UNIVERSITY OF BIRMINGHAM

HEALTH AND SUPPORTIVE CARE NEEDS OF SURGICAL LUNG CANCER PATIENTS, AND THE PROGNOSTIC SIGNIFICANCE OF SMOKING

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Abstract

Aims This thesis investigated the health and supportive care needs of surgical lung cancer patients to address gaps in the evidence base and inform future service developments. Additionally, the prognostic significance of smoking behaviour was investigated.

Methods Semi-structured interviews were conducted with 29 surgical (VATS and thoracotomy) lung cancer patients to explore health, functioning, smoking, satisfaction with recovery and preferences for a tailored rehabilitation programme. Interviews were analysed using framework approach. Systematic literature searches were conducted to review evidence of the association between smoking history or continued smoking after diagnosis and prognosis. Survival estimates were combined where possible using a random effect inverse variance model.

Results Most participants experienced difficulty during recovery. Breathlessness and pain emerged as dominant health challenges. Participants were open to being offered smoking cessation support. From 78 and 10 studies, preliminary evidence was found that both smoking history and continued smoking are associated with prognosis, respectively. Analyses indicated that smoking-associated increased risk may be mediated through cancer-related pathways.

Conclusions Many surgical lung cancer patients' supportive care needs are not being met. Well developed treatments and services for management of breathlessness, pain and smoking cessation may improve quality of life and health outcomes after lung cancer surgery, and require further testing.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ASA American Society of Anaesthesiologists

BHH Birmingham Heartlands Hospital

BMI body mass index

BS borg scale

BT breathlessness typology

BTS British Thoracic Society

CHD coronary heart disease

CI confidence interval

CNS clinical nurse specialist

CO carbon monoxide

CO2 carbon dioxide

COPD chronic obstructive pulmonary disease

CR cardiorespiratory

CRF Cancer Reform Strategy

ECOG Eastern Cooperative Oncology Group

EGFR epidermal growth factor receptor

EORTC European Organisation for Research and Treatment of Cancer

FEV1 forced expiratory volume

FVC forced vital capacity

HPV human papillomavirus

HR hazard ratio

HTO Healthtalkonline

IASLC International Association for the Study of Lung Cancer

IASP International Association for the Study of Pain

MDT multidisciplinary team

MRC Medical Research Council

NCRI National Cancer Research Institute

NCSI National Cancer Survivorship Initiative

NICE National Institute for Health and Clinical Excellence

NRT nicotine replacement therapy

NSAID non-steroidal anti-inflammatory drug

NSCLC non-small cell lung cancer

NSPCR National School of Primary Care Research

PID patient identification

ppts participants

PT pain typology

QOL quality of life

ROC Rehabilitation for Operated lung Cancer programme

SCLC small cell lung cancer

TNM tumour, node, metastasis

UHB University Hospital Birmingham

VATS video-assisted thoracic surgery

VEGF vascular endothelial growth factor

WRI Worcester Royal Infirmary

CHAPTER

ONE

INTRODUCTION

1.1 Thesis aims and outline

The aim of this thesis is to investigate key issues surrounding the health and supportive care needs of lung cancer patients treated with surgery for curative intent. It has been recognised that lung cancer receives less research attention than other cancers,[1] and there are gaps in the evidence base regarding the supportive care needs of this population. The investigations reported in this thesis were conducted with the intention of addressing some of these gaps, and to aid tailoring of supportive care to the needs of this patient group in future service developments. Within other areas of medicine, rehabilitation programmes form an important part of supportive care, for example cardiac, stroke or pulmonary rehabilitation.[2–4] In addition to describing the health and supportive care needs of patients during the first year after surgery, patients' attitudes towards health behaviour change and also preferences regarding the content and format of a tailored rehabilitation programme are also explored. Although the causal role of smoking in the development of lung cancer is well known, there is no consensus regarding prognostic significance of smoking history, or of continued smoking after diagnosis. As understanding the

prognostic significance of smoking is relevant to patient counselling and rehabilitation, this was also investigated by means of two systematic reviews of the evidence relating to these areas. I will now summarise the aim and content of each chapter of this thesis to help orientate the reader, and to explain how I have addressed these issues of investigation.

The aim of Chapter 1 is to introduce the broad topics that this thesis refers to. Using the latest available statistics, the current epidemiological profile of lung cancer is presented, along with predictions for growth of the lung cancer survivor population over the next three decades. A brief overview of the processes involved in thoracotomy and video assisted thoracic surgery (VATS) is presented, along with treatments that are commonly used in conjunction with surgery. Next, I present an overview of what is already known regarding specific issues that underpin the investigations presented in this thesis, namely health and functioning of surgical lung cancer patients and health behaviours with a focus on smoking. I then summarise some of the landmark developments that have occurred within cancer services over the past two decades and describe key activities that have been ongoing as a result of government strategy to improve the care of cancer survivors in general. Finally, I outline the rationale for developing supportive care services for surgical lung cancer patients and summarise the thesis aims.

Chapter 2 - 4 presents a qualitative interview study conducted with surgical lung cancer patients recruited from Birmingham Heartlands Hospital. This study had four aims. First, participants' experiences of health and functioning during the first year after surgery are explored, in order to understand the main challenges that these patients face during this time and identify potential needs to be addressed by supportive care services. Second, participants' attitudes towards smoking and smoking cessation, and the role of the NHS in providing support for smoking cessation as part of the cancer care pathway is investigated. Third, with participants that received standard care, attitudes towards recovery, supportive care received and preferences for the content and format of a tailored rehabilitation programme are explored. Fourth, with those who participated in a rehabilitation programme that was being piloted at the time of the qualitative interview study, attitudes towards recovery, supportive care received as part of the programme and design

changes needed to improve tailoring are explored. The interview findings related to each of these aims are discussed in the context of other relevant published studies and suggestions for a rehabilitation programme are presented.

Chapter 5 investigates the relationship between smoking history and the prognosis of lung cancer by means of a systematic review, meta-analysis and meta-regression using longitudinal observational data. There are many studies that have reported observational data on the relationship between smoking history and prognosis, but results are mixed and a review is warranted. Longitudinal observational studies are the best evidence available to consider this relationship, although allow inference of association only rather than confirmation of a causal link. It is biologically plausible that smoking history may confer a greater risk of disease progression, cancer-related death or death due to co-morbid disease. Mediation of risk through pathways related or unrelated to cancer is investigated along with the importance of recency and heaviness of smoking history.

Chapter 6 aims to investigate the case for smoking cessation support as an integral part of surgical lung cancer patient care. Specifically, based on similar methods to the review reported in chapter 5, the association between continued smoking and prognosis is investigated by means of a systematic review with meta-analysis. This review has been published by the BMJ in January 2010. In the absence of randomised controlled trials of smoking cessation interventions with lung cancer patients that measure prognostic outcomes, this relationship is also investigated using data from longitudinal observational studies. Indications that smoking cessation even at this late stage could be beneficial to prognosis would be an important message to give to patients, and would strengthen the case for smoking cessation support to be an integral part of cancer care.

Finally, the aim of chapter 7 is to bring together the findings of the studies reported in chapter 2 - 6 to draw overarching conclusions and make recommendations for future research.

1.2 How cancer develops

Cancer is initiated by critical changes to the genome of an individual cell.[5] Once initiated, these pre-neoplastic lesions are understood to move through distinct phases in which a tumour mass develops and then spreads to colonise other parts of the body, a process known as metastasis.[6] The biological processes involved from genetic change through to development of the neoplastic and metastatic phenotypes are many and diverse, and not completely understood. However, rapid advances in research and technology are leading to ever more detailed understandings, and driving forward development of more effective treatments.[7]

In 2000, Hanahan and Weiberg published a seminal peer-reviewed work proposing that in order to develop and spread a tumour must acquires six functional capabilities, the so called 'six hallmarks of cancer.'[8] Although different tumour types may gain these capabilities through different mechanisms, tumour survival and development is dependent on these capabilities of evading apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, sustained angiogenesis, limitless replicative potential and tissue invasion & metastasis.[8]

Genetic drivers of lung cancer development are thought to primarily involve mutation of genes that encode for the epidermal growth factor receptor (EGFR) and K-Ras proteins. Mutations of genes coding for EGFR are more commonly associated with non-smoking related lung tumours,[9] and are thought to lead to over-expression or activation of the EGFR receptor.[10] Activation of the EGFR pathway plays an important role in cell proliferation, apoptosis, angiogenesis and invasion.[9] The *ras* gene family encodes for membrane bound GTPase binding proteins that regulate cell growth, differentiation and apoptosis, and mutations may lead to deregulation of these processes.[11, 12] Other frequent mutations associated with lung cancer, as well as other tumours, are of genes encoding the tumour suppressor protein p53 and the vascular endothelial growth factor (VEGF) signal protein.[13]

1.3 Epidemiology of lung cancer

1.3.1 Incidence and histological classification of lung tumours

In the UK, the annual incidence of lung cancer is second only to breast cancer, and in 2010 accounted for over 42 000 new cancer diagnoses.[14] Histological classification of lung tumours fall into two main categories; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for around 85% of incident lung tumours,[15, 16] and can be sub-divided into three main histological types: squamous cell carcinoma (35-45% of NSCLC tumours), adenocarcinoma (35-40% of NSCLC tumours) or large cell carcinoma (around 10% of NSCLC tumours).[17] Generally, squamous cell tumours arise from cells that are located within the central bronchi, whereas adenocarinoma and large cell tumours are located peripherally.[18] Small cell carcinoma arises from neuroendocrine cells located more centrally within lung tissue and is the most aggressive histological type of tumour.[19] Historically, incidence rates have been highest for squamous cell carcinoma.[18] However, during the 1970s and 1980s, the incidence of squamous cell carcinoma began to decrease whereas incidence of adenocarcinoma increased.[20, 21] It is thought that this change in trend may have been partly due to the introduction of porous wrapping paper and perforated filters for manufactured cigarettes which allowed deeper inhalation of smoke.[18, 22, 23] Other rarer histological types of lung cancer include adenosquamous, sarcomatoid, carcinoid and salivary gland lung tumours.[17, 24]

1.3.2 Risk factors for the development of lung cancer

Smoking is the main risk factor for lung cancer, increasing risk of developing all main histological sub-types.[25, 26] In countries which have seen a high prevalence of smoking, currently around 90% of lung cancer diagnoses are attributable to smoking.[27] Smoking is most strongly associated with the development of small cell carcinoma and squamous cell carcinoma, followed by large cell and adenocarcinoma.[26] The risk of lung cancer associated with smoking

has most commonly been studied in terms of lung cancer death, rather than lung cancer incidence.[23, 28–31] Over the past 50 years, the age-adjusted risk of death from lung cancer in men and women who smoke has increased as successive cohorts have started to smoke earlier in their lifetime, and people have developed more regular and heavier smoking behaviours.[23] The earliest evidence regarding the size of increased risk came from men, as smoking behaviour became established earlier in men than in women.[32] In the past there has been uncertainty as to whether the risk of death is as great for women who smoke as it is for men, as women were not yet demonstrating the same burden of risk.[23] However, a recent US study found that women have now 'caught up' with men in terms of risk. Age-adjusted estimates based on current smokers aged 55 years and above between 2000-2010 showed that men had a 27 fold increased risk of dying from lung cancer and for women the increased risk was 26 fold compared to never smokers (men RR 27.32 (24.30, 30.70), women RR 26.18 (23.65, 28.98)).[23]

Other environmental risk factors for the development of a lung tumour include exposure to asbestos, ionising radiation and air pollution.[27] Although these environmental factors increase the risk of developing a lung tumour, host susceptibility has also long been recognised as being important.[33] Not all who are exposed to risk factors develop lung cancer, and evidence from case-control and cohort studies show that family history of lung cancer predicts risk.[27, 34] Racial disparity of incidence relative to smoking prevalence is particularly notable for African-American males, and it is thought that this group may carry genetic susceptibility to the carcinogenic effects of tobacco smoke.[27, 35]

1.3.3 Temporal trends of lung cancer incidence

Lung cancer incidence has changed dramatically within demographic strata over the 20th century, largely based on changes in smoking prevalence 20-30 years previously.[27, 36, 37] In the first two decades of the twentieth century lung cancer was a rare disease. However, incidence began to rise sharply in men in the 1930s until the 1950s, after which it began to steadily fall. Females followed with a rise in incidence that began in the 1960s and as yet, continues to

climb.[27] Currently, more men than women develop lung cancer: in 2010, a total of 23 175 men were diagnosed with a lung tumour whereas 18 851 female cases were recorded in the UK.[14] It is predicted that over the coming years incidence in women will begin to outstrip incidence in men.[27, 38]

The rise in incidence seen since the 1930s has mainly been in the older age groups.[39] Incidence rate remained relatively low for people in their 40s and 50s. However, incidence in people diagnosed above 60 years of age increased.[39] Over the past decade, there has been a marginal decrease in incidence rates in men for most age groups, apart from those age 70-79 years who have seen a more marked decline. Today, incidence is highest in age 80 or above (see figure 1.1).[14] For women, every 10-year birth cohort from age 60 upwards has seen a steady increase in incidence over the past decade, most markedly so in those aged 60-69 and 80+. Again, incidence is highest in women aged 80 or above (see figure 1.2).[14]

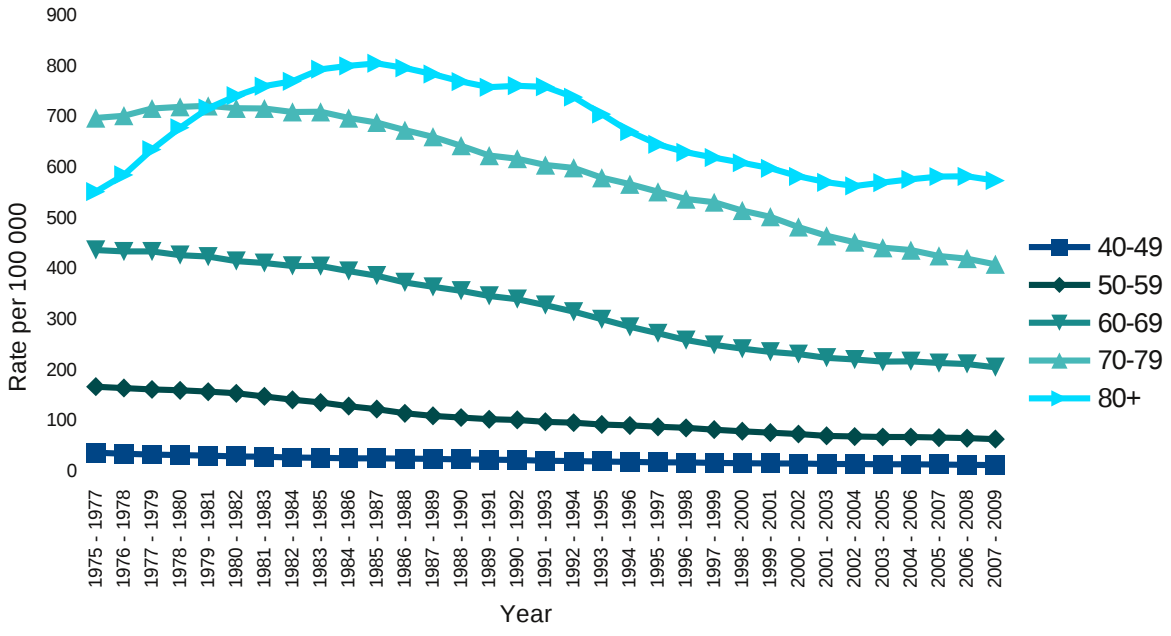


Figure 1.1: European age-standardised incidence rates per 100,000 population in males by age in Great Britain. [Source: Cancer research UK, cancer statistics]

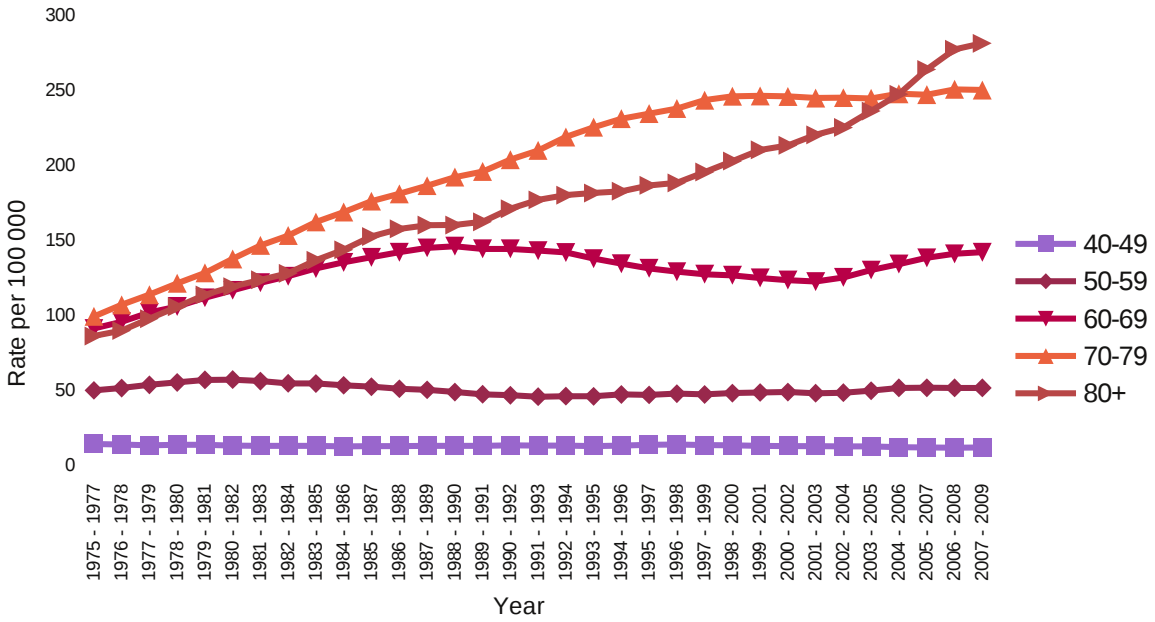


Figure 1.2: European age-standardised incidence rates per 100,000 population in female by age in Great Britain. [Source: Cancer research UK, cancer statistics]

1.3.4 Predicted future prevalence of lung cancer survivors

1.3.5 Survival rates

Lung cancer is the largest cause of cancer death, accounting for 22% of all cancer deaths in the UK in 2010.[41] Unlike other cancers, 5-year survival rates in the UK have shown only marginal improvement over the past four decades, and survival rates are lower than most other European countries as well as Australia and Canada.[42, 43] Of the 21 most common cancers, lung cancer has the second lowest survival rate, with around 30% of patients surviving for one year and 8% for 5 years.[41]

Histological cell types of lung tumour grow at different rates, and faster growing tumours have poorer survival rates.[18] A lung tumour is thought to be detectable after 30 cell division cycles. However, symptoms usually arise later than this and diagnosis is often delayed. Fatality occurs after 40 cycles.[39] Small cell tumours are the fastest growing tumour, doubling monthly whereas squamous cell tumours double every 3 months and adenocarcinoma doubles every six

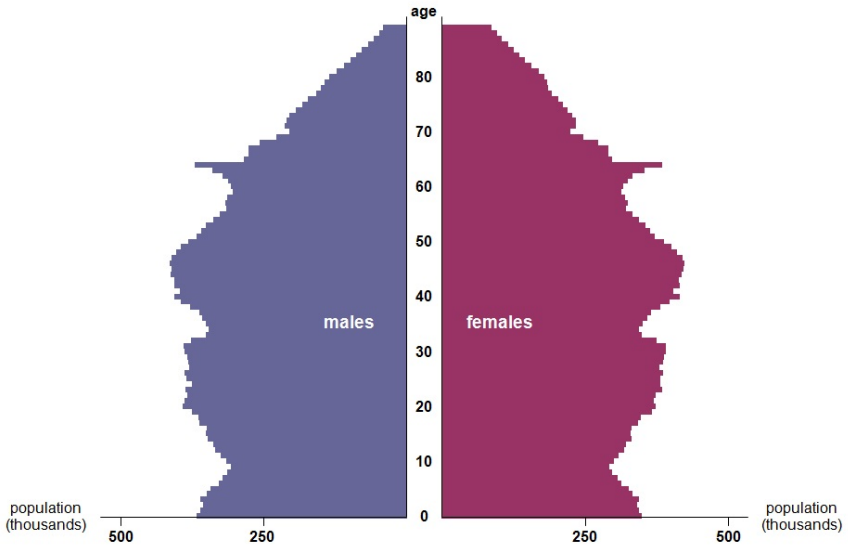


Figure 1.3: Population pyramid for England and Wales, mid 2011. [Source: Office for National Statistics][40]

months.[39] As such, small cell tumours progress from being detectable to causing death within 6 months - 1 year, whereas this occurs within 1-2 years and 2-4 years for squamous cell and adenocarcinoma tumours respectively.[39]

Treatment with surgery, radiotherapy or chemotherapy significantly increases survival.[44] Currently, over 70% of lung cancer tumours are diagnosed at an advanced stage and are unable to receive curative treatment.[14] However, around 20-30% of NSCLC tumours are diagnosed at a stage eligible for surgery, and the 5-year survival of this group can be as high as 73%.[45] In addition to tumour stage, a number of other factors are taken into account before surgical treatment is decided upon, such as a patients' age, co-morbidity and performance status (see section 1.4).[46, 47] Not all patients with potentially operable tumours are fit for surgery, and on average 14% of lung cancer patients in Great Britain and Northern Ireland underwent radical surgery in 2010.[48] Most cases of small cell lung cancer are diagnosed in advanced stages. Treatment with chemotherapy or radiotherapy can extend survival for those in early stages. However, given the aggressive nature of the disease the prognostic benefit is small.[46]

Looking in more detail at lung cancer survival rates within demographic stratum some patterns can be seen, particularly for age and socio-economic group. In 2010, 5-year age-standardised

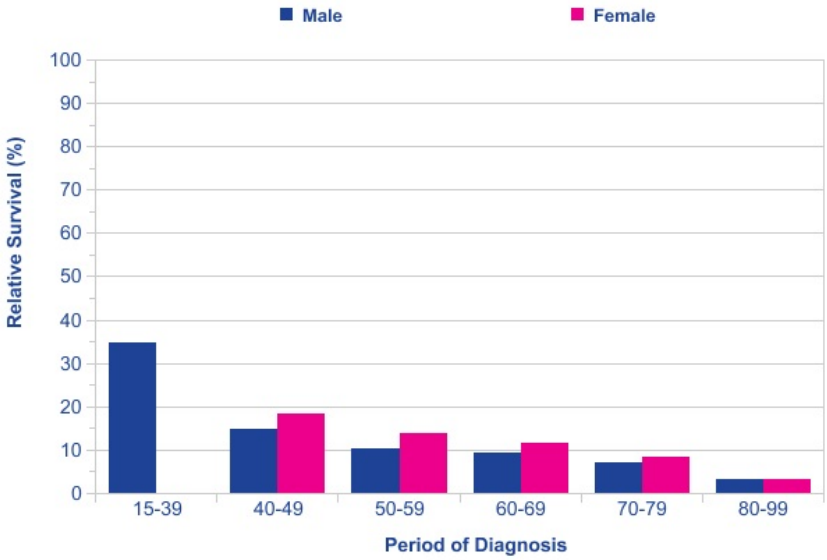


Figure 1.4: Five-year relative survival rates by age and gender.
(Average relative survival for years 2005-2009, data for females aged 15-39 not available. [Source: Cancer research UK, cancer statistics])

survival rates for men and women in the UK were both low at 6%. When looking at men and women combined, relative survival rates decrease with increasing age (see figure 1.4).[49] Relative survival takes into account deaths from other causes, as the survival rate is calculated relative to the number of deaths that would be expected in corresponding demographic strata in the general population. Therefore, this difference represents an excess risk of death due to lung cancer rather than being explained by normal age-related increased risk of death.[50, 51]

Inequalities in survival by socio-economic status have also been reported, particularly in men. A recent UK population-based study reported a significant 1.4% difference in relative survival between men in the highest and those in the lowest strata of deprivation, who were diagnosed between 1986 and 1990.[52] Although this number is small, given the large number of men who are diagnosed with lung cancer each year this results in an important rise in the number of deaths within more deprived groups.[49] The deprivation gap between women was smaller and non-significant.[52] Socio-economic inequalities in survival may be due to a number of factors, including later presentation [44], lower probability of receiving timely active treatment [53] and lower rates of use of the NHS in deprived groups.[54, 55]

1.3.5.1 Lung cancer staging systems

Treatment is strongly indicated by stage at diagnosis, which describes the extent to which a tumour has developed and spread. A patients' tumour may be staged based on clinical observations, for example using imaging or bronchoscopic investigations or on pathological investigation.[46] There have been a number of iterations of the classification system of tumour stage.[45] Classification of a NSCLC tumour is based on assessment of T (tumour), N (node) and M (metastasis) components, and tumours are further classified into five stage groups based on the size and positioning of the tumour, extent of metastasis to regional lymph nodes and to distant sites (see table 1.1 for description of TNM classifications, and table 1.2 for description of stage grouping). This staging system has some applicability to SCLC, but often a tumour is simply classed as being of 'limited' or 'extensive' stage.[56] Survival differs by stage at diagnosis. A recent study based on more than 81 000 patients from 19 countries reported survival rates based on clinical or pathological staging. For NSCLC, five year survival rates ranged from 43 - 73% for patients diagnosed with a stage I tumour, 25-46% for patients diagnosed in stage II, 7-9% for patients diagnosed in stage III and ranged from 2-13% for patients diagnosed with a stage IV tumour.[45] In contrast, 25% of patients diagnosed with limited stage SCLC survive for 2 years, and less than 5% of patients survive for 5 years with extensive SCLC.[41]

1.3.6 The prognostic significance of smoking exposure for surgical lung cancer patients

The single most important arbiter of prognosis is receipt of curative treatment, which is largely determined by tumour stage at diagnosis.[57] The main stay of curative treatment for lung cancer is surgery.[46, 47] Although successful surgery increases survival, rates are still lower than in corresponding demographic strata of the general population.[58] Some studies have described the risk of various causes of death after lung cancer surgery. It is likely that risk of death after surgery remains higher than the general population due to risk of disease relapse and

Table 1.1: Definitions for T, N and M descriptors: International Associations for the Study of Lung Cancer (IASLC) lung cancer staging classification

TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a	Tumour 2 cm in greatest dimension
T1b	Tumour 2 cm but 3 cm in greatest dimension
T2	Tumour 3 cm but 7 cm or tumour with any of the following features (T2 tumours with these features are classified T2a if 5 cm) Involves main bronchus, 2 cm distal to the carina. Invades visceral pleura associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumour 3 cm but 5 cm in greatest dimension
T2b	Tumour 5 cm but 7 cm in greatest dimension
T3	Tumour 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial) effusion
M1b	Distant metastasis

Table 1.2: TNM stage groupings based on IASLC classification

Occult tumour	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a, b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1,T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a, b

cancer related death, although studies indicate that up to half of patients treated with surgery die from co-morbid disease.[59–64] Complications after surgery also elevate the risk of death, and in particular surgical lung cancer patients are at an increased risk of dying from major infections.[65] The causal role of smoking in the development of lung cancer is widely recognised, but it is also possible that smoking exposure (i.e. smoking history or continued smoking after diagnosis) may be associated with prognostic outcome after lung cancer surgery by either increasing the risk of disease progression and death from cancer, or by increasing the risk of non-cancer related death due to co-morbid disease.[31, 61] Smokers are also more likely to develop complications after lung cancer surgery.[66] However, the prognostic significance of smoking exposure for surgical lung cancer patients has not been reviewed. Chapter 5 and 6 of this thesis report two systematic reviews that sought to investigate the relationship between smoking exposure and prognosis, focusing on prognostic significance of smoking history and of continued smoking after diagnosis, respectively.

1.4 Lung cancer treatment

1.4.1 Curative treatment

The mainstay of curative treatment for lung cancer is surgery. Radical surgery is considered firstline treatment for patients with NSCLC who are diagnosed between stage I-IIIa.[46, 47] Patients with stage IIIa NSCLC tumours may also undergo surgery with curative intent, al-

though this is often supplemented with adjuvant therapy.[44, 47] Patients with limited-stage SCLC (T1-2a, N0, M0) may be considered for surgery. However, it is rare that SCLC tumours have not developed beyond this stage at presentation.[46] Depending on the stage and position of the tumour, surgery can involve removal of a small section of lung tissue (wedge resection, or segmentectomy), a whole lung lobe (lobectomy) or a whole lung (pneumonectomy).[67]

An alternative curative treatment to surgery is radical radiotherapy. This is offered to patients who are too unwell to undergo surgery and have an unacceptable risk of post-surgical complications.[46, 47] It may also be offered to patients who are unwilling to undergo surgery, or who have an early stage tumour which is inoperable. [68]. During radical radiotherapy treatment, ionizing radiation is delivered to affected areas of the body by an external beam.[69] Conventionally, direction/coverage of the beam has been determined from 2-D imaging. Advances have led to an improvement in the precision of the delivery of external beam radiation, notably using sterotactic techniques which involved 3-D imagining.[70, 71] Radical radiotherapy treatment regimes occur over a shorter period of time than radiotherapy given as an adjuvant palliative treatment. Radiation may be delivered as daily treatment for up to 7 weeks, or a more intensive regime of continuous hyper–fractionated accelerated radiotherapy (CHART) delivered over the period of 12 days.[68, 69, 71] Even though this treatment is considered to be curative, in general survival rates are lower that those seen after radical surgery. [68, 72] However, advances such as stereotatic techniques promise to lead to improvements in survival.[70, 73, 74]

Given that the aims of this thesis are to consider the supportive care needs of lung cancer survivors (i.e. of patients treated curatively rather than palliatively), it would be relevant to explore both patients treated with radical surgery and radiotherapy. However, I have been unable to collect or use data from patients treated with radical radiotherapy. This was due to difficulties during recruitment to the qualitative interview study (for details see section 2.3.2). Similarly, no studies included in the systematic reviews of the effect of smoking history or continued smoking after diagnosis were conducted on patients who received radical radiotherapy (for details see section 5.4.1 and 6.4.1). Therefore, this thesis has concentrated on assessing the supportive

care needs and the prognostic significance of smoking for surgically treated lung cancer patients only.

1.4.1.1 Surgical treatment

Surgical procedures Surgery for lung cancer can either be performed via thoracotomy or thoroscopically (video assisted thoracic surgery, VATS).[46] Thoracotomy involves a 15-25cm incision between the 5th and 6th ribs, cutting through skin and all layers of intercostal muscle (figure 1.5a). Depending on the location of the tumour, entry to the thoracic cage may be made under the arm (axillary), from the back to the side (posterolateral) or under the breast (anterolateral). In order to gain sufficient access necessary to resect lung tissue, ribs are spread using metal retractors or sometimes excised (figure 1.5b).[75] VATS does not require retraction of the rib cage, and involves small 2.5 cm incisions for the insertion of a camera and surgical tools (figure 1.6a and 1.6b).[76] The tumour mass is palpated (thoracotomy) or located (VATS) (figure 1.5c and 1.6c). Ligamentous attachments are dissected. Significant blood vessels and bronchial tubes are isolated, ligated and transected, to free the lung tissue and interrupt the vascular supply to the area for resection (figure 1.5d, 1.5e). Transection of larger vessels is performed using a stapling device (figure 1.5f and 1.6d), eventually freeing the lung tissue for resection (figure 1.5h). In the case of a VATS procedure, the resected lung tissue is bagged and removed through one of the openings to the thoracic cavity (figure 1.6e and 1.6f). If necessary, lymph nodes are dissected (figure 1.6g). To prevent air leakage, the remaining lung tissue is stitched together (figure 1.5h). In order to prevent the build up of air (pneumothorax) and fluid (pleural effusion) within the intrathoracic space, a chest drain is inserted for a few days after surgery after both thoracotomy and VATS (figure 1.6h).[77]

Assessment for suitability for surgery Guidelines for deciding patient suitability for surgical treatment are published by the British Thoracic Society[47] and the National Institute for Health and Clinical Excellence (NICE).[46] In order to identify patients at high risk of perioperative death, a cardio-vascular event or unacceptably high levels of post-surgical breathlessness,

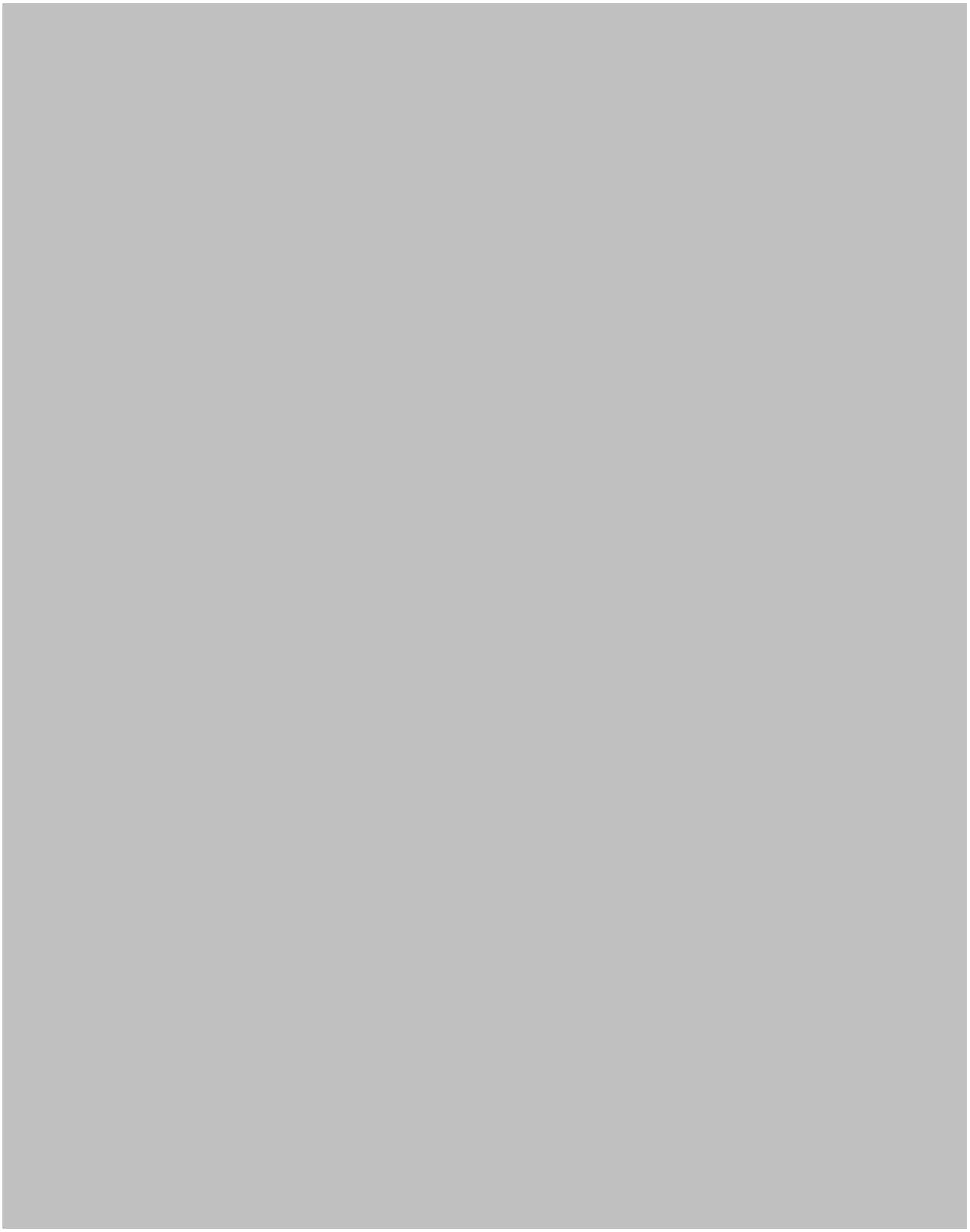


Figure 1.5: Lung lobe resection via thoracotomy. Source:
http://www.youtube.com/watch?v=OJbgWFt1jWg]

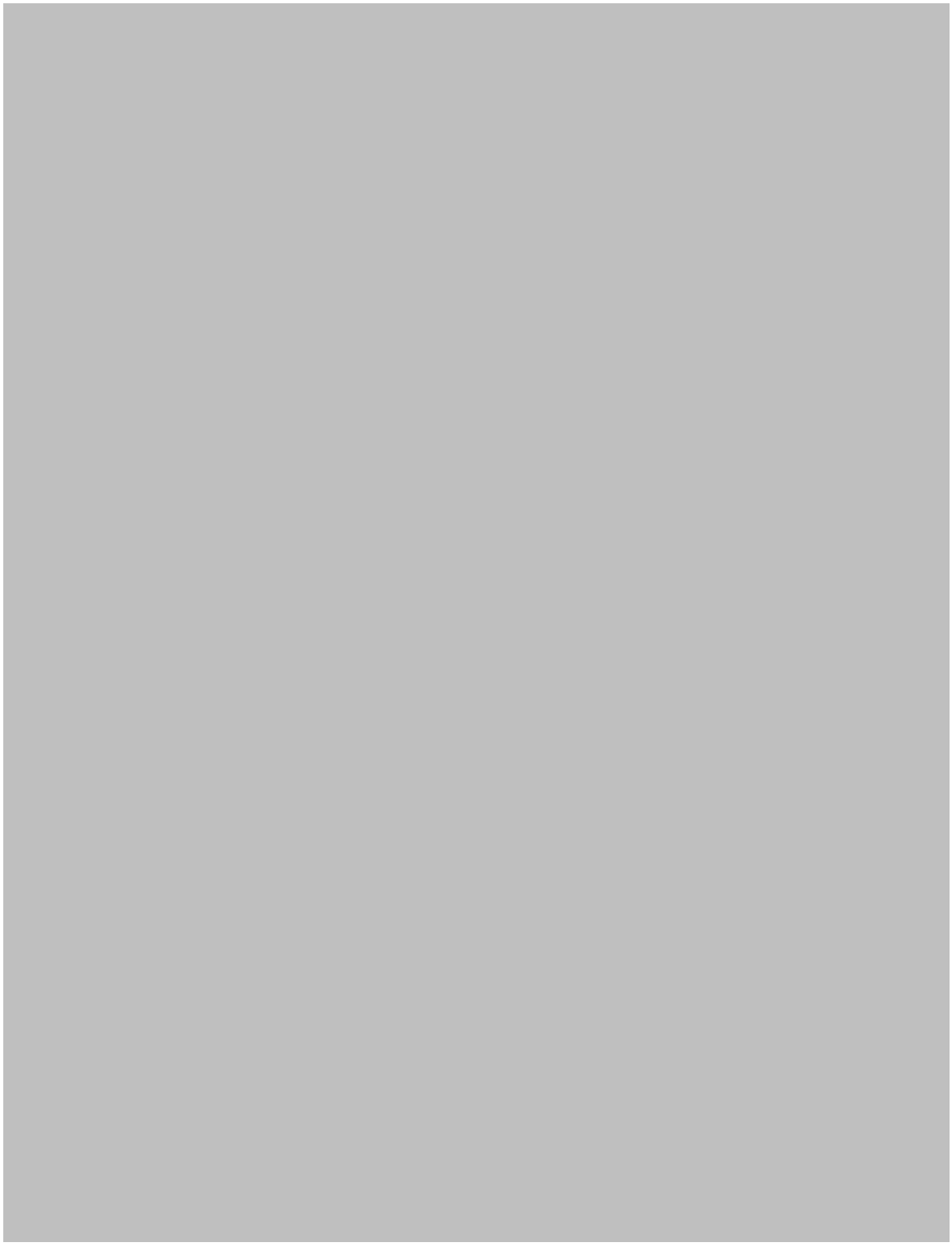


Figure 1.6: Removal of lung lobe via VATS procedure. [Source: http://www.youtube.com/watch?v=SlG8Mf5RdCY]

these guidelines recommend that several tests are performed to assess patients' fitness before decisions about surgical treatment are made. These include a range of respiratory function tests and exercise tolerance tests to test cardio-pulmonary fitness. Tests used to assess respiratory function include those that measure ventilation, including spirometric measures such as FVC (forced vital capacity), FEV_1 (force expiratory volume in 1 sec) and FVC/FEV_1 ratio and those that test gaseous exchange such as oxygen saturation tests and CO_2 transfer (DLCO). The shuttle walk test and cardio-pulmonary exercise tests are also recommended as a functional assessment and to assess cardio-pulmonary fitness. [1] In addition, guidelines recommend the calculation of the thoracoscore which indicates risk of perioperative mortality,[78] and is based on age, gender, American Society of Anaesthesiologists (ASA) score (classifies extent of systemic disease), performance status classification (measures extent to which patients' day to day activities are effected by disease symptoms), MRC breathlessness score, priority for surgery (elective/emergency), extent of resection, malignant/benign disease and number of co-morbidities.

As a general guideline, in order to tolerate lobectomy or pneumonectomy, patients must demonstrate an (FEV_1) of >1.5L or >2L respectively.[79] A post-operative predicted FEV_1 of $\geq 30\%$ is generally considered to be the cut off for those at low or medium/high risk of developing post-surgical breathless.[46, 47] However, the latest British Thoracic Society (BTS) and NICE guidelines have a more permissive stance on acceptance for surgery than previous guidelines.[46, 47] Cut off levels for acceptable scores on fitness for surgery tests have remained the same, or in the case of thoracoscore are not given, but guidelines stress that patients must be informed about level of risk of adverse post-surgical outcomes and then be given the choice as to whether to proceed or not. Therefore, it is possible that in the future, greater numbers of patients of borderline fitness may undergo surgery, with the consequence of more patients experiencing high levels of post-surgical breathlessness.

[1] During a shuttle walk test, patients walk around two cones placed 10m apart to the pace of auditory beeps. The pace is gradually increased and exercise tolerance/breathlessness are assessed.

1.4.2 Adjuvant treatment

For many years, it has been standard practice to supplement surgery with adjuvant chemotherapy regimes for other tumours, but there has not been sufficient evidence to recommend this for lung tumours.[44] However, over the past decade strong evidence has emerged to recommend adjuvant chemotherapy for patients after resection of early NSCLC [80]. Current BTS guidelines recommend offering a cisplatin-based combination therapy regimen to patients with T1-3N1-2M0 NSCLC, and recommend also considering this treatment for patients with a T2-3N0M0 NSCLC tumour >4 cm diameter.[46, 47] The role of adjuvant radiotherapy after lung cancer resection has also been controversial over past decades, with mixed evidence of its effectiveness.[81, 82] Currently, radiotherapy is not indicated for patients with complete resection of early stage tumours, but is recommended when microscopic evidence of disease spread is found within the resected tumour margins. For patients with T1-4N0-M0 limited stage SCLC tumours, chemotherapy and radiotherapy are both indicated. Chemotherapy and radiotherapy are recommended to run concurrently for those patients with good performance status, or sequentially for those who would not tolerate combined treatment.[46, 47]

1.5 Health and functioning of lung cancer patients during the first year after surgery

It has been noted that there is a lack of research outlining the 'natural history' of cancer survivorship in terms of health experiences (see section 1.7.2). The first aim of the qualitative interview study that is documented in chapters 2 to 4 of this thesis was to explore patients' experiences of health and the effect of health on functioning during the first year after surgery for lung cancer. Previously published literature in this area was reviewed before commencing the qualitative interview study in order to help with construction of the interview guide (see table 2.2). An overview of what is already known about the health and functioning of lung cancer

patients after surgery is presented below.

1.5.1 Quantitative quality of life (QOL) studies

Historically, research exploring QOL has focused on patients surviving childhood cancers. However, during the past decade there has been an increasing focus on the QOL of adult survivors.[83] Even so, the survivorship experience of lung cancer patients has been studied less than patients with other cancers.[83, 84] There have been a variety of tools developed to assess QOL, some of which have been developed specifically to capture lung cancer specific issues and have been validated in this patient group. A review published in 2012 found that the most widely used validated tools in lung cancer are the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ C-30), a generic tool for assessing health related quality of life in cancer patients, and the EORTC QLQ LC-13 which is a lung cancer specific quality of life tool.[85] The C-30 questionnaire contains 30 questions and is used to calculate five functional scales (physical, role, cognitive, emotional, and social), eight symptoms (fatigue, pain, nausea and vomiting, dyspnoea, loss of appetite, insomnia, constipation and diarrhoea), a global health status / QOL scale and perceived financial impact of the disease. The LC-13 questionnaire contains 13 questions regarding lung cancer specific symptoms. Other generic QOL tools, such as the SF-36, have been used to assess QOL in lung cancer patients which calculates scores for vitality, physical function, bodily pain, general health, physical role, emotional role, social role functioning and mental health.

During preparations for conducting the qualitative study, twelve studies [86–97] measuring QOL in surgical patient populations were identified that had been published between 1995 and 2009. For a summary of these studies see table 1.3. All twelve studies showed that patients experience reduced QOL in comparison to baseline scores in various domains as well as lung cancer specific symptoms for at least 1 month after surgery. However, there was mixed evidence on the amount of functional impairment, severity of symptoms, and the length of duration of impairment/ symptoms. In particular, studies indicated that physical, role and social function

can remain impaired and that patients may also experience prolonged breathlessness, pain and fatigue for twelve months or more. Generally, impairment/symptoms were found to be greater and endure longer for those undergoing pneumonectomy compared to lobectomy or wedge resection,[87, 88] for thoracotomy compared to VATS procedure [86] and for those experiencing disease progression.[93] Lung cancer QOL has also been shown to be worse compared to patients with other cancers [98] and the general population.[90, 92] Most of the studies (7/9) were conducted in samples smaller than 150 patients, and no studies had taken account of differences in baseline characteristics when comparing groups. However, these studies indicate some of the most prevalent quality of life issues facing lung cancer patients during their first year after surgery.

Given the differences reported in these scores, recruitment of patients to the interview study reported in chapters 2 - 4 aimed to represent both patients who had undergone thoracotomy and those who had undergone VATS as well as those who had received more or less conservative tissue resection. Other sub-groups were also represented in the sample (see section 2.3.4).

Table 1.3: Summary studies measuring QOL in lung cancer patients during the first year after surgery

Author, date (country of study)	Lung cancer population comparisons	*n*	QOL scale used	When measured	Main findings
Aoki, 2007 (Japan)	1. VATS 2. Thoracotomy	33	SF-36	3 months 12 months (also 36 months)	VATS - General health and physical function remained impaired at 12 months although not significantly. Thoracotomy - Physical function, Role-physical, Role- emotional and general health remained significantly impaired at 12 months after thoracotomy
Balduyck, 2007 (Beligium)	1. Wedge resection 2. Lobectomy 3. Pneumonectomy 4. VATS 5. Thoracotomy	100	EORTC QLQ-C30 and LC13	Pre-surgical 1 month 3 months 6 months 12 months	Wedge resection and lobectomy - Decrease in functioning and increase in pain after 1 month, lobectomy patients also have an increase in breathlessness at 1 month. By 3 months, all scores returned to baseline, apart from pain after lobectomy Pnemonectomy - no return to baseline in physical function, role function, pain or breathlessness during first 12 months. VATS and thoracotomy - physical function, QOL and thoracic pain improvements in VATS compared to thoracotomy. Posterolateral thoracotomy more painful than anterolateral thoracotomy

Table 1.3: cont.

Author, date (country of study)	Lung cancer population comparisons	*n*	QOL scale used	When measured	Main findings
Balduyck, 2008 (Belgium)	1. Sleeve lobectomy 2. Pnemonectomy	30	EORTC QLQ-C30 and LC13	Pre-surgical 1 month 3 months 6 months 12 months	Sleeve lobectomy - decrease in role and physical function at 1 month after which all score returned to baseline Pneumonectomy - Breathlessness, general pain, thoracic pain, shoulder dysfunction remained significantly impaired at 12 months
Balduyck, 2009 (Belgium)	1. Lobectomy (age 70-79) 2. Pneumonectomy (age 70-79)	60	EORTC QLQ-C30 and LC13	Pre-surgical 1 month 3 months 6 months 12 months	Lobectomy - All scores returned to baseline 3-6 months after surgery, apart from physical function and breathlessness that remained impaired at 12 months Pnemonectomy - All scores returned to baseline at 1 months, apart from breathlessness and general pain that returned to baseline at 3 and 6 months, respectively.
Brunelli, 2007 (Italy)	1. Thoracotomy 2. General population	156	SF-36	Pre-surgical 1 month 3 months	Physical composite score reduced at 1 months and returned to baseline at 3 months. Mental composite score remained unchanged

Table 1.3: cont.

Author, date (country of study)	Lung cancer population comparisons	*n*	QOL scale used	When measured	Main findings
Dales, 1994 (Canada)	1. Thoracotomy, malignancy confirmed 2. Thoracotomy, no malignancy	117	Pnemonoconiosis research unit index (PRU)	Pre-surgical 1 month 3 months 6 months 9 months	31% with severe breathlessness at 3 months, but returned to approximate baseline levels (10%) after 9 months. Impairment greater for those who had been diagnosed with cancer compared to those with no confirmed malignancy
Handy, 2002 (USA)	1.Thoracotomy and VATS 2. Matched healthy patients	139	SF-36 Ferrans and Powers QLI	Pre-surgical 6 months	Some domains remained significantly impaired after 6 months - physical function, role-physical, bodily pain and mental health QOL significantly impaired compared to healthy controls
Kenny, 2008 (Australia)	1. Stage I or II NSCLC surgical patients without recurrence 2. Stage I or II NSCLC surgical patients with recurrence	173	EORTC QLQ-C30 and LC13	Pre-surgical Discharge 1 month 4 months 8 months 12 months (also 16, 20, 24 months)	No recurrence - improvement up to 4 month after surgery in overall QOL and functioning, but physical, role and social function remained below pre-surgical levels. Pain, fatigue and breathlessness score remained significantly impaired at 4 months. 53% and 40% had worse breathlessness and fatigue after 12 months compared to baseline Recurrence group - some post-surgical recovery but deterioration in all domains after recurrence apart from emotional functioning.

Table 1.3: cont.

Author, date (country of study)	Lung cancer population comparisons	*n*	QOL scale used	When measured	Main findings
Salati, 2009 (Italy)	1. Thoracotomy (age 70+) 2. Thoracotomy (age <70)	218	SF-36	Pre-surgical 3 months	QOL scores back to baseline values by 3 months No difference in scores between elder and younger groups
Schulte, 2009 (Germany)	1. Bilobectomy/ lobectomy 2. Pneumonectomy	159	EORTC QLQ-C30 and LC13	Pre-surgical 3 months 6 months 12 months (also 24 months)	For all patients - most QOL indicators deteriorated during first 3 months after surgery and then a returning to baseline levels by 12 months, apart from physical function, pain and breathlessness Pneumonectomy - significantly slower returning to baseline compared to after bi-lobectomy/lobectomy in physical and social function, role, global health, pain.
Win, 2005 (England)	1.Thoracotomy (lobectomy and pneumonectomy)	110	EORTC QLQ-C30 and LC13	Pre-surgical 1 month 3 months 6 months	Global QOL deteriorated at 1 month but had returned to baseline by 3 months Fatigue, nausea, pain and breathlessness deteriorated at 1 months and returned to baseline at 6 months.

Table 1.3: cont.

Author, date (country of study)	Lung cancer population comparisons	*n*	QOL scale used	When measured	Main findings
Zieren, 1996 (Germany)	1. Thoracotomy (lobectomy and pneumonectomy)	72	EORTC QLQ C30	Pre-surgical 11 days 3 months 6 months 9 months 12 months	QOL domains deteriorated after discharge by returned to baseline levels within 3-6 months after surgery in recurrence free patients.

1.5.2 Specific symptoms reported by surgical lung cancer patients

1.5.2.1 Breathlessness

One commonly reported sequelae of pulmonary resection is breathlessness.[99] There is mixed evidence regarding the length of time after surgery that patients continue to experience breathlessness based on quantitative QOL studies. Some studies found that breathlessness returns to baseline scores within 3 months after surgery and others report continuing breathlessness a year after surgery (see table 1.3). There is also data to suggest breathlessness can be reported for up to five years for a significant proportion of patients. Sarna et al. investigated the presence of respiratory symptoms in lung cancer survivors 5 or more years after surgery. Among 142 patients, 63% reported breathlessness and 10% were unable to leave the house due to breathlessness. These authors also reported that breathlessness significantly predicted physical functioning, physical role and social functioning scores.[100]

There has been little published research examining the causes of breathlessness after surgery for lung cancer or of effective treatments. The ventilatory processes involved in breathing have two main functions, moving air in and out of the lungs and secondly gaseous exchange between the airspace of alveoli and the blood.[39] Respiratory control is complex, and requires highly co-ordinated orchestration of several conscious and autonomic processes that detect oxygen saturation levels in the blood and regulate the mechanical processes of breathing.[101] It is possible that surgical incision and damage to intercostal muscles may result in deconditioning.[102] Clearly, surgery also removes lung tissue, reducing the surface area for exchange of oxygen and carbon dioxide which may also contribute to breathlessness.[103] Post-surgical reduction in forced expiratory volume in one second (FEV_1) has been shown to be directly related to the amount of lung resected in those who have undergone surgery for lung cancer, with a 15% reduction seen in lobectomy patients six months after surgery in comparison to a 35% reduction after pneumonectomy.[104] However, it is well known that self reported levels of breathlessness do not always correlate with spirometric measures of respiratory function, or

Table 1.4: The modified Borg scale

Grade	Degree of breathlessness related to activities
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5 - 6	Severe
7 - 8	Very severe
9	Very very severe (almost maximal)
10	Maximal

Table 1.5: The MRC breathlessness scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking 100 yards or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

other physiological tests such as oxygen saturation and arterial blood gases.[105] Guidelines recommend that spirometric measures should not be used in isolation to determine respiratory function, but rather should be used in conjunction with patient self report.[47]

Measures of breathlessness that form part of QOL tools are single items that rate breathlessness on a Likert scale. These tools have been developed for clinical trials rather than clinical care.[85] Two of the most widely used, generic clinical tools for measuring breathlessness are (1) The modified Borg scale and (2) The MRC breathlessness scale. The Borg scale is a measure of perceived breathlessness that quantifies severity on a scale from 0-10, where 0 represents 'no breathlessness at all' and 10 represents 'maximal breathlessness'.[106] The MRC breathlessness scale does not quantify the severity of breathlessness, but rather classifies the associated limitation in function on a scale of 1 to 5.[107] The descriptions of each of these scores can be found in table 1.4 and 1.5.

Qualitative explorations of patients' experiences of breathlessness have been conducted in patients with end stage disease receiving palliative care.[108] However, the experience of breath-

lessness and effect on function has not been qualitatively explored in lung cancer patients who have undergone surgery. In chapter 3 - 4, patients' experiences of breathlessness are explored, and interpreted in the light of the MRC breathlessness scale and Borg scales.

1.5.2.2 Pain

Thoracotomy is recognised as being one of the most painful surgical procedures, akin to limb amputation.[109, 110] Surgical damage to skin, soft tissue, bone and muscle results in an inflammatory response, and pain signals are transmitted through the intercostal nerves. Intercostal nerves themselves may also be damaged during the surgical procedure, and in addition constant motion due to breathing continually aggravates the area.[111] The International Association for the Study of Pain (ISAP) has stated that pain after thoracotomy is *"characterised by an aching sensation in the distribution of the incision that usually resolves in the two months following the surgery."* [112] Although in the past it was thought that persistent pain was only experienced in the case of tumour recurrence, it is now recognised that a proportion of patients do develop persistent pain independently of tumour recurrence, or post-thoracotomy pain syndrome (PTPS).[111] PTPS has been described as persistent pain which has an aching, burning dysaesthesia and/or a pleuritic component.[113, 114] The merriam-webster medical dictionary defines dysaethesia as *'impairment of sensitivity, especially to touch.'* Pleuritic is defined as *"of, relating to, or affected with pleurisy"*, which is a condition in which the lining of the pleural cavity of the lungs becomes inflamed and is associated with sharp, shooting pains on inhalation. Shoulder pain is also common after thoracotomy although the reasons for this are not completely understood.[87]

Dajczman et al published the first data in a small group of patients demonstrating the existence of chronic post-thoracotomy pain in disease free patients, in 1991.[115] Fifty-six patients were interviewed between 2 months and 5 years post-thoracotomy. In this group, 73% of patients were still experiencing pain after two years and 30% reported pain at 5 years. Since then other studies have confirmed the existence of chronic post-thoracotomy pain, but estimates of

incidence range from 11% to 80%.[111] There are mixed reports in QOL studies of the length of time that patients continue to experience pain (see table 1.3), with some studies reporting that pain scores return to baseline within the first three to six months after surgery and others finding evidence of pain persisting for twelve months after surgery. It has been estimated around 5% of patients continue to experience pain that is incapacitating 12 months after surgery.[113, 116, 117]

Control of post-surgical pain is important not only from a QOL point of view, but pain can also prevent patients from mobilising, can inhibit coughing and can cause shallow breathing.[118, 119] These factors increase the risk of atelectasis and retention of secretions which can lead to hypoxaemia, hypercapnia and respiratory failure. In addition, immobilisation increases the risk of deep venous thrombosis and pulmonary embolism.[120] As such, the goal of acute pain control after thoracotomy is for patients to be able to move, breathe deeply and cough without experiencing high levels of pain.[119, 120] The World Health Organisation developed what is commonly referred to as the 'three-step analgesic ladder' as a guide to the management of cancer-related pain.[121] The first step includes simple analgesics such as paracetamol and non steroidal anti-inflammatory drugs (NSAIDs). If pain persists or increases, other treatment is added. The second step of treatment adds weak opioids, for example tramadol or codeine, and then the third step adds strong opioids such as morphine or pethidine. Non-pharmacological interventions may also be used such relaxation, hypnosis and acupuncture.[122]

Prediction of those who will experience greater pain related to thoracic surgery is complex, as the cause of pain is multi-factorial. Pain experiences may differ due to variation in the surgical technique used, positioning of the incision and patient specific anatomical differences, responses to analgesia and psychological responses to pain.[120] Some studies have shown that experience of acute post-surgical pain predict PTPS.[123–125] The aetiology of PTPS is not known, however pain descriptions are consistent with intercostal nerve damage, and this is considered to be an important cause.[111]

There are no measures that have been developed to specifically describe patient reported post-

thoracotomy pain. Similar to breathlessness, pain experience is captured within QOL scales using a single item scale. Other studies have generally used generic visual analogue scales, Likert scales and/or tools such as the McGill pain questionnaire (MPQ) to describe post-thoracotomy pain.[114, 115, 117, 126] The MPQ allows patients to identify words that described their pain that fall into three classes of description: sensory, affective and evaluative. The words used to describe pain denote the intensity and are associated with a score. In addition, patients rate their present pain intensity on a 5 point scale. This questionnaire had been used to interpret descriptions of pain experiences reported by interview participants in the qualitative study reported in chapter 2 - 4. The MPQ can be found in appendix A.1.

1.5.3 Prevalence of co-morbidities in lung cancer survivors

Multi-morbidity is likely to be high in lung cancer patients due to the association of this tumour with both age and smoking. This issue is important not only for predicting prognosis but also has implications for the planning of services, clinical decision making and patient management.[127, 128] One US study including patients that had received curative or non-curative treatment described the prevalence of 56 co-morbidities in 1 155 lung cancer patients.[129] Prevalence within this sample was highest for chronic obstructive pulmonary disease (COPD) (29%), connective tissue disease (22%) and peripheral vascular disease (10%). Another study conducted in the US found that 30% of patients had co-morbid cardio-vascular disease, 36% hypertension and 37% had co-morbid respiratory disease. The stage at diagnosis and treatment received by patients in this study was not reported.

Two known studies have described prevalence of co-morbidity in surgically treated lung cancer patients. One study conducted in Spain described the frequency of 5 specific co-morbid diseases in 2 992 consecutive patients and found that 50% of patients had an additional diagnosis of COPD, 16%, 13% and 10% of patients had atrial hypertension, cardiac disease or peripheral vascular disease, and 9% of patients had diabetes.[130] The second study was conducted in the US with 451 patients who had undergone surgery for pathological stage I NSCLC.[60]

Co-morbidity was measured using the Kaplan-Feinstein Index. This measure classifies co-morbidity as absent, mild, moderate or severe based on the number of individual diseases present and the extent to which the disease is advanced. Thirty three percent did not have a co-morbid condition at diagnosis with lung cancer, whereas 33%, 26% and 10% were described as qualifying for mild, moderate or severe KFI score. However, the authors did not describe the prevalence of individual co-morbid diseases. Although more studies are needed to describe the prevalence of co-morbidities in lung cancer patients treated in the UK, it is likely that a significant minority, if not the majority, are affected by at least one co-morbid disease.

1.6 Health behaviours of lung cancer patients after surgery

The second aim of the qualitative interview study documented in this thesis was to describe patients' health behaviours after surgery and explore their attitudes towards behaviour change. This was with a particular view to exploring patients' preferences for the inclusion of support for health behaviour change within a rehabilitation programme. The role of health behaviours in improving patient health, management of treatment sequelae and improving disease outcomes for cancer survivors has received increasing attention over the past few years.[131] However, the majority of research has focused on survivors of breast, prostate and colorectal cancers.[132] A previous review of the evidence relating to the health behaviours of lung cancer patients, and the relationship between post-diagnosis behaviours and health outcomes found no research regarding exercise, diet or alcohol consumption.[133] However, some studies regarding post-diagnosis smoking behaviour and health outcomes were reported and showed that smoking cessation may lead to both short term benefits (e.g. shorter length of hospital stay[134], better quality of life [135] and lower levels of reported pain[136]) and longer term prognostic benefits,[137] (see chapter 6 for a review of the evidence for prognostic benefits of smoking cessation).

Given the lack of evidence surrounding health behaviours other than smoking, the following sections will focus on some of the key issues that inform incorporation of smoking cessation

into a rehabilitation programme for surgical lung cancer patients. First, it is important to know the prevalence of current smoking at the time of diagnosis and how many continue to smoke after diagnosis. It may be that many patients with a smoking history have already quit by this stage or quit as a reaction to their diagnosis. However, even if a minority of patients continue to smoke, it is worth investigating patients' attitudes towards their smoking and towards being offered smoking cessation support. Second, there has been considerable debate in the literature as to the optimum timing of smoking cessation before surgery in terms of post-surgical pulmonary complications. Despite mounting evidence that smoking cessation may lead to improved outcomes in both the short and the long term, there has been a concern that quitting immediately before surgery may cause a paradoxical increase in risk of surgical complications. If patients express a preference for being offered support to quit smoking, it is important to understand the optimum time for quitting before surgery. These two topics are discussed in the following sections.

1.6.1 Prevalence of smoking in patients diagnosed with lung cancer

Eight known studies have described the prevalence of smoking in surgical lung cancer patients (see table 1.6).[138–145] Three of the eight studies retrospectively questioned patients about their smoking status at diagnosis and found that at least 85% had a history of smoking and between 44 and 100% were smokers at diagnosis. The study reporting 100% current smokers had selected patients based on their smoking behaviour, therefore this prevalence is not representative of surgical lung cancer patients in general at diagnosis. On average, patients were surveyed between two and ten years after diagnosis and between 13 and 46% were smoking at follow up. Two of these retrospective cohorts[138, 140] relied on self report of smoking status only, and the third included biochemical validation of smoking status at the time of interview.[139] Biochemical validation is considered the gold standard in confirming smoking abstinence, and is considered stronger evidence than self report only.[146] These studies provide weak evidence of the prevalence of smoking at diagnosis and continued smoking after diagnosis, but indicate

that smoking behaviour is still relevant to lung cancer patients at and beyond diagnosis.

Five studies used a prospective cohort design to capture smoking behaviour during the first year after diagnosis, providing stronger evidence.[141–145] However, biochemical validation of smoking status was only used in two studies.[141, 145] As with the retrospective studies, the prospective cohort studies reported that around 90% of patients diagnosed with lung cancer had a history of smoking and that a significant number still smoked at diagnosis. Two of these studies were conducted in the US more than twenty years ago and it is possible that smoking prevalence has changed since this time.[142, 143] Gritz et al. reported smoking behaviour in 840 patients by combining data from three clinical trials of adjuvant therapy which recruited patients between 1977 and 1987.[143] All patients had been diagnosed with NSCLC and were treated with surgery. This study found a high prevalence of smoking at diagnosis, at 60%. However, only 4% were reported as current smoking at an average of 4 years after diagnosis. It is not clear from this study how many patients were lost to follow up due to death and in addition smoking status was ascertained by self report. Dresler et al. recruited 363 surgical lung cancer patients between 1992 and 1996.[142] This study reported that just under half of patients were smoking at diagnosis and 13% of patients were smoking at longest follow up, which on average was one and a half years after surgery.

Three more recent studies were also conducted in the US.[141, 144, 145] One of these studies[145] recruited patients between 2001 and 2005 but included only patients who were smokers at diagnosis and therefore prevalence could not be assessed. This study reported that 80% were biochemically confirmed as quit one year after surgery. Cooley et al followed up 94 stage I-IIIA patients 1, 2 and 4 months after they had undergone surgery between 2002 and 2006.[141] Thirty seven percent of patients were smoking at time of diagnosis. Some patients who had quit before diagnosis relapsed after treatment and were smoking at 4 months follow up, along with others who had been smokers at diagnosis such that 48% were smoking at follow up. Logistic regression modelling showed that young age, less than high school education, quitting fewer than 6 months before diagnosis and high pain scores were predictive of smoking at follow up in

Table 1.6: Smoking prevalence at diagnosis and the proportion of patients smoking at long term follow up

Author	*n*	Ever smokers (%)[a]	Smokers at diagnosis (%)[a]	Smoking at longest or mean fu (%)[b]	Longest or mean fu/yrs (SD or range, if known)	Data collection time points post-surgery	Smoking abstinence measure
Retrospective cross sectional studies							
Davidson, 1982	52	50 (96)	22 (44)	24 (46)	5	Time of survey	Self report
Evangelista, 2003	142	120 (85)	99 (70)	19 (13)	10 (3)	Time of survey	Self report and urinary cotinine validation
Walker, 2004*	43	43 (100)	43 (100)	13 (30)	2.8 (0.8)	Time of survey	Self report
Prospective cohort studies							
Cooley, 2009	94	84 (89)	35 (37)	45 (48)	0.3	1m, 2m, 4m	Self report and urinary cotinine validation
Dresler, 1996	362	344 (95)	175 (48)	44 (12)	1.5 (0.1–5.6)	Every 3m for 2 yrs and 6m thereafter	Self report
Gritz, 1991	1268	1206 (95)	758 (60)	57 (5)	4	Every 3m for 2 yrs and 6m thereafter	Self report
Park, 2011	2456	2210 (90)	925 (38)	335 (14)	0.4	Diagnosis and 5m	Self report
Walker, 2006	154	154 (100)	154 (100)	31 (20)	1	3m, 6m, 12m	Self report and salivary cotinine validation

[a]Number of ever smokers and smokers at diagnosis expressed as a percentage of the total number in the study
[b]Number of smokers at longest follow up expressed as a percentage of the number smoking at diagnosis

this study. Finally, Park et al published the largest cohort study to date in lung cancer patients. However, only around half of the sample had undergone surgery.[144] Overall, 38% of patients were found to be smokers at diagnosis and 13% were smoking at 5 months follow up. In a univariate logistic regression, those who had surgery were found to be 36% less likely to smoke at 5 months follow up than those who had not had surgery (OR 0.64 (95%CI 0.45-0.90)).

In summary, three retrospective and five prospective cohort studies have provided evidence of a falling prevalence rate of current smoking amongst surgical lung cancer patients over the past decades, but that currently over a third of patients may smoke at diagnosis. A significant minority of these patients may continue to smoke after treatment. The proportion of continued smokers reported in previously published studies has varied, but this is likely to be due to differences in follow up periods, bias introduced due to the study methodology and lack of biochemical validation of smoking status. There was some indication that age, education and performance status were related to the likelihood of continued smoking, and in particular those who had quit within a year of diagnosis appeared to be at higher risk of relapse to smoking after treatment than those who had quit more than a year before diagnosis. This picture of smoking prevalence amongst surgical lung cancer patients confirms that smoking cessation support is likely to be relevant to many patients and is potentially an important component of a rehabilitation programme.

1.6.2 Optimum timing of smoking cessation for surgical lung cancer patients

Smokers are at an increased risk of post-surgical complications compared to non-smokers.[147–151] In particular, smoking has been associated with increased anaesthetic dosage, increased risk for local wound complications, pulmonary and cardiac complications, post-surgical intensive care admission and longer periods of hospitalisation compared to non smokers.[147, 152–155] Patients who undergo pulmonary resection are most vulnerable to pulmonary complications including pulmonary infection, atelectasis, bronchospasm, and prolonged ventilation.[134,

156, 157] It is thought that smoking may elevate risk of respiratory complications by decreasing ciliary action, macrophage activity and small airways function, and causing an increase sputum production.[147, 158]

Although it is advisable for patients to quit smoking before surgery, even if only temporarily [159], there has been considerable debate in the literature as to how long before surgery a patient must quit in order to see a reduction in risk of complications, and regarding the optimal timing of smoking cessation before surgery.[160] Studies have compared risk within different surgical populations, between different time windows of pre-surgical quitting, for several types of complication, with mixed results. An in depth appraisal and discussion of all the literature on this topic is outside the scope of this thesis. However, I will summarise some of the key studies within this debate that are relevant to understanding the optimum time for quitting before thoracic surgery.

One of the main issues of contention within the debate has been the safety of quitting smoking within 2 months leading up to surgery.[134, 160, 161] Two studies conducted 20-30 years ago in non thoracic surgery patients [162, 163] and one more recent study conducted in patients undergoing lung surgery [164] found that quitting within this time window (<8 weeks before surgery) was associated with an increased risk in complications. An additional study found that smoking cessation may temporarily increase sputum production above the level produced as a smoker,[165] thus indicating a potential mechanism by which those who quit immediately before surgery may be at greater risk of pulmonary complications.[156, 161] Although many additional studies have shown no increased risk, or a decrease in risk, concern still persists amongst some surgeons and anaesthetists and some local surgical guidelines have recommended that smokers do not quit within this time window.[161]

Several authors have published narrative reviews, or systematic reviews with meta-analyses in this area.[147, 153, 156, 159–161, 166–170] The most up to date systematic reviews were published in 2011 [168] and 2012 [169]. Myers et al, included two RCTs and seven observational studies that *'allowed comparisons of post-surgical complications in patients who stopped*

smoking 8 weeks or less prior to surgery (recent quitters) with those who continued to smoke (continuers). All types of post-surgical complications were considered from all specialities and populations.'[168] Two of the studies included in the review were observational studies on patients that had undergone pulmonary resection.[158, 171] Relevant data from all studies were pooled to assess risk of any complication or pulmonary complication which showed no significant difference between recent quitters and continuers (Any complication RR 0.78 (95%CI 0.57, 1.07), Pulmonary complication RR 1.18 (95% CI 0.95, 1.46). Individual study estimates for the two studies conducted on patients who had undergone pulmonary resection of risk of any complication or risk of pulmonary complications did not show any significant difference. However, a small number of patients were contributing to these analyses (Barrera, 2005 [158] $n = 52$, Groth, 2009 [171] $n = 39$) Although this review found no cause of concern for quitting before surgery in terms of an increased risk of complications, it combines data for all those who quit at any point in the 8 weeks preceding surgery. In some studies patients had quit within two weeks of surgery whereas others had quit six or eight weeks before. If risk was only elevated for those who quit within 2 weeks, this may be masked by combining these data. Although this review gives reassuring evidence, an elevated risk for those quitting more immediately before smoking cannot be ruled out.

Wong et al [169] used similar inclusion criteria to Myers et al., but extended inclusion to studies with participants who quit within 6 months rather than just 2 months before surgery. This review included 25 studies in total (2 RCTs, 7 prospective cohort studies, 16 retrospective cohort studies). Five of the studies had been conducted on patients who had undergone pulmonary surgery,[66, 158, 164, 171, 172] which includes the 2 studies found by the Myers review. Similar to Myers et al, data in this review are combined for all types of surgery. However, rather than comparing those who quit any time within 8 weeks to those who continued to smoke, this review compared five categories of smoking behaviour (current smoker, quit <2 weeks, 2-4 weeks, >4-8 weeks and >8 weeks before surgery).

Compared to those who continued to smoke, the risk of respiratory complication was found to

not significantly differ for those who quit <2 weeks (RR 1.20 (95% CI 0.96, 1.50; 3 studies, 559 ppts) or 2-4 weeks before surgery (RR 1.14 (95% CI 0.90, 1.45; 3 studies, 2210 ppts) and was significantly reduced for those who quit >4 weeks - 8 weeks (RR 0.77 (95% CI 0.61, 0.96; 4 studies, 5659 ppts) and >8 weeks before surgery (RR 0.53 (95% CI 0.37, 0.76; 5 studies, 1426 ppts). When directly comparing risk in those who quit <2 weeks before surgery with those who quit between 2 and 4 weeks, no significant difference was found (RR 1.04 (95% CI 0.83, 1.30; 3 studies, 2170 ppts). This indicates that quitting at any point within 4 weeks of surgery is associated with the same level of risk as for those who continue to smoke. However significant decreases in risk of pulmonary complications were found for those who quit >4 weeks compared to <4 week (RR 0.65 (95% CI 0.46, 0.93; 3 studies, 5592 ppts) and for those who quit >8 weeks compared to those who quit <8 weeks before surgery (RR 0.47 (95% CI 0.29, 0.74; 5 studies, 1309 ppts). Similarly, those who quit smoking >3-4 weeks before surgery had a lower risk of developing wound complications than those who quit smoking <3-4 weeks before (RR 0.74 (95% CI 0.56, 0.98; 7 studies, 845 ppts). This indicated that patients need to quit at least 4 weeks before surgery in order to reduce their risk of complications, and for those who quit even earlier the benefits are greater. However, the authors state that the findings should be interpreted with caution because many of the studies did not score highly on quality measures. Many studies posed a possible risk of bias because smoking status was based on self report and outcome assessor was not blinded to smoking status. Out of 17 studies that contributed to the estimates quoted here, 13 reported differences in baseline characteristics and in two these characteristics were not assessed. In addition, crude rates of complication were included in the meta-analyses which may be subject to confounding.

No review has conducted sub-group analyses combining studies that have been performed on patients undergoing pulmonary surgery only. Of the 5 studies that have been identified by systematic reviews that have been carried out in this population, four recruited a total of 300 patients or fewer and only a proportion of these patients quit smoking within the time window of interest to this discussion. However, one study conducted in adult patients undergoing primary resection for lung cancer [66] was large ($n = 7990$) and is worthy of note. In this study, data

regarding risk of the occurrence of pulmonary complication (prolonged ventilation >48hr post-surgical, need for reintubation, atelectasis requiring bronchoscopy, tracheostomy, pneumonia and development of acute respiratory distress syndrome) were prospectively obtained. Smoking behaviours were split into 5 categories: current smokers ($n = 1595$) and those who quit >14 d-1 months ($n = 404$), 1-12 months ($n = 940$), >12 months (n4026) before surgery and those who never smoked ($n = 1025$). Data were derived from several hospitals. The authors report a significant difference in the distribution of age, gender, BMI, zubrod score (tool for assessing performance status), spirometry measures and resection type between the 5 smoking behaviour groups. However, the methods of assessing differences was not described, and post-hoc tests did not ascertain which groups differed. Crude measures of risk of pulmonary complications showed a trend of decreasing risk for increasing periods of cessation before surgery (current smoker = 6.9%, quit >14d-1m = 6.2%, quit 1-12m = 6.4%, quit >12m =5.8% and never smoked = 2.6%). To account for baseline differences, the authors conducted a multivariable analysis using a non parsimonious mixed model with logit link which included 20 variables. As with other reviews, the authors used never smokers as the reference category and found that both current smokers and those who quit within a month surgery were at increased risk of complications (current smoker OR 3.5 (95% CI 1.1, 11), >14d ays-1m OR 4.6 (1.2, 18). Indirectly comparing current smokers to those who quit 2-4 weeks before surgery did not find any significant difference (OR 1.31 (95% CI 0.26-6.7)

Taken together, these reviews and studies indicate that smokers who quit within a month before surgery are not at an increased risk of pulmonary or wound healing complications. In addition, quitting at least four weeks before surgery appears to be associated with risk reductions and the longer the length of time a patient has quit before surgery the better. There is reasonably strong evidence that this is also the case specifically for patients undergoing pulmonary surgery. However, although some of the studies included in these reviews were relatively large (over 1000 patients), most did not score highly in quality measures and findings may be subject to bias and uncontrolled confounding. Notwithstanding the limitations of data, reviews in the area have concluded that surgeons should not be deterred from offering smoking cessation at any

point up until surgery. These data provide a strong case that smoking cessation support should be offered to patients as soon as possible before surgery.

1.7 Evolution of cancer services over the past two decades

1.7.1 The Calman-Hine report and The Cancer Plan

Over the past 2 decades, there have been marked changes in the way cancer services are organised and delivered. The Calman-Hine report,[173] published in 1995, was the first ever comprehensive review of UK cancer services and recommended changes to national service configuration and delivery. One of the driving factors that led to this comprehensive review was the inequality in service provision and cancer outcomes that was apparent across the country.[173] In response to these difficulties, the Calman-Hine report set out what has been referred to as seven innovative and ground breaking principles which heralded a more patient-centred approach and equitable service:[174]

1. access to uniform high-quality care in the community or hospital
2. early identification of cancer and availability of national screen programmes
3. patients to be given clear information at all stages
4. services to be patient centred
5. centrality of primary care and effective communications
6. psychological aspects of care are important
7. cancer registration and monitoring of treatment and outcome are essential.[174]

The content of the Calman-Hine report underpinned 'The Cancer Plan' 2000, the first political document of its kind to set out a comprehensive programme of service reforms that encompassed changes in prevention, diagnosis, treatment, care and research,[175] and this programme

was updated in 2004 in 'The NHS plan and the new NHS: providing a patient-centred service'.[176] These documents have provided the vision and acted as a catalyst to many positive developments within cancer care, including the formation of cancer networks (organisations tasked with driving change and improvement in cancer services for the population of a specific geographic area), the integration of clinical expertise in the form of multidisciplinary team (MDT) meetings in which individual cases are discussed and clinical decisions are made, the emergence of national screening programmes to improve rates of early detection of tumour development and the formation of cancer registries where data regarding diagnosis, treatment and outcome of disease are systematically collected and recorded.[44]

Specific to lung cancer, as a result of these reforms and accompanying financial investments, services have developed to centre clinical decision making around lung cancer MDTs, and lung cancer clinical nurse specialists (CNS) are assigned to individual patients to provide tailored support as they progress through the system. In addition, the evidence base for treatments has improved and developments in technology have improved techniques for disease staging and delivering treatments.[44] These developments have been incorporated into national guidelines for the diagnosis and treatment or lung cancer.[46, 47]

1.7.2 The Cancer Reform Strategy and The National Cancer Survivorship Initiative (NCSI)

Due to improvements that have been made in early detection, treatment and survival rates, along with the ageing population, the prevalence of people living with cancer is now increasing.[177] In 2008, it was estimated that there were 2 million cancer survivors living in the UK and that this number is rising annually by an estimated 3.2%.[63, 178] Modelling of cancer prevalence has predicted that by 2040 almost one quarter of people living in the UK who are aged 65 and above will have received a cancer diagnosis, rising from one eighth of that age group in 2008.[178] In recognition of this significant increase and the changing needs of this population, cancer survivorship care has been placed more firmly on the agenda of cancer research and service de-

velopment. Additional to improvements brought about by The Cancer Plan, the Cancer Reform Strategy published in 2007 highlighted the need to develop services for those 'living with and beyond cancer'.[179] Previous care pathways had focused on detection, diagnosis, treatment and palliation, but the needs of curatively treated patients have been largely overlooked.[177, 180]

The National Cancer Survivorship Initiative (NCSI), a partnership between the English DH and Macmillian Cancer Support, and supported by NHS improvement, was set up to deliver the aspirations set out by the Cancer Reform Strategy for those living with and beyond cancer. The NCSI was launched in September 2008 with the explicit goal of taking *"the necessary steps to ensure that those living with and beyond cancer get the care and support they need to lead as healthy and active a life as possible, for as long as possible"*. Figure 1.7 demonstrates the position and scope of survivorship care within the complete cancer care pathway.

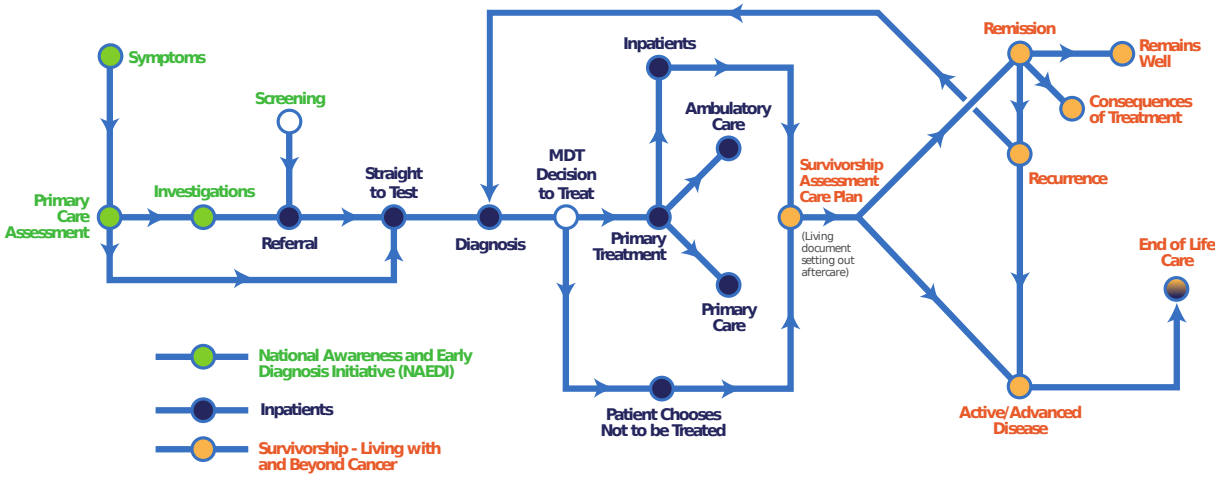


Figure 1.7: Complete pathway of cancer care, including survivorship [Source: NHS Improvement - Cancer, 2011]. [181]

To fulfil this mandate, the NCSI commenced a stream of work that began with assessing and filling gaps in the existing evidence base. In brief, this work confirmed that current care in the UK was not addressing patients' survivorship or supportive care needs.[182] A survey of cancer services throughout England showed that care pathways were often ill defined after treatment, and were focused on surveillance of disease rather than involving holistic assessment of need. In addition, there was found to be a lack of co-ordination between primary and secondary

care.[183] In their vision document published in January 2010, the NCSI set out 5 shifts that were necessary to adapt to the needs of the cancer survivor population :[177]

1. a cultural shift in the approach to care and support for people affected by cancer to a greater focus on recovery, health and well being
2. a shift towards assessment, information provision and personalised care planning. This is a shift from a one-size fits all approach to follow up to personalised care planning based on assessment of individual risks, needs and preferences
3. a shift towards support for self management. This is a shift from a clinically led approach to follow up care to support self-management, based on individual needs and preferences and with the appropriate clinical assessment, support and treatment
4. a shift from a single model of clinical follow up to tailored support that enables early recognition of and preparation for the consequences of treatment as well as early recognition of signs and symptoms of further disease
5. a shift from an emphasis on measuring clinical activity to a new emphasis on measuring experience and outcomes from cancer survivors through routine use of Patient Reported Outcome Measures (PROM) in after care services.[177]

During the lifetime of this doctoral study, significant strides forward have been made in defining and testing new 'risk stratified' models of care for cancer patients. Building on the findings of initial ground work, this pathway was tested within lung, breast, colorectal and prostate cancer groups.[184] The lung cancer specific model was first described after I completed the interviews that form part of the empirical work reported in this thesis (see chapter 2 - 4).[181] At the foundation of this model, a personalised care plan is created with the patient and reviewed on a regular basis. Based on patient need, follow up may take one of three levels of intensity: self management, shared care or complex care. As the needs of patients change, they may move between these levels of care. It was estimated that 15%, 60% and 25% of all lung cancer patients would need each of the three levels of care respectively. The lung cancer risk stratified

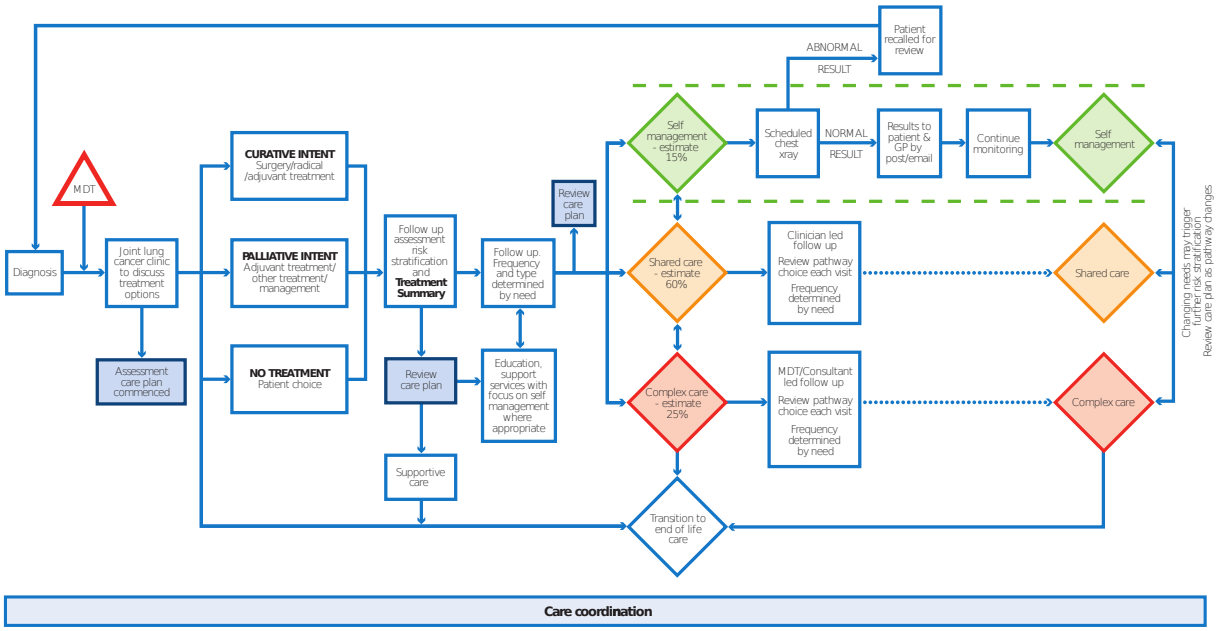


Figure 1.8: Lung cancer risk stratified lung cancer pathway. [Source: NHS Improvement - Cancer, 2011].[181]

pathway is shown in figure 1.8 below.

The feasibility of implementing a risk stratified pathway was piloted with lung cancer patients by two teams based at Hull and East Yorkshire Hospitals NHS trust and Brighton and Sussex University Hospitals NHS trust, and the findings were published in September 2012.[184] In brief, this involved piloting a health and wellbeing clinic to identify patient needs and referral on to other services. Also, for patients still under outpatient care, a more flexible approach to consultant led clinic appointments was trialled, including a pre-clinic telephone assessment one week prior to clinic to allow for re-scheduling based on patient need. This work indicated that all patients required some form of professional led care, but that also many could self manage for periods during the pathway. Clinical support services that patients were most frequently referred to included physiotherapy/breathlessness clinics, nutritional and psychological services, district nursing, occupational therapy/wheelchair services and home oxygen services. Pre-clinic telephone calls resulted in around a quarter of appointments being cancelled and rescheduled. Also, about one fifth of appointments were arranged at patient or professional request, and potentially avoided emergency admissions. This work was geared towards lung cancer patients with 'active or advanced disease', and therefore it is unknown how the findings relate to the

needs of surgical lung cancer patients in particular. No estimation of the stratification of needs for surgical lung cancer patients has been made.

In addition to defining and piloting new models of care, the NCSI research workstream have made a series of recommendations for research emphasising that *"the highest priority for research in cancer survivorship is to understand the 'natural history' of survivorship and to create risk stratification tools for all cancers and for survivors of all ages"*.[185] Recent reports by the NSCI and also the National Cancer Research Institute (NCRI) have noted a lack of research in all areas of lung cancer research in particular. In 2011, Mick Peake, the National Clinical Lead for lung cancer, explained *"The issue of how best to follow up lung cancer patients is difficult. This is because it is almost an evidence-free area, as has been recognised in the recently updated NICE Lung Cancer Guidance."*[181] This includes a specific lack in a description of the natural history of health experiences after treatment and investigations surrounding the supportive care needs of lung cancer survivors.[1, 46, 182, 186]

1.8 Current and future supportive care for lung cancer patients after surgery

1.8.1 Terminology used to describe models of after care

The concept of supportive care and rehabilitation within the NHS is not unprecedented. Rehabilitation programmes are offered as standard to patients with coronary heart disease,[2] stroke [4] and COPD.[3] Throughout research literature, strategy and guideline documents, several terms have been used to describe care for patients that is additional to primary treatment, including 'survivorship care', 'after care', 'rehabilitation', 'supportive care', 'follow up care', 'enhanced recovery' and 'palliative care'. There are various definitions for these terms, but many overlap and the distinction between them is often blurred.[187] The NCSI/NHS Improvement have not given a definition of supportive care as included in figure 1.8. Within the documen-

tation arising from the work of these organisations, various terms have been used to describe care, including survivorship care, after care, follow up care and supportive care.

Within this thesis, the terms rehabilitation and supportive care have been chosen to identify the type of care that is being investigated. The term rehabilitation is used to refer to a programme that is conducted for a finite period of time before, during and/or after discharge. The aim of cancer rehabilitation is to:[188]

> *"help a person with cancer to help himself or herself to obtain maximum physical, social, psychological, and vocational functioning within the limits imposed by disease and its treatment."*

The term supportive care is used as an umbrella term for the services that help support patients (and their family), of which a rehabilitation programme may be one aspect. As such, this follows the definition given by NICE:[189]

> *"helps the patient and their family to cope with cancer and treatment of it, from pre-diagnosis, through the process of diagnosis and treatment, to cure, continuing illness or death and into bereavement. It helps the patient to maximise the benefits of treatment and to live as well as possible with the effects of the disease. It is given equal priority alongside diagnosis and treatment."*

Although this definition of supportive care also includes aspects of palliative care (i.e. dealing with the issues presented by terminal illness and death) and emphasises support given to family as well as the patient, this thesis focuses on the needs of patients within the first year after surgery only. In addition, it should be noted that although supportive care is denoted as being separate to the risk stratified follow up care in figure 1.8 by the NCSI, for the purposes of this thesis and based the NICE definition, supportive care includes the activities that form the risk stratified area of this care pathway and is interchangable with the concept of survivorship care.

1.8.2 Current supportive care - national guidelines

Current BTS guidelines[47] on the radical management of patients with lung cancer do not include any recommendations regarding appropriate supportive care for surgical lung cancer patients, and the only post-surgical considerations included relate to adjuvant chemotherapy and radiotherapy. In order to minimise post-surgical complications and reductions in quality of life, guidelines advocate the least invasive form of surgery possible, including using VATS or muscle sparing thoracotomy procedures if possible. In addition, for patients with smaller tumours and of borderline fitness, lung parenchymal-sparing surgery is advocated. More extensive resection is only indicated if this in the only means by which a clear surgical margin around the tumour can be obtained. NICE guidance for the diagnosis and treatment of lung cancer has acknowledged the importance of supportive care through every stage of the cancer care pathway.[46, 190] Within the section on 'Palliative interventions and supportive and palliative care', this guidance advocates that services should follow recommendations given in a related NICE guidance document for supportive and palliative care in cancer patients.[189] Whilst these guidelines recommend that patients should receive holistic care, including access to psychological, social, spiritual and rehabilitation support services, no specific recommendations regarding the supportive care needs of surgical lung cancer patients are detailed.

The 2005 NICE guidance for the diagnosis and treatment of lung cancer made further recommendations for supportive care specific to lung cancer, but these were largely based on needs of patients with advance disease (e.g. management of endobronchial obstruction, brain metastasis, pleural effusion, spinal cord compression etc) although it was also recommended that *"other symptoms, including weight loss, loss of appetite, depression and difficulty swallowing, should be managed by multidisciplinary groups that include supportive and palliative care professionals."* The updated version of this guidance published in 2011 has additional recommendations that patients receive a specialist follow up appointment within 6 weeks of completing treatment to discuss ongoing care and regular appointments thereafter, that patients with a life expectancy greater than 3 months should also receive a follow up care led by a lung CNS, that patients are

able to contact the nurse between their hospital appointments and that lung CNS appointments should be scheduled by the hospital rather than relying on patients to book appointments when they experience symptoms. In addition, the updated guidance includes recommendations regarding smoking cessation. Specifically, patients should be advised to stop smoking as soon as a diagnosis of lung cancer is received as smoking increases the risk of pulmonary complications after surgery, and patients should be offered support to quit including prescriptions of nicotine replacement therapy (NRT) or varenicline. The guidance further advises that surgery should not be postponed in order for patients to stop smoking.

These recommendations advocate the current gold-standard for supportive care after lung cancer surgery. However, it is not known to what extent patients receive this support, or the quality of the support given in standard care. Although increased support by a lung cancer specialist nurse is advocated, the specific needs of surgical lung cancer patients have not been defined. In the updated NICE guidance, additional recommendations regarding communication and enhanced information were made, but none of these recommendations address patients' informational needs regarding the effects of surgery and what to expect during recovery. In addition, no specific recommendations regarding rehabilitation have been made, rather this was highlighted as a priority for further research. In particular, research regarding the effect of pulmonary rehabilitation, optimisation of drug treatment and enhanced recovery programmes before and after surgery on mortality, pulmonary complications, pulmonary function and quality of life was recommended.[46]

1.8.3 Future rehabilitative care: tested programmes based on pulmonary rehabilitation

As has been previously discussed (see section 1.5), there is evidence that lung cancer patients experience a range of health challenges after surgical treatment. Given the respiratory involvement, it has been hypothesised that post-surgical lung cancer patients may benefit from pulmonary rehabilitation and NICE has recommended further research to measure these poten-

tial benefits.[191–193] Pulmonary rehabilitation is a programme of tailored exercise and self management education that was developed for patients with chronic obstructive and non obstructive pulmonary disease, and is routinely offered as part of treatment.[194] It is possible that pulmonary rehabilitation may improve pulmonary function and reduce the risk of pulmonary complications. In a cohort of 331 patients who underwent wedge resection, lobectomy or pneumonectomy, predictive post-surgical FEV_1 was shown to be the strongest indicator of risk for development of post-surgical complications [195] and patients with COPD have also been shown to be at an increased risk of pulmonary complications after lung cancer surgery compared to patients without.[196]

Three rehabilitation programmes based around principles of pulmonary rehabilitation for COPD have previously been piloted with lung cancer patients. Spruit and colleagues tested an 8-week in-patient programme of exercise 3 months after surgery in an uncontrolled pilot trial. The trial enrolled 10 patients, nine of whom had undergone surgical treatment. Exercise training was conducted in a group setting along with COPD patients and consisted of daily cycling, treadmill walking, weight training and stretching exercises. Pulmonary function (measured by FEV_1), 6-min walking distance and peak cycling load were measured before and after the programme. No significant change in FEV_1 was found, however patients showed a significant increase in exercise capacity at the end of the programme compared to baseline.[191]

Similarly, Cesario et al. tested an inpatient programme with 25 surgical lung cancer patients. The programme was offered to 211 eligible patients, but the majority declined to participate and were treated as controls. The programme included five daily 3 hour supervised sessions each week, up to a maximum of 20, during a hospital stay for the first month after surgery. Sessions included 30 min of continuous cycling, abdominal muscle activities, inspiratory resistive sessions, treadmill, upper and lower extremities training and full arm circling. Twice weekly education sessions were also available coving the topics of pulmonary physiopathology, pharmacology of medications, dietary counselling, relaxation and stress management techniques, energy conservation principles, and breathing retraining. Those accepting the offer to partic-

ipate in the trial had significantly worse baseline performance status and respiratory function, and therefore direct comparison found that controls had better functional and respiratory function scores after one month. However, comparing one month scores to baseline within group, borg scale on exertion, FEV_1, distance walked and oxygen saturation after 6 minute walk test all showed improvement for those who received treatment, and deterioration for controls.[192]

A pilot trial of outpatient pulmonary rehabilitation delivered before surgery has also been associated with improvements. Bobbio et al. piloted a four week programme with 12 patients who were eligible for lung cancer surgery, but showed evidence of obstructive pulmonary disease on pre-surgical respiratory function tests and maximal oxygen consumption by a cardio-pulmonary exercise test was found to be $\leq$15 ml/kg/min. The programme involved daily 1.5 hour hospital appointments, five days a week for four weeks. Patients were taught breathing exercises and incentive spirometry, and participated in aerobic exercise in the form of stationary cycling for 40 minutes. After four weeks, resting pulmonary function and diffuse lung capacity of patients was unchanged, however exercise capacity increased with a significant improvement in maximal oxygen consumption of 2.8 ml/kg/min.[193]

These pilot trials have shown improvements in exercise capacity and breathlessness scores in the short term but have been conducted in small groups of self selecting patients. These approaches remain to be assessed in terms of patient acceptability and definitively tested for long term effectiveness.

1.9 Rationale for investigating the health and supportive care needs of surgical lung cancer patients

Of the 41 000 new lung cancer cases in 2008, it was estimated that 12 000 survived for at least a year and were in need of rehabilitative care.[63] Most patients that survive for longer than one year will have received curative treatment, the mainstay being surgery.[82] As has been discussed previously (see section 1.3.4), although survival rates in lung cancer have only

marginally improved over the past decades, there is an expected rise in incidence due to the ageing population.[38] In addition, it is possible that in the future, more patients of borderline fitness will be offered surgery as a result of changes in the national guidelines whose recommendations are more permissive, and advocate greater patient choice in the decision to operate.[46, 47] Taken together, this indicates that the number of lung cancer patients undergoing surgical treatment and potentially in need of supportive care is set to rise in the coming years.

It has been acknowledged that the current system of cancer care follow up is unsustainable and does not meet the need of the growing population of cancer survivors.[177] In the first phase of piloting pathways of care, led by NHS improvement, two medical teams in Hull and Brighton were invited to test newly developed pathways of care for lung cancer. However, the focus was to test a proactive management approach to those with active or advanced disease and did not specifically focus on the needs for surgical patients.[181] Future work by the NCSI in defining and piloting new pathways of care will be taken forward with breast, colorectal and prostate cancer only, and is no longer going to focus on lung cancer. [182]

It has been noted that there is a lack of research detailing the 'natural history' and care needs of lung cancer survivors, and these research areas have been identified as a priority by the NCSI, NCRI and NICE.[1, 46, 186] Past studies using quantitative and qualitative methods to explore the health experiences of lung cancer patients have mainly focused on those receiving palliative care or survivorship issues 1-5 years after radical treatment. Although survey and quality of life data indicate that surgical lung cancer patients often experience health challenges such as breathlessness and pain after surgery, there are conflicting reports on the duration of these health challenges. No qualitative exploration of recovery after lung cancer surgery has been published, nor patients' evaluation of or attitudes towards their recovery. Although some description of the prevalence of health behaviours such as smoking, exercise and diet of cancer survivors exists, again there has been little focus on lung cancer patients specifically and no previous study has aimed to explore surgical patients views on health behaviours and behaviour change after diagnosis. Some pilot trials of rehabilitation programmes designed for lung cancer patients

based on pulmonary rehabilitation have been tested, and report on physiological outcomes. Patients' experience of the programme or attitudes towards their post-surgical supportive care needs have not been explored.

Given the lack of evidence surrounding the health of surgical lung cancer patients and their supportive care needs, coupled with the growing number of this patient group, an exploration of these issues is warranted. The purpose of this thesis is to explore these issues in order to contribute to the evidence base from which tailored services can be designed and tested in the future.

1.9.1 Thesis aims

In brief, this thesis documents research activity that sought to investigate key health and supportive care issues for surgical lung cancer patients in order to contribute to future developments in supportive care services for this patient group. Below are the specific aims of the investigations of this thesis:

1. Describe patients' experiences of health and functioning during the first year after surgery.
2. Describe patients' health behaviours during the first year after surgery and explore attitudes to health behaviour change.
3. Explore patients' satisfaction with recovery and level of supportive care received.
4. Describe key design features (i.e. content and format) for a tailored rehabilitation programme, based on patients' needs and preferences.
5. Assess the strength of evidence that smoking history affects prognosis, and if risk of death is mediated through pathways that are related or unrelated to cancer.
6. Assess the strength of evidence that continued smoking after a diagnosis of lung cancer affects prognosis, and the likely contribution of cardiovascular risk and cancer-specific risk.

CHAPTER

TWO

LUNG CANCER PATIENTS' PERSPECTIVES ON HEALTH AND SUPPORTIVE CARE NEEDS AFTER SURGERY: A QUALITATIVE STUDY

2.1 Purpose and aims of the study

This qualitative interview study was conducted to inform the development of supportive care services for surgical lung cancer patients, and identify important design features of a tailored rehabilitation programme based on patients' expressed needs and preferences. In line with these purposes, the study aimed to explore the following, relating to the first 12 months after surgery:

1. Participants' health experiences and effect on function.
2. Participants' health behaviours, health behaviour change and NHS support to change behaviour.
3. With participants receiving standard care - attitudes towards recovery, supportive care received and preferences for the content and format of a tailored rehabilitation programme.

4. With participants enrolled on a pilot rehabilitation programme - attitudes towards recovery, supportive care received and rehabilitation programme design change.

This chapter includes the introduction to this study, including the philosophical and methodological underpinning, justification for the methods used and a detailed account of the methods. The subsequent two chapters document the results and the discussion/conclusion, respectively. This study has been split over three chapters due to the volume of results.

2.2 Introduction

Meeting the needs of cancer survivors has become a focus of national service development since publication of the Cancer Reform Strategy in 2007 (see section 1.7.2). The rationale for developing services for surgical lung cancer patients has been discussed in the main introduction (see section 1.9). In order to develop tailored programmes, understanding the 'natural history' of the patients' health experiences and also patients' attitudes regarding the content and design of services is key.[186] These issues have not previously been qualitatively explored with surgical lung cancer patients.

Qualitative exploration of patients' perspectives is necessary for two main reasons. First, although some quantitative instruments have been used to measure QOL and specific symptoms in lung cancer patients, the ability of these instruments to capture the varied experience of surgical patients is unknown.[177] Investigating participants' experiences qualitatively may shed further light on the nature of the multifaceted reality of health and functioning after lung surgery, and indicate if commonly used instruments adequately represent these descriptions. Second, current policy aimed at 'modernising' healthcare puts the patient 'at the heart of the NHS'.[197] Understanding patients' attitudes towards/preferences for health care is therefore recognised to be an essential component of developing services that meet their needs.[177, 197, 198]

2.2.1 Ontological, epistemological and methodological stance: identification and justification

Qualitative research began to flourish in the latter half of the 20th century (the so called post-modern era) and past decades have seen the establishment of an array of different underlying beliefs and approaches to this type of inquiry.[199] In particular, qualitative researchers may differ regarding their beliefs about the nature/characteristics of reality and what is possible to be known about it (ontology), how it is possible to know about the nature of reality and what constitutes 'knowledge' (epistemology), and also by their approach used to attempt to find knowledge regarding reality (methodology).[200, 201] Many have sought to formulate a definition of qualitative research that, despite the diversity of beliefs and approaches, captures its essence. A widely quoted definition was formulated by Denzin and Lincoln who explained that qualitative researchers *"study things in their natural settings, attempting to make sense of, or to interpret, phenomena in terms of the meanings people bring to them."* [202] In addition to this, Richie and Lewis suggested that qualitative methods are best used *"to address research questions that require explanation or understanding of social phenomena and their contexts. They are particularly well suited to exploring issues that hold some complexity and to studying processes that occur over time."*[200] Since its emergence, beliefs and approaches to qualitative inquiry have evolved such that today, qualitative research is an umbrella term for a variety of different approaches that may take different philosophical positions, guiding the actions of the researcher.[203, 204]

It has been acknowledged that *"there is no one, single accepted way to approach or carry out qualitative research"*[200]. Establishing a perspective is not a "clear-cut" exercise because different perspectives may be required.[199] However, before embarking on a line of qualitative inquiry, it is necessary to identify which philosophical perspectives the researcher holds to, or the paradigm that will be used to inform data collection, analysis and interpretation. Denzin and Lincoln (1994) describe a paradigm (or world view) as the *"net that contains the researcher's epistemological, ontological, and methodological premises"*. It is the philosophical stance that

provides *"a basic set of beliefs that guides action"*.[202] In the following sections, I will explain which philosophical positions and methodological approach I took, as well as the specific methods that I used, in the context of some of the main alternatives, and justify why those I have chosen are appropriate for pursuit of the aims of this study.

2.2.1.1 Ontology and epistemology

Positivist thinking dominated science from the renaissance until the 20th century, and it is from this tradition that paradigms of qualitative inquiry have evolved. Ontologically, positivists hold the belief that reality exists externally or independently to the observer, and is not formed through the value that the observer or the observed places upon it, so called 'realism'.[200] Epistemologically, positivists believe that knowledge about these underlying truths or phenomena can only be obtained through empirical methods of inquiry (i.e. observation through the five human senses of sight, touch, hearing, smell, taste); deductive, hypothesis driven observation and experimentation uncovers the 'what', 'when' , 'why' and 'how many' of a phenomenon which is represented in numerical form.[204] The aim of the positivist researcher is to uncover a single 'objective truth', distanced from bias or interpreted value that may skew the observation. Although this tradition remains active within quantitative approaches, challenges to this paradigm began to arise at the end of the 19th century, particularly by researchers in the fields of the social sciences.[199] In the second half of the 20th century, alternative ontological and epistemological positions have been advocated by qualitative researchers and the methods used to gain knowledge based on these underlying beliefs have increasingly become accepted as having an important role within the field of health research.[204]

Generally, qualitative inquiry could be described as interpretivist.[200] Unlike positivism, interpretivism encompasses the belief that knowledge can be gained through other means than the senses, specifically through the 'interpretations' or 'constructions' of individuals or groups of people based on their experience and influenced by their cultural context. This epistemological position is taken along side the ontological view that rather than there being one underlying re-

ality which is objective, there may be several different versions of reality.[202] At the extreme end of this ontological spectrum, some researchers believe that reality does not exist externally but is solely the substance of people's interpretations; that truth is entirely relative. This has been referred to as 'relativism' or 'idealism'.[199, 200] The most conservative of qualitative researchers maintain that some of the tenets of positivism can be applied to the social world as well as the physical worlds (e.g. biological, mechanical, astrophysical worlds) within which empirical methods were developed. However, moving on from conservative positivism they believe that there could be more than one underlying reality depending on the perspective of the observer, thus retaining *"an ontological realism while accepting a form of epistemological constructivism and relativism"* and accepting the *"possibility of alternative valid accounts of any phenomenon"* Maxwell, 2008 [199]). Regardless of where researchers place themselves on this ontological spectrum, qualitative inquiry is considered to be more strongly suited to answering 'why' and 'how' questions, and to uncovering meaning.[203, 204]

In order to investigate the aims of this project, I have taken on the approach developed by the National Centre for Social Research, namely Framework Approach.[200] This approach has been developed over several decades specifically for use within the field of applied policy research, and has been recommended and successfully employed within the field of health research.[198, 205, 206] It is based on 'subtle realism', as described by Hammersley [207], which posits that the phenomena under investigation exist independently of participants' interpretations. However, different perspectives (or realities) held by participants are acknowledged in the belief that *"different vantage points will yield different types of understanding"*[200] and helps the researcher to understand different ways in which reality has been experienced to convey a *"full ... picture of the nature of that multifaceted reality."* [200] In other words, although the phenomena that this project aims to investigate could be considered to exist on a purely biological or practical level (i.e. health, health behaviour, functioning, health services), and measured independently of participants' interpretations to some degree, this project acknowledges that different realities exist based on interpretation of those experiencing these phenomena (ontological position) and seeks to understand the nature of these underlying phenomena from the

perspective of individual patients (epistemological position), thereby gaining a greater understanding of patients' attitudes towards these things.

2.2.1.2 Methodological approaches

There are a variety of methodological approaches to qualitative inquiry which are underpinned by the philosophical positions outlined above. I will briefly describe three commonly used methodologies, and then compare and contrast these approaches to the framework approach which has been employed in this study. Here, I use the term methodology to refer to the 'theory' behind method rather than the practical specifics of data collection and analysis itself (e.g. interviewing, focus groups, case studies, coding, identification of themes etc.),[208] which I describe afterwards. The first approach is 'constant comparison', which has its roots in grounded theory methodology developed by Glaser and Strauss [209], and more lately has developed to include thematic analysis, naturalistic enquiry and interpretive description.[210] Qualitative inquiry that uses the constant comparative method proceeds by comparing newly collected data with data that was collected previously. Instances of a phenomenon are compared within and between participants to understand how it is the same or different. This method is concerned with describing the range and patterning of manifestations of the phenomenon and what factors it might be related to. Often, particularly with grounded theory, no pre-existing theory or structure is imposed on data collection; rather patterns and theories are formed through the iterative process of data collection and constant comparison. This is often referred to as inductive reasoning.[200] However, pre-existing theories or knowledge can also been applied using these methods, particularly when using thematic analyses, which deductively lead to the acquisition and exploration of the range and patterning of the phenomena/experience based on a pre-existing hypothesis-driven framework.[208]

The narrative approach to qualitative research involves encouraging participants to 'tell their story', normally in chronological order. Rather than comparing phenomena within and between participants to identify patterns of experience, this approach typically focuses on one or a lim-

ited number of participants to provide an in depth illumination of the phenomenon of interest. Stories are viewed as a vehicle by which underlying lived experience can be represented and this approach is concerned with how choice of language reveals the underlying lived experience and reveals how people make sense of the phenomenon.[203] Discourse analysis, a type of narrative approach, draws on the fields of sociolinguistics and cognitive psychology to understand what is being communicated. It looks in more detail at not only the choice of language, but at the way participants respond to questions (e.g. pauses, silences, avoidance etc.) and how societal influences may bring meaning to phenomena through language.[211]

Phenomenological approaches to qualitative inquiry seek to uncover the essence of a phenomenon by in depth study of several individuals, as opposed to only one or two as is the case with narrative research. Ontologically, this approach appears to veer towards positivism, in that it seeks to find the single essence of a universal phenomenon through lived experiences, for example that of insomnia, grief, anger or undergoing a medical procedure.[203] Epistemologically, phenomenology asserts that reality is a function of consciousness and only exists through the perceived meaning derived from lived experience. Using this approach, research attempts to uncover, across many participants, a universal description of 'what' was experienced and 'how' they experienced it in order to give a detailed description of the phenomenon of interest.[212]

Framework approach, as used in this study, contains elements of these approaches, but most closely resembles a constant comparative, thematic analysis approach.[200] As with the narrative approach, participants are encouraged to 'tell their story' in chronological order as a means of eliciting and understanding of the phenomena of interest. However, rather than focusing on the choice of language within a limited number of individuals, participants 'stories' and the instances of experiences/attitudes are compared and contrasted in order to understand the range of experiences and attitudes that are exhibited, and to identify common themes. Although framework approach takes interpretive ontological and epistemological positions (i.e. there are many versions of reality, and knowledge is gained about these versions through the channel of peoples' interpretations), aspects of positivism remain (hence the 'subtle realism' classifi-

cation). Specifically, the researcher aims to be as neutral as possible and rather than learning about the phenomenon under study by becoming part of the social world experiencing it, remains an impartial observer of the interpretations of others. In addition, rather than taking a purely inductive approach to understanding experience, experience can be deductively explore based on preceding understandings and identified research priorities.

This qualitative study arose from pre-determined research priorities and in addition potential areas of importance had been identified based on a search of published literature (see sections 1.5- 1.6). Based on the capacity to combine deductive and inductive analytical frameworks, the pragmatic approach to data collection and the successful use by other studies exploring heath and healthcare issues, the framework approach was considered the most suitable approach to adopt for this study.

2.2.1.3 Data collection and analysis methods: Identification and justification

There are various options in terms of qualitative data collection approaches, ranging from the more intensive approaches of ethnography where a researcher becomes part of the social world understudy through to more time conserving approaches of conducting individual interviews and focus groups.[203] Given the individual nature of the health experiences and that the aim of the research was not to understand group influences on experiences, I decided to interview patients on a one to one basis. A semi-structured interview format was chosen over structured or unstructured interviewing as there were a range of specific topics that I wanted to address with participants, but it also gave participants' an opportunity to introduce areas of discussion not dictated by the researcher. Richie and Lewis [200] described five interlinking processes to data collection and analysis using framework approach:

1. Familiarisation with the data - immersion in a pragmatically selected portion of the data
2. Identifying a thematic framework - deductively identify a thematic framework/index for analysis using the structure of the interview and inductively from findings in stage 1

3. Indexing - apply all data collected to the identified thematic framework in textual form, with iterative changes made to the index (and framework) as data collection progresses
4. Charting - summarising data under themes identified by the framework.
5. Mapping and interpretation - map the range and interpret the findings, including finding associations and defining typologies.[15]

Reflections on the processes that have been involved in conducting this study have been discussed in section 4.2.

2.3 Methods

The following sections describe the methods used for the study, including data collection and analysis. Interviewees are referred to as 'patients' until they consented to the study, after which they are referred to as 'participants'.

2.3.1 Funding/Collaboration

This study was funded by the National School of Primary Care Research (NSPCR). The funding application and confirmation of funding letter can be found in appendix A.2. The University of Birmingham acted as sponsor (see appendix A.3). A stipulation for being awarded funding was to form a collaboration with another primary care department within the NSPCR. I collaborated with the Healthtalkonline (HTO) team within Primary Care Health Sciences at the University of Oxford, and arrangements were made to dovetail the aims of this project with a contribution to their website. The HTO website contains *"a unique database of personal and patient experiences through in-depth qualitative research into over 50 different illnesses and health conditions."*[213] The HTO venture has been running for over a decade. Patients are interviewed regarding their experiences of health and treatment, the interviews are video recorded, and visual or audio clips from the videos are published on the website. At the time of this

project, the HTO website did not include interviews conducted with lung cancer patients who had undergone VATS. Three participants (HTO1, HTO2 and HTO3) who had undergone VATS were interviewed following procedures in the HTO manual, and the interviews were video taped in addition to an audio recording. Clips from the video recordings of interviews with HTO1 and HTO2 are both posted on the HTO website.[214][215]

2.3.2 NHS recruitment sites

Prior to the commencement of this qualitative research project, the research team that I was working with had an established collaboration with the thoracic surgery centre at Birmingham Heartlands Hospital NHS trust (BHH). The idea for the project had been discussed with a thoracic surgeon at BHH, and the initial focus was set to be surigcally treated lung cancer patients. However, as the project developed, it was decided that it would be a beneficial addition to also recruit patients treated with radical radiotherapy. This was because survival rates are improved after both of these curative treatments, and it was considered that in addition to surgical patients, radical radiotherapy patients may also be in need of additional supportive care after treatment. No previous study was identified that had qualitatively investigated the health and supportive care needs of lung cancer patients treated with radical radiotherapy. As such, a collaboration was set up with University Hospital Birmingham NHS Foundation Trust (UHB) who treat lung cancer patients with curative radical radiotherapy, and a substantial amendment to recruit patients from this site was granted (see section 2.3.3).

There was one clinical oncologist at UHB that treated lung cancer patients with radical radiotherapy. Unfortunately, although this oncologist agreed to facilitate recruitment of eligible patients, I was only sent details of and recruited one patient treated this way. During the course of the project, I made numerous attempts to engage the clinical oncologist, or enlist the help of a secretary, to improve recruitment but was unable to make progress. As there was only one radical radiotherapy patient recruited, it was decided that this patients would be excluded from this analysis. Although this is not ideal as the patient had consented to having data taken and

was expecting it to be used, I felt that this was the best course of action as it was not possible to conduct a representative analysis of patients who had received this treatment. Therefore, this project returned to a sole focus on surgically treated lung cancer patients.

2.3.3 Ethics and R&D approval

As this study involved NHS patients and their data, ethical approval to conduct the study was sought from Birmingham, East, North and Solihull Research Ethics Committee. A favourable opinion was given on the 11th March, 2009 (see appendix A.4). During the course of the study I applied for approval of two substantial amendments. The first amendment involved a change in the interview schedule, and the second was to extend recruitment to patients treated with radical radiotherapy from an additional hospital trust, the University Hospitals Birmingham NHS Foundation Trust. Favourable opinions were given on the 21st September 2009 and 9th May 2011, respectively (see appendices A.5 and A.6). As patients were only identified by the hospital trust, and interviews took place at patients' homes rather than on the premises, it was not necessary to apply for an honorary contract for each trust, but rather a letter of access was granted by Heart of England NHS trust and the University Hospitals Birmingham NHS Foundation Trust (see appendices A.7 and A.8).

The HTO project was granted ethical approval by Berkshire Research Ethics Committee on 22nd May, 2009 (see appendix A.12). Although I did not need to seek for ethical approval to conduct interviews according to the HTO manual with HTO1, HTO2 and HTO3, I applied to the Heart of England NHS trust for an additional letter of access to conduct these interviews (see appendix A.13).

2.3.4 Patient sample

Lung cancer patients were recruited from a tertiary referral thoracic surgery centre, based at Birmingham Heartlands Hospital (BHH).[1] A list of all patients that were eligible to take part in the study was generated by a secretary attached to the thoracic surgery team at BHH from the hospital computerised patient record system. Patients were recruited at interview between February 2010 and November 2011, and a list was generated a number of times over the course of recruitment to capture new patients that were becoming eligible. Criteria for eligibility were as follows:

1. Diagnosis of non-small cell or small cell lung cancer
2. Removal of lung tissue via surgical procedure (VATS or thoracotomy)
3. Surgical procedure conducted between 3 and 12 months previous to the date of interview
4. No confirmed recurrent tumour

The rationale for recruiting patients between 3 and 12 months after surgery, rather than all at 12 months, was to contemporaneously explore patients experiences throughout this period. It was anticipated that this would give a more reliable overall understanding of the diversity of health experiences and health behaviours, by minimising recall bias. Although one year survival rates after surgery are high at around 80%,[216–218] sampling patients at various points along the 12 month pathway also minimised any impact that survival bias may have on the representativeness of the sample throughout the study period. The strengths and weaknesses of this approach have been explored in the discussion to this study (see section 4.2).

Patients were purposively selected for initial contact from the list of eligible patients generated by the secretary. Identification of patients and initial contact was carried out by the research nurse/physiotherapist, under my direction. The aim of sampling was to recruit patients to rep-

[1] BHH thoracic surgery unit receives referrals from 11 individual hospitals in the West Midlands, Worcestershire, Herefordshire and Gloucestershire areas: BHH, Solihull Hospital, Good Hope Hospital, Walsall Manor, City Hosptial, UHB, Sandwell General Hospital, Alexandra Hospital (Redditch), Hereford County Hospital, Worcester Royal Infirmary and Cheltenham General Hospital.

resent a range of characteristics that may affect the experience of recovery and views regarding care including age, gender, primary incision procedure (VATS v thoracotomy procedure) and extent of resection (wedge resection v lobectomy v bilobectomy v pneumonectomy). As patients were specifically selected for these characteristics, recruitment was not random or consecutive.[219] Patients were not purposefully sampled based on smoking status, as their smoking status was unknown before the time of the interview. However, a diverse range of behaviours (i.e. never, former, current at diagnosis, and continued, relapsed or quit after diagnosis) were represented in the sample (see section 3.1).

During the initial contact, the research nurse/physiotherapist briefly introduced the study, and asked if patients would be willing for their contact details to be sent to a researcher at the University of Birmingham who would tell them more about the study and set up an interview time. In the brief introduction to the study, the research nurse/physiotherapist explained that the purpose of the study was to talk about their recovery after surgery and about their experience of and views regarding aftercare.

During the recruitment period for the interview study, a pilot trial of a rehabilitation programme for surgical lung cancer patients (the ROC programme - **R**ehabilitation for **O**perated lung **C**ancer) began recruiting patients who had been treated surgically at BHH (see section 2.3.4.1 for full details of the ROC programme). The thoracic surgery centre received patient referrals from twelve different hospitals in the region. Patients who had been referred from either by BHH, Solihull Hospital or Worcester Royal Infirmary (WRI) were eligible to take part in the ROC programme. Eligible patients were identified at MDT meetings and were recruited at their first visit to a thoracic surgery/respiratory clinic after the MDT meeting, before surgery.

The first patient was recruited onto the ROC programme on the 6th May, 2010. Patients who were enrolled in the ROC programme were not excluded from the interview study, if they fulfilled the interview study eligibility criteria. PID1-14 from the interview study had been identified for surgery in an MDT before the ROC programme began recruiting patients, and therefore had not participated in the programme. PID15-31 and HTO1-3 were all identified at an MDT

whilst the ROC programme was running, and some of these patients had been referred from either BHH, Solihul Hospital or WRI and therefore had taken part in the ROC programme. Recruiting both patients who had received and who had not received the ROC programme gave the opportunity to compare the experiences and views of patients who had received these different levels of care. The research nurse/physiotherapist who initially contacted patients for interview did not have any prior knowledge of patients who had receive standard care, but were involved in running the ROC programme and therefore had prior knowledge of some of the ROC patients. The implications of this and have been discussed in section 4.2.

2.3.4.1 The ROC programme

The ROC programme was designed by a multidisciplinary team of health professionals involved in surgical lung cancer patient care at BHH and WRI.The development of the programme was led by Mr Babu Naidu, a thoracic surgeon. The aim of the programme was to modify risk factors for post-operative pulmonary complications and to improve patient experience through enhanced information giving and self management education. Modifiable risk factors were identified based on previous published evidence from the team.[157] Specifically, it was decided that the ROC programme would be designed to address COPD, BMI and smoking status. Exercise-based rehabilitation programmes have been shown to be effective in optimising recovery in other cancers,[221] cardiovascular disease[2] and have shown promise for lung cancer patients specifically.[192, 193, 196] Based on this evidence, and coupled with clinical judgment and expertise, the multidisciplinary team designed the ROC programme which was embedded within pulmonary rehabilitation services for COPD patients being provided by BHH and WRI.

Participants that enrolled on the ROC programme joined physiotherapist-led pulmonary rehabilitation exercise training and education sessions and received additional enhanced information sessions tailored to the needs of surgical lung cancer patients from a physiotherapist and lung CNS. In addition, participants were assessed for nutritional and smoking status and if appropriate were referred to a Macmillan dietician or specialist smoking cessation advisor. The

programme was run locally at BHH hospital gym for participants referred for surgery from BHH and within the community at Worcester for participants who had been referred for surgery from WRI. Participants were encouraged to attend sessions twice a week for as many weeks as possible prior to surgery. Surgery was not delayed in order for patients to participate in the pre-surgery component of the programme. Participants were invited to return for a further six, weekly supervised exercise and education sessions, four weeks after discharge. Sessions lasted for two hours, with one hour for exercise and one hour for education.

Exercise and educational sessions were delivered in a group setting, although participants exercised at their own pace and received individual feedback from physiotherapists. The content of exercise and educational sessions are shown in Table 2.1.

Table 2.1: Exercise and education sessions received by participants enrolled in the ROC programme

Exercise session (1st hour)	Educational sessions (2nd hour)
Participants were encouraged to engage in all of the following exercises:	Each education session focused on one of the following topics:
Lower body manoeuvres	Need for lifestyle change (smoking cessation, healthy diet)
Walking	COPD and co-morbidities
Cycling	Benefits of exercise
Step-ups	At home advice on exercise
Marching on the spot	How to deal with breathlessness
Sit to stand	Chest clearance
Upper body manoeuvres	Oxygen and inhalers
Upright wall press-ups	
Ball bouncing	
Backstroke	
Upper body twists whilst sitting	
Double arm lift with exercise ball	
Pulley	

Participants received two additional one-to-one information sessions which were specifically tailored to the needs of lung cancer surgical patients. The first was delivered at the point of recruitment by a lung CNS, which occurred at the first clinic attendance after a patient was identified as a candidate for surgery at the multidisciplinary team meeting (MDT). During this session, a lung CNS explained in more detail what to expect before, during and after surgery,

the surgical procedure, physical side effects of surgery and how their pain would be managed whilst an inpatient and on discharge. In addition, participants were given lifestyle advice and at this point participants who were smoking or had lost more than 10% of their weight over the previous three months were referred for specialist smoking cessation and dietary intervention. The second tailored information session was delivered by a physiotherapist during the hour previous to the participant's first pulmonary rehabilitation session. This session began with an assessment of activity/fitness/limitations and health behaviours. Depending on the findings of the assessment, the physiotherapist briefly covered the topics of the main educational sessions (see table 2.1), and in addition gave a detailed explanation of lung physiology. Figure 2.1 gives an overview of the ROC programme.

2.3.5 Recruitment

Patients were invited to participate in batches over the period of the study. The characteristics of the included participants were monitored throughout this process to ensure maximum variation in the characteristics of interest (i.e. age, gender, primary incision procedure, extent of resection and also type of supportive care (standard v ROC programme)). Patients who had given consent for their details to be passed to a researcher after initial contact from the research nurse/physiotherapist were contacted by myself, by telephone. More detail about the aims of the interviews were given and patients were invited to participate in the study.

Patients who were undecided were sent a patient information sheet (PIS) (see appendix A.10) in the post and given the option of thinking about their decision to participate for 1 week, after which they were re-contacted for a decision. For those who agreed to be interviewed, I set up an appointment time for the interview to take place at the patient's home, and the PIS, along with an appointment letter, were sent out to the patient's address. Patients were given at least 48 hours after receiving the PIS before the interview occurred. Most patients did not request further details about the interview, but some wanted to know more about the topics that would be covered. In this case, I gave a verbal account of the information in the PIS (see appendix

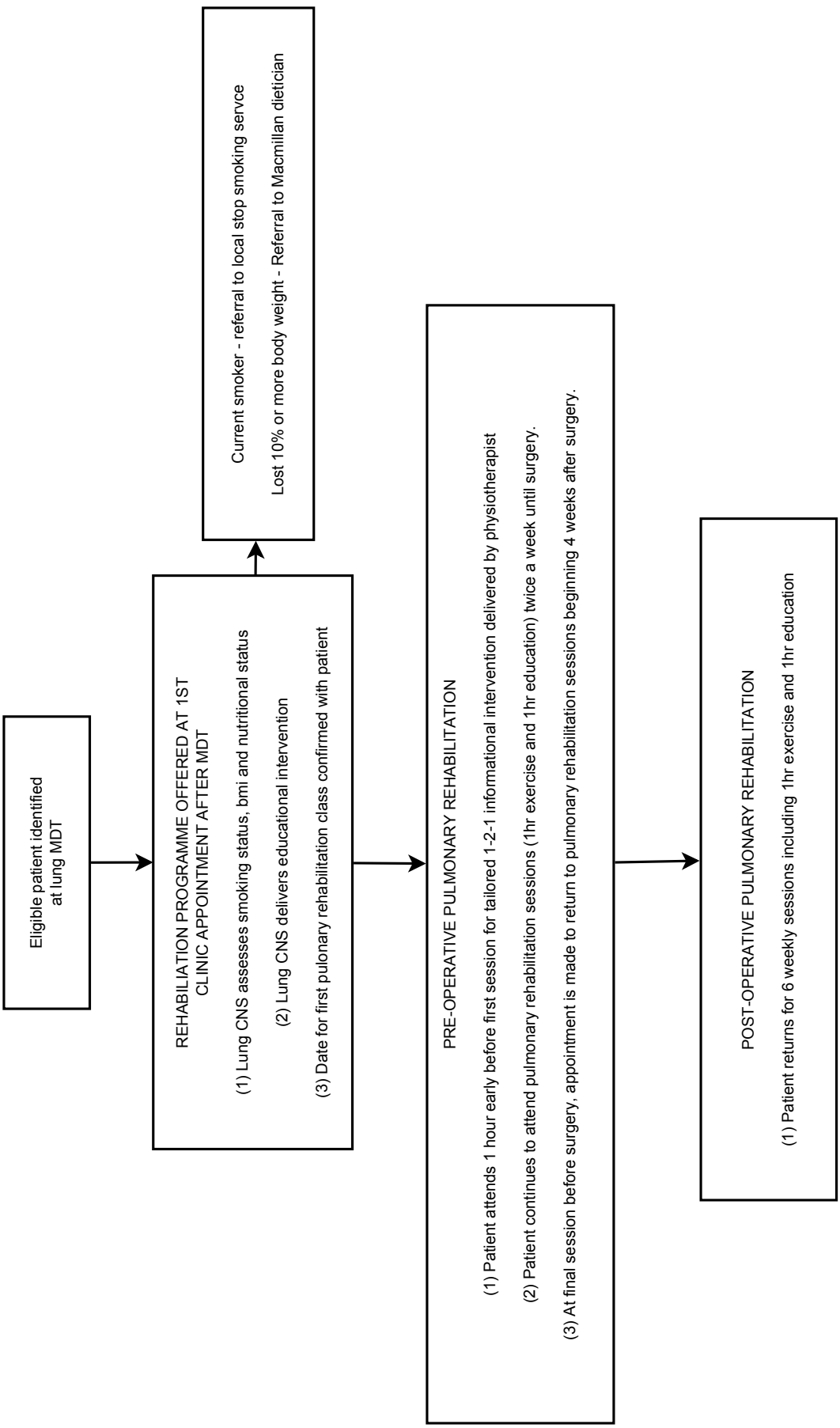


Figure 2.1: The ROC programme

A.10). Patients were informed that they could withdraw from the project at any time before, during or at the end of the interview. HTO1, HTO2 and HTO3 were sent the HTO PIS (see appendix A.15) in addition to the PIS developed for this project, and the potential that interview material could be used for the HTO website was explained. As with other patients, interviews were arranged at least 48 hours after receiving the study associated paper work.

2.3.6 Consent

On the day of interview, I checked that patients had read and understood the PIS. Patients who had not read the PIS were given the opportunity to do so before consenting to take part. I also gave patients the opportunity to ask questions about the study. Patients were then shown the consent form and asked to read and sign. The consent form reminded patients of the rights to withdraw from the study at any time, that relevant sections of their medical notes may be used by researchers, that the interview would be recorded and that records would be kept confidentially. HTO1, HTO2 and HTO3 signed additional consent forms that had been approved by Berkshire REC (see appendices A.9 and A.14).

Although the aim of the interview was to focus on patients only, rather than to explore experiences and views of partners or other family members, in some cases a third party was present when I arrived at the patients' home (see table 3.1). If participants requested that the third party remained present at the interview, this was granted. Third parties did not fill out an additional consent form but gave verbal consent to participate in the study. Third parties present in the interview were not asked questions directly, but sometimes they added additional detail to descriptions given initially by the participant. Additional data generated from participation of third parties in an interview were transcribed along with the rest of the interview material, and relevant data were included in the analysis whilst attributing the data to the third party.

2.3.7 Interview

Before commencing, participants were reminded of the aims of the interview. Three possible difficulties were anticipated and I sought to ameliorate their effect during the set up and delivery of the interview. Firstly, talking about cancer and treatment may have been upsetting. I reminded participants that they could stop the interview at any time or decline to discuss particular topics. Secondly, due to the links between smoking and lung cancer, the topics of smoking behaviour and treatment was raised sensitively. I aimed to convey a non-judgemental attitude and encouraged participants to be honest about their smoking behaviour. Thirdly, it was possible that participant responses would be subject to social desirability bias. To overcome this, before the interview commenced, I explained that patients could be frank about their experiences and attitudes related to their health and treatment, and reminded them that the interview findings would be anonymised and were being used to help improve services rather than being used 'against' the NHS.

Interviews proceeded in a semi-structured fashion. To put the recovery experiences into context, all interviews began with the question *"So to start off with, can you tell me what first made you think there was something wrong?"* and participants were encouraged to tell their story of diagnosis and treatment. Subsequently, several topics were addressed, although the order and the wording of questions sometimes differed from participant to participant, depending on how the interview had progressed. The interview topics and questions are found in table 2.2. Although some closed questions were used, I generally aimed to use open ended, non-leading questions.

After the interview, participants were given a leaflet signposting organisations which offer information and support to people who have been treated for lung cancer (see appendix A.11). All interviews were recorded using a dictophone. The interviews were transcribed and anonymised by a third party, and then edited for completeness and accuracy by myself. The transcribed audio file of the interview was the only source of data used in the analysis.

Table 2.2: Interview topics and questions raised with participants

Interview topics	Example interview questions
Preamble - describe the context	"What first made you think there was something wrong"
Aim 1: topics raised	"When did you first notice X was a problem?"
- Breathlessness	"Can you describe what X felt like (physically)?"
- Pain	"Is X still a problem? How did/does X affect your day to day functioning?"
- Effect of health challenges on function	"How does X affect you emotionally/psychologically?"
	"Would you say you are back to normal?"
	"In what ways are you not back to normal?"
Aim 2: topics raised	"Are you smoking at the moment?"
- Smoking	"How did the cancer and treatment affect your appetite and diet?"
- Diet	"Have you engaged in any exercise since your surgery?"
- Exercise	"Did the staff at the hospital talk to you about your smoking/exercise/diet?"
	"Has anything helped improve your breathlessness/pain/fatigue etc."
	"Would you feel able to tell your doctor that you were still smoking? Why/why not"

Table 2.2: cont.

Interview topics	Example interview questions
Aim 3: topics raised (Standard care only)	"Did you feel prepared for surgery and for your experiences during your recovery?"
- Satisfaction with recovery	"Was there anything that you had been struggling with that you felt you weren't helped with?"
- Attitudes towards supportive care received	"What kind of extra support do you think that you would have benefited from?"
- Need for additional supportive care	"What do you think would be important aspects to include in a rehabilitation programme?"
- Preference for content and format of tailored rehabilitation programme	"At what point after surgery should a rehabilitation programme take place?"
	"Would you prefer to be part of a group or individual rehabilitation sessions?" "If you were offered help to stop smoking/with your diet/to exercise would you accept it? Why/Why not"
	"At what point after surgery do you think is the best time to get help with smoking/diet/exercise. Why?"
Aim 4: topics raised (ROC programme only)	"Did you find the ROC programme helpful? In what ways was it helpful/unhelpful?"
- Satisfaction with recovery	"Do you think that participating in the programme helped you to recover? Why/why not?"
- Attitudes towards supportive care received	"Did you feel that the exercise level was right for you?"
- Suggested design changes for the ROC programme	"Did you feel adequately prepared for surgery and recovery?"
	"Was there anything that you had been struggling with that you felt you weren't helped with?"
	"How did you feel about an offer of help to quit smoking, or help with diet?'
	"What were the best things about the programme?"
	"What was the worst thing about the programme"
	"Was there anything that you thought needed to be done differently?"

2.3.8 Post-interview data gathering

The research nurse completed a clinical information form for each participant interviewed from information in their medical notes, detailing diagnostic and lung cancer surgery characteristics, prescriptions for inhaled steroid or bronchodilators given on discharge, demographic information, co-morbidities (history of COPD, ischaemic heart disease, cardiac failure, hypertension), breathlessness and Eastern Cooperative Oncology Group (ECOG) performance status recorded in the pre-operative clinic. Breathlessness was measured using the MRC breathlessness scale. ECOG performance status included grade 0-5 of activity, with 0 being 'fully active, able to carry on all pre-disease performance without restriction' and 5 being 'dead'. For a full description of these grades see section 1.5.2.1.

2.3.9 Interview pilots and iterative changes

The first two interviews were used as a pilot for the interview structure and delivery. Participants were informed that their interview was a pilot and were asked to give feedback. Neither participant suggested changes, and felt that the interviews allowed them to express all information that they felt was relevant. They did not find the content or tone of the interviews distressing. As the number of interviews completed increased, I became more familiar with the subject area, and made iterative changes to the preamble to the interview (increasing the directness of the explanation of the focus and purpose of the interviews), wording of questions (used more terms that were commonly used by participants, improved on construction of non-leading questions) and simplified the interview schedule (see appendix A.16 for first version of interview script. Final collection of questions that were used are found in table 2.2).

2.3.10 Analysis

When conducting qualitative research, the stages of data collection and analysis inform each other, and data collection undergoes iterative changes due to findings from concurrent analysis.[200] In order to facilitate this, as interviews were completed, transcribed and checked, I noted emerging themes. Data were managed using NVivo 9.2 (2011 QRS International) which was developed in collaboration between QRS International and NatCen FrameWork software developers, and for the first time includes the capability to construct framework matrices. Coding node trees were constructed, and each interview transcript was coded. Iterative changes were made to the organisation of the coding tree as new themes emerged from interview data. In addition, I began to construct framework matrices based on some of the main themes of the interviews. This process allowed me to see what each participant had said about each theme, and helped to identify areas that needed further clarification in future interviews. Interviews were continued until it was considered that no new themes were emerging (saturation of themes)[208] and the interview aims had been explored in full.

During the early stages of coding, five transcripts were coded independently by an experienced qualitative researcher. Assignment of codes was found to correspond highly, but any differences in coding were discussed and resolved. After all data had been collected and coded, and in order to complete framework matrices, I carried out some additional data coding checks. This was done by conducting broad context queries in NVivo to retrieve interview data regarding five main themes of analysis: breathlessness, pain, fatigue & sleep, appetite & weight loss and smoking. This retrieved all interview data that included the terms of the query along with surrounding text. The query results were cross-checked with the coded data to ensure full retrieval of relevant material and framework matrices were constructed based on the final coded data. Queries were not carried out to check coding of participants' views regarding attitudes to recovery and supportive care due to lack of a finite list of key words that would identify these data. Data were summarised along with illustrative quotes in the matrices for the overarching themes and sub-themes listed in table 3.4.

Types of experiences of breathlessness and pain were categorised based on commonly used clinical tools to measure them (see table 3.6 and 3.9). Specifically, categorisation of breathlessness experiences was based on the MRC breathlessness scale and the Borg Scale. Categorisation of pain experience was based on the McGill Pain Questionnaire (MPQ) and descriptions of post-thoracotomy pain syndrome (PTPS) given by the International Association for the Study of Pain (IASP) (see section 1.5.2 for description of scales and PTPS). A typology of breathlessness and pain experience was constructed from patterns across several categories of experiences that emerged whilst comparing accounts between participants, summarising the extent to which participants were affected by these health challenges.

CHAPTER

THREE

QUALITATIVE INTERVIEW RESULTS

This chapter describes the characteristics of participants interviewed for the qualitative study, the peri-surgical and post-surgical supportive care that participants received, the main topics and themes for analysis and then presents the results for each of the four aims of the study (see section 2.1).

3.1 Characteristics of participants

From the list of eligible patients generated by the medical secretary from computerised patients records, a total of 46 patients were identified with the range of characteristics that had been identified for sampling and were approached to participate in the study. From this a total of 34 participants were consented into the study and interviewed. One consented participant (PID2) had undergone radical radiotherapy two years before removal of an additional tumour via thoracotomy at BHH. Searching the medical notes after interview, it became clear that there was uncertainty over metastatic disease and this participant was excluded from the analysis (see section 2.3.4). Two interviews (PID7 and PID8) were accidentally deleted from the dictaphone

before they were saved onto a server, and one further interview (PID27) did not record successfully due to technical failure of the equipment. One participant was recruited from UHB after undergoing curative radiotherapy for a primary tumour (PID22). This participant was excluded from the analysis as I was unable to arrange other interviews with participants who had received this treatment. Therefore, a total of 29 participants were included in the analysis, all of whom had undergone radical surgery and represented a range of demographic and clinical characteristics (see table 3.1 and 3.2, and figure 3.1).

In total, 14/29 participants were male and the mean age at interview was 70 years (range 39-82 years). . Twenty three participants' primary procedure was thoracotomy, and 6 participants had been resected via VATS. Twelve participants had undergone wedge resection (with one or two wedges being removed) and fourteen participants underwent lobectomy (with one or two lobes being removed). One participant had undergone a lobectomy with an additional wedge resection and two participants had undergone a complete pnemonectomy.

There is no national data available regarding the demographics of surgically treated lung cancer patients with which to compare the sample for representativeness. The 2011 National Lung Cancer Audit (2010 patient cohort) gives a mean (SD) age of 71.4 (10.7) for all lung cancer cases,[48] and this is consistent with the age range interviewed in this study. There is no data on ethnicity or SES breakdown. The 2013 National Lung Cancer Audit (2012 patient cohort) describes national figures for the number of patients receiving different types of surgical resection between 2008-2012.[222] During this period, 90% of patients received either lobectomy, wedge resection, pnuemonectomy or bilobectomy. Therefore, as far as it is possible to tell, the demographic and surgical characteristics of the patients interviewed are representative of these characteristics in surgical lung cancer patients in general.

The goal was to recruit patients with confirmed lung cancer between 3 and 12 months after surgery. Tumour histology was obtained from the medical notes for all but two of the participants. Most participants had been diagnosed with non-small cell lung cancer (12 adenocarinoma, 3 squamous cell, 1 large cell, 3 mixed NSCLC cell types), two participants had small

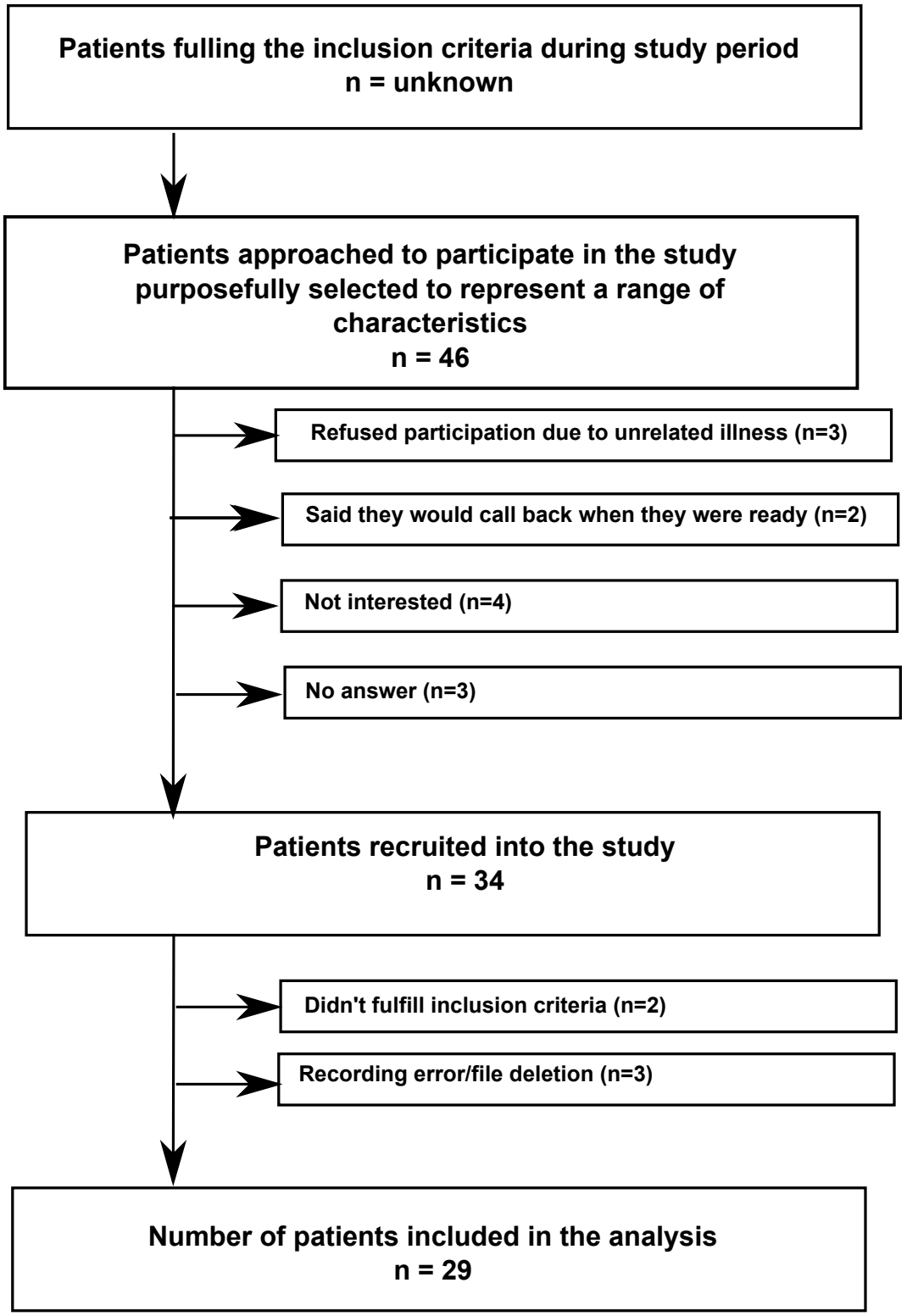


Figure 3.1: Flow chart of patient sampling

cell lung cancer, two participants had a carcinoid tumour and two participants had been diagnosed with a mixed non-small cell and small cell lung tumour. Again, these histological types are representative of the range of histological diagnoses for lung cancer in general.[14] One participant, however, was found to have no malignancy (PID23). In addition, all patients were interviewed between 3 and 12 months after surgery apart from one who was interviewed at 14 months after surgery (PID 4). After consideration, PID23 and PID4 were included in the analysis. For PID23, this was based on the assumption that although his suspected lung cancer was not confirmed, after surgery he would be phenotypically the same as other patients for whom cancerous tissue had been removed via the same procedure. PID4 had confirmed lung cancer, and although was interviewed at 14 months provided descriptions of her experiences during the first 12 months which were relevant to the analysis.

Participants' pre-surgical ECOG performance status[223] grade[1] ranged from 0 (fully active, able to carry on all pre-disease performance without restriction) to 3 (capable of only limited self-care, confined to bed or chair more than 50% of waking hours), with a median score of 0. Ten participants had been diagnosed with COPD before surgery and five of these participants were prescribed inhaled bronchodilators and/or steroids on discharge. A further four participants were diagnosed with asthma and all were prescribed with inhaled bronchodilators and/or steroids on discharge. Ten participants had been previously diagnosed with hypertension, four had been diagnosed with ischaemic heart disease and one with chronic cardiac failure. MRC breathlessness score ranged from 1 to 4, with a median of 1. MRC breathlessness score for only participants diagnosed with COPD or asthma also ranged from 1-4, but participants had a median score of 2 for COPD and 1 for asthma (for description of MRC breathlessness score see section 1.5.2.1).

Most participants (26/29) had a history of smoking. At diagnosis, 11 were current smokers,

[1]Eastern cooperative oncology group (ECOG) performance status is a widely used measure to assess to what degree patients are affected by disease. Grade 0 = fully active, able to carry on all pre-disease performance without restriction, 1= restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work, 2 = ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours, 3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours, 4 = completely disables. Cannot carry on any self-care. Totally confined to bed or chair, 5 = dead.

15 participants had quit smoking between two months and 40+ years previously and three participants were never smokers. The majority of ex-smokers had quit over 10 years before their diagnosis.

Table 3.1: Participant characteristics: demographics, smoking behaviour and care

PID[1]	M/F[2]	3rd Party	Age[3]	Standard/ Enhanced[4]	MPS[5]	Smoking status[6]	smoker at diagnosis	Description of smoking behaviour (cpd = cigarettes per day)
HTO1	M	No	70	standard	3	Ex	N	Ex-smoker of 11 yrs
HTO2	F	No	81	standard	4	Ex	N	Ex-smoker of 20+ yrs (cpd20)
HTO3	F	No	73	ROC	4	Ex	N	Ex-smoker of 3 yrs
PID1	M	No	62	standard	11	Ex	N	Ex-smoker of 20+ yrs
PID3	M	Wife	67	standard	10	Relapse	Y	Quit and relapsed after surgery to smoking 20 cpd
PID4	F	No	61	standard	12	Relapse	N	Quit 2 months before surgery and relapsed to 40cpd 3 months after surgery. Had started new quit attempt 2 weeks before interview
PID5	M	No	77	standard	6	Cont	Y	Continued smoking after surgery (20cpd)
PID6	F	No	66	standard	11	Abs	N	Ex-smoker of 8 months
PID9	F	No	71	standard	9	Cont	Y	Cut down to 15cpd on patches, but continued smoking
PID10	F	No	39	standard	7	Ex	N	Used to smoke "years" ago.
PID11	M	Sister	70	standard	4	Ex	N	Ex-smoker of 10+ yrs
PID12	M	Wife	76	standard	5	Ex	N	Ex-cigarette smoker of 30+ years, occasionally smokes a cigar

[1]HTO = Participant also completed “Health talk online” consent form, PID = Patient identification
[2]M = male, F = female
[3]Age at time of interview
[4]Standard = standard care, ROC = participated in the ROC programme
[5]MPS = months post-surgery
[6]Ex = ex-smoker i.e. quit before diagnosis, Relapse = quit for surgery but relapsed after discharge, Cont = did not try to quit for surgery and continued to smoke on discharge, Abs = abstinent from surgery to interview

Table 3.1: cont.

PID[1]	M/F[2]	3rd party	Age[3]	Standard/ ROC[4]	MPS[5]	Smoking status[6]	smoker at diagnosis	Description of smoking behaviour (cpd = cigarettes per day)
PID13	F	No	66	standard	5	Relapse	Y	Quit a few days before surgery, relapsed 3 months after returned home. Trying to quit with e-cigarette, but reading between the lines she was also still smoking.
PID14	M	Wife	82	standard	5	Ex	N	Ex-smoker of 16 years
PID15	M	Wife	75	ROC	5	Abs	Y	Did not smoke whilst in hospital, was put on patches by doctor, has had 1 or 2 cigarettes in total since discharge but not relapsed.
PID16	F	No	58	standard	5	Relapse	Y	Did not smoke in hospital, smokes the "odd" cigarette now but does not smoke at work or in front of her children. Uses patches to help, OTC.
PID17	F	No	73	ROC	5	Never	N	Never smoker
PID18	M	No	81	ROC	3	Never	N	Never smoker
PID19	F	No	71	ROC	6	Ex	N	Very occasional social smoker in the past
PID20	M	Wife	80	standard	3	Abs	Y	Been smoking for 60+ years, gave up the day he went into hospital for his surgery, hasn't smoked since
PID21	F	No	63	standard	3	Cont	Y	Was not smoking in hospital, but started smoking again as soon as she was discharge. Back to smoking 20-30cpd
PID23	M	No	75	ROC	3	Relapse	Y	Quit for 2-3 weeks after surgery, but started to feel well and went back to 40cpd

Table 3.1: cont.

PID[1]	M/F[2]	3rd party	Age[3]	Standard/ ROC[4]	MPS[5]	Smoking status[6]	smoker at diagnosis	Description of smoking behaviour (cpd = cigarettes per day)
PID24	F	No	66	standard	3	Ex	N	Ex smoker of 5-6 years
PID25	M	Wife	76	ROC	3	Ex	N	Ex-smoker of 20 yrs
PID26	M	No	61	ROC	7	Cont	Y	cut down, smokes half of what he did
PID28	F	No	76	ROC	3	Never	N	Never smoker
PID29	F	No	60	ROC	3	Ex	N	Ex-smoker of 16 years
PID30	F	Husband	72	ROC	4	Abst	Y	Quit from the moment she found out she had cancer.
PID31	M	No	74	standard	4	Ex	N	Ex-smoker of 30+ years ago

Table 3.2: Participant characteristics: clinical

ID	Histology[6][7]	Stage[7][8]	Primary Procedure	Incision Procedure	Position[7]	LOS[9] (days)
HTO1	NSCLC (adenocarcinoma)	T1b N0 Mx	VATS	Lobectomy	Left, lower	4
HTO2	NSCLC (adenocarcinoma)	T2a Nx Mx	VATS	Wedge resection	Left, lower	3
HTO3	NSCLC (squamous cell carinoma)	n/a[7]	VATS	Wedge resection	Left, upper	8

[6]NSCLC = non-small cell lung cancer, SCLC = small cell lung cancer
[7]n/a = not available
[8]For TNM description refer to table 1.1
[9]LOS = length of stay

Table 3.2: cont.

ID	Histology[67]	Stage[78]	Primary Procedure	Incision Procedure	Position	LOS[9] (days)
PID1	Carcinoid	n/a	Thoracotomy	Wedge resection	Right, middle	9
PID3	Mixed (Large cell neuroendocrine and SCLC)	T1 Nx Mx	Thoracotomy	Wedge resection	Right, lower	35
PID4	SCLC	T1 Nx Mx	Thoracotomy	Wedge resection	Left, upper	6
PID5	NSCLC (squamous cell carcinoma)	n/a	Thoracotomy	Wedge resection	Right	11
PID6	NSCLC (Poorly differentiated adenocarcinoma)	pT2 N1 Mx	Thoracotomy	Pneumonectomy	Left	8
PID9	SCLC	T1 M0 Nx	VATS	Wedge resection	Right, upper	4
PID10	Carcinoid	T2 a N0 Mx	Thoracotomy	Bi-lobectomy	Right, middle and lower	6
PID11	NSCLC (squamous cell carcinoma)	T2b N0 Mx	Thoracotomy	Bi-lobectomy	Right, middle and lower	4
PID12	NSCLC (Large cell)	T2a N0 Mx	Thoracotomy	Lobectomy	Left, lower	10
PID13	NSCLC (adenocarcinoma)	T2a N0 Mx	Thoracotomy	Bi-wedge resection	Left, anterior and apico-posterior	3
PID14	n/a	T2 N2 Mx	Thoracotomy	Bi-lobectomy	Right, middle and lower	9
PID15	NSCLC (adenocarcinoma)	T1b N0 Mx	Thoracotomy	Lobectomy	Right, lower	6
PID16	NSCLC (adenocarcinoma)	T2a N0 Mx	Thoracotomy	Lobectomy	Right, upper	5
PID17	Mixed (adenocarinoma and SCLC)	T2a N0 Mx	Thoracotomy	Lobectomy	Right, upper	4
PID18	NSCLC (adenocarcinoma with BAC features)	pT1a N0 Mx, pT2a N0 Mx	Thoracotomy	Bi-lobectomy	Right, middle and upper	5

Table 3.2: cont.

ID	Histology[67]	Stage[78]	Primary Procedure	Incision Procedure	Position	LOS[9] (days)
PID19	NSCLC (adenocarcinoma)	T2a N0 Mx	Thoracotomy	Lobectomy	Left, upper	8
PID20	NSCLC (endobronchial, squamous)	Stage 2a	Thoracotomy	Pneumonectomy	Left	4
PID21	NSCLC (adenocarcinoma)	T1a N0 Mx	Thoracotomy	Lobectomy	Right, upper	14
PID23	No malignancy	n/r	Thoracotomy	Wedge resection	n/a	9
PID24	n/a	n/a	VATS	Wedge resection	Left, lower	4
PID25	NSCLC (adenocarcinoma)	T1b N0 Mx	Thoracotomy	Wedge resection	Right, lower	16
PID26	NSCLC (Poorly differentiated adenocarcinoma)	T2 N2 Mx	Thoracotomy	Lobectomy	Left, upper	5
PID28	NSCLC (adenocarcinoma)	T1b N0 Mx	Thoracotomy	Lobectomy	Left, upper	6
PID29	n/a	n/a	Thoracotomy	Lobectomy and wedge resection	Right, upper and middle	4
PID30	NSCLC (adenocarcinoma, non-mucinous BAC)	T2a N0 Mx	Thoracotomy	Bi-wedge resection	Right, upper and lower	4
PID31	NSCLC (adenocarinoma)	T2 N2 Mx	VATS	Lobectomy	Left, lower	1

Table 3.3: Co-morbidity status

ID	primary	ECOG[1]	MRC[2]	COPD[3]	Asthma	IHD[4]	CHF[5]	Hyper[6]	Prescribed inhaler TTH[7]
HTO1	VATS	0	1	0	0	0	0	0	None
HTO2	VATS	1	3	0	0	0	0	1	None
HTO3	VATS	1	3	1	0	0	0	0	Terbutaline, Seretide, Tiotropium
PID9	VATS	0	1	0	1	0	0	0	Seretide
PID24	VATS	2	2	0	0	0	0	1	None
PID31	VATS	0	1	0	0	0	0	1	None
PID1	Thoracotomy	0	1	0	0	0	0	0	None
PID3	Thoracotomy	3	2	1	0	0	0	0	Salbutamol, Fluticasine, Salmetarol
PID4	Thoracotomy	1	3	1	0	0	0	0	Salbutamol, Tiotropium
PID5	Thoracotomy	0	1	1	0	0	0	1	None
PID6	Thoracotomy	0	1	0	1	0	0	0	Salbutamol, Ipratropium, Symbicort
PID10	Thoracotomy	0	1	0	0	0	0	0	None
PID11	Thoracotomy	1	2	1	0	0	0	0	Salbutamol, Seretide
PID12	Thoracotomy	1	1	1	0	1	1	0	None
PID13	Thoracotomy	1	2	0	0	0	0	0	None
PID14	Thoracotomy	0	1	0	0	0	0	0	None
PID15	Thoracotomy	0	1	1	0	1	0	1	None
PID16	Thoracotomy	0	1	0	0	0	0	0	None
PID17	Thoracotomy	0	2	0	0	0	0	0	None
PID18	Thoracotomy	0	1	0	0	0	0	1	None
PID19	Thoracotomy	0	1	1	0	1	0	1	None
PID20	Thoracotomy	0	1	0	0	0	0	1	None
PID21	Thoracotomy	1	1	0	0	0	0	1	None
PID23	Thoracotomy	1	3	1	0	0	0	0	Seretide, Salbutamol
PID25	Thoracotomy	2	4	1	0	1	0	0	None
PID26	Thoracotomy	0	2	0	0	0	0	0	None
PID28	Thoracotomy	2	1	0	0	0	0	1	None
PID29	Thoracotomy	2	4	0	1	0	0	0	Salmeterol, Beclometasone
PID30	Thoracotomy	1	1	0	1	0	0	0	Seretide, Salbutamol

[1]ECOG performance status score 0 to 5
[2]MRC breathlessness scale score 1 to 5
[3]Chronic obstructive pulmonary disease, 1 = present, 0 = absent
[4]Ischaemic heart disease, 1 = present, 0 = absent
[5]Chronic heart failure, 1 = present, 0 = absent
[6]Hypertension, 1 = present, 0 = absent
[7]TTH = to take home

3.2 Description of peri- and post-surgical supportive care received by interviewed participants

Participants who underwent thoracotomy were admitted for a median of 6 days (range 3-35) and those who underwent VATS were admitted for a median of 4 days (range 1-8). Eighteen participants received standard peri- and post-surgical supportive care (see below for description), and 11 participants were enrolled in a rehabilitation programme (for a full description of the ROC programme see section 2.3.4.1).

Participants receiving standard care and the rehabilitation intervention were admitted on the day of surgery, apart from PID3 who was admitted a week before with the aim of increasing his fitness for surgery. As part of standard care, nurses/physiotherapists aimed to mobilise participants on day one after surgery. Participants were medicated for pain control (including intravenous morphine or epidural in cases of severe pain). To improve lung function and aid expansion of the remaining lung tissue into the void created in the thoracic cavity after resection, participants were taught breathing exercises by physiotherapists whilst inpatients. In addition, they were given breathing exercise instructions and an incentive spirometer[2] to be taken home on discharge for continued use. In order to be considered fit for discharge, all participants had to demonstrate ability to climb stairs, under the supervision of a physiotherapist. Participants were assessed by a clinician before discharge and, along with other medications, were prescribed pain medication as deemed necessary. Once discharged, participants receiving standard care were followed up at an outpatient clinic at regular intervals with the primary aim of checking for a second primary or recurrent tumour.

Participants of the ROC programme pilot received additional supportive care. Briefly this involved twice weekly exercise sessions before surgery and six weekly sessions after surgery, education sessions, and referral to the stop smoking service or a Macmillan dietician if neces-

[2] An incentive spirometer is a device which measures the strength of an exhaled breath. In order to achieve high scores, a patient must breath in deeply and exhale strongly, thus exercising the lungs.

sary (see section 2.3.4.1 for detailed description of the ROC programme).

3.3 Overarching topics and themes for framework analysis

To help orientate the reader through the following sections, a table of the main topics and themes for analysis are shown in table 3.4. Main topics and themes were based on the interview aims and areas of interest identified during the literature search (see sections 1.5 - 1.6). In addition, some themes and also sub-themes emerged from interview. Although the second aim was to explore health behaviours and behaviour change including smoking, diet and exercise, diet and exercise have been omitted in the analysis. This is because although some participants reported experiencing decreased appetite and weight loss, questions regarding diet and healthy eating generated little data and was not a topic that was given priority by participants. Many participants did report increasing their engagement in exercise, but this was discussed in the context of recovery from breathlessness, or participation in the ROC programme, and as such is referred to within the first and fourth main topics. Therefore, the second main analysis topic focuses on smoking and smoking cessation only.

Dictated by the volume of data, six framework matrices were created for main topics or themes to aid with data analysis (see table 3.4). Within each of the main topics and themes, qualitative differences between key participant sub-groups were also considered. For the numbers of participants belonging to key participant sub-groups, see table 3.5.

The conventions used for quotations throughout this results section are as follows

- An ellipsis (. . .) is used to indicate a pause in the interview, or omission of words not relevant to the quote
- () indicate a word that has been added to clarify the sense
- [] indicates anonymised words
- **bold font** indicates interviewer speaking

Table 3.4: Main topics and themes for framework matrix analysis

Main topics	Themes
Interview aim 1 Health and function	*All participants ($n = 29$):* 1. Breathlessness (framework matrix 1) 2. Pain (framework matrix 2) 3. Other health challenges (framework matrix 3)
Interview aim 2 Smoking (framework matrix 4)	*Participants with a smoking history only ($n = 26$):* 1. Attitudes towards smoking and smoking cessation 2. Reasons for relapse to smoking after discharge 3. Views about NHS intervention for smoking cessation
Interview aim 3 Recovery, supportive care received and rehabilitation programme design (framework matrix 5)	*Standard care only ($n = 18$):* 1. Satisfaction with recovery 2. Attitudes towards supportive care received 3. Preferences for the content and format of a tailored rehabilitation programme
Interview aim 4 Recovery, supportive care received and rehabilitation programme design (framework matrix 6)	*ROC programme only ($n = 11$):* 1. Satisfaction with recovery 2. Attitudes towards supportive care received 3. Suggested design changes for the ROC programme

Table 3.5: Number of patients belonging to key sub-groups

Extent of resection	Standard care ($n = 18$)		Enrolled in ROC programme ($n = 11$)	
	Thoracotomy ($n = 13$)	VATS ($n = 5$)	Thoracotomy ($n = 10$)	VATS ($n = 1$)
Pneumonectomy	2	0	0	0
Lobectomy	6	2	7	0
Wedge resection	5	3	3	1

3.4 Main topic 1: health experiences and effect on function

Two health challenges dominated most participant interviews and arose largely without prompting: breathlessness and pain. Other health challenges described by participants included loss of appetite, weight loss, altered sleep and fatigue. Individual health challenges often affected specific activities and in many cases led to limitation of function. The following sections (3.4.1 - 3.4.4) explore accounts of breathlessness, pain and other less commonly reported health challenges. Each sub-section summarises the experiences of all consented participants, regardless of clinical or treatment characteristics, after which qualitative differences between key participant sub-groups are considered. In addition, a typology of breathlessness and pain experiences is presented (see table 3.7 and 3.10).

3.4.1 Main topic 1, theme 1: breathlessness

Post-surgical breathlessness was reported by 25/29 participants. Descriptions of experience were complex and analysis revealed that there were seven dimensions (or sub-themes) of reported breathlessness experience. Comparing interview accounts, categories of experience (or sub-sub-themes) emerged within each dimension of breathlessness (see table 3.6). For two dimensions (5 - physical experience and 7 - other triggers) categories were discrete, and for the remaining five dimensions categories lay on a continuum of severity. Where experiences lay on a continuum, they are described from most favourable experience to the least favourable experience. Experiences are described using the dimension and category names found in table 3.6. In the following sections, dimensions 1-4 are presented in combination, giving a description of the extent to which breathlessness affected a participant. In order to help orientation of the reader, this is done under the headings of the typology which was constructed from these accounts, which is described in the section that follows these accounts (section 3.4.1.1.1). Finally, dimensions 5-7 are discussed separately in light of this typology.

Table 3.6: Categories of experience within seven dimensions of breathlessness

No	Dimension	Category name and description (equivalence in Borg Scale (BS) and MRC breathlessness scale (MRC))
1	Level of severity	Examples of descriptive words used to convey level of breathlessness: 1. ABSENT - no breathlessness (BS = 0–1) 2. LOW - mildly, somewhat, a little (BS = 1–2) 3. MEDIUM - quite, very (BS = 3-6) 4. HIGH - very, very or gasping (BS = 7–10)
2	Effect on function	Activity level affected by breathlessness: 1. DEMANDING - strenuous activity such as sport and DIY (MRC = 1) 2. MODERATE - activities such as gardening, housework, shopping, carrying, climbing the stairs and walking more than 1 mile (MRC = 2–4) 3. BASIC - activities of daily living such as talking, grooming, walking between rooms on the same floor of the house (MRC = 5)
3	Duration	Breathlessness resolved within: 1. SHORT - 2 weeks after surgery 2. MEDIUM - between 2 weeks and 3 months after surgery 3. LONG - was not resolved 3–12 months after surgery
4	Trajectory	1. IMPROVING - steady reduction in level of breathlessness over time 2. MAINLY IMPROVING - general trend of reduction over time, with setbacks 3. NO CHANGE - no improvement over time 4. DETERIORATION - Deterioration in breathlessness over time
5	Physical manifestation	1. Rapid shallow breathing 2. Tightness 3. Reduction in lung capacity
6	Emotional response	1. Pragmatic outlook, not distressed 2. Distressed
7	Other triggers	1. Smoking environments 2. Change in weather/temperature 3. Pain or fatigue

3.4.1.1 Level of severity, effect on function, duration and trajectory (dimensions 1-4)

Most participants, regardless of pre-existing breathlessness due to infection or disease, reported noticing a marked increase in breathlessness immediately after surgery. Almost without exception, participants described experiences in terms of the specific physical activities that provoked an increased level of breathlessness. In addition, they gauged their progress in recovery by improvements, or otherwise, in the level of breathlessness experienced whilst engaging in these activities and how long it took to improve. Thus level of severity, effect on function, duration and trajectory of breathlessness were generally interconnected within participants' accounts. After comparison of participants' accounts, the extent to which participants were affected by breathlessness was found to lie on a continuum from those not affected to those severely affected.

Not affected by breathlessness For a small number of participants, surgery was not accompanied by a noticeable increase in breathlessness and this health challenge did not feature in their descriptions of recovery. For example, after being asked if they had suffered from breathlessness after surgery, two participants *(PID19 - THORACOTOMY, LOBECTOMY, 6MPS; PID31 - VATS , LOBECTOMY, 4MPS)*[3] stated that they experienced no breathlessness at all and one participant *(PID24- VATS, WEDGE RESECTION, 3MPS)* described experiencing breathlessness that was so *"light weight"* that she was not sure if it was real or imagined. PID9 *(VATS, WEDGE RESECTION, 9MPS)* had suffered with TB as a child and reported having suffered with *"chest weakness"* all of her life. She explained that although she experienced some breathlessness, she did not think that it was *"any worse now than it used to be"* before surgery.

Mildly affected by breathlessness Some participants found that they experienced low[4] levels of breathlessness after surgery, but became breathless only when engaging in demanding

[3]MPS = months post-surgery at time of interview

[4]For definition of words use to describe level of severity, activity level affected, duration and trajectory of breathlessness (e.g. low, medium, high level of severity, demanding, moderate, basic level of activity etc.) please refer to table 3.6

physical activities by the time of interview. For example, PID18 *(THORACOTOMY, BILOBECTOMY, 3MPS)* reported low levels of breathlessness associated only with playing tennis or walking up hills using the words *"slightly"*, *"a bit"* and *"somewhat"*. He added:

PID18: *"It's never stopped . . . It's not disappeared . . . it's just probably gradually improving I should say, yes, it definitely is."*

He was a life-time non smoker and was the only participant who reported choosing to play sport after surgery. Although his breathlessness had improved, he felt that he was still experiencing more breathless then he would normally experience, and reported feeling 75% recovered at interview.

PID26 *(THORACOTOMY, LOBECTOMY, 7MPS)* was a smoker at diagnosis, and continued to smoke after his treatment. He explained that he was *"surprised about how capable he felt"* after surgery. He had been able to manage the stairs easily in hospital and added:

PID26: *"I was quite happy at how quick the recovery was, and in the first few weeks particularly on week 2 and 3 I was quite pleasantly surprised at how I could go for walks in a morning."*

After seven months, he reported that he did not get breathless *"in the general course of things"*. However, at the time of interview he was decorating his house and explained that he would need to stop regularly due to breathless, when painting the ceiling for example.

A small number of participants reported experiencing medium levels of breathlessness provoked by moderate activities after leaving hospital. However, the breathlessness improved over time and resolved within the first three months after surgery. For example, HTO1 *(VATS, LOBECTOMY, 3MPS)*, an ex-smoker of 11 years, found it easy to climb the stairs with the physiotherapists whilst an inpatient. When he returned home, he went walking with his dog in a nearby park on a daily basis which had made him feel breathless, but he noticed that over time the walking was provoking lower levels of breathlessness. Three months after surgery, he reported that the

breathlessness had disappeared:

HTO1: *"When I first started walking up the hill, I was having to stop half way, then I found that if I forced myself by striding out a bit stronger, I could get to the top. I was very breathless when I got there, but it didn't take long to recover, didn't take long at all. But now I can just stroll at one even pace . . . without having to stop at all"*

Moderately affected by breathlessness The majority of participants reported medium or high levels of breathlessness ('quite', 'very', 'very very', 'gasping') that were provoked by moderate levels of activity (stairs, walking outside, housework etc.). After leaving hospital, all of these participants described gradual improvements, although at different speeds. In addition some participants reported setbacks in their recovery due to pulmonary complications (e.g. infection, pulmonary embolism). For all of these participants, breathlessness was still present at the time of interview to a certain extent.

Four participants (PID1, PID10, PID16, PID29) fitting this description were in employment before they were diagnosed and three (PID10, PID16, PID29) were able to return to work. All three participants who returned to work reported limitations in their ability to cope with the physical demands due their health, and this was due to breathlessness for two (PID16 and PID29). PID29 *(THORACOTOMY, LOBECTOMY AND WEDGE RESECTION, 3MPS*) was diagnosed with asthma a number of years before her cancer diagnosis. She described experiencing a series of chest infections before diagnosis, and had been given a rating of 4 on the MRC breathlessness scale at a pre-surgical assessment. However, at interview she explained that, other than when she had an infection, she had felt well before surgery. After surgery she noticed experiencing an increased level of breathlessness. She explained that she had not felt 100% since the surgery due to breathlessness, even when going back to work. Her work place had lightened her work load to accommodate her needs, but she explained that she still found it difficult. She further explained:

PID29: *"(I) can't go shopping. I started to go around the shop, by the time I'd gone down the first aisle, I had to say to my husband, take me back to the car. So I leave the shopping, he takes me back to the car, he goes back and does the shopping. Then there's... when the grandkids come in. "Nanny, can you come down and do" "No, darling I can't get down there because I can't get up. If I try to get up, it's really hard with my breathing" "Could you collect me from school"... "No, I can't do that darling, 'cos I can't get up you know"...* ***So when you go to the shops, and you need to go back to the car, in what way do you feel not well..?*** *It's because of the breathlessness, I just couldn't walk around, and we can't always get wheelchairs... they have set amount. And then if there isn't one, you're stuck."*

PID16 *(THORACOTOMY, LOBECTOMY, 5MPS)* was a smoker at diagnosis and continued to smoke after surgery. She explained how since the surgery and going back to work she was *"finding everything twice as hard physically"* because of breathlessness. She particularly found it difficult to climb the stairs which was something she couldn't avoid at her workplace. She also noted breathlessness when working in her garden, and was still experiencing these difficulties.

In contrast to those who had been able to return to work, PID1 (*THORACOTOMY, WEDGE RESCTION, 11MPS*) was unable to return to a manual labour job because of breathlessness and loss of physical strength. Despite looking for other jobs, he had not been able to find anything at the time of interview. On discharge from hospital, he started walking on a daily basis, sometimes walking to the next town, and reported that 11 months after surgery this continued to provoke medium levels of breathlessness:

PID1: *"I walk everywhere... If I have to go to [the next town], I walk, I very rarely catch the bus. And if I don't have to pick up something then I'll try and walk back ... you can walk slow ... because there's no rush ... you get out of breath, but there is always somewhere for you to sit down for five minutes and get your breath back and have a rest and then get up and go and carry on."*

Other participants that continued to experience medium/high levels of breathlessness at the

time of interview, provoked by moderate activities, had not been in employment before their diagnosis, but had mostly led active lives. For example PID11 *(THORACOTOMY, BILOBECTOMY, 4MPS)*, an ex-smoker of 10 years, had enjoyed fishing as a hobby. He had co-morbid COPD and scored 2 on the MRC breathlessness scale on a pre-surgical assessment. He reported experiencing increased levels of breathlessness after surgery, and that climbing stairs and walking made him very breathless. Four months after his surgery, he reported a *"slight improvement"*, but explained that the bronchodilator and corticosteroid inhalers that he had been prescribed for COPD were helping. He had been unable to return to his hobby of fishing due to concerns about breathlessness:

PID11: *"I used to go fishing. Now I'm frightened of going any distance fishing.* ***Why is that?*** *Because I'd be out of breath ... I daren't, I can't even go on the rivers, because I can't walk with all them lumps ..."*

PID4 *(THORACOTOMY, WEDGE RESECTION, 12MPS*) had led an active life visiting friends and going out socialising. She had been a lifelong smoker, although had quit two months before surgery. Three months after returning home she relapsed to smoking 40 cigarettes per day, although had begun a new quit attempt just prior to her interview. She had previously been diagnosed with COPD and scored 3 on the MRC breathlessness scale in a pre-surgical assessment. Twelve months after her surgery she was still struggling with breathlessness, although was not housebound and was able to carry out activities of daily living: PID4 *(THORACOTOMY, WEDGE RESECTION, 12MPS*) had led an active life visiting friends and going out socialising. She had been a lifelong smoker, although had quit two months before surgery. Three months after returning home she relapsed to smoking 40 cigarettes per day, although had begun a new quit attempt just prior to her interview. She had previously been diagnosed with COPD and scored 3 on the MRC breathlessness scale in a pre-surgical assessment. Twelve months after her surgery she was still struggling with breathlessness, although was not housebound and was able to carry out activities of daily living:

PID4: *"I mean it's taken me a whole 12 months just to walk from here and get up to the top. I've got to walk to the end of this road, go up a bit of a hill, come up [road1] back where the shops are. It's just when I hit [place2] … because it's like that [demonstrates a hill], I'm frightened for my breath. I mean I only do little steps now, I can't walk brisk like I used to, I can't do none of that."*

Severely physically affected by breathlessness At the worst end of the spectrum, some participants experienced high levels of breathlessness provoked by basic activities of daily living and moving about in the house. For instance, PID20 *(THORACOTOMY, PNEUMONECTOMY, 3MPS)* had been an active person who was smoking at diagnosis but had not smoked since that time. He was a smoker until diagnosis, but had not previously been diagnosed with COPD. He was one of two participants who had undergone a pnemonectomy. Unlike other participants, he reported that he became progressively more breathless over time. Three months after surgery he reported being housebound, and that basic activities of daily living and moving around the house provoked high levels of breathlessness:

PID20: *"**How limited are you, would you say?** Very limited. At the moment. Very limited. I don't do nothing, for myself … anything really strenuous, I have to get [wife] to do it for me. As I say … I'd be out of breath by the time I get to the front room … it takes me a good ten minutes to get upstairs at night, to get to bed. And I'm sitting there gasping for another ten minutes, to try and get my breath before I can actually get into bed and try and relax."*

PID3 *(THORACOTOMY, WEDGE RESECTION, 10MPS)* had been largely housebound for 10 months since discharge from hospital. Before his surgery he had been working as a manual labourer, although had experienced recurrent chest infections in the 3-4 years preceding his diagnosis. He described himself as not experiencing breathlessness before his surgery, other than when he had a chest infection. However, he was a lifetime smoker with a previous diagnosis of COPD and was rated MRC breathlessness scale of rating of 2 (i.e. short of breath when hurrying or walking

up a slight hill). He described experiencing an increase in breathlessness since his surgery, and reported that he had not been able to continue working because of his health. He relapsed to smoking after being discharged home. PID3 described how 10 months after surgery, walking between two rooms on the ground floor of his house left him *"gasping"* for breath, as did his morning and evening routines. He reported that over time his breathing had improved *"a little, not much"*.

PID3: *" **What have been the main difficulties you have experienced since your operation?** Difficulty breathing. Any kind of stress and getting up, getting dressed [laughs] . . . Getting undressed. At night I'll get ready for bed. Have a wash, brush my teeth and whatever. Then I have to have what ten - fifteen minutes of oxygen to clear my chest and then get into bed after that. And of a morning I'm coughing continually for about half an hour, bring everything up and more oxygen."*

3.4.1.1.1 Typology of post-surgical breathlessness experiences In summary, the way in which breathlessness affected participants varied by level of severity, effect on function, duration and trajectory. Some participants were not affected by breathlessness. However, many participants without a COPD diagnosis experienced breathlessness after surgery, and those with COPD described a worsening of their experience of breathlessness after surgery. For many, breathlessness limited their daily functioning for more than three months. In the most severe of cases, participants found activities of daily living difficult and were largely housebound, or else they were able to leave the house but still became breathless when engaging in moderate activities such as walking, shopping, climbing stairs for example. Breathlessness prevented three participants from returning to work, and made life difficult for others who did return to work.

Neither the MRC nor the Borg scales of breathlessness could describe breathlessness experiences in their entirety. The MRC scale describes 'effect on function' but only describes a small range of functions in which participants were limited. The Borg scale describes 'level of severity' only.

Building on these scales, a typology was constructed to represent emerging patterns of the extent to which participants were affected by the experience of breathlessness (see table 3.7).

There were several clinical characteristics of participants that could have plausibly influenced the extent to which participants were affected by breathlessness. These were:

1. Type of surgical procedure (thoracotomy v VATS)
2. Extent of resection (pneumonectomy v lobectomy v wedge resection)
3. Smoking behaviour (smoking v not smoking after treatment)
4. Inflammatory lung condition (present v absent)
5. Participation in the ROC rehabilitation programme pilot, which included physiotherapist led gym sessions and educations about breathing and chest clearance.

Distribution of these participants characteristics within each level of the breathlessness typology is described in table 3.8. There was a marked qualitative difference between the experiences of those who had undergone thoracotomy compared with the six participants who had undergone VATS. Two participants (PID24, PID31) who had undergone VATS reported no or negligible breathlessness after surgery. A further two participants (HTO1, HTO2) described medium levels of breathlessness, when walking for example, that had resolved within 3 months. The final two participants (PID9, HTO3) experienced breathlessness before surgery due to pre-existing lung conditions and reported breathlessness that was no worse or had improved after surgery. Thus, all patients who had undergone VATS were examples of not affected or mildly affected by breathlessness. Conversely, although some participants were not affected at all or were mildly affected by breathlessness after undergoing thoracotomy, most reported being moderately or severely affected by breathlessness.

It has previously been reported that extent of resection is associated with post-surgical spirometric measures.[104] However, no obvious pattern of breathlessness experience was found with resection type for participants who had undergone thoracotomy. Similarly, no pattern of experience emerged based on smoking status, on pre-surgical MRC breathlessness score or on

Table 3.7: Typology of breathlessness in terms of level of severity, effect on function, duration and trajectory over the first 12 months after surgery

Type (MRC breathlessness scale score)	Description (Borg scale score)	Standard care participants[a]	ROC programme participants
Not affected by breathlessness	Negligible or no breathlessness	**PID9**, **PID24**, **PID31**	PID19
Mildly affected by breathlessness (1)	Any level of breathlessness (0 -10) provoked only by strenuous activities such as sport , or low/medium level breathlessness (1-6) provoked by moderate activities that largely resolves within 3 months of surgery.	**HTO1**, **HTO2**, PID5	**HTO3**, PID18, PID23, PID26
Moderately affected by breathlessness (2-4)	Medium/high (3-10) levels of breathlessness that continues to be provoked by moderate activities 3-12 months after surgery, although generally improves.	PID1, PID4, PID6, PID10, PID11, PID12, PID13, PID14, PID16, PID21, PID28, PID29, PID30	PID15, PID17, PID25,
Severely affected by breathlessness (5)	Severe levels of breathlessness (9-10) provoked by basic activities of daily living that had not resolved by the time of interview, that shows little improvement or deterioration.	PID3, PID20	

[a] **bold** ID indicates VATS patient

presence of inflammatory lung condition. Most of those enrolled the ROC programme pilot were examples of being mildly or moderately affected, and none described being severely affected. It is possible that participation in the rehabilitation programme changed the severity of breathlessness experienced or increased speed of recovery although it was not possible to investigate this using these data. Participants perceptions of how the rehabilitation programme affected their breathlessness are discussed in section 3.7.1.

3.4.1.2 Description of the physical manifestation of breathlessness (dimension 5)

When describing breathlessness, some participants demonstrated being out of breath and found it difficult to explain the experience in words. The demonstration was always of rapid shallow breaths, and participants indicated that this was a necessary action to rectify the experience of not having enough breath. All participants that gave this demonstration were people who continued to be moderately affected by breathlessness at the time of interview. In addition, they had all undergone thoracotomy. For example, PID14 *(moderate - THORACOTOMY, BILOBECOTOMY, 5MPS)*[5] explained that although his breathlessness had improved, he still needed to take rapid shallow breaths when walking:

PID14: *"you feel as though something's going to happen and you go <demonstrates quick, shallow breathing in and out> like this all the time and I still get it now but not as bad as it used to be … my wife makes me get up and have a walk around and by the time I'm finished I'm sat down <demonstrates quick, shallow breathing in and out> I'd have to do that, you know."*

Four participants (PID11, PID21, PID28, PID30) described a sensation of *"tightness"* that developed in response to physical activity or talking. Again, all participants who reported this experience were examples of being moderately affected by breathlessness and had undergone thoracotomy. PID11 *(moderate - THORACOTOMY, LOBECTOMY, 4MPS*) and PID30 *(moderate - THORACOTOMY, BI-WEDGE RESECTION, 4MPS)* were both ex-smokers and had a co-morbid inflammatory

[5] mild, moderate, severe refers to breathlessness typology category the participant belongs to

Table 3.8: Participant and treatment characteristics of participants within each level of the breathlessness typology

ID	Gender	Age	Primary Procedure	Incision Procedure	Standard/ROC	Dyspnoea Grade	COPD	Asthma	Smoking After Surgery[a]
Not affected by breathlessness									
PID9	F	71	VATS	Wedge resection	Standard	1	0	1	Continuous
PID19	F	71	Thorocotomy	Lobectomy	ROC	1	1	0	Ex-smoker
PID24	F	75	VATS	Wedge resection	Standard	2	0	0	Ex-smoker
PID31	M	74	VATS	Lobectomy	Standard	1	0	1	Ex-smoker
Mildly affected by breathlessness									
HTO1	M	70	VATS	Lobectomy	Standard	1	0	0	Ex-smoker
HTO2	F	81	VATS	Wedge resection	Standard	3	0	0	Ex-smoker
HTO3	F	73	VATS	Wedge resection	ROC	3	1	0	Ex-smoker
PID5	M	77	Thorocotomy	Wedge resection	Standard	1	1	0	Continuous
PID18	M	81	Thorocotomy	Bi-lobectomy	ROC	1	0	0	Never
PID23	M	66	Thorocotomy	Wedge resection	ROC	3	1	0	Relapsed
PID26	M	61	Thorocotomy	Lobectomy	ROC	2	0	0	Continuous
Moderately affected by breathlessness									
PID1	M	62	Thorocotomy	Wedge resection	Standard	1	0	0	Ex-smoker
PID4	F	61	Thorocotomy	Wedge resection	Standard	3	1	0	Relapsed
PID6	F	66	Thorocotomy	Pneumonectomy	Standard	1	0	0	Abstinent
PID10	F	39	Thorocotomy	Bi-lobectomy	Standard	1	0	1	Ex-smoker
PID11	M	70	Thorocotomy	Bi-lobectomy	Standard	2	1	0	Ex-smoker
PID12	M	76	Thorocotomy	Lobectomy	Standard	1	1	0	Ex-smoker
PID13	F	66	Thorocotomy	Bi-wedge resection	Standard	2	0	0	Relapsed
PID14	M	82	Thorocotomy	Bi-lobectomy	Standard	1	0	0	Ex-smoker
PID15	M	75	Thorocotomy	Lobectomy	ROC	1	1	0	Abstinent
PID16	F	58	Thorocotomy	Lobectomy	Standard	1	0	0	Relapsed
PID17	F	73	Thorocotomy	Lobectomy	ROC	2	0	0	Never
PID21	F	63	Thorocotomy	Lobectomy	Standard	1	0	0	Continuous
PID25	M	76	Thorocotomy	Wedge resection	ROC	4	1	0	Ex-smoker
PID28	F	76	Thorocotomy	Lobectomy	ROC	1	0	0	Never
PID29	F	60	Thorocotomy	Lobectomy and wedge resection	ROC	4	0	0	Ex-smoker
PID30	F	72	Thorocotomy	Bi-wedge resection	ROC	1	0	1	Abstinent
Severely affected by breathlessness									
PID3	M	67	Thorocotomy	Wedge resection	Standard	2	1	0	Relapsed
PID20	M	80	Thorocotomy	Pneumonectomy	Standard	1	0	0	Abstinent

[a]For definitions, refer to table 3.14

lung condition. Along with preventative therapy (Seretide), they had been prescribed a broncodilator (Ventolin) and reported that acute administration helped:

PID11: *"Tight, it goes tight. You can feel it. I can feel it myself when..I start to breathe and anything like that you can feel, something inside, you know like tight."*

PID30: *"it clears the tubes, piece of magic, absolute magic [signals to ventolin inhaler] . . . talking takes my breath away but they are magic, I couldn't do without them . . . You feel it going all up like tightening here [points at the chest] and all the airwaves"*

Finally, two participants (PID10 and PID20) described feeling that their lungs did not have the physical capacity to take deep breaths as they felt necessary, or as they had been able to previous to their surgery. PID10 *(moderate - THORACOTOMY, BI-LOBECTOMY, 7MPS)* explained:

PID10: *"I can't take a deep breath, it kind of just stops dead and that's it . . . when I really need to take a deep breath in I can't do it, it just doesn't happen."*

Similarly, PID20 *(severe - THORACOTOMY, PNEUMONECTOMY, 3MPS)* explained:

PID20: *"I can't seem to fill my lungs with air. And my lung . . . seems very shallow all the time with the breathing"*

In summary, necessity for rapid shallow breathing, tightness and limited lung capacity were given as descriptions of the physical experience of breathlessness. All such descriptions were given by participants who had undergone thoracotomy and had been moderately or severely affected by breathlessness. There was no other discernible pattern indicating sub-group factors that were associated with particular descriptions of the sensation of breathlessness, except it was noted that participants describing limited capacity had both had 2 lobes of lung tissue removed (PID10 = right bi-lobectomy, PID20 = left pneumonectomy).

3.4.1.3 Emotional response to the experience of breathlessness (dimension 6)

When talking about breathlessness, some participants demonstrated a pragmatic, stoic outlook, stating that it was an obvious consequence of lung resection and that it was something they had to live with or get on with. For instance HTO1 *(mild - VATS, LOBECTOMY, 3MPS)* explained that in the first weeks after his surgery he was breathless but felt that was *"part and parcel of this type of operation"*. He added:

HTO1: *"it does leave you a little breathless, which is something I can live with anyway, I can live with that. But I'm getting better every day"*

Some participants who had been moderately affected by breathlessness, were also pragmatic about the experience, and did not seem overly distressed about it. For example, PID12 *(moderate - THORACOTOMY, LOBECTOMY, 5MPS)* described not being able to walk up a hill. However, he explained *"I just accept the fact is what I can't do, I can't do."*

However, some participants described the physical experience of breathlessness as frightening. For instance PID4 *(moderate - THORACOTOMY, WEDGE RESECTION, 12MPS)* described her emotional response to becoming breathless when outside:

PID4: *"I'm alright on the flat, but because it's just up a bit, the way I walk [place2], I'm frightened for my breath ... It's like being claustrophobic really because you're trying to get your breath because it comes on all of a sudden, well it's not all of a sudden I suppose. I think I'm stronger than I am and obviously I'm not."*

PID10 *(moderate - THORACOTOMY, BILOBECTOMY, 9MPS)*, although nine months on from surgery, described feeling scared about exercising or engaging in activities that would make her breathless. She described an acute episode of coughing whilst at dancing club with her daughter which had been traumatic. She had felt that she was unable to breath properly, and a friend had offered her the use of a ventolin inhaler which she reported had helped. She reported that she was *"getting used to things now"* but still felt scared:

PID10: *"I'm scared to do a lot of things. I'm scared of getting out of breath . . . . I'm just getting used to things now and slowly it will get better but I am scared to exercise. I don't know what the strength is there, I don't know if I'm going to pull it. I'm scared of over exerting myself at the moment."*

PID14 *(moderate - THORACOTOMY, BILOBECTOMY, 5MPS)* had been very breathless when discharged from hospital, but gradually improved such that he could engage in activities of daily living without becoming unduly breathless at the time of the interview. However, he described an experience where his wife had encouraged him to take a trip to the local shops, but after half an hour he had to come back home because he became severely breathless. Since that episode, he had not had the confidence to go outside again:

PID14: *"We was only out half an hour. And I came back, took me coat off, sat here and I was like this [demonstrates shaking] and I was fighting for me breath wasn't I? And I thought well, if that's going be the case, I'm not going to go out anymore. For the time being anyway. But, uh, I haven't been out since . . . it scares you, that's what scared me . . . when I came back from the walk, that's what scared us, when I was fighting for me breath. I was shaking like a leaf, I don't know why."*

PID21 *(moderate - THORACOTOMY, LOBECTOMY, 3MPS)* had been housebound since discharge and reported lacking confidence to leave the house. She explained that breathlessness was partly responsible:

PID21: *"**What do you think knocks your confidence?** [pause 8 sec] I don't really know. It's just a mixture of like, will I be able to breathe if I walk far or um, am I going to knock my side, am I going to get the shooting pains . . . it's a mixture really."*

PID20 *(severe - THORACOTOMY, PNEMONECTOMY, 3MPS)* and PID3 *(severe - THORACOTOMY, WEDGE RESECTION, 10MPS)* were both distressed by the level of breathlessness they continued to experience, and emphasised this with tone of voice and the words that they chose to describe their breathlessness such as *"gasping"*, *"really, really struggling"* and *"fighting"* for breath. Both

explained that they could not do most things for themselves anymore and they were dependent on their wives. PID20 in particular seemed low in mood as he explained how his life had changed since surgery:

PID20: *"Oh I sold my car . . . 79 now, and I've been driving since I was 17. I'm not going to drive again . . . I'll probably surrender me licence next time . . . Fishing. That's all done . . . there's no way I could do that now."*

In summary, there was a clear divide in terms of emotional response to breathlessness, based on the extent to which participants were affected. Those who had been mildly affected and some patients who had been moderately affected adopted a pragmatic, accepting attitude and were not distressed. The remainder who were moderately and severely affected, were more likely to report being distressed by the experience. Distress was mainly caused by the acute experience of feeling breathless but also participants reported distress relating to reduced ability to function.

3.4.1.4 Other triggers of the experience of breathlessness (dimension 7)

Most descriptions of breathlessness were reported to be in conjunction with physical activity (see section 3.4.1.1). However, other triggers of breathlessness were also described. For instance, two participants *(HTO3 (moderate - THORACOTOMY, BI-WEDGE RESECTION, 4MPS), PID30 (moderate - THORACOTOMY, BI-WEDGE RESECTION, 4MPS))* reported that extra cold or hot temperatures, windy weather conditions and dry heat from central heating affected their breathing. Both of these participants had a co-morbid inflammatory lung condition.

For others, the experience of breathlessness was associated with pain and fatigue. For instance, PID3 *(severe - THORACOTOMY, WEDGE RESECTION, 10MPS)* reported that whilst an inpatient he found breathing difficult because of pain. In particular, he recounted an experience of not being able to defecate *"because (he) couldn't breathe properly, because of pain"*. PID13 *(moderate - THORACOTOMY, BI-WEDGE RESECTION, 5MPS)* had co-morbid rheumatoid arthritis and found that the pain associated with illness had lead to breathlessness on physical exertion, even before

her lung resection. She did not specifically report breathlessness in conjunction with surgery related pain, but found it difficult to distinguish changes in her experience of breathlessness after surgery because of the breathlessness she had experienced in association with arthritic pain before surgery. When reflecting on her experiences of breathlessness, PID10 *(moderate - THORACOTOMY, BILOBECTOMY, 9MPS)* suggested that it contributed to tiredness, reporting that *"the two sort of go together"*.

Finally, a small number of participants that smoked conceded that it was likely that their breathing would be better if they were not smoking, or noticed that when they quit/relapsed their breathing was affected (see section 3.5.2.1). Other participants who were non-smokers or ex-smokers gave examples of finding it difficult to breath when being in a smoky atmosphere. For example PID10 *(moderate - THORACOTOMY, BILOBECTOMY, 9MPS)* explained:

PID10: *"I went to a really big ... funeral about a month ago and literally as soon as we came out ... I think 90% of the people ... lit a cigarette up ... and I thought my chest was going to explode. I just couldn't get enough breath in you know"*

Similarly, HTO1 *(mild, VATS, LOBECTOMY, 3MPS)* also reported experiencing breathlessness when at a friend's bonfire:

HTO1: *"we were there for a couple of hours and ... I couldn't live with the smoke that this bonfire was generating ... I was getting lungfulls of the stuff ... so we came home..."*

In summary, breathlessness was mainly associated with physical activity, but was also reported in association with hot, cold and dry temperature or weather conditions, pain, fatigue and smoking/smoky atmospheres. These triggers were only described by participants that had undergone thoracotomy. It is possible temperature or weather conditions triggering breathlessness may be explained by presence of co-morbid COPD or asthma, although these participants noted an increase in breathlessness after surgery.

3.4.2 Main topic 1, theme 2: pain

Pain management was an integral part of post-surgical care, and participants described receiving analgesic pharmacotherapy via intravenous, epidural and/or oral routes of administration. Although participants were largely unaware of the specifics of the analgesic pharmacotherapy regime they had been prescribed, many mentioned that they received morphine as an inpatient. In addition to pain management whilst in hospital, participants were often prescribed further analgesic pharmacotherapy to use at home over the first few weeks after discharge. However, no additional assessment or treatment of pain was pro-actively offered in standard care or as part of the rehabilitation intervention.

Despite prescribed pharmacotherapy, 25/29 participants reported experiencing pain after surgery at some point during the first 12 months. As with breathlessness, participant descriptions of pain were complex, and they varied in seven dimensions (or sub-themes). Comparing participant accounts, categories of experience (or sub-sub-themes) emerged within each dimension of pain (see table 3.9). For three dimensions (severity, duration and emotional response), categories lay on a continuum, whereas categories of effect on function, triggers and physical experience were discrete. The level of pain experienced over time (trajectory) fluctuated for many participants, possibly in part due to use of analgesia.

Due to differences in the level of surgical invasion during VATS and thoracotomy, experiences are considered separately for these procedures. As with breathlessness, in the following sections pain experiences are described using the dimension and category names found in table 3.9. In order to help orientation of the reader, within both VATS and thoracotomy sub-sections, this is done under the headings of a typology constructed from the combined findings from dimensions 1-5 (see table 3.10). Finally, dimensions 6-7 are discussed separately in light of the typology.

Table 3.9: Categories of experience within seven dimensions of pain

	Dimension	Category name and description (equivalence in McGill Pain Questionnaire (MPQ))
1	Level of severity	Example of descriptive words for level of pain: 1. ABSENT - None (MPQ = no equivalent score) 2. LOW - A little, no great pain, discomfort, sore, tender (MPQ strength of pain= 1-2) 3. MEDIUM - A lot, quite painful (MPQ strength of pain = 3) 4. HIGH - Agony, tremendous, terrible (MPQ strength of pain = 4-5)
2.	Effect on function	1. Activity level not reduced 2. Activity level reduced 3. Altered sleep
3	Triggers/ associated with	1. Breathing, coughing, other movements that stretch the wound site 2. Touching the wound site 3. Generally present
4	Duration	Pain resolved within: 1. SHORT - 2 months after surgery (threshold for definition of PTPS) 2. MEDIUM - Between 2 and 6 months after surgery 3. LONG - continued for more than 6 months after surgery
5	Trajectory	1. IMPROVING - Pain in hospital which continued, but improved, after discharge 2. INTERMITTENT - No pain in hospital, but pain experienced after discharge, which was intermittent but gradually improved 3. NO CHANGE - Constant pain which did not improve
6	Physical experience	1. Discomfort, a bit of pain (MPQ = no equivalent) 2a. Static cramping/tightening/pulling sensation (MPQ = group 5 and 6 description) 2b. Moving cramping/tightening/pulling sensation (MPQ = no equivalent) 3. Dull and numb sensation (MPQ = group 8 description) 4. Sharp sensation (MPQ = group 2, 4 and 14 pain description)
7	Emotional response	1. Pragmatic, logical, accepting outlook, "to be expected" 2. Distressed (frightening, scary)

3.4.2.1 Level of severity, effect on function, duration and trajectory (Dimensions 1-5)

Participants gave accounts of the pain that they experienced as an inpatient and also described experiences and their duration after discharge. It was noted that there was correlation between the level of pain experienced in hospital and that experienced after discharge. Those experiencing no pain in hospital reported no pain or a low level of pain severity once discharged. Those who had reported experiencing a low level of pain in hospital continued to experience low levels of pain or the pain disappeared. All reporting high levels of pain in hospital continued to experience high levels of pain when discharged. Pain after discharge lasted for varying lengths of time, with some participants still experiencing moderate or high levels of pain at the time of the interview.

3.4.2.1.1 Pain experiences after VATS

Not or mildly affected by pain Whilst in hospital and after discharge, all participants who had undergone VATS reported experiencing either no pain or a low level of pain. For example, PID9 *(VATS, WEDGE RESECTION, 9MPS)* was advised to undergo adjuvant treatment with chemotherapy but she felt strongly that she did not want to accept it. Whilst describing her reasons, she reported having experienced no pain so far throughout her whole patient journey and she did not want to experience the side effects. HTO1 *(VATS, LOBECTOMY, 3MPS)*, HTO3 *(VATS, WEDGE RESECTION, 4MPS)* and PID24 *(VATS, WEDGE RESECTION, 3MPS)* all experienced low levels of pain severity using the words *"discomfort"*, *"a little pain"* and *"sore"* whilst in hospital which continued for a short period of time (up to three weeks) after discharge, after which it disappeared. Both HTO1 and PID24 emphasised that the surgery had been nothing to worry about. PID24 compared the experience to having tonsils removed:

PID24: *"... I felt it, obviously, for a couple of days ... to get out of the bed, whenever you pulled it you could feel that area. I mean if you were to have your tonsils out, your throat would be iffy for a couple of days, and this was no more."*

PID31 *(VATS, LOBECTOMY, 4MPS)* reported not experiencing pain in hospital (note: he was only in hospital for one night). However, he explained that *"everything felt like a boulder, on the way home in the taxi"*. He added:

PID31: *"The only time I knew I'd done it was if I turned . . . when I'd lie in bed at night . . . it woke me up . . . but then, after a couple or three weeks it didn't wake me up . . . I had far more pain having my dentures fitted . . . the word is discomfort not pain you occasionally get an 'oops' but not an 'oh no, I can't move!.'"*

Similarly, HTO2 *(VATS, WEDGE RESECTION, 4MPS)* noted that when she came round from surgery she was in no pain, but experienced some numbness. She reported that as the analgesia she had been prescribed to take at home had *"worn off"* she began to feel soreness. Unlike participants who had undergone VATS, she described how three months after surgery, she had developed *"sharp pains"* at the site of the surgical incision which were still ongoing.

3.4.2.1.2 Pain after thoracotomy

Not affected by pain Two participants *(PID5 (THORACOTOMY, WEDGE RESECTION, 6MPS) , PID15 (THORACOTOMY, LOBECTOMY, 5MPS))* that had undergone thoracotomy reported experiencing no pain in hospital or after discharge.

Mildly physically affected by pain A few reported that their pain was initially well controlled, but that they began to experience low level pain severity on reduction or removal of analgesia either in hospital or after discharge. For example, PID12 *(THORACOTOMY, LOBECTOMY, 5MPS)* reported waking up in no pain after surgery. However, he was being administered with mechanically regulated intravenous morphine. A few hours after it was taken away, he reported realising that he was still in pain and requesting for the medication to be restarted. After discharge he reported experiencing medium level pain severity, particularly triggered by breathing deeply or coughing, which gradually reduced. PID17 *(THORACOTOMY, LOBECTOMY,*

5MPS) explained that after 6-8 weeks she began to experience *"discomfort of the inner wound"*, which she attributed to *"inner healing"* taking place. PID11 *(THORACOTOMY, BILOBECTOMY, 4MPS)* reported experiencing *"discomfort"* that had continued when he was discharged home. He explained that in his understanding the continuing pain originated from damage to his rib cage:

PID11: *"They said "the actual operation is nothing really . . . that will get better right away . . . but your ribs always take a damn sight longer." . . .* ***And was that true?*** *It was true, but it wasn't all that long. And you can't say I had pain, it's just discomfort at times.* ***So when you coughed, that was when the-?*** *Only, that didn't last long. But, it's only down here, by the side of the ribs. It didn't last long at all."*

All of these participants were no longer in pain at the time of interview and had not experienced pain for longer than two months.

Moderately physically affected by pain However, for some the pain lasted longer and they reported low/medium level pain throughout their inpatient stay, which continued for up to six months after discharge. For instance, PID13 *(THORACOTOMY, BI-WEDGE RESECTION, 5MPS)* noted that it was painful when she did deep breathing exercises whilst in hospital, and this continued after discharge although she reported not being in any pain at the time of interview. However, she added that she was taking analgesic medication for arthritis and that this may have been keeping the pain *"under control"*. PID14 *(THORACOTOMY, BI-LOBECTOMY, 5MPS)* described first being aware of pain in hospital, and reported still being in *"a bit"* of pain at the time of interview, and reported that pressure applied to the wound site triggered pain; for example, when turning over in bed at night.

Other participants described experiencing high levels of pain in hospital, that continued after discharge and gradually subsided to lower levels or had largely disappeared by the time of the interview. For example, PID1 *(THORACOTOMY, WEDGE RESECTION, 11MPS)* was administered with morphine whilst in hospital, and reported being sent home in a lot of pain with a weeping

wound. His GP organised for him to be readmitted to a different hospital where he was treated for the infection. He described being in a lot of pain until the infection had gone, which took at least 3 weeks. After that, the scar began to heal and he reported having no further problems. PID16 *(THORACOTOMY, LOBECTOMY, 5MPS)* explained that she had been experiencing high levels of pain for up to six weeks after the operation. However, this was not associated with infection:

PID16: *"I was in a lot of pain after the surgery . . . for a lot of weeks . . . . the pain was really, really acute . . . I could hardly lift myself, . . . I was constantly having to take painkillers . . . the pain's just, it was just horrendous . . . it was really, really sharp. Agonising pain.* ***And was it constant? Or. . .*** *Yes it was constant. The only thing that helped was the painkillers. And that only dulled it, it didn't get rid of it . . . it was constantly there.* ***But you're not in pain now?*** *No, I'm not in pain now.* ***So how did that happen?*** *Gradually, yeah. It just went gradually over, I think it was about like four weeks after I'd had surgery . . . Maybe longer than four. Four to six weeks . . . it was a really long process pain wise."*

PID29 *(THORACOTOMY, LOBECTOMY AND WEDGE RESECTION, 3MPS)* explained that after surgery if she laughed, took a deep breath or *"had a good cough"* she would have to support her chest because of the pain. She added:

PID29: *"you notice it less and less each time, unless you do something silly, like cough"*

Severely physically affected by pain PID3 and PID19 both reported high levels of pain severity in hospital and after discharge which was associated with an infection of the wound. In both cases, pain continued for many months after discharge and was associated with a reduction in general activity levels. PID3 *(THORACOTOMY, WEDGE RESECTION, 10MPS)* explained that he was in a *"tremendous amount of pain"* whilst in hospital which prevented him from being able to cough when asked to do so by physiotherapists. Eventually he was able to cough with a

rolled up towel under his arm to support his chest, in addition to local injections of morphine around the wound site. Once he was able to cough, he reported producing black phlegm. After discharge, he reported being in *"absolutely agony"* until he was referred by chance to a pain management clinic by a chemotherapy nurse seven months after surgery. After eight days of treatment he was pain free and the pain had not returned at the time of interview:

PID3: *"I had a rolled up towel on there [signals to back of the arm chair] constantly, so I could hold myself in whilst I coughed. Now I don't need it . . . So basically I had been suffering since the operation. Absolute agony. When I was coughing it was literally doubling me up . . . "*

PID19 *(THORACOTOMY, LOBECTOMY, 6MPS)* described her wound site as *"a gaping hole"* that was seeping fluid and that she was in a lot of pain whilst in hospital. She reported that the dosage of her pain medication was increased in hospital, which had made her feel *"lifeless"* and was in her understanding an overdose:

PID19: *"they said to me that I could go home! . . . and I said, "But I've still got this hole . . . I felt absolutely awful.* ***In what way did you feel awful?*** *Well . . . I just felt lifeless . . . I was just in pain, uncomfortable and this was seeping stuff all the time."*

After discharge she was referred to the care of community nurses rather than readmitted to hospital. The community nurses visited her everyday to *"scrape the top off"* the wound. After a few weeks she saw the surgeon's registrar who had performed her surgery. He told her that the community nurses shouldn't be scraping the wound and advised her to tell them to stop. PID19 reported that although she relayed this information to the nurses, they disregarded it, stating that *"These surgeons and registrars, they don't know what they're talking about . . . All they know about is cutting people open . . . they don't know a thing about . . . getting closed up again."* After many weeks of this continuing situation, she finally refused entrance to the nurses and her wound began to heal. She reported that it took a long time for the wound to heal (although didn't specify a time on probing), and that she was in some pain but she wasn't overly

concerned about it and didn't feel that she needed medication to control it.

PID10 *(THORACOTOMY, BI-LOBECTOMY, 7MPS)* reported that she experienced *"horrendous"*, *"awful pain"* in hospital. There was no evidence that this high level of pain was caused due to infection. During the first month after discharge, she described not being able to move without pain, and that despite being on pain killers she had to sit on the living room sofa with her arms constantly propped up with pillows in order to avoid pain. Over time the pain subsided, but she reported experiencing ongoing low level pain severity seven months after discharge:

PID10: *"Later on in the day I don't wear a bra because it swells all here, I just put ... the old kind of vest tops on. Because I get swelling like around it here [indicates surgical wound site] and that gets quite tender still."*

Two participants (PID4, PID21) reported high levels of pain that had not subsided at the time of the interview. There was no evidence that their continuing pain was associated with infection. PID21 *(THORACOTOMY, LOBECTOMY, 3MPS)* reported experiencing a collapsed lung during a CAT scan guided biopsy that was performed before her thoracotomy. She reported that the necessary equipment to re-inflate her lung was not in the room where the biopsy had taken place, and she explained:

PID21: *"The result of that [no equipment immediately to hand] was that I had to have a terrible procedure done, where they gave me no anaesthetic whatsoever, they took me on a ward, and they held me down, actually physically held me down, and re-inflated my lung by cutting me inside and putting a tube, a drain, into my lung ... I screamed the place down."*

She was subsequently diagnosed with cancer and underwent thoracotomy with lung resection, but had to undergo a second surgery within the same admission period due to a second lung collapse. She was receiving intravenous morphine drip whilst in hospital but described experiencing high levels of pain that continued when she was eventually discharged two weeks after surgery. During the three months after her surgery, she had been housebound, partly due to pain

and described why she was unable to exercise as she felt she ought:

PID21: *"I lie down a lot because it's easier, and I know I'm supposed to exercise but with all the different pains I get, it's difficult. I lie there and I think, I didn't know I should have pains here and . . . I'm numb down here but I've got pain here and I think how can I . . . be numb and have pain at the same time?"*

Finally, PID4 *(THORACOTOMY, WEDGE RESECTION, 12MPS)* described continuing pain although, unlike any other participant, in addition to pain associated with the wound site, she described that her bones *"really, really ache"*. She reported going to bed in pain and waking up in pain and explained that she found this wearing. She had experienced aching before her surgery associated with an accident where she had fallen out of her loft. However, she reported that the aches and pains were much worse after her cancer treatment, and she particularly associated the experience with radiotherapy treatment.

3.4.2.1.3 Typology of post-surgical pain experiences In summary, despite medication, many participants experienced post-surgical pain, although at varying levels of severity and lasting for varying amounts of time after surgery. High levels of pain were often reported by participants who had an infected thoracotomy wound. Others experienced high levels of on-going pain in the absence of infection, although this was associated with complications that required additional surgery in the case of one participant. In general, participants were particularly aware of the pain when they were breathing, coughing or when pressure was applied to the site of the wound. Some participants also reported that it was painful when lying in bed or sitting in a chair, and those who experienced high level of pain severity reported that their activity level was generally limited.

A typology was constructed to represent emerging patterns of the extent to which participants were affected by the experience of pain (see table 3.10). The International Association for the Study of Pain (IASP) define post-thoracotomy pain syndrome (PTPS) as pain that persists for longer than 2 months. Most participants ($n = 17$) were moderately or severely affected by pain

and therefore fitted this description.

As with breathlessness, there was a marked qualitative difference between the experiences of those who had undergone thoracotomy compared with those who had undergone VATS, with the latter being more likely to report no pain or mild pain and the former being more likely to report moderate or severe pain. No other qualitative differences were noted for other sub-groups based on participant or treatment characteristics (see table 3.11).

3.4.2.2 Physical experience of pain (dimension 5)

A range of different sensations of pain were described. Some participants described a clamping/tightening/pulling sensation that travelled along the incision scar. Although this sensation was only reported by those who had undergone thoracotomy, it was experienced by those that were mildly, moderately and severely affected by pain. These descriptive words for pain are classified by the MPQ as constrictive pressure (group 5) and traction pressure (group 6) pain. For instance, PID4 *(severe - THORACOTOMY, WEDGE RESECTION, 12MPS)*[6] described this experience occurring regularly:

PID4: *"I had this funny feeling when I was in hospital … it comes from the back all the way round and I just put it down to the nerve endings … It's like a clamp with the pain but it sort of starts in the back where the scar is and then all of a sudden you can feel it, it's stiff … it goes hard … and you can feel it working its way around and it stops about here [indicates front of the chest wall] …* ***Are you feeling that right now or?****It's stiff but not the pain. I get the pain in the morning mostly and mostly on a night. And … if I sit in a certain way it comes on as well.""*

PID25 *(moderate - THORACOTOMY, WEDGE RESECTION, 3MPS)* described the same experience, but explained that *"to be honest it's been easier lately. It's not so bad at all."* PID12 *(moderate - THORACOTOMY, LOBECTOMY, 5MPS)* described a moving pain; however, it moved over several

[6]mild, moderate, severe refers to pain typology category that participants belong to

Table 3.10: Typology of pain in terms of level of severity, effect on function, duration and trajectory over the first 12 months after surgery

Type	Experience	Standard care participants	ROC programme participants
Not affected by pain	No pain as an inpatient or after discharge	PID5, **PID9**, PID20	PID15
Mildly affected by pain	Low levels of pain (MPQ "how strong" scale 1-2) starting in hospital, or no pain in hospital but low levels of pain after discharge. No reported restrictions in activity level. Pain largely resolved within 2 month of surgery, or lasted in total for no longer than 2 months.	**HTO1**, PID6, PID11 **PID24**, **PID31**	**HTO3**, PID18, PID23
Moderately affected by pain	Low/medium levels of pain severity (MPQ "how strong" scale 1-3) starting in hospital or after discharge. Pain largely resolved between 2-6 months of surgery. Or high level pain (MPQ "how strong" scale 4-5) that resolves within 2 months. May be associated with some restriction in activity level.	**HTO2**, PID1, PID12, PID13, PID14, PID16	PID17, PID25, PID26, PID29
Severely affected by pain	High levels of pain severity (MPQ "how strong" scale 4-5) in hospital that continued or subsided but was still present after 6 months (or at time of interview). Level of activity restricted.	PID3, PID4, PID10, PID21	PID19, PID28, PID30

Table 3.11: Participant and treatment characteristics of participants within each level of the pain typology

ID	Gender	Age	Primary Procedure	Incision Procedure	Tumour Position	Standard/ROC	Smoking After Surgery
Not affected by pain							
PID5	M	77	Thoracotomy	Wedge resection	Right	Standard	Continuous
PID9	F	71	VATS	Wedge resection	Standard	Right upper	Continuous
PID20	M	80	Thoracotomy	Pneumonectomy	Left	Standard	Abstinent
PID15	M	75	Thoracotomy	Lobectomy	Right, lower	ROC	Abstinent
Mildly affected by pain							
HTO1	M	74	VATS	Lobectomy	Left, lower	Standard	Ex-smoker
HTO3	F	73	VATS	Wedge resection	Left, upper	ROC	Ex-smoker
PID6	F	66	Thoracotomy	Pneumonectomy	Left	Standard	Abstinent
PID11	M	70	Thoracotomy	Bi-lobectomy	Right, middle and lower	Standard	Ex-smoker
PID18	M	81	Thoracotomy	Bi-lobectomy	Right middle and upper	ROC	Never
PID23	M	66	Thoracotomy	Wedge resection	N/d	ROC	Relapsed
PID24	F	75	VATS	Wedge resection	Left, lower	Standard	Ex-smoker
PID31	M	74	VATS	Lobectomy	Left, lower	Standard	Ex-smoker
Moderately affected by pain							
HTO2	F	81	VATS	Wedge resection	Left, lower	Standard	Ex-smoker
PID1	M	62	Thoracotomy	Wedge resection	Right, middle	Standard	Ex-smoker
PID12	M	76	Thoracotomy	Lobectomy	Left, lower	Standard	Ex-smoker
PID13	F	66	Thoracotomy	Bi-wedge resection	Left, lower	Standard	Relapsed
PID14	M	82	Thoracotomy	Bi-lobectomy	Right, middle and lower	standard	Ex-smoker
PID16	F	58	Thoracotomy	Lobectomy	Right, upper	Standard	Relapsed
PID17	F	73	Thoracotomy	Lobectomy	Right, upper	ROC	Never
PID25	M	76	Thoracotomy	Wedge resection	Right, lower	ROC	Ex-smoker
PID26	M	61	Thoracotomy	Lobectomy	Left, upper	ROC	Continuous
PID29	F	60	Thoracotomy	Lobectomy and wedge resection	Right, upper and middle	ROC	Ex-smoker
Severely affected by pain							
PID3	M	67	Thoracotomy	Wedge resection	Right, lower	Standard	Relapsed
PID4	F	61	Thoracotomy	Wedge resection	Right, middle	Standard	Relapsed
PID10	F	39	Thoracotomy	Bi-lobectomy	Right, middle and lower standard	Standard	Ex-smoker
PID19	F	71	Thoracotomy	Lobectomy	Left, upper	ROC	Ex-smoker
PID21	F	63	Thoracotomy	Lobectomy	Right, upper	Standard	Continuous
PID28	F	76	Thoracotomy	Lobectomy	Left, upper	ROC	Never
PID30	F	72	Thoracotomy	Bi-wedge resection	Right, upper and lower	ROC	Abstinent

weeks rather than happening daily. PID10 *(severe - THORACTOMY, BI-LOBECTOMY, 7MPS)* also described experiencing a clamping sensation, but did not report any movement of the sensation:

PID10: *"I still get ongoing pain around here [indicates wound site] and even at the end of the day it feels as though my back on this side concertinas sort of thing like that, you just want to go like that [demonstrates stretching]."*

In addition, PID10 recounted a further similar experience:

PID10: *"At one stage I had a lump come up here and I was in ever such a lot of pain with it.. what had happened was the nerves had got really agitated and pulled the diaphragm up here . . . you could see it on the X-ray."*

Finally, PID14 *(moderate - THORACOTOMY, BI-LOBECTOMY, 5MPS)* reported a *"clinging"* sensation *"as if someone had grabbed him and pulled him down"* around the wound site, although again he did not report that this sensation moved along the scar.

Some participants described sharp, shooting pains which were described as *"vicious"* or *"like a butcher's knife"*. These descriptive words for pain are classified by the MPQ as spatial (group 2), incisive pressure (group 4) and punishing (group 14) pain. For example, PID3 *(severe - THOROCOTOMY, WEDGE RESECTION 10MPS)* described experiencing this sensation when he coughed:

PID3: *"When I was coughing it was literally doubling me up.* ***What kind of pain was it?*** *Vicious . . . It was like. . . someone sticking a knife in-between my ribs."*

In addition, some participants reported that rather than feeling pain, they described sensations of *"numbness"*, *"feeling a bit funny"*, *"tingly"* and *"strange"*. These descriptive words for pain are classified within MPQ brightness (group 8) pain group.

Some participants reported that they experienced more than one type of pain. For example, PID21 *(severe - THORACOTOMY, LOBECTOMY, 3MPS)* and PID3 *(severe - THORACOTOMY, WEDGE RE-*

SECTION, 10MPS) explained:

PID21: *"I've got three different types of pain ... sometimes it's like a nagging ache. Sometimes it's shooting pains. And all the while continuing, it's like I've got something stuck between my ribs that's there all the while."*

PID3: *"It's completely numb all the way down the centre, could stick a pin in it. But if I press it, it hurts. Sometimes I get it like someone's just stuck a branding iron on my leg occasionally and that hurts"*

Often participants noted that the site of the chest drain was particularly painful, more so than the site of the lung resection. For instance, PID10 *(severe -THORACOTOMY, BILOBECTOMY, 9MPS)* reported being in *"utter pain"* when she came round from surgery and further explained:

PID10: *"... it was awful because I'd got two drains coming out of me with a big swing on them as well ... that was the worst pain from the drains. There was a big swing on the drains like a constant pulling ... and I was in utter pain."*

PID19 *(severe - THORACOTOMY, LOBECTOMY, 6MPS)* felt that the pain from the drains was worse than giving birth:

"I couldn't get over having the drains in, that was horrendous..I think it's worse than when I had two daughters. It's horrible."

In summary, it was noted that participants that had undergone a VATS procedure did not use adjectives to describe their pain that belonged to any of the descriptive groups specified by the MPQ. The only exception to this was HTO2 who developed shooting pains a few weeks after discharge. The remaining participants used the words *"discomfort"* or *"a bit of pain"*. In contrast, most participants who had undergone a thoracotomy, particularly those who had been moderately or severely affected by pain, used adjectives recognised by the MPQ to describe their

pain experiences. From the sample included in this study, there was no discernible pattern to the manifestation of these sensations in terms of extent of resection or length of time since surgery. Regardless of the level of pain reported, some participants noted that the site of the chest drain (rather than the incision through which part of the lung was resected) was the most painful. A number of participants described experiencing a cramping/tightening/pulling sensation that moved along the incision scar. Movement of these sensations is not described by the MPQ.

3.4.2.3 Emotional response to pain (dimension 6)

There was a clear contrast between participants that reported not being affected or being mildly/ moderately affected by pain and those who were severely affected by pain. Generally, when describing experiences that fitted the mildly and moderately affected categories, participants spoke pragmatically about their pain. For example HTO1 *(mild - VATS, LOBECTOMY, 3MPS)*, PID13 *(moderate - THORACOTOMY, BI-WEDGE RESECTION, 5MPS)*, PID24 *(mild - VATS, WEDGE RESECTION, 3MPS)* and PID29 (*moderate - THORACOTOMY, WEDGE RESECTION AND LOBECTOMY, 3MPS)* all explained that it was *"to be expected"* and that they were not worried about it.

However, as would be expected, when participants experienced a high level of pain they found it distressing whether it resolved quickly (moderately affected) or continued (severely affected). This was reflected in their tone of voice and also choice of words to describe the pain such as *"tremendous"*, *"terrible"*, *"awful"*. A few participants reported that they had found it painful to cough as an inpatient, or had found it difficult to mobilise themselves from their bed and wash in the bathroom. Some participants felt that the staff had not been understanding of the amount of pain that they were in. One participant *(PID26 moderate - THORACOTOMY, LOBECTOMY, 7MPS)* went as far as describing this as bullying:

PID26: *"in the first couple of days.. the physios . . . were getting me to cough . . . and it was very painful from the wound sort of stretching and it felt like the wound was going to burst open and they kept saying come on you need to try harder . . . and the pain was excruciating and I was still trying, and I was thinking "this is bullying this is because I'm in real pain here"' . . . then at one point I just said "I'm not going to do it any more so you might as well go away" and I was in tears, I was crying for some reason."*

PID3 *(severe - THORACOTOMY, WEDGE RESECTION, 10MPS)* also recounted an experience which he had found distressing as an inpatient, the day after his surgery:

PID3: *"her and another nurse, frog marched me down to the bathroom, stood me in front of the sink, no oxygen, nothing. She said have a wash, get yourself washed. Course I was dropping onto the basin, couldn't breathe, gasping for breath. I finally settled down and I just swilled my face basically and she came in, have you finished yet? I said I want to go to the toilet. So she put me on to the toilet, but I couldn't do anything because I couldn't breathe properly because of pain. She come back down and frog marched me back to the bed. Sat me in the chair, put the oxygen back on and that were it."*

Some participants also expressed that they had not expected the severity of pain that they experienced. For example, PID10 *(severe - THORACOTOMY, BI-LOBECTOMY, 7MPS)* explained:

PID10: *"Looking back, I didn't realise how big an impact the operation would have and how harsh the operation - it's really bad. I've had caesareans, I've had a hysterectomy, I've had little minor surgeries and I thought I'd walk it, I thought I'd be OK. Oh my God, honestly, I felt as though I'd been in a car crash. It was horrid. Horrid. It really is a nasty operation, I didn't realise it . . . "*

PID21 *(severe - THORACOTOMY, LOBECTOMY, 3MPS)* disclosed that she had contemplated suicide, and that if she had known how much she was going to suffer she would have chosen to go the

palliative care route:

PID21: *"if I'd have known what was involved and how I was going to suffer, I wouldn't have bothered… it's been so difficult, the pain has been terrible … I'd have either gone into [hospice 1] and just gone under their sort of niceness, or, to be perfectly frank, if I hadn't got my cat, it would've been an exhaust on the car job."*

Unexpected, enduring high levels of pain also led some participants to worry that 'something had gone wrong'. For example, PID28 *(severe - THORACOTOMY, LOBECTOMY, 3MPS)* described being *"shocked"* by what had happened as a result of the surgery, and added:

PID28: *"You don't know, whether it's normal to be sort of coughing and the pain but then, I suppose they don't know either really do they? I think it's just the fear of the unknown. I'd sort of get a pain or it would be something that I hadn't had before and you think oh gosh, is everything okay?"*

PID21 (*severe - THORACOTOMY, LOBECTOMY, 3MPS)* was also worried about the significance of her pain experiences. She described experiencing three types of pain, and additionally described a 'moving pain' similar to those described in section 3.4.2.2:

PID21: *"But, sometimes it actually feels like something's moving round in there … and I think, God's sake, what's going on in here! You know what I mean … and it's frightening, it's worrying. I mean the pain moves around. And I started to think, well why? … you imagine all sorts of stuff, 'cause I was starting to think, there's something gone wrong here."*

In summary, only patients who had experienced high levels of pain severity after thoracotomy reported feeling distressed by their experience. No patients who had undergone VATS reported high levels of pain and they did not report feeling distressed by the pain that they experienced. Often high levels of pain severity that continued for a protracted length of time (severely affected) were unexpected and led participants to worry that something had gone wrong. Of those

who had been severely affected, both those who had received standard care and those who had participated in the rehabilitation programme pilot reported being worried about the significance of their pain experience.

3.4.3 Main topic 1, theme 3: other health challenges

Although breathlessness and pain were the most commonly reported health challenges, some participants reported additional post-surgical health challenges including: reduced appetite, weight loss, altered sleep and general fatigue.

Appetite and weight loss Thirteen participants reported loss of appetite and some had also lost weight. For all participants, appetite had improved over time but many still felt that they didn't have their full appetite back at the time of interview. Although participants were often uncertain about the cause of their loss of appetite, there were a range of factors that were reported as possible contributors. Both PID29 *(BT moderate, PT moderate*[7] *-THORACOTOMY, LOBECTOMY AND WEDGE RESECTION, 3MPS)* and PID31 *(BT absent, PT mild - VATS, LOBECTOMY, 4MPS)* described loss of appetite and nausea concurrent to chemotherapy, although neither reported significant weight loss. PID29 added that she had been making an effort to eat in order to *"keep (her) weight up"*. PID10 *(BT moderate, PT severe -THORACOTOMY, BILOBECTOMY, 7MPS)* reported that she did not have much of an appetite until her pain medication was changed, after which she started to put on weight. PID17 *(BT moderate, PT moderate -THORACOTOMY, LOBECTOMY, 5MPS)* noticed that she was *"never ready for any meal"* and that she had lost her sense of taste. She was not sure whether she was experiencing this as a side effect of the anaesthetic or chemotherapy:

PID17: *"It's only probably about the last six weeks that I began to feel that I've gone back onto taking some foods that I just couldn't stand the sight of . . . Nothing tasted . . . But my appetite has got much better . . . it has improved, but I can't say, still say, that I'm hungry or ready for a meal. I'm not, (but) it's much better than it was."*

[7] BT = breathlessness typology, PT = pain typology

PID20 *(BT severe, PT absent -THORACOTOMY, PNEUMONECTOMY, 3MPS)* reported loss of appetite after being discharge from hospital although he was not sure what was causing it. However, this participant had been severely affected by breathlessness and was largely housebound as a result, he also demonstrated low mood. He was not undergoing adjuvant therapy and neither had he lost a significant amount of weight. He explained:

PID20: *"I've gone off my food . . . Just don't feel like eating, and when I do, it's only certain things I like to eat like, [person 1] put some dinner out yesterday. I ate the mash potatoes, struggled with the vegetables. I had one piece of the chop. And that's all I could eat. I couldn't eat anymore . . . I used to have a fairly good appetite at one point but, when I look at things, for some reason, (I) think I don't want that. It's strange."*

PID14 *(BT moderate, PT moderate -THORACOTOMY, BILOBECTOMY, 5MPS)*, PID16 *(BT moderate, PT moderate -THORACOTOMY, BILOBECTOMY, 5MPS)* and PID21 *(BT moderate, PT severe - THORACOTOMY, LOBECTOMY, 3MPS)* all reported losing an amount of weight that they were concerned about, and they were actively trying to gain weight. PID14 reported having his full appetite back at interview, however PID16 and 21 were still not back to normal in terms of appetite. Although PID14 did not offer a possible cause, PID16 cited the effect of chemotherapy on her sense of taste. PID21 suggested that it was due to the combined stress of her cancer treatment and also a difficult relationship. She explained:

PID21: *"The eating has been a problem . . . people may be at risk from malnutrition, I don't think I'm that far down the road but like, I've got no appetite . . . I buy myself all nice things . . . but I've not got a lot of appetite . . . I've always been tiny, but it's got ridiculous . . . nothing fits, and I'm hard pressed to find something to get dressed in. And, I think, well, shall I buy a pair of size six? But then I was online looking when you came and it's difficult to find."*

In summary, about a third of participants reported loss of appetite and for some this was still

present at the time of interview. Loss of appetite was more often reported by those who had undergone thoracotomy, but participants specifically stated a range of other reasons for loss of appetite including chemotherapy, pain medication, stress and change in routine. Weight loss only occurred in a few participants, and these participants reported being concerned about it and were actively trying to regain weight.

Altered sleep Eleven participants reported disturbances in their sleep. Some were able to sleep at night but found themselves needing more sleep than usual, and/or were also falling asleep during the day. HTO1 *(BT mild, PT mild - VATS, LOBECTOMY, 3MPS)* reported being *"shattered"* on the first day he was discharged from hospital and sleeping more than he normally would on his first night at home. He felt that his tiredness was due to lack of sleep in hospital:

HTO1: *"I arrived home about six o'clock in the evening, and I desperately wanted to watch the football highlights at 10.30pm (but) I was in bed at 9.30pm . . . and I woke up the following morning at about eight o'clock, I couldn't believe the time . . . "*

Four participants (PID3 *(BT severe, PT severe - THORACOTOMY, WEDGE RESECTION, 6MPS)*, PID10 *(BT moderate, PT severe - THORACOTOMY, BILOBECTOMY, 7MPS)*, PID19 *(BT absent, PT severe -THORACOTOMY, LOBECTOMY, 6MPS)* and PID21 *(BT moderate, PT severe - THORACOTOMY, LOBECTOMY, 3MPS)*) who had undergone thoracotomy also reported needing more sleep than normal, but in contrast to HTO1 it lasted for a much longer length of time. Two participants (PID3 and PID19) both described sleeping because of tiredness, or running out of energy. PID3 explained that after his surgery he started sleeping heavily, *"for hours and hours"* because *"there's just nothing left."* His wife added:

PID3: *"[Wife: You still do that now. He can have his first sleep until 11 o'clock. Then he'll have his lunch then he'll sleep again and then he'll sleep again during the evening and it's like he just switches off]."*

PID19 reported not sleeping during the day but getting very tired towards the evening and going

to bed earlier than had been normal for her before surgery.

PID21 reported needing up to 16 hours of sleep a day after she was discharged from hospital, but referenced the fact that she was on *"heavy drugs"* (including morphine). PID10 had been able to return to work, but described how she often came home feeling exhausted and would fall sleep. She explained that she thought the tiredness was due to shortness of breath:

PID10: *"I'd work till 2, come home and go to sleep. Literally come in the door, go up the stairs, sit on the bed and fall asleep ... even now I only work a Wednesday and a Friday, I come home from work on a Friday I literally go upstairs, have a quick shower get my pyjamas on and then I don't move because ... I'm just so tired, I get physically exhausted quite easily. Like a nanny ... I think probably the tiredness comes from the shortness of breath the two sort of go together I think."*

One participant who had undergone VATS and also some participants who had undergone thoracotomy reported not being able to sleep properly during the night. Again, this situation resolved within days for the participant who had undergone VATS, but was a protracted problem for those who had undergone thoracotomy. PID29 *(BT moderate, PT moderate - THORACOTOMY, LOBECTOMY AND WEDGE RESECTION, 3MPS)*, PID30 *(BT moderate, PT severe - THORACOTOMY, BI-WEDGE RESECTION, 4MPS)* and PID31 *(BT absent, PT mild - VATS, LOBECTOMY, 4MPS)* all reported that the cause of their disturbed sleep was pain when moving position. Each also described that they had needed to change from their normal sleeping positions in order to avoid triggering pain, which had initially disturbed their ability to sleep. PID20 described how he had not had a *"good night's sleep"* for a long time but due to breathlessness rather than pain:

PID20: *"And I'm struggling for me breath at night, most nights, it's been ages since I've had a good night's sleep. Ages.* ***What's stopping you from sleeping?*** *Breathing ... I've got to get comfortable ... I sit up most of the time ... because I found ... if I lay ... on my sides ... I was really struggling to get me breath. So I found it best to sit up, pack my pillows behind me ... even then I have trouble ... last night ... about five o'clock, I moved that side, and lay on some pillows. I just found ... a nice position, where I found me breathing a lot easier. And I dosed off for a couple of hours. That's very rare that is."*

PID14 *(BT moderate, PT moderate - THORACOTOMY, BI-WEDGE RESECTION, 5MPS)* found himself waking up multiple times a night for a few weeks after discharge. However, he couldn't understand why, and reported not being in any pain. The situation resolved after he was prescribed a course of sleeping pills by his GP. PID4 *(BT, moderate PT, severe - THORACOTOMY, WEDGE RESECTION, 12MPS)* reported finding it difficult to sleep at night, and that instead she was sleeping in the day. This had been a difficulty since the treatment and had not resolved after 12 months. PID21 *(BT moderate, PT severe - THORACOTOMY, LOBECTOMY, 3MPS)* also reported sleeping more than normal during the day when she was first discharged from hospital, and that then she started to find it difficult to sleep at night. Both PID4 and 21 felt that their sleep disturbances were rooted in anxiety, with PID21 adding that she often experienced nightmares.

In summary, some participants reported needing more sleep than normal, whereas others found it difficult to sleep during the night. Alterations in sleep were reported to arise due to a range of reasons, including pain, breathlessness and anxiety. This difficulty resolved quickly for those who had undergone VATS but was a protracted problem for those who had undergone thoracotomy.

General fatigue Five participants described a general feeling of fatigue, and in particular reported that activities left them feeling more tired than usual, or that they got tired more quickly. These participants did not report that their sleep was also affected, although they were not probed directly about this. For example, PID9 *(BT absent, PT absent - VATS, WEDGE RESCTION,*

9MPS) reported that she was not greatly affected by surgery and was able to return to her employment as a care worker, although she had changed her working hours. She later explained this was because of tiredness. PID16 *(BT moderate, PT moderate - THOROCOTMY, LOBECTOMY, 5MPS)* also described how she had returned to work but five months after surgery was still finding that she returned home feeling *"really, really tired"*:

PID16: *"I'm still getting very tired . . . after the work, I come home and I'm really really tired . . . it's just one of these things you've just got to [pause 1 sec], I mean they're very supportive at work. I have thought about reducing my hours if I can't cope and I'm sure they're fine with that and I asked if I can say maybe work one day a week from home so, I am trying to think of things to sort of help me get back to normal. But I know it's going to take time."*

PID17 *(BT moderate, PT moderate - THOROCOTMY, LOBECTOMY, 5MPS)* described experiencing *"lethargy"* as a side effect of chemotherapy, and that sometimes if she had done too much during the day she *"suddenly slumps"* and has to rest:

PID17: *"But it's something about . . . stamina, I hadn't got the stamina I was used to having . . . the main side effect (of chemotherapy) . . . has been the breathlessness and terrible tiredness on days six seven and eight . . . then I might have an occasional day, when perhaps I've done too much and I suddenly have to, I suddenly slump. And I have to sit down."*

PID1 *(BT moderate, PT moderate - THOROCOTMY, WEDGE RESECTION, 11MPS)* and PID28 *(BT moderate, PT severe - THOROCOTMY, LOBECTOMY AND WEDGE RESECTION, 5MPS)* described feeling tired although they did not know why. PID28 had experienced tiredness since surgery and reported that although she was recovered in other ways at the time of interview she still felt more tired than usual:

PID28: *"But I do find now that I want to get on and do things but I get so tired . . . I don't know why . . . just sort of weary . . . making the effort to do things . . . I still get tired, at the end of the day I think, you know, glad that's over."*

In summary, fatigue was reported by both one participant who had undergone VATS and by four participants who had undergone thoracotomy. It appeared that regardless of surgery type, fatigue was an ongoing challenge that remained in the background at the time of interview. Unlike other physical challenges, descriptions suggested that this 'background level' of fatigue did not improved over time and also for many the phenomenon was not linked with a particular trigger.

3.4.4 Summary of participants health experiences during the first 12 months after surgery

Although a typology of breathlessness and pain experiences emerged from the reported experiences of participants in this study, no unifying typology was evident. A summary of the health experiences of individual participants during the first year after surgery are found in tables 3.12 and 3.13. The extent to which these findings confirm and extend existing, commonly used measures of breathlessness and pain will be addressed in the discussion.

3.5 Main topic 2: smoking

Most participants (26/29) had a history of smoking. Eleven patients were current smokers at diagnosis, 15 participants had quit smoking between two months and 40+ years previous to diagnosis and three participants were never smokers. All 11 participants smoking at diagnosis reported abstinence throughout hospitalisation. Of those 11, three remained abstinent until interview, four attempted to remain abstinent but had relapsed, and four chose to resume smoking on discharge and were still smoking at interview. Of the two participants that had quit in the

Table 3.12: Health experiences during the first year after lung resection of participants who received standard care

PID	Incision procedure	MPS[1]	Breathlessness	Pain	Appetite/ WL	Disturbed sleep	Fatigue
VATS							
HTO001	Lobectomy	3	Mild	Mild	N	Y	N
HTO002	Wedge resection	4	Mild	Moderate	N	N	N
PID9	Wedge resection	9	Absent	Absent	N	N	Y
PID24	Wedge resection	3	Absent	Mild	N	N	N
PID31	Lobectomy	4	Absent	Mild	Y	Y	N
Thoracotomy							
PID1	Wedge resection	11	Moderate	Moderate	Y	N	Y
PID3	Wedge resection	10	Severe	Severe	Y	Y	N
PID4	Wedge resection	12	Moderate	Severe	Y	Y	N
PID5	Wedge resection	6	Mild	Absent	N	N	N
PID6	Pneumonectomy	11	Moderate	Mild	N	N	N
PID10	Bi-lobectomy	7	Moderate	Severe	Y	Y	N
PID11	Bi-lobectomy	4	Moderate	Mild	N	N	N
PID12	Lobectomy	5	Moderate	Moderate	N	N	N
PID13	Bi-wedge resection	5	Moderate	Moderate	N	N	N
PID14	Bi-lobectomy	5	Moderate	Moderate	Y	Y	N
PID16	Lobectomy	5	Moderate	Moderate	Y	N	Y
PID20	Pneumonectomy	3	Severe	Absent	Y	Y	N
PID21	Lobectomy	3	Moderate	Severe	Y	Y	N

[a]MPS = months post-surgery

Table 3.13: Health experiences during the first year after lung resection of participants who enrolled in the ROC programme

Participant	Incision procedure	MPS	Breathlessness	Pain	Appetite/ WL	Disturbed sleep	Fatigue
VATS							
HTO003	Wedge resection	4	Mild	Mild	N	N	N
Thoracotomy							
PID15	Lobectomy	5	Moderate	Absent	N	N	N
PID17	Lobectomy	5	Moderate	Moderate	Y	N	Y
PID18	Bi-lobectomy	3	Mild	Mild	Y	Y	N
PID19	Lobectomy	6	Absent	Severe	N	Y	N
PID23	Wedge resection	3	Mild	Mild	N	N	N
PID25	Wedge resection	3	Moderate	Moderate	N	N	N
PID26	Lobectomy	7	Mild	Moderate	Y	N	N
PID28	Lobectomy	3	Moderate	Severe	N	N	Y
PID29	Lobectomy and wedge resection	3	Moderate	Moderate	Y	Y	N
PID30	Bi-wedge resection	4	Moderate	Severe	N	N	N

year leading up to their diagnosis (PID4, two months and PID6, 8 months), only PID6 remained abstinent after discharge.

In the following sections, the attitudes of participants towards smoking, smoking cessation and NHS services for smoking cessation support is considered in the light of smoking behaviour groups (see table 3.14). Never smokers were not included in the analysis as they provided no relevant data. Participants were assigned to groups as follows:

Table 3.14: Smoking behaviour groups

Smoking behaviour group	Participants
Ex-smoker at diagnosis	HTO1, HTO2, HTO3, PID1 PID4[1], PID6, PID10, PID11, PID12, PID14, PID19, PID24, PID25, PID29, PID31
Smoker at diagnosis – continuous abstinence after discharge	PID15, PID20, PID30
Smoker at diagnosis – quit and relapsed after discharge	PID3, PID4[1], PID13, PID16, PID23
Smoker at diagnosis – continuous smoking after discharge	PID5, PID9, PID21, PID26

3.5.1 Ex-smoker at diagnosis

3.5.1.1 Main topic 2, theme 1: attitudes towards smoking and smoking cessation

Ex-smokers generally reported that they had no desire to smoke. Those who had quit smoking more than 1 year before surgery felt that smoking cessation support was not relevant to themselves. They did not express concern about being asked about their smoking during their cancer care, and were able to answer the question with ease. No ex-smoker of eight months or more reported benefits that they perceived to be associated with smoking and some expressed their dislike of smoking, explaining that they were thankful that they no longer smoked and some

added that they wish they had never started in the first place. Regardless of the stress experienced due to their diagnosis and treatment, ex-smokers of 8 months or more found that they were not tempted to start smoking again at diagnosis. For example, PID1 who had quit 20+ years before diagnosis explained that smoking *"didn't bother (him) whatsoever"*. PID6 *(THORACOTMY, PNEUMONECTOMY, 11MPS)* quit smoking eight months before she was diagnosed, and she reported that *"it never occurred to (her) to smoke again"*. She explained that the first two months of quitting had been difficult, but now she *"couldn't stand the smell of (smoke)"*. PID4 quit two months before diagnosis, but found it difficult to not smoke after she was discharged from hospital and relapsed to smoking 40 cigarettes per day three months after discharge. When discussing her views towards smoking, unlike other ex smokers, she emphasised the benefits of smoking, such as her belief that it provided stress relief (see section 3.5.2.1).

There was some evidence that ex-smokers felt stigma attached to the diagnosis of lung cancer, which was deemed to be unfair. PID10 *(THORACOTMY, BI-LOBECTOMY, 7MPS)* had a history of smoking, but had not smoked for many years. She was particularly worried at the beginning of her cancer journey that people would assume she had *'smoked herself a tumour'*. She was the youngest participant (diagnosed at age 39) and believed that her diagnosis was not related to smoking:

PID10: *"That's a big thing as well ... I felt a stigma, and it's a dirty cancer ... I felt, it feels terrible to say that word but it did feel like a dirty cancer from smoking, and it's not. That's how I perceived that people saw me at the beginning."*

Similar to participants who were smoking at diagnosis (see section 3.5.2.1), PID6 *(THORACOTMY, PNEUMONECTOMY, 11MPS)*, who had stopped smoking eight months prior to diagnosis, explained that she felt ashamed when asked by doctors if she was smoking, although she later pointed out that often doctors and nurses are seen smoking outside of hospitals and she felt that this did not set a good example.

PID6: *"I felt ashamed. I've done this to myself you know. It's my fault I've got it. But it was my own fault, wasn't it . . . I don't think anyone realises how addictive it is and I feel it should be banned, cause it's a drug, you know . . . I couldn't give it up so . . . I did in the end, but too late."*

Despite finding it uncomfortable to answer questions about her smoking behaviours, PID6 explained that she thought that it was the rightful place of doctors to ask those questions, and that it did not offend her. No other ex-smokers described feeling guilty about their past smoking or expressed feeling a weight of responsibility for their diagnosis. However, some did wonder if smoking had contributed to their diagnosis.

3.5.2 Current smoker at diagnosis

3.5.2.1 Main topic 2, theme 1: attitudes towards smoking and smoking cessation

The attitudes of current smokers towards smoking and smoking cessation fell into three main categories: a resolute desire to quit, internal conflict with regards to desire to quit and resolute desire not to quit.

Resolute desire to be quit The majority of participants who were smoking at diagnosis stated that they would prefer to be a non-smoker. For some participants, this desire was expressed resolutely, with no evidence of an internal conflict of attitude. For example, two of the three participants who were continually abstinent after diagnosis explained that they had 'just decided' that they would no longer smoke, and that they would never smoke again. PID30 *(THORACOTMY, BI-WEDGE RESECTION, 4MPS)* explained that from the moment she was first told that she had cancer, she stopped smoking and was able to *"just throw away her cigarettes"*. She reported that she could not describe how she felt, but that she *"felt like a different person"* and wished that she had stopped like that years before. PID20 *(THORACOTMY, PNEUMONECTOMY, 3MPS)* was continually abstinent after discharge and explained that he had made this decision due to his

health:

PID20: *"When I had this operation, I thought, smoking isn't going to do me any good at all, I've only got one lung, if something happens to that I'm going be in trouble, so I just said I wouldn't smoke anymore. And I won't . . . I shan't smoke again . . . I wish I could have taken that (decision) thirty years ago but there you are, that's hindsight isn't it."*

Internal conflict with regards to desire to quit In addition to expressing concerns regarding their smoking behaviour and the desire to be a non-smoker, some participants also expressed conflicting attitudes. There were a variety of conflicts described by participants including: lack of will power/ability to overcome addiction, concerns about impact on physical health, reflecting on smoking with fondness and beliefs that smoking helps maintain mood, deals with acute anxiety and relieves boredom.

Some who had relapsed back to smoking after a period of abstinence, or who had returned to smoking immediately after discharge cited no benefits for continuing to smoke, and explained that the only thing standing in the way of quitting was a lack of will power to overcome the addiction. For example, PID21 *(THORACOTMY, LOBECTOMY, 3MPS)* explained that, after returning home, she immediately resumed smoking although she felt that this was *"stupid"*:

PID21: *"I knew I'd got a pack somewhere. And I sat here for quite a while. And I thought, I wonder if it'll hurt if I, I wonder if it'll actually I mean physically hurt. I thought, I've got to have a cigarette. And I did, and it didn't hurt, so you know, stupid. Don't make any sense whatsoever."*

She also reported feeling guilty about her smoking, explaining that the care that she had received from the NHS must have cost *"thousands upon thousands"* of pounds and that it was necessary because of her smoking behaviour. She added:

PID21: *"Not only that but I mean, obviously I'd probably be breathing a lot better if I didn't continue smoking. Um, [pause 2 sec] I just feel bad about it, but I can't do anything about it . . . . I've got the best intentions in the world, I could open a cupboard there, and show you every stop smoking product known to mankind. But none of them work . . . (cigarettes are) the thing I reach for."*

PID3 *(THORACOTMY, WEDGE RESECTION, 10MPS)* relapsed to smoking a short while after discharge. He explained that he would like to be able to quit smoking, but he felt that he did not have enough will power and that the only way he would be able to quit now was by undergoing hypnotherapy. However, he also defended his smoking explaining that smoking helped him to cough and clear his lungs of mucus. He felt that he had reduced the risk of his smoking by cutting down. When probed to explain what he meant by the term 'cutting down' he explained that he no longer inhaled the smoke into his lungs:

PID3: *"I've got no will power now . . . I don't want to give it up so I'll carry on doing what I'm doing, take the smoke into my mouth and blow it out again rather than take it all the way down and I'll carry on like that. And eventually one day I will be able to."*

Some who expressed a desire to be a non-smoker also reflected on smoking with fondness. For example, PID15 *(THORACOTMY, LOBECTOMY, 5MPS)* had quit since being admitted to hospital for his surgery and his GP had prescribed him patches to help maintain abstinence. He reported having two cigarettes since being discharged, although his wife 'told him off' and they had made him vomit. Although he was determined to stay quit, he described smoking as *"an old friend"*. PID23 *(THORACOTMY, WEDGE RESECTION, 3MPS)* explained that he was an addicted smoker, but was *"not proud of the fact"*, stating that he was *"guilty as charged"* and that smoking was his *"biggest enemy"*. He added:

PID23: *"I hate myself for smoking, really do. There's not a day goes by that I don't think I'm going to stop it today. I'm going to smoke that pack, then that's it . . . but there you go. I'm just a bad example."*

Despite feeling this way he explained that a beer and a cigarette outside in the sunshine was *"like seventh heaven"* and that three weeks after discharge he had returned to smoking 40 cigarettes per day. Similarly, PID5 *(THORACOTMY, WEDGE RESECTION, 6MPS)* consulted with his GP prior to his surgery and was prescribed patches, but decided not to use them. He continued to smoke after he was discharged from hospital, although described it as *"stupidity"*, adding *"but there are all kinds in this world young lady!"*. He started smoking whilst still a teenager in the air force and he explained:

PID5: *"We all did . . . like a load of idiots I suppose . . .* ***Have you been a smoker for the rest of you life?*** *Yeah. No one to complain, only my stupid self. Like I say I've had my fun, keep it quiet, I've had my kicks . . . I'll kick it tomorrow [laughs]."*

PID4 *(THORACOTMY, WEDGE RESECTION, 12MPS)* described how she had relapsed to smoking 40 cigarettes per day two months after discharge. She regretted having relapsed and explained that *"it played on (her) mind and (she) felt guilty about it . . . terrible about it"* adding that she hadn't been enjoying smoking. Two weeks before the interview, she had started a new quit attempt and felt confident that this time she would be successful. However, she also defended her smoking with strong feeling, arguing that it had kept her sane:

PID4: *"But . . . you've got to put yourself in my position . . . it's like your own little prison, your own little world . . . And when you've got nothing else and you've got no one to talk to . . . I always called my cigarette my comfort hat . . . Anytime you feel wound up or anything, have a cigarette. And that's how I felt about smoking . . . and I know it's no good for your lungs . . . but people need to understand it is a calmer . . . it keeps you together sometimes . . . I know it's a drug . . . but at the end of the day it keeps you sane."*

PID13 *(THORACOTMY, BI-WEDGE RESECTION, 5MPS)* had found it easy to not smoke whilst in hospital, and had continued to be abstinent for two or three weeks after discharge but then relapsed. She explained that she *"tried not to"* smoke, and knew that she should not, but she

did still smoke. However, she also defended her smoking by explaining that she was concerned that quitting may be harmful to her health, and that smoking made her happy:

PID13: *"it's frightening . . . because I know people that have smoked for a long time and they pack up smoking and their body can't cope. I know people have strokes and everything.* ***So you're worried about what will happen to your body?*** *And . . . the weight, because the steroids have piled the weight on me . . . the weight's no good for my arthritis. It's all a jumble of things really . . . and I'm sixty six, Amanda! I don't expect to live much longer. And when you see this world, I don't know whether I want to. [Pause 4 sec], I'm alright . . . . [Pause 4 sec].I just want to be happy and if a cigarette makes me happy, why shouldn't I have one. . . . I know I'm naughty and I shouldn't do it and . . . [pause 3 sec] but I'm ok."*

Resolute desire not to quit Finally, unlike other participants, PID9 *(VATS, WEDGE RESECTION, 9MPS)* defended her decision to smoke and did not raise any concerns associated with smoking or express any remorse. After her diagnosis, she reported having *"made herself think about (smoking)"* and that she had cut down the number that she smoked at the time of surgery, with the aid of patches. Ultimately, however, she reported that she could not stop smoking and neither did she want to. She worked (and had returned to work after surgery) as a care worker, providing respite care. She expressed concern at the possibility of becoming like her clients, dependent and unable to do things for themselves. She expressed a preference for just *"dropping dead"* as her husband had done years before, rather than being dependent. Her family had expressed their wishes for her to quit smoking but she explained:

PID9: *"I said "[daughter], I'm sorry, being on my own", (it's been) 11 years since my husband died, "if I haven't got my cigarettes I might as well just pack up." **Pack up?** Pack up life … I've always got something I'm doing, and if they were going to make me sit here and do nothing then I didn't see any reason for me to live. And those were the doubts … I took the chance … Yes I was lucky, yes it was caught in time, but I don't want to live another 20 years. At least I know I'm still driving and I'm still able to work."*

In summary, all but one of the smokers at diagnosis reported that they wished that they were not smoking, or were glad that they had managed to quit. There was evidence that many who continued to smoke felt guilty about their smoking. For those who had managed to quit, they were often regretful that they had not managed to quit earlier. Some participants were resolute in a desire to not smoke and these were more likely to be abstinent. However, the majority also expressed a range of conflicting desires and beliefs that supported continued smoking (see table 3.15).

3.5.2.2 Main topic 2, theme 2: reasons for relapse to smoking after discharge

Most smokers at diagnosis found it easy to be abstinent whilst an inpatient, and stated that they had not thought about smoking or that they had felt too ill to smoke whilst in hospital and it was when they got home that the cravings had returned. An exception to this was PID21, a smoker of 40 cigarettes per day. Although using nicotine replacement patches, she had found it difficult to be abstinent in hospital, and had found herself reaching out for a cigarette packet on the bedside table out of habit.

Four participants (PID3, PID13, PID16, PID23) who had been abstinent since diagnosis or admission for surgery, and one participant (PID4) who had been abstinent for two months prior to diagnosis, relapsed to smoking after trying to remain abstinent when discharged home. For each of these participants, relapse occurred within the first three months after discharge. Three described just smoking one cigarette, or a reduced number, but then relapsing back to smoking

regularly as they had done before surgery. Four out of five explained that they had returned to smoking to help them cope psychologically. For instance, PID4 and PID13 lived on their own and were both too unwell to live active lives. Both explained that smoking helped to relieve the boredom of sitting at home alone. PID4 *(THORACOTMY, WEDGE RESECTION, 12MPS)*, in particular, had received many visits from friends and family after she was discharged home, but explained how after a while the visits became less frequent and she was left on her own:

PID4: *"You get the fuss when you first come out, everybody's knocking the door, people come to see you, you have visitors every night, so many every day and then it all wears off and you're left suddenly on your own . . . two, three days sometimes you won't see anybody and I think that's why. I started off with 10 and I ended up now since last year going up to 40. . . don't forget I wasn't able to do anything, much cleaning or anything because I was too weak . . . I was too tired so I was just lying about most times. You know, you can't watch the telly 24/7 . . . so that was the reason why I think I started to smoke again, boredom. Just boredom."*

PID3 *(THORACOTMY, WEDGE RESECTION, 10MPS)* explained how stress related to ongoing health care needs *"built up"* over time and he found himself wanting to smoke:

PID3: *"Something made me start worrying I think . . . it just started building up, having to ring for ambulances to get to the hospital for blood and this that and the other. And it more or less got on top of me an all. I've got to have a cigarette, so I did. I had one and then of course the craving came back 3 o'clock in the morning, I've got to have a fag. I need a fag. But you don't give in. Same first thing in the morning. Got to have a fag. But the craving's there all the time . . . "*

After first of all resisting the urges to smoke, PID3 relapsed to smoking 20 cigarettes per day. PID16 *(THORACOTMY, LOBECTOMY, 5MPS)* explained how family related stress, and in particular the death of her father, had made it difficult for her to cope and although she felt she had done well in maintaining abstinence during her surgery and chemotherapy, she had relapsed back

to smoking *"the odd cigarette"* a day by the time of interview. Finally, PID23 *(THORACOTMY, WEDGE RESECTION, 3MPS)*, unlike the other participants, stated that stress was not the reason that he returned to smoking, but he became vulnerable to relapse when he started feeling well again:

PID23: *"When I did stop smoking I felt marvellous, because I did stop for about three weeks, not long, but I felt so good. "Well one won't hurt" because I felt so well ... it's when I feel well, that's my danger time. I mean it's not when I'm stressed ... It's when I feel good I think."*

In summary, despite finding it easy to remain abstinent whilst in hospital, and a resolve to remain abstinent after discharge, many smokers who quit subsequently relapsed. The most vulnerable time for relapse appeared to be within the first three months after discharge. There was evidence that the challenges of being alone and psychological factors played a major role in the reason for relapse. In total, four categories of reasons for relapse and benefits for continued smoking cited by participants were noted that supported continued smoking behaviour.

Table 3.15: Participant held beliefs and challenges that support continued smoking behaviour

Category	Explanation
Lack of will power	Unable to overcome the drive to smoke.
Pleasurable	Described as "an old friend", "like seventh heaven", "if I can't smoke there is no pleasure in life."
Maintenance of mood	Encourages feelings of happiness, helps to cope with acute anxiety, helps overcome boredom/loneliness.
Health concerns	Fear of health consequence of quitting, including stroke, weight gain. Smoking helps to clear airways of mucus.

3.5.2.3 Main topic 2, theme 3: views about NHS intervention for smoking cessation

Many participants stated that throughout their cancer care they had not been asked their smoking status. However, without exception, all participants felt that it was the responsibility of the clinical staff involved in their cancer care to discuss smoking with them. Despite feeling this

way, for those who were asked about smoking, some explained that it had made them feel uncomfortable. One participant *(PID4 - relapsed)* reported not telling the truth when asked by her GP if she was smoking in a consultation after she was discharged from hospital. Her records showed that she was a non-smoker and she admitted that it had taken her about 12 months to *"confess"* to having relapsed. She explained:

PID4: *"It's hard because (my GP has) been very good with me. You feel like you're wasting their time, you feel guilty but she was great with me and she ... asked me what I wanted to go on."*

Despite the possibility of feeling uncomfortable, participants reported that being asked about smoking was not offensive to them. For example PID5 *(continued)* stated:

PID5: *"Whether it was size, whether it was brand, whether it is the count, it wouldn't offend me."*

PID9 *(continued)* and PID21 *(continued)* both expressed the view that although it was acceptable for a doctor to ask about smoking, the way in which it was approached was important. PID21 stated that she did not mind being asked about her smoking but she continued to explain that her ex-partner had nagged her and she had found that irritating. She emphasised the importance of a health professional showing understanding of how difficult it is to quit. A number of clinical staff had asked PID9 about her smoking, and the majority had been sympathetic and given her a choice which she felt was the right approach. However, she was told by one member of staff that if she did not stop smoking then the surgeon would not operate on her. She felt that this was unjust given that she was a law abiding citizen who had paid her taxes, and it made her feel angry. She later explained that she did believe that it was the place of the doctor to ask their patients about smoking, but felt that they shouldn't *"hold it over (your) head."* She added

PID9: *"I think that they should know because, yes they are going to take the risk of the anaesthetic and the operation and I don't hide it ... I know that I shouldn't do it but I can't give it up but why should they hold it over my head? And I think it's so unfair and they turn around to me and say you're fit and healthy ... but because you smoke we're not going to operate on you. Hello."*

Five participants that were current smokers at diagnosis (PID3*(relapsed)*, PID4 *(relapsed)*, PID5 *(continued)* , PID21 *(continued)*, PID26 *(continued)*) described being offered stop smoking support. Three (PID4, PID5, PID21) were offered help by their GP in a consultation after discharge. PID26 was offered referral to the local stop smoking service as part of his participating in the ROC programme, although he declined the offer. PID3 was admitted to hospital one week before surgery to undergo respiratory conditioning in preparation for surgery and during that time he was prescribed patches to help him maintain abstinence. However, no follow up smoking cessation care was arranged after discharge. The remaining participants (6/11) that were smokers at diagnosis were not offered help either during their cancer treatment or by their GP. Most participants specifically indicated that it would not offend them to be offered the help, even if they thought that it would not work for them or that they did not need the extra support. For example, PID5 *(continued)* expressed the feeling that maybe it was *"too late in the day"* for him to try and quit but stated he would not mind being asked if he wanted help. PID26 *(continued)* explained that although he thought treatment would not be helpful to him, he understood that it might be useful to other people:

PID26: *"I don't mind being offered that sort of help because it might be the right thing for the next person and nobody knows until the help is offered, so I could quite understand why I was offered the help but it just didn't work."*

Others indicated that not only would they not be offended, they felt it was important and necessary. PID4 explained:

PID4: *"The way I look at it is that you do need help, you do need someone to stop you from doing it really but I mean it's easier said than done … It was about 3 months after (surgery) I started to smoke (again) … It would have been nice to have been able to contact someone you know. They may have been able to talk me through or come out and give you patches at the time cause, don't forget I couldn't get to the doctors because I was too ill, I couldn't do anything really for myself them early days. So it would have been nice for them to say well, we'll send … the district nurse round with some patches … but no, you just had to do it on your own didn't you."*

As with being asked smoking status, participants commonly underlined the importance of an understanding approach by health practitioners offering smoking cessation help. In addition, there was evidence that feelings of guilt and shame could act as a barrier to participants telling their doctor that they had relapsed after a quit attempt. For example, PID23 *(relapsed)* explained that he felt uncomfortable returning to his GP to ask for help for additional support after a relapse:

PID23: *"And I didn't have the nerve to ask her again because I felt so, like a failure. So I wouldn't ask her again, because … I am conscientious … I really do not want to waste her time. But I would like to stop. Yes, I would like to stop smoking."*

All participants felt that smoking should be addressed as soon as possible within the cancer care pathway. For example, PID3 felt that patients should be given help a month before surgery to give enough time for cutting down. PID4 felt that offering of smoking cessation support should be considered as *"part and parcel"* in the diagnostic consultation. She further highlighted the importance of intervention at the bedside. She explained:

PID4: *"I reckon it should be done there at the bedside. Not wait for the office after you've been discharged. I think it should start being drummed into the patients there and then who are smokers… if you're smoking … we can help you with it and things like that. I think straight, at the bed, you know as soon as they are well enough to take it … on board … You know the seriousness of it and everything else."*

Other participants explained that it was important for support to continue after discharge:

PID16: *"Obviously you're not smoking in hospital and from the point of that, which you've done so well, it should continue, so straight away after you've come out of hospital. I mean if you've managed to do it for that long, that's probably what you need [pause 1 sec] . . . to inspire you to carry on. So straight away."*

PID23: *"You're on a very tender hook when you stop smoking. And you can go either way at any time. But I wasn't craving for cigarettes, in the hospital, (it was) when I came out."*

In summary, regardless of smoking status (ex-smoker or current smoker at diagnosis) participants were open to discussing their smoking status and being offered help to quit smoking where appropriate. Universally, participants accepted that it was the place of health professionals to discuss smoking with them, although some acknowledged the importance of health professionals adopting an understanding and approachable attitude. There was some evidence that participants felt 'like a failure' if they had returned to smoking and that this could act as a barrier to them reporting their true smoking status or pro-actively seeking help. Participants highlighted the importance of smoking cessation support as soon as possible, and that continued support after discharge was vital.

3.6 Main topic 3: attitudes towards recovery, supportive care and rehabilitation programme design from the perspective of participants receiving standard care

The previous sections have explored in detail the nature of specific health challenges that participants faced during the first year after surgery, and the attitudes of participants with a smoking

history towards smoking, smoking cessation and NHS stop smoking support. This section explores the attitudes of participants who had received standard care ($n = 18$) towards their recovery after surgery, focusing on the way in which participants evaluated their recovery in general rather than the specific challenges that they faced. In addition, attitudes of participants towards the level of supportive care that they had received after surgery and their opinions about the optimum content/format of a rehabilitation programme are presented. There was a clear divide in attitudes between participants who had undergone VATS compared to those who had undergone thoracotomy. Therefore, the findings are considered separately by primary procedure sub-group.

3.6.1 Main topic 3, theme 1: satisfaction with recovery

3.6.1.1 VATS

All participants who had undergone VATS described being highly satisfied with the surgical procedure, and also with their recovery. Often participants indicated that they were surprised at how little an impact the surgery had made and the speed at which they had recovered. For instance, HTO1 *(BT=mild, PT=mild)* explained how all the way through his cancer journey *"health wise (he) felt fine"*. He explained:

HTO1: *"Nothing's changed really ... I feel absolutely fine. (I feel) so, so lucky, I really do ... I tell everybody I feel so lucky, I do honestly."*

HTO2 *(BT=mild, PT=moderate)* added:

HTO2: *"I'm thankful that they have done it. Honest to God, I feel really healthy."*

When asked how she felt physically after being discharged from hospital, PID9 *(BT=none, PT=none)* responded:

PID9: *"How was I? Oh I just got back to work and drove my car and everything..."*

Some participants acknowledged that they had felt nervous about undergoing surgery but, after describing how little it had impacted their health and functioning, stated that it was nothing to be worried about. HTO2 *(BT=mild, PT=moderate)* added that she *"would never be afraid of it again"*. Most participants explained how family and friends 'could not believe' how quickly they had recovered. In addition some participants described how their GP or other health professionals involved in their cancer care remarked on how quickly they had recovered. All participants who had undergone VATS described being fully recovered within 3 months of surgery, and HTO2 *(BT=mild, PT=moderate)* and HTO3 *(BT=mild, PT=mild)* described feeling better than before they had undergone surgery. Despite being almost back to normal, at interview HTO2 continued to experience occasional shooting pains and PID9 experienced tiredness (see section 3.4.2 and 3.4.3). However, neither of these participants reported feeling distressed by these experiences and they were satisfied with their recovery.

3.6.1.2 Thoracotomy

Like those who had undergone VATS, a minority of participants who had undergone thoracotomy indicated that the surgery had not affected them greatly. For instance, when asked how he was feeling after his surgery, PID5 *(BT=mild, PT=absent)* denied experiencing any effects from the surgery:

PID5: *"(I was) alright. Memory good, hearing good, eyesight good. Didn't affect any other parts of my body like, as I know of."*

He repeated many times through the interview that the health professionals involved in his care were *"nice people"* and that they had *"done a good job"*. Although it was explained to him that it would be normal to feel some effects from surgery, and that this would not be taken as a bad reflection on those involved in his care, he maintained that the surgery had not affected

him. On probing, he did admitted that sometimes he felt breathless. However, he also stated that he could *"still run like a rabbit"*.

PID12 *(BT=moderate, PT=moderate)* had not lived an active life before surgery due to a co-morbid heart condition, and described feeling philosophical that for the past few years he had *"not (been) able to do the things (he) used to do"* and he was satisfied with his recovery. Despite reporting some pain and breathlessness over the first 4-5 months after discharge, his main concern was the effect of his diagnosis on the price of holiday insurance. He reported that on a visit to his GP three weeks after his surgery, his doctor remarked *"well I never would have thought you'd just had a serious operation"*. Five months after surgery, PID12 added:

PID12: *"I could feel myself getting better all the while ... my breathing and everything, it's just stabilised now like ... everything seems alright, I'm not worried about anything, I weren't worried about anything before, it's just one of them things."*

In contrast, all other participants who had undergone thoracotomy and received standard care (PID1, PID3, PID4, PID6, PID10, PID11, PID13, PID14, PID16, PID20, PID21) described a difficult and protracted recovery period, and were not back to normal by the time of interview . Many of these participants had described feeling emotional distress regarding the health challenges that they had experienced (see section 3.4). Some specifically stated that they were dissatisfied with the level and speed of their recovery. For example, PID14 *(BT=moderate, PT=moderate)* had been left with moderate breathlessness, low level of pain, had experienced loss of appetite, significant weight loss and also disturbed sleep after surgery. He was the eldest participant, at 82 years of age, and he reported having decided not to leave the house for the foreseeable future after a negative experience. He explained:

PID14: *"I'd much rather go back to what it was like before the operation, but ... [doctor 1] did apologise to me when I went. He said "I'm very, very sorry I've got you in this state, as you're in now" he says "but I had to make a decision and" he says "I think I've took the right decision." ... [pause 1 sec] it isn't his fault ... but as I say, I'd much rather go back to what I was before."*

PID10 *(BT=moderate, PT=severe)* was the youngest participant, at 39 years of age. Although she had returned to work, seven months after surgery she reported that she was not back to normal and that she had struggled both mentally and physically during her recovery. She explained:

PID10: *"I just wanted to get back to normal and I'm always struggling to try and get back to normal and then you push yourself too far and I feel myself flying backwards . . . I feel a little bit angry that I can't get back to normal. I realise that I'm probably not going to be the same again, I'm not going to be able to do as much as I wanted to . . . I felt really disabled . . . and I rushed to get back to work to avoid that. I went back . . . too quickly and so I've been steadily using up annual leave ever since."*

For some participants, health challenges resulting from surgery were compounded by side effects of chemotherapy and/or radiotherapy. For example, PID4 had undergone surgery and adjuvant radiotherapy. She described experiencing breathlessness, aching bones, sleep disturbance and weight loss that were still present 12 months after her surgery. She explained that after evaluating what had happened to her, she had told her son *"I don't think I can go through it again"*, referring to the possibility of the cancer recurring. She added:

PID4: *"Oh yeah it certainly knocked the socks off me, I mean I'm not the same person I was over 12 months ago you know what I mean. No way."*

3.6.2 Main topic 3, theme 2: attitudes towards supportive care received

3.6.2.1 VATS

All participants that had undergone VATS and received standard care were highly satisfied with the level of care and felt that they did not need additional support after discharge to aid their recovery. For instance, HTO2 *(BT=mild, PT=moderate)* explained that she had been able to do exercises by herself and felt fitter than she had for many years. PID31 *(BT=absent, PT=mild)*

reported that he felt *"as if (he) could pick up the phone and talk to a face (he) knew"*. However, he had never needed to do that during his recovery. In addition, participants who had undergone VATS felt they had been fully informed about the nature of their surgery. They expressed no concerns regarding a mismatch between information or explanations they received prior to surgery to their actual experience of surgery and recovery. Interestingly, although they had been informed, two participants explained that they had not really understood what was going to happen during the procedure. However, they were not concerned about this. In particular, HTO1 explained that although the consultant had *"tried his best"* to explain what was going to happen, he had not been able to process the information. He explained:

HTO1: *"I think your mind is in such turmoil, you don't take it in . . . nothing registers. He was excellent really, smashing guy, and he explained in detail what was going to happen, but it never registered."*

3.6.2.2 Thoracotomy

When asked if they felt that they had needed more support after discharge, some participants (PID1, PID5, PID12, PID14) who had undergone thoracotomy took a similar view, reporting that they were able to manage their own recovery. They expressed the opinion that the information about breathing exercises that they were given on discharge by physiotherapists, and follow up phone call(s) from a lung CNS were sufficient for their needs. Interestingly, although two of the participants expressing this view had described a relatively easy recovery (PID5 and PID12), two participants (PID1, PID14) described difficulty during recovery, but maintained that they preferred to manage things on their own. PID1 *(BT=moderate, PT=moderate)* explained:

PID1: *"I would rather do it on my own . . . I don't need anyone to motivate me. I can do it myself."*

PID14 *(BT=moderate, PT=moderate)* praised the hospital team that had cared for him and explained

that they had been *"very helpful"*. He added:

PID14: *"We do have (neighbour) comes, to check if we want anything, which we don't. We don't want anything really."*

However, the majority of participants that had undergone thoracotomy and received standard care expressed the view that additional support after being discharged from hospital was needed. Some described feeling abandoned on discharge, that they were left to recover from major surgery without the knowledge and support that they had needed. Some indicated this by stating that they felt they had been discharged too soon. When probed as to why they felt this, they all described feeling too ill to cope when leaving hospital. PID3 explained:

PID3: *"Anyway they decided to send me home and they didn't give me a thing. Because they were talking about oxygen and this thing and the other and they sent me out with a few tablets. And I think they sent me home far too early.* ***What made you feel like that?*** *Well the way I was. I was still struggling to walk. I couldn't really climb a flight of stairs . . . I felt so vulnerable . . . I couldn't cope."*

Although PID3 and his wife reported that contact with the lung CNS had been very valuable, they felt that contact was removed too soon. His wife stated that she *"felt like (her) right hand had been cut off when (she) lost her"* support, and at one point she reported that she got to the stage where she did not feel she could cope supporting her husband on her own.

PID6 expressed her surprise at being sent home seven days after surgery as she thought she *"should have been in longer"*. She was worried that she would be too ill to manage at home, and she did in fact find it difficult to cope. She explained that for the first few days she had not been able to climb the stairs to get to the bathroom in order to have a shower. She further added:

PID6: *"I thought perhaps I would have a nurse come in when I come out for a while but no there's nothing afterwards . . . I mean I had a phone number that I could have rung the ward if I'd needed it, obviously I could have rung my doctor but I just thought perhaps a nurse would have come and checked me over or something, you know, after having major surgery. That's the only thing."*

PID20 reported that although he had wanted to come home from hospital, he didn't feel ready when he was discharged and he also felt that he had been *"sent (home) a little bit too early"* and that he *"didn't have enough backing"*. He further explained:

PID20: *"I . . . never had no contact with anyone from the . . . hospital since I came out, I got macmillan nurses round me when I was there and once I'd left the hospital, I never had another contact at all. As regards assistance or helping . . . I still think . . . there should be more aftercare, or assistance . . . (the) way they just threw me out and then nothing, no anyone . . . after that."*

When probed about the specific type of assistance, PID20 explained that he needed both help to improve his breathing but also equipment such as cushions and padding to prevent bed sores and a wheelchair. Due to severe breathlessness he was largely housebound and immobile at the time of interview, but he reported that *"nobody wanted to know"* and that he would have to fund or organise these things himself. He had consulted with his GP who was sympathetic to his situation, but was not proactive in organising care. He explained:

PID20: *"I've seen my doctor, she seems to think I should have, pulmonary therapy is it? . . . and the next appointment I've got with the surgeon, which is probably in a couple of months time, she asked me to mention it to him if I could get any assistance in that way . . . what you want is a normal breath . . . that's what I was looking for . . . so I was wondering whether there's anybody that's capable of giving advice on that."*

PID10 *(BT=moderate, PT=severe)*, who had struggled with both breathlessness, pain and fatigue until the time of her interview, acknowledged that breathing exercises given by physiotherapists

and contact with the lung specialist nurse had both been helpful but explained that it had not provided enough support. She also remarked on how there had been no contact with anybody once the follow up phone calls had stopped, until she went back to clinic. She stated:

PID10: *"I'd gone home ... the lung specialist nurse (called), but that was it. That was all the after care and I just think that for something so big that it would be good to have a little more. I'm not saying you should have, it's the NHS, it's limited you know, it's not your right to have everything laid at your feet but it would be nice ... I think everybody has the right to know as well ... I just think it would be good if people were able to prepare themselves."*

Finally, PID16 *(BT=moderate, PT=moderate)* stated that she *"thought there was a real blip in the follow-up from surgery"*, and that she *"felt as if (she) had the surgery and then there was nothing ... no after care"*. She explained:

PID16: *"I felt a bit on my own for a while. Then I decided to go to my GP because I was still in a lot of pain and (then) it was down to the GP to follow-up my care."*

However, although she had accessed support from her GP to help with pain, she still felt that more support was needed, particularly emotional support. She added:

PID16: *"I think that cancer, I think there needs to be a follow-up service because the cancer just doesn't stop ... does it? ... it's not like ... having your tonsils out and that's it, that's the end of it. In cancer, it's very emotional and there is a lot that falls out of it ... I think once you've had it, it's there for life. And it becomes part of your life."*

PID1, PID10, PID11, PID16, PID20 and PID21 all emphasised during interview that they did not feel fully informed or prepared for the impact that surgery would have on them, or the length of time it would take to recover. For example, PID1 *(BT= moderate, PT=severe)* had experienced enduring breathlessness after surgery. He reported that health professionals involved in his care

had said *"as time goes on and the more exercise you do, your lungs will get stronger"* and *"you will get over it"*. Although he did report that his breathlessness improved, eleven months after surgery he protested that it was not true that he had 'got over it'. He explained:

PID1: *"He [a health professional] said ... "it will take time obviously ... but you will get over it". I can't, I can't, because I was in the industrial cleaning, that was my job, and there's no way I can do industrial cleaning (now)."*

PID10 *(BT=moderate, PT=severe)* explained that she had underestimated the impact that the surgery would have and that it was a *"nasty operation"*. She felt that she had underestimated the impact because she had not received accurate information from those involved in her care. She explained:

PID10: *"Instead of using the word pain, I think they used the word discomfort too much. To me discomfort is period pain ... or a migraine ... this isn't discomfort, it was horrendous, honestly, it was awful pain and ... I do think there is more that can be done to prepare people for it ... I never knew how bad it was. I just thought they would get through that hole, I didn't realise how ... obviously, you know it's going to be invasive but I didn't realise how much, it was quite barbaric ... I thought I would be back to normal in about 3 months. And I wasn't ... "*

In addition, PID10 explained that she had imagined waking up after the surgery lying in bed with small nasal tubes inserted. However, instead she described feeling *"intimidated (by) the amount of equipment (she'd) got going on around (her)"*. She explained:

PID10: *"I had ... a thermal blanket underneath, these boots on my feet to keep my feet warm and probes on my feet, drains coming off ... bigger than I imagined. It wasn't (how I imagined). It was a lot different to that."*

In summary, there was a stark difference between the attitudes of participants who had undergone a VATS procedure and the majority of those who had undergone thoracotomy. Although,

similar to all those who had undergone VATS, a few participants who had undergone thoracotomy did not see a need for additional follow up care, or felt that they would prefer to manage their recovery alone, most reported that the level of standard care was not sufficient for their needs. Many reported feeling under prepared for what to expect or how to manage their recovery. Many used language that suggested that they felt abandoned after discharge, and that they felt vulnerable. In particular, participants highlighted that they had struggled with day to day living immediately after discharge and would have found a home visit from a nurse helpful. There was also an indication that, for those most severely affected, participants would have also benefited from an occupational health assessment and access to mobility aids. Participants also indicated that they felt they needed help to manage specific symptoms, such as breathlessness and pain. Although some felt strongly that more help should be available, many participants also added the caveat that the health professionals involved in their care had 'done a good job' and expressed the attitude that they did not feel they could demand entitlement to care. Although some participants indicated that they were aware that they could approach their GP, or phone the hospital, there was evidence of reticence to do this. Those who did approach their GP indicated that their needs were still not completely met.

3.6.3 Main topic 3, theme 3: preferences for the content and format of a tailored rehabilitation programme

In general, although participants clearly articulated health difficulties that they had faced during their recovery and many participants felt that they had needed more information and additional care, most found it somewhat difficult to formulate and express preferences for the design of a tailored rehabilitation programme. For instance, a few participants did not answer the question when asked to specify their service preferences in order for their needs to be addressed. Instead, they responded tangentially, continued to explain the difficulties that they had faced or said that they did not know. When given examples of what a rehabilitation programme may contain and asked if they thought that would be beneficial they responded by saying 'probably yes',

'maybe', 'makes sense' or 'I'm sure that would help'. Therefore, it was not clear if they were agreeing because they believed it would be helpful or whether their answers were influenced by social acceptability bias. PID11 *(BT=moderate, PT=mild)* was forthright in answering that it was not his place to comment on somebody else's job, and that *"they are the experts"*. He further added that if somebody had told him how to do his job, he would have told them to [go away]. He said that he would not know what would help until he tried it. Despite it being made clear that any thoughts shared on how services could improve would not be regarded as a criticism, when asked how things could be improved participants often stated that the team in charge of their care had done their best.

However, some participants (only those who had undergone thoracotomy) did discuss specific content preferences for a tailored rehabilitation programme. Some expressed preference for structured and supervised exercise. For example, PID4 *(BTmoderate, PT=severe)* explained:

PID4: *"**Do you think you would have found it helpful to have someone help you to get back onto your feet again?** Well it would have been nice, you know, even if you went to a day centre for a day and did a bit of exercise... even to be able to go use their machines, one day a week even... things like (exercise bikes) or for them to give us gentle exercises."*

PID10 *(BT=moderate, PT=severe)* also felt that supervised exercise would have been helpful to her. Although she attended the gym and had a personal trainer before she was diagnosed with lung cancer, she felt that she now needed specialist support from a health professional who understood the consequences of thoracic surgery:

PID10: *"Some kind of rehabilitation, to be in a controlled place, to have somebody who knows what they are doing to say, "you can do this", "push this", "do that" … "this is what you are able to do" and perhaps some real physio … I don't know what I'm capable of and I don't know what muscles are what and how I … need to work on them to get some strength back and mobility in my sides."*

PID20 *(BT=severe, PT=none)* felt that it would have been useful to have additional support to improve his breathing:

PID20: *"Well, somebody probably got some idea, of how I could best . . . breathe, to get . . . the air where it should be going."*

Some participants felt that emotional support had been lacking in their care and would have been a helpful addition. PID10 *(BT=moderate, PT=severe)* explained:

PID10: *"I've got a good group of girls but you don't want to share . . . {it's} too deep I think to share with other people and {it's} too frightening and I think... if you could talk to someone who was not emotionally involved or you could have someone to just listen to you that would be good."*

and PID16 *(BT=moderate, PT=moderate)* added:

PID16: *"I think there should be some follow up care . . . somewhere to go to talk if you got problems or just somebody to say you're doing fine. Because you don't know, do you? . . . you're just left on your own."*

Some participants expressed a preference for more accurate information regarding how they would be affected by surgery and a realistic picture of the length of recovery. PID4 felt that she had asked questions but she stated that she would *"have liked more answers"*. PID10 *(BT=moderate, PT=severe)* added:

PID10: *"I think for me. . . it's the not being as prepared as I could have been perhaps for how big it was and have realistic expectations for getting back to normal and the time it took to get better . . . I suppose it would be nice to sort of be a bit more prepared and know how to deal with it."*

Although many participants had also been in pain, and some had experienced appetite and weight loss, none suggested incorporating pain or dietetic review/management into a rehabili-

tation programme.

All participants who expressed an opinion felt that the start of a rehabilitation programme would need to be delayed after surgery as they would not feel well enough to participate straight away, or to give time for the wound to heal. The length of delay stated by participants was normally between 1-2 months. However, one participant *(PID4 - BT=moderate, PT=severe)* said that she would not have felt well enough to participate in a rehabilitation programme for the first year after her surgery. In addition to not feeling well enough, PID10 *(BT=moderate, PT=severe)* explained that immediately after surgery it would be difficult to focus on a rehabilitation programme. She added:

PID10: *"I don't think it would sink in. Everything is still for me ... full of "oh my god, it's done, it's done, I'm over", do my breathing exercises, take my pain killers that was it and I think that was probably for the first month and I think probably from then. It's to get over the shock of the operation, is a big one."*

However, when talking specifically about the timing of support for smoking cessation, all who smoked at diagnosis stated this help should be given straight away, with one participant advocating it to be 'part and parcel' of the diagnostic consultation, and others emphasising the benefits of having support to reduce or quit before surgery and of continued support after discharge (see section 3.5.2.1).

When asked whether they would prefer a rehabilitation programme to take place at either the hospital or locally, participants opted for the hospital. However, the reason for this was that they felt it was important to have access to health professionals who knew about their care so far. For instance, PID11 *(BT=moderate, PT=mild)* explained:

PID11: *"I think the hospital would be better (to host rehab programme) because they know a lot more. Your dates, all your records and everything."*

PID20 *(BT=severe, PT=none)* also expressed a preference for having continued access to help from

health professionals that had been involved in his care. When asked how additional help could best be given he explained:

PID20: *"Well ... just somebody to keep in touch with you. Somebody from [hospital 1] basically ... involved in the operation. Knows the score, what's going to happen, to just keep in touch and ask you how's it going and if you want ... well anything in general really to try and help you out, that's all."*

Finally, there was a mixture of responses to preferences for group rehabilitation or individual contact. Some participants did not express greater preference for one format over the other. Where participants did express a preference, most favoured individual contact stating that groups 'were not their thing' or that they would not feel comfortable in a group setting. This was particularly true for smoking cessation support. However, one participant *(PID10 - BT=moderate, PT=severe)* did express preference for rehabilitation to be delivered in a group setting, as she would value the opportunity to learn and draw comfort from people in a similar situation. She stated that it would help her feel less abnormal. PID10 was the youngest interviewee at 39 years of age, significantly younger than the average age at which patients are diagnosed with lung cancer. Despite the probability of a large age gap, she still felt that group sessions would be preferable. She explained:

PID10: *"I probably would feel a little bit different ... but even listening to someone else, it doesn't matter if they are 15 years older than me or whatever. If they were saying I had this, did you have that? And knowing that someone else gets the same no matter how old you are (is helpful)."*

In summary, most participants were unable to offer specific preferences for the content and format of a tailored rehabilitation programme. However, some participants did express specific preferences and these are summarised in table 3.16.

Table 3.16: Preferences regarding content and format of a future rehabilitation intervention from participants who had received standard care

Content	(1) Exercises to improve lung and general strength (2) Emotional/psychological support (3) Information regarding surgery and recovery (4) Smoking cessation support (5) Support on discharge from community nurse (6) Occupational health assessment and access to mobility aids
Delivered by	Health professionals who know about previous care and are able to answer questions specific to the impact of lung surgery
Timing	Start 1-2 months after surgery
Group or individual	Both equally acceptable

3.7 Main topic 4: attitudes towards recovery, supportive care and rehabilitation programme design from the perspective of participants enrolled in the ROC programme

Eleven of the 29 participants interviewed had taken part in a rehabilitation programme that was being piloted at Birmingham Heartlands Hospital (BHH) and Worcester Royal Infirmary (WRI). For full details of the ROC programme content see section 2.3.4.1. This programme contained many elements that participants who had received standard care identified as being important to met their needs (see table 3.16), and provides the opportunity to explore participants' assessment of and attitudes towards receiving such an intervention.

Participants attended an average of two pre- and four post-surgery sessions and, on average, returned for their post-surgery sessions four weeks after discharge. One participant had undergone VATS (and also had been diagnosed with COPD four years previously) and the remaining participants had undergone thoracotomy. No participants had been referred for smoking cessation or dietary support, although one participant was offered a referral to the stop smoking

service and declined.

3.7.1 Main topic 4, theme 1 and 2: satisfaction with recovery and attitudes towards supportive care received

All participants enrolled in the ROC programme spoke about the programme with enthusiasm and felt that it had been worthwhile. They stated that it was a *"very good programme"*, *"the exercises were great"*, *"the physiotherapy was great"*, *"it certainly had the effect of helping"* or *"it really helped"*. For example, PID29 *(BT=moderate, PT=moderate)* added:

PID29: *"The rehabilitation programme is one of the best things going, to be honest, as long as there is money around for those sort of things, I think then that's fantastic."*

In addition, when asked to describe the worst aspects of the ROC programme sessions, PID26 *(BT=mild, PT=moderate)* responded:

PID26: *"I can't really say there was a worst thing about them, because as I say, I quite enjoyed them"*

Although the exercise sessions were run in a group, participants followed a set exercise programme on an individual basis and were also given one-to-one support when requested within the session. Commonly, participants commented on how they were 'able to go at their own pace', and that they highly valued this approach as it made the programme enjoyable. Some participants remarked that it was 'unlike school', and that they felt that they were treated like adults. PID15 *(BT=moderate, PT=none)* explained:

PID15: *"As regards to the exercise and what have you, they don't pressure you to do it. They ask you to do it. And if you don't want to do it, you don't do it."*

HTO3 *(BT=mild, PT=mild)* explained that she had found an exercise particularly painful around

the surgical scar, and had talked to the physiotherapist to find out how she should proceed. She reported that the physiotherapist demonstrated a different exercise which might be less painful but advised her to *"take it easy and if it still hurts, don't do it"*. HTO3 explained that she found this very comforting and added *"so yes they don't push you to do things that are painful"*.

In contrast to participants that had received standard care, participants also spoke positively about their recovery, and were generally satisfied with the progress they were experiencing. They mainly attributed this to participation in the programme, and in particular described physical, motivational, informational and emotional benefits to participation. Participants most readily attributed these benefits to the exercise classes, rather than the group educational sessions or extra contact from a lung CNS/physiotherapists. However, there was evidence that both the exercise and educational/support elements of the rehabilitation sessions had been beneficial from the point of view of participants.

Physical Most participants reported that they believed the exercise programme had made them feel generally fitter and had strengthened their lungs. HTO3 *(BT=mild, PT=mild)*, a COPD sufferer, added that she had noticed that she was becoming less breathless when engaging in activities:

HTO3: *"... My breathing is probably better than it has been for a long time so that definitely helps and I would recommend that to anyone ... I can get up the stairs a lot better now. Before the operation I would be puffing and panting when I got to the top of the stairs. Now I can go up and down with no problems. I can walk a better distance on a flat not too good on hills still but I can walk on the flat ok. It's just general breathing is much better.* ***Since the operation?*** *Yes and since the physio as well."*

As well as improving health and levels of breathlessness, some participants reported that they used the techniques that they had learned during the educational sessions to deal with acute episodes of breathlessness whilst at home, and also to help with chest clearance. For example, PID25 *(BT=moderate, PT=moderate)* explained:

PID25: *"Since I've (participated in the ROC programme), I can breathe better, and phlegm, I can get that out easier."*

Motivational Participants commonly expressed the view that attending the programme had increased their motivation to work on their recovery, with participants often continuing to exercise at home. PID25 *(BT=moderate, PT=moderate)* explained that he had found the sessions motivational and that *"they made you want to get back on your feet"*. PID17 *(BT=moderate, PT=mild)* described how the ROC programme had *"encouraged (her) to get as fit as (she) could"* before her surgery. She had also decided to follow a walking regime at home after discharge, in addition to attending the rehabilitation exercise classes. She explained that during her walking regime she would deliberately get breathless as she had been instructed to do in the classes.

PID29 *(BT=moderate, PT=moderate)* explained that she would not have found the motivation to exercise during her recovery at home on her own. She admitted that:

PID29: *"If I'd have been sat down, ... doing nothing ... I think I would have given up, I would not have wanted to do anything, I would have found breathing even more difficult because I'm not getting up, and getting my lungs to even try and work to their full capacity."*

She felt that the classes gave her *"the incentive, it makes you do that one more little stand and sit or whatever it is that we are doing at the time"*.

Informational The majority of participants reported that they were happy with the information that they received with regards to the surgical procedure and its impact. For example, PID30 *(BT=moderate, PT=severe)* stated that one of the benefits of the ROC programme was that *"they could tell you what was going to happen"*. PID17 *(BT=moderate, PT=mild)* explained that the one hour one-to-one session with the physiotherapist before she had started the exercise sessions had *"allayed (her) fears"*, and that it had refreshed her memory of the anatomy of the lungs and put her surgery in context. She also reported that the physiotherapy sessions were an

ideal opportunity to ask questions, and she also found that comments made by the physiotherapists during the exercise sessions had helped her:

PID17: *"One physiotherapist said, "your lungs are big enough to fill this room. So the fact that . . . you're going to have a bit missing, it's neither here or there really. But your body's just got to mend from it." So, you know, there were lots of kind of, if you like, offhand comments that really help . . . when you do a job like that, you're so used to it, sometimes you don't realise, that a throw away remark really helps somebody."*

There was evidence that participants believed that they would not have been able to have facilitated their own recovery as well if they had not participated in the ROC programme. This was partly due to an increase in motivation, but also because of what they had learned during the programme. PID29 *(BT=moderate, PT=moderate)* found that as a result of what she had learned during the classes, she was building gentle exercises into her day:

PID29: *"At home here, I can sit here and watch TV and go like that [demonstrates shoulder rolls] and I'm exercising my shoulder blades, and I'm stretching my lungs. I wouldn't have thought of things like that, had I not gone to this, and been told about it. And just by standing up in the kitchen, washing up, marching on the spot, gets the blood pumping, keeps the legs going, that stops blood clots if you are sitting down quite a bit. It's all these things that I would never ever have taken into consideration."*

PID30 *(BT=moderate, PT=severe)* also explained:

PID30: *"You can carry on, on your own (at home)."* ***Do you think that would have been something that you would have done. . .*** *"Oh no, I wouldn't have even known what to do. No they teach you, if you listen, you learn."*

Although the majority of participants reported that they were satisfied with the level of information that they had received, one participant *(PID28 - BT=moderate, PT=severe)* indicated that she

was not satisfied. She reported that although she had been given an explanation of the surgical procedure and what to expect during recovery, she had not fully understood it. She reported feeling as though she was *"in the dark"* and that she had not *"quite realised what (she) would feel like afterwards"*. She further explained:

PID28: *"(it's) just the uncertainty and the not knowing, they give you this leaflet of what you can do over the four weeks and eight weeks and everything but, I mean I don't know what my GP must have thought but I think I've been to see her three times, because you panic. Because you don't know. Um, and you know, I go off and see her.* ***You don't know?*** *Whether it's normal to be sort of coughing and the pain and, but then I suppose they don't know either really do they? But you know, I mean she was always very nice, you know, "don't worry you can always come and see me". But, I think it's just the fear of the unknown. Um, you know, if you sort of wake up in the middle of the night and you can't breathe, you panic. You know, if they'd said before that this might happen, I think that may have helped, I don't know."*

Emotional Generally, participants reported that participating in the ROC programme had been a positive experience and had helped them to remain optimistic throughout their recovery. In addition, participants felt that the physical exercise had increased their confidence and information had addressed their fears. In particular, participants generally found it supportive to be part of a group with other patients who were 'in the same boat', especially as some were further on in the treatment pathway and could therefore provide insight on what they were about to go through. For instance, PID29 *(BT=moderate, PT=moderate)* explained:

PID29: *"It is absolutely fantastic that you can go to something, where there are other people exactly the same as you, we've all got breathing difficulties of different varying degrees."*

Some participants reported that they had received encouragement not only from the health professionals, but from other members of the group. PID17 *(BT=moderate, PT=mild)* explained:

PID17: *"It was actually being part of a group . . . and meeting other people . . . hearing, and noticing how people supported each other . . . that was really good."*

In addition, some participants reported that they found it somewhat comforting to compare themselves with others in the group. For instance, PID30 *(BT=moderate, PT=severe)* explained:

PID30: *"That lady's a lot older than you, there's one there 86, and look, "They've come through this". And its such a help. And this was before your op, so that was really nice. "Oh you'll be alright, look at me, I've had it." It's a good thing that is. You were able to talk to other patients, oh yes . . . we all spoke to each other, it was really nice, really nice."*

3.7.2 Main topic 4, theme 3: suggested changes to the design of the ROC programme

Similar to participants that had received standard care, participants found it difficult to make specific suggestions for changes necessary to improve tailoring of the ROC programme to their needs. However, four negative aspects associated with participation in the programme were reported. The first two were the additional cost of parking at the hospital and demand on time, which was a concern expressed by one participant *(PID15 - BT=moderate, PT=none)*. However, although there had been an additional cost, he felt that overall it was worth it. He explained:

PID15: *"Park the car and your time . . . it's a bit much but apart from that if I can get up, I don't care. I can do anything they've asked me to, simple as that. If I think it helps me, I'll do it."*

The third concern was expressed by two participants and related to the pre-surgery sessions. Both participants had felt well and not at all breathless before surgery, and so found it difficult to understand why it was necessary to attend the exercise classes in the run up to surgery. PID26

(BT=mild, PT=moderate) explained that he had *"felt a bit of a fraud"* and had felt *"embarrassed"* that he was able to walk at a fast pace during the six minute walk test, he was concerned that it gave the impression that he was *"showing off"*. PID28 *(BT=moderate, PT=severe)* explained that the pre-surgery exercise sessions had felt pointless, as at the time she had not fully realised how she would be affected by surgery. Related to this, PID28 went on to highlight the forth concern. She reported that sharing rehabilitation sessions with other participants with severe COPD had been disconcerting. She explained

PID28: *"The first time I went, I thought, you see these old peoples' homes on the television and these people sitting in chairs doing things, and I thought oh my goodness, is this what I've come to . . . I'm sure a lot of people there are far worse than me, they have oxygen cylinders and things. . . . I found that very difficult . . . because I thought oh gosh is that what I'm going to be like?"*

The ROC programme design features that participants valued and also expressed preferences for change are summarised in the table below.

Table 3.17: Participants preferences regarding the content and format of the ROC programme, including suggestions for change

Content	(1) Exercises to improve lung and general strength, deal with acute breathlessness, and aid chest clearance - Participants value following the programme on an individual basis giving them the flexibility to tailor the exercises to their ability and go at their own pace. They also valued being treated like an adult rather than feeling like they were back at school. (2) Information - Participants value having a greater understanding of the nature of the surgical procedure, what to expect/ how to deal with health challenges during recovery and to understand the boundary between 'normal' and indication of something wrong.
Delivered by	Health professionals who are able to answer questions specific to the impact of lung surgery.
Timing	Restart 1–2 months after surgery was acceptable to participants.
Group or individual	Support from group members who are in a similar position is valued by participants.
Potential challenges Suggestions for change	Some participants may find it difficult to travel to rehabilitation sessions due to ill health or lack of funds for travel/parking. Some participants may find it unsettling to be placed in a group with other patients who are seriously ill. Some participants may not understand why they are exercising before the surgery and need further explanation.

CHAPTER

FOUR

QUALITATIVE INTERVIEW: DISCUSSION AND CONCLUSIONS

This chapter is split into three main sections. In the first section (section 4.1) the findings regarding the four study aims/main topics are crystallised, integrated and interpreted in light of findings from previously reported studies. This section ends with the design features of a tailored rehabilitation programme that were identified as important, based on participants' expressed needs and preferences. The second section (section 4.2) considers the strengths and weakness of the study, and reflections on my experience of conducting the study. Finally, the third section (section 4.3) summarises the conclusions to be taken from the findings of the study and identifies priorities for further research

4.1 Discussion of findings

4.1.1 Participants' health experiences during the first year after surgery and effect on function (interview aim/main topic 1)

This study found that many participants experienced ongoing health challenges during the first 12 months after surgery, particularly after thoracotomy. Although some participants were not greatly affected by surgery, for many recovery was difficult and protracted, and they were not back to normal at the time of interview. The most commonly reported health challenges were breathlessness and pain, which were normally discussed without any prompting from the interviewer. Although participants also described other health challenges, breathlessness and pain were the first to be described, and usually dominated the interview. Given the priority that participants gave breathlessness and pain in terms of order and time devoted at interview, findings from this study add to the literature by indicating that these health challenges are of importance to participants in terms of improving recovery experience. Indeed, some participants explicitly stated that breathlessness or pain had been of the greatest concern to them during recovery (see section 3.6).

Breathlessness The descriptions of experience of breathlessness were complex and rich in detail. Some QOL instruments include measures of breathlessness, but involve rating general levels of breathlessness on a scale. The exploration of experience complexity in this study adds further detail to the evidence available from these previously published studies. Experiences of breathlessness were found to vary in seven dimensions (see table 3.6). Variations in experiences within the dimensions of 'level of severity', 'effect on function', 'duration' and 'trajectory' were able to be grouped together to form a typology of experience which categorised participants as being either not affected or being mildly, moderately or severely affected by breathlessness (see table 3.7). Some participants in this study reported either not being affected by breathlessness, or being midly affected. Participants were classified as mildly affected if breathlessness limited

only strenuous activities such as sport or DIY, or else mild breathlessness was experienced when engaging in moderate activities such as walking, carrying shopping or climbing stairs, for example. Although these participants felt that their functioning was somewhat limited in the immediate days/weeks after surgery, they were back to normal by 3 months post-surgery and they described coping well with the course of their recovery. They were not distressed by their experiences of breathlessness as they felt that it was to be expected, and on the contrary often expressed a positive emotional response including relief that they had not been greatly affected and that they felt 'lucky'.

Most participants in this study were classified as being either moderately or severely affected by breathlessness. Those who were moderately affect experienced medium or high levels of breathlessness when engaging in moderately strenuous activities that had not disappeared by three months and for some was still ongoing up to 12 months after surgery. As moderate activity was a normal part of day to day life for most of these participants, they often felt that their life had been significantly disrupted and were sometimes not satisfied with the level of their recovery. Some participants who had received standard care expressed concern that they had not realised that they would be affected after surgery to such an extent and their experience caused them emotional distress. Largely, participants did not receive any support from primary or secondary care health practitioners for breathlessness and participants reported setting up their own 'programmes' to aid recovery, particularly daily walking routines. Participants who were enrolled on the ROC programme generally felt more prepared for their experience of breathlessness after surgery and felt that exercising helped their breathing. A small number of participants had access to prescribed steroid and bronchodilator inhalers due to co-morbid diagnoses of COPD or asthma. All participants that used this type of pharmacotherapy reported that it was helpful in managing their breathlessness after surgery. For participants that were severely affected by breathlessness, activities of daily living such as washing, dressing, sleeping and moving from one room of the house to another proved difficult. Two participants fell into this category. These participants were interviewed at three months and 10 months after surgery. Both were largely housebound and felt distressed by their experience. In addition, they

described feeling alone and unsupported because help was difficult to secure and was achieved through their own efforts only.

Although this study was able to elicit rich detail regarding participants' experiences sampling was purposeful and therefore the distribution of breathlessness severity may not be representative of surgical lung cancer patients on the whole. Quantitative QOL studies with patients that represent different clinical or demographic sub-groups have given mixed reports regarding the length of time that breathlessness remains elevated above baseline levels. However, these studies confirm that most experience breathlessness for at least one month, but for many it continues for more than 3 months and some groups of patients (particularly those who undergo pneumonectomy) may experience breathlessness for 12 months or more after surgery (see section 1.5.1). This general pattern is consistent with the distribution found in this study, and confirms that breathlessness remains a problem for many for at least 3 months after surgery.

It is possible that some of the breathlessness described by participants could be explained by pre-existing cardiorespiratory diseases, most notably COPD and CHD. However, those with pre-existing disease were not more likely to report being more affected by breathlessness. One of the participants who described being severely affected by breathlessness was a life time smoker who relapsed back to smoking after surgery. He had also been diagnosed with COPD previous to developing lung cancer and was receiving oxygen therapy. It is possible that this had predisposed him to be more severely affected. However, he reported noticing a marked increase in breathlessness after surgery, suggesting that his experience could not be completely explained by co-morbid COPD. This finding was also noted for other participants who did, and those that did not, have pre-existing lung conditions. Almost without exception, all participants who experienced breathlessness noted that this symptom notably increased, or first emerged immediately after surgery. This finding supports the position that over and above pre-existing cardiopulmonary disease and functioning, most patients experience breathlessness after surgery and further investigation is necessary to identify causes and appropriate treatment and care.

Breathlessness is a symptom, and therefore represents participants' subjective experience of

being *"unable to breath easily."*[39] Breathlessness has been noted as a common problem in advanced cancer,[108, 224] both for patients with primary or metastatic involvement of the lungs and also those with disease that does not involve the lungs.[105] Increasingly, the causal roots are being recognised as a complex interplay between physical, psychological, emotional and functional factors.[108] Palliative care medicine utilises a range of techniques to alleviate breathlessness, as well as both pharmacological and non-pharmacological treatments. These include radiotherapy to reduce tumour volume or drainage of pleural effusions and use of bronchodilators, inhaled steroid, oral opioids, anxiolytics such as benzodiazepines or oxygen therapy. Non-pharmacological treatment includes controlled breathing exercising, anxiety management and patient counselling.[105, 189, 225–227]. In the context of advance disease, anxiety and emotional factors may have an important role in the exacerbation of breathlessness, but it is unknown if this applies to surgical patients. Although it is not captured in the academic literature, anecdotally there is evidence that health care practitioners have often attributed breathlessness after surgery to a 'loss in confidence' or being 'anxiety driven'.

A striking feature of the descriptions of breathlessness was that many participants in this study had not anticipated the degree to which they would be affected. It was quite common for participants to say that they became breathless when rushing around, forgetting that they had undergone a serious operation (although this was confined to those who were mildly and moderately affected). In addition, many participants were motivated to strengthen their lungs and increase their exercise tolerance by exercising daily, and reported experiencing breathlessness in this context. This is important for two reasons. Firstly, the lack of awareness indicates an informational gap which needs to be addressed in a rehabilitation programme, in order to prepare patients for what to expect after surgery and to support them if they do experience breathlessness. A general feeling amongst participants was that they were more able to deal with health challenges if they had been told to expect them and had been reassured that it was a normal experience, although they also suggested it was difficult to assimilate information in the diagnostic consultation. Secondly, the unexpected nature of breathlessness and the experience of breathlessness in the face of attempts to exercise is an interesting finding to consider when

speculating on the potential cause of breathlessness. During interview some participants did specifically refer to anxiety and loss of confidence and it may be that psychological and emotional factors have some role to play. However, that the majority of participants actively exerted themselves and still experienced breathlessness, and did not expect the experiences they had, indicates that for this group of patients breathlessness seems mainly rooted in physical causes.

Additional findings that support this hypothesis are the descriptions that participants gave of the physical experience of breathlessness. Often participants explained that they felt a tightening of the airway, that they had increased difficulty in breathing when lying down in bed at night, in extremes of temperature and in smoking environments. These are descriptions that are indicative of inflammatory lung conditions such as asthma and COPD.[228] However, although some participants were diagnosed with an inflammatory lung condition this did not adequately account for the experience of breathlessness. The cytokine network is recognized to play a pivotal role in inducing the acute phase inflammatory response to surgical trauma,[229–231] and raised inflammatory cytokines have been found to circulate in the blood after lung resection.[231, 232] VATS procedures have been associated with a reduced level in these inflammatory markers.[231, 233] It is thought that this may account, in part, for lower pain levels experienced compared to thoracotomy.[231] However, the presence, cause and role of pulmonary inflammation during the first year after surgery in post-surgical breathlessness has not been investigated. Some participants in this study had been prescribed corticosteroid inhalers and bronchodilators, and felt that this helped them manage their breathlessness. Some also felt that participating in a COPD-rehabilitation programme improved and helped them manage breathlessness. It is possible that surgical lung cancer patients may benefit from a respiratory assessment and access to treatments that are widely available for other respiratory conditions, although the design of this study was not able to assess this. The benefit of pulmonary rehabilitation and inhaled anti-inflammatory pharmacotherapy needs to undergo definitive testing in this patient group.

Another indicator that breathlessness may be rooted in physical causes was participants' descriptions of not being able to expand the lungs fully in order to breathe to a satisfactory depth.

This may in part be down to technique or possibly psychological barriers. However, descriptions did not convey that. For instance, PID10 reported: *"I can't take a deep breath, it kind of just stops dead and that's it ... when I really need to take a deep breath in, I can't do it, it just doesn't happen"*. This participant had undergone bilobectomy, indicating that physical reduction in lung volume may be the reason.

No known clinical instrument has been specifically designed to measure breathlessness experienced by surgical lung cancer patients. Commonly, history taking for patients with respiratory symptoms includes use of the Borg scale and the MRC breathlessness scale. Categories of breathlessness experiences that have been described in this study mapped on to these two scales of breathlessness. These scales take into account the severity of breathlessness (e.g. slight, moderate, severe, maximal breathlessness) and the effect on function respectively. The Borg scale was found to sufficiently describe the levels of breathlessness experienced by participants in this study. However, the MRC breathlessness scale described breathlessness in terms of strenuous exercise, walking and undressing only and therefore was not sensitive to the range of activities that may be limited by breathlessness.

From accounts of participants in this study, combined with findings from other studies, assessment and management of breathlessness emerges as a priority for a tailored rehabilitation intervention to target. Further work is needed to understand the root causes of breathlessness and to assess the effectiveness of pharmacological and non-pharmacological treatments in managing breathlessness. In addition, the suitability of common measures of breathlessness needs to be assessed from the patients' perspective, and measures developed that indicate the need for intervention and can capture improvements in the experience of this symptom.

Pain As with breathlessness, participants' descriptions of pain experiences were complex and rich in detail. Participants received varying regimens of analgesia whilst in hospital and to cover the first weeks at home, although participants were not able to reliably recount the specifics of these regimens. It has been reported that despite the availability of a range of analgesia and routes of administration, acute and chronic post-thoracotomy pain remains a frequent clinical

presentation.[118] This was found to be true for the participants in the present study.

A typology was constructed that classified participants as being either not affected, or being mildly, moderately or severely affected by pain. Participants were classified as mildly affected if they had experienced low levels of pain (e.g. a little, discomfort, sore) that had largely resolved within 2 months after surgery, or had lasted for no more than 2 months in the case of participants who were pain free in hospital but developed some pain after discharge, once analgesic prescriptions had been used and the effect had 'worn off'. Participants were classified as being moderately affected by pain if they reported either low or medium levels of pain severity (e.g. a little, discomfort, sore, a lot of pain, quite painful) that continued for more than 2 months but had disappeared within 6 months, or else they experienced high levels of pain (e.g. agony, tremendous, terrible) that had resolved within 2 months. High levels of pain lasting less than two months was included in this category as participants experiencing pain of this description were generally distressed by the experience and pain significantly impacted activity levels, therefore moderately affected was chosen as a more adequate description than mildly affected. Participants that experienced high levels of pain severity that continued for longer than 6 months, either at the same level of severity or at lower levels, were classified as being severely affected by pain.

Similar to breathlessness, pain is a subjective experience and its aetiology is complex (see section 1.5.2.2).[234] It is a commonly held clinical belief that pain after thoracotomy is transient.[111, 112, 118] It is recognised that some can experience post-thoracotomy pain syndrome (PTPS), which is defined as persistent pain that continues for longer than two months after thoracotomy (see section 1.5.2.2). Two months was used to define the transition from mildly to moderately affected in the typology of pain experiences presented in this thesis, in order to map on to this definition. There was a clear divide in the extent to which participants in this study were affected by pain based on primary surgical procedure. Those who had undergone VATS procedure reported either not being affected or being mildly affect by pain, whereas most were moderately or severely affected after thoracotomy (i.e. the majority fulfilled the criteria

for PTPS). This is consistent with other work that has indicated that compared to thoracotomy, VATS is associated with less reported post-surgical pain.[232, 235] As with breathlessness, the distribution of the participants within levels of the typology may not be representative of the underlying population. However, other studies have also found that many continue to experience pain for more than 2 months after thoracotomy (see section 1.5.1). If most patients do experience pain for at least two months after surgery, this calls into question the clinical belief that development of PTPS is the 'exception' and highlights the need to improve identification of patients with PTPS and to investigate effectiveness of treatments. .

The current description of type of pain experienced by those with PTPS did not adequately describe the pain experiences reported by participants in this study. PTPS has been described as an aching, burning dysaesthesia and/or having a pleuritic component which is largely confined to the thoracotomy incision.[111] Participants in this study described aching, sharp pains and impairment in sensitivity (dysaesthesia). However, no participant described a burning sensation. Words used by participants to describe pain were largely captured by the categories of spatial, pressure and punishing pains of the McGill Pain Questionnaire. However, participants also described movement of a clamping/cramping pain along the thoracotomy scar which is not described by the MPQ. In addition, a common observation from participants in this study was that the site of the chest drain had been particularly painful, with some going as far as to say that this site had caused the most pain. Many also experience ipsilateral shoulder pain, which may be partly caused by the extended period of time for which the arm is extended and held in a brace in order to allow access the thoracic cage.[236] Largely, therefore, although the description of pain experienced by those with PTPS fitted some of the participants' descriptions of pain, much was not described by this definition.

There were two other points of interest regarding participants' accounts of pain. The first is the effect of pain on activity levels and functioning. It has been acknowledged that there is limited evidence available that describes the impact of post-thoracotomy pain on patients' activity.[111] As in the hospital setting, adequate long term pain control is desirable to enable participants to

rehabilitate and resume their normal levels of activity as soon as possible, in order to reduce the risk of developing complications (see section 1.5.2.2). Participants in this study described the impact of pain on activity and function, and there was a noticeable qualitative distinction between the accounts of the effects of breathlessness and pain on this dimension. Whereas breathlessness was most often experienced as a result of and during physical activity, and limited the extent to which participants could continue with or the speed at which they completed the activity, pain was most often reported in association with breathing, coughing, or when pressure was applied to the wound whilst lying in bed or sitting in a chair, for example. When the pain provoked was either at a low or medium level, participants did not report that it limited their degree of activity, and they continued as normal despite the pain. There was some evidence of slight sleep disturbance due to low or moderate pain experienced when changing position, but overall participants spoke pragmatically about this stating that it was to be expected. However, high levels of pain severity often caused a general reduction in participants' activity level leaving them vulnerable to the adverse consequences of immobility, and decreasing their confidence to go outside.

Secondly, the two main dimensions of pain experience that seemed to differentiate emotional response were level of severity and duration. There appeared to be a 'two tier' emotional response; the first being acute distress and the second being anxiety regarding the cause of pain. As would be expected, even when experienced for a short amount of time, those who experienced high levels of pain found this acutely distressing. However, when severe pain lasted for longer than two months or lower levels of pain lasted longer than six months, some participants reported that they began to worry about what was causing the pain and whether 'something had gone wrong'. This anxiety was augmented by the fact that often participants had not expected to experience pain to the level or for the length of time that they did. Some participants reported that they had not been given an accurate picture of what to expect after surgery regarding pain. This added to the shock, and one participant even disclosed that she had contemplated suicide. Those who had managed to speak to a health professional involved in their care after starting to feel anxious found it reassuring, and wished that they had been able to have the conversation

sooner.

The findings from this study, combined with past studies, indicate that many patients experience persistent pain for more than two months after surgery. This indicates that assessment and management of pain is also a priority target for a tailored rehabilitation intervention. Evidence from this study indicates that the current definition and description of PTPS may not be accurate or useful, and that further work is needed to define this clinical problem and also to improve identification, communication and management of the issue.

Other health challenges In addition to breathlessness and/or pain, some participants also reported experiencing sleep disturbance, fatigue, loss of appetite and/or weight loss, to varying degrees. For the majority, these topics did not dominate the interview but some participants were concerned, particularly if the experiences severely affected day to day functioning and/or were enduring. In addition, some participants reported experiencing anxiety related to their experiences. There was some evidence that these experiences may have been secondary to adjuvant treatments, to analgesia, or to experiences of breathlessness and/or pain. For instance, it was not uncommon for participants to note that pain and breathlessness experienced when lying down at night disrupted their sleep. Also, the extra exertion involved in daily activity and the struggle for adequate breath left some participants feeling fatigued. Often participants felt that they lost their appetite, or that their sense of taste was impaired, whilst undergoing radiotherapy or chemotherapy regimens, or taking high dose analgesia. Anxiety and psychological distress associated with cancer diagnosis, treatment and health challenges during recovery from surgery were laced through some participants' accounts, and again it was not uncommon for participants to feel that they had lost weight because of anxiety or to report that their sleep was disrupted. In short, from a combination of the physical and psychological affects of diagnosis and treatment, participants generally experienced a complex of one or more of these health challenges after surgery. However, priority in participants accounts was given to breathlessness and pain.

As with breathlessness and pain, little research has focused on investigating causes of or potential treatments for these additional health challenges for surgical lung cancer patients.[186]

However, there is some evidence to suggest that exercise may improve symptoms of fatigue, as it has been demonstrated to improve exercise tolerance and fatigue both in health populations and those with long term conditions.[187] Fatigue is a symptom that affects 70-100% of cancer patients. A recent Cochrane review summarised the findings from 56 studies that investigated the effect of exercise on fatigue in cancer patients. This review found that engaging in aerobic exercise either during or after adjuvant treatment led to a significant reduction in fatigue score rating at the end of treatment.[187] However, most studies in this review were conducted on patients with breast cancer whose average age at diagnosis is younger, and treatment differs. No research investigating the effect of exercise on fatigue has focused on surgical lung cancer patients, and further studies are needed to assess the benefits of exercise in this group not only on respiratory function and breathlessness but also on measures of fatigue.

Differences between sub-groups There are various participant or treatment characteristics that could have influenced the extent to which participants were affected by health challenges. The nature of the primary incision (VATS or thoracotomy) and the extent of lung resection (wedge resection, lobectomy, pneumonectomy) have previously been shown to be associated with worse QOL scores (see section 1.5.1). In addition, a study investigating QOL in lung cancer patients found that persistent smoking behaviour after diagnosis was also associated with poorer QOL compared with those who did not smoke.[135] It was also considered likely that participants with a pre-existing cardiorespiratory disease may experience higher levels of breathlessness.

When comparing the qualitative descriptions of health during the first 12 months after surgery between participants of difference sub-groups in this study, the only factor that clearly differentiated reports was the nature of the primary incision. Participants who had undergone VATS were more likely to report either not being affected or being only mildly affected by health challenges. These findings add to a growing body of literature indicating advantages of VATS compared to thoracotomy (see section 1.4.1.1). Some have expressed concern that this procedure is not more widely available to patients.[232, 233, 237] Despite the potential for improved

outcomes from this minimally invasive procedure it is not specifically recommended for use in current BTS guidelines.[47] Barriers to nationwide use of this technique include some concerns that VATS may result in inferior disease progression and survival outcomes[238], although systematic reviews showing comparable prognostic outcomes for VATS and thoracotomy exist.[218, 239] The findings of the present study, in addition to previous studies, indicate that VATS may have an important role in improving the treatment and recovery experience of eligible lung cancer patients, and underline the urgent importance of further research that will lead to definitive answers regarding its potential as a less invasive, oncologically comparable alternative treatment.

During the lifetime of this PhD, a review of QOL studies in surgical lung cancer patients has been published.[240] In addition to the studies that were reviewed in the introduction (see section 1.5.1), a further five studies were identified that had been published since 2009.[241–245] Considering findings from all identified studies (pre- and post-2009), this review concluded that lobectomy was associated with a deterioration in QOL with partial recovery over time. However, pneumonectomy was associated with a greater deterioration which did not improve, or in some cases deteriorated further over time. This is consistent with the experience that was described by one participant who had undergone a left pneumonectomy via thoracotomy in this study (PID20). This participant was severely affected by breathlessness, and was the only participant to report deterioration over time. However, one other participant who underwent pneumonectomy, and others who underwent bi-lobectomy via thoracotomy described being mildly and moderately effected by health challenges, as did those who underwent lobectomy and wedge resection in this qualitative study. Although not identified in this study it is possible that there are important qualitative differences between other sub-groups, particularly between patients who undergo pneumonectomy compared to lesser resections.

4.1.2 Participants' attitudes towards smoking, smoking cessation and NHS stop smoking support (interview aim/main topic 2)

Around half of the participants in this study were smokers at the time of diagnosis and although some were able to quit, others continued to smoke immediately after discharge or relapsed within the first three months after discharge. Although participants were purposefully sampled (however, not on the basis of smoking behaviour), this findings supports previously published studies that indicate a notable proportion of lung cancer patients continue to smoke after diagnosis (see section 1.6.1). Most participants stated that they would rather smoking was not a part of their life and that they would like to quit, but also expressed conflicting beliefs/attitudes that were supportive of continued smoking behaviour. Reasons for relapse or continued smoking after discharge are likely to have involved a number of factors, but predominantly participants cited reasons of enjoyment, lack of will power, psychological coping and living alone. These findings have important implications for smoking cessation support as they indicate that surgical lung cancer patients are no different to the general public in terms of desire to quit and reasons for smoking.[246, 247] Regardless of participants' attitudes towards smoking and smoking behaviour after diagnosis, all participants felt that it was the place of health professionals to ask about smoking behaviour and to offer smoking cessation support.

Given that notable numbers continue to smoke and openness to intervention, these findings indicate that smoking cessation support is of relevance to many in this patient group and needs to be addressed. No study has quantified the proportion of surgical lung cancer patient smokers that are offered support either within primary or secondary care in the UK, but a survey conducted with clinician members of the International Association for the Study of Lung Cancer (IASLC) showed that low numbers of clinicians offered smoking cessation support as a standard aspect of their practice.[248] Most participants in the present study reported that they were not offered support to quit smoking, despite recommendations by NICE that smoking cessation support should be offered to lung cancer patients.[46] It is likely that in practice there is a gap for most surgical lung cancer patients between the need for support and the level of smoking cessation

support provided within cancer services.

Patient, physician and service barriers to accessing smoking cessation treatment There are a few possible factors that may be acting as barriers to patients accessing smoking cessation support within cancer services. This study found that some participants reported feeling stigma and guilt associated with smoking. This is consistent with a previous qualitative study that reported lung cancer patients often feel stigmatised, whether smokers or not, due to the link between smoking and lung cancer and that some who continue to smoke after diagnosis experience guilt and shame due to their continued smoking.[249] Some participants in this study explicitly stated that feelings of guilt and shame had prevented them from being truthful about their smoking status and from seeking support. Stigma, guilt and shame experienced by patients whose behaviour is linked to ill health has also been reported in other clinical contexts, and these feelings can prevent help seeking behaviour.[250–253] These findings underline the importance of sensitive, proactive management of smoking by health professionals. As identified by participants in this study, a non-judgemental approach is key, allowing patients to feel they can be honest about their smoking behaviour and to return for further support after relapse.[254] Further it suggests that biochemical validation of smoking status may be important in this patient group. Biochemical validation has been shown to be a more reliable method of assessing smoking status than self report.[255] Monitoring of CO levels in exhaled air are used as standard within specialist smoking cessation clinics and anecdotally it is known to be acceptable to patients.

It has previously been reported that clinicians also hold concerns that may be acting as barriers. In general, clinicians report a lack of time, training and resources to engage in smoking cessation activities with patients.[254, 256, 257] Relapse rates after attempts to quit are high,[258] and this may be de-motivating to both a patient and clinician.[254] These concerns may be compounded in this particular context by nihilism born out of an historically poor outlook for lung cancer patients as a whole, and smoking cessation is not seen as a priority by health professionals.[1, 259–261] Whilst it is possible that smoking cessation is not associated with improved

outcomes in patients with advanced disease, there is mounting evidence that smoking cessation after a diagnosis of early stage lung cancer is associated with short and long term health benefits in addition to improvements in quality of life (see section 1.6, also the strength of evidence for the association between smoking cessation and prognosis in early stage lung cancer patients is investigated in chapter 6 of this thesis), indicating that smoking cessation may be worthwhile in this patient group.

A cancer diagnosis has often been referred to in the literature as a 'teachable moment', where patients may be more receptive to intervention, and indeed there have been calls to capitalise on this time and make smoking cessation support an integral part of cancer treatment.[254, 262–264] The legal ban of smoking in enclosed spaces in July 2007 [265] means that patients are no longer able to smoke whilst in hospital, providing an external imperative to be temporarily abstinent. This has the potential to provide added impetus to initiate and support a quit attempt, although no study has been conducted to assess the impact of UK smoke-free legislation on smoking attitudes and behaviour amongst hospitalised patients. Given the notable proportion of continuing smokers, the potential benefits of quitting to health, the proximity of patients to health services whilst receiving treatment for cancer and the willingness of surgical lung cancer patients to be offered support, there is a strong rationale for the incorporation of smoking cessation support into standard care for this group. Despite this, today in the UK, smoking cessation is not explicitly recommended in the BTS guidelines for the radical management of lung cancer patients [47], and general practitioners are not incentivised by the Quality and Outcomes Framework (QOF) to arrange smoking cessation support for cancer patients. The latest version of NICE guidance for the diagnosis and treatment of lung cancer recommends that patients should receive support to stop smoking, but smoking cessation care is still not embedded within standard cancer care pathways.

Anecdotally it is known that secondary care health professionals do not perceive smoking cessation support or referral to be part of their responsibility,[254, 266] and smoking cessation is poorly integrated into secondary care services generally. NICE are currently drawing up guid-

ance for smoking cessation in secondary care, which is due to be published in October 2013. This will be the first version of guidance on this topic and promises to increase impetus for embedding smoking cessation into secondary care pathways for all patients, and also to improve communication between secondary care, primary care and specialist smoking cessation services. In terms of lung cancer patients specifically, added to improved service infrastructure for identifying and supporting smokers to stop, awareness needs to be raised amongst health professionals that patients are open to discussing their smoking behaviour and would like help to quit. Health professionals need to have access to training which would increase their knowledge of how to tackle this issue, and reassure them that sensitive management of the issue would not affect the patient-health professional relationship.

Timing, content and level of intensity of smoking cessation services for surgical lung cancer patients: participants' preferences and evidence Smokers in this study indicated that they would prefer support for smoking cessation to be initiated as soon as possible during their cancer care, with some specifically stating that support to quit before surgery would be best. No strong preferences were expressed by participants for type of pharmacological support. No known previous studies have tested the effectiveness of smoking cessation interventions with surgical lung cancer patients, but there is no reason to believe that effectiveness of treatments are likely to differ for this population compared to the general population. Many participants had tried several available pharmacological products without success in the past. Some indicated that they would be open to trying these treatments again. Indeed, some had attempted to quit again using NRT patches or varenicline as offered by (usually) their GP. An interesting observation from participants' accounts was that although some found it difficult, many reported that it was easy to be abstinent whilst an inpatient as they felt too ill to smoke or because they *'just did not think about it'*. Many left hospital with good intentions to continue their abstinence, although often with minimal or no support, but found that within the first three months of discharge they had relapsed. Although no strong preferences regarding type of pharmacological were expressed, many had a strong preference for extended support during the immediate

post-surgical period, because of particular vulnerability to relapse during this time.

There are several reasons to suggest that quitting before surgery and extended follow up would be beneficial, in addition to being preferred by patients. As was discussed at length in the introduction, there is evidence that quitting smoking immediately before surgery does not increase risk of post-surgical complications (see section 1.6.2), and quitting smoking more than four weeks before surgery and continual abstinence after treatment may lead to reductions in risk.[66, 169] In addition, two systematic reviews provide evidence that extended follow up significantly increase long term quit rates. A Cochrane review that assessed the effectiveness of smoking cessation interventions in hospitalised patients found that of five levels of intervention intensity, the only level that resulted in a significantly increased long term quit rate (6+ months) started at the bedside and continued for at least one month after discharge (RR 1.37 (95% CI 1.27 to 1.48; 25 trials).[267] This level of support was also significantly improved with supplementation of NRT. (RR 1.54 (95% CI 1.34 to 1.79); six trials)

A second Cochrane review [170] reporting evidence from 5 trials ($n = 535$) on the effect of a pre-surgical smoking cessation intervention on smoking cessation reported similar findings. None of these trials were included in the first Cochrane review because the intervention was initiated before hospitalisation. Although both brief intervention (1 face-to-face or by post contact as part of routine pre-surgical assessment) and intensive intervention (weekly counselling for between 4 and 8 weeks) significantly increased the number who had quit at time of surgery (Intensive RR 10.76 (95% CI 4.55, 25.46) and brief RR 1.41 (95%CI 1.22, 1.63)), intensive intervention only led to significantly increased quit rates at 12 months (RR 2.96 (95% CI 1.57, 5.55). Interestingly, this review also reported data on risk of any complication or wound complications and for both analyses, only the intensive intervention led to significant reductions in risk (Any complication RR 0.42 (95% CI 0.27, 0.65), wound healing complication RR 0.31 (95% CI 0.16, 0.62)). These interventions initiated quit attempts within 8 weeks of surgery.

In summary, combining the findings from this study and evidence from previously published studies, it appears that a notable proportion of lung cancer patients continue to smoke after

diagnosis and are open to support to quit. Research evidence has shown that initiation of support before surgery and continuation for at least 1 month after surgery is the most effective, and this was also the preference for care expressed by participants in this study. A proactive non-judgemental approach by health professionals may be important to help patients overcome feelings of guilt and shame associated with their smoking behaviour. The rationale for prioritising smoking cessation support for surgical lung cancer patients is strong. However, further work is required to embed smoking cessation support into standard care. Previous and pending NICE guidance needs to catalyse the development of improved infrastructure for identifying and referring patients for smoking cessation support. In addition, training of health professionals is needed to equip them with the knowledge and understanding necessary to implement the guidance.

4.1.3 Participants' attitudes towards recovery and supportive care received (interview aims/main topics 3 and 4)

VATS A finding that has emerged throughout this chapter is the stark difference in experience between those who had undergone VATS compared with most who had undergone thoracotomy. In line with this, when evaluating their general experience of recovery, all participants who had undergone VATS were highly satisfied with their recovery, and felt that standard care had met their needs. This lends further weight to the argument that, wherever clinically possible, VATS should be surgicial procedure of choice, from the point of view of the patient reported outcomes. However, as described in section , there remains uncertainty as to whether oncological outcomes (e.g. recurrence, mortality) are equivalent or superior for patients undergoing VATS compared to thoracotomy. .

The NSCI have defined a new model of follow up which stratifies patients to one of three levels of care based on needs (see section 1.7.2). The first level of care is 'self-management'. Within this pathway, patients who do not have complex on going needs will be given the support and information necessary to manage their own recovery, with the caveat that they may receive more intensive follow up if the need arises. The second level of care involves 'shared care' and is appropriate for patients who have ongoing needs that they would not be able to manage alone and need contact either with primary care or nurse/clinician led secondary care. The third level is termed 'complex care', which will be led by consultants. It is thought that this will be necessary for a minority of patients who have complex ongoing needs. Findings of this study, in combination with previous studies, indicate that patients who have undergone VATS are likely to have less complex needs than patients who have undergone thoracotomy. Participants who had undergone VATS in this study were able to self-manage health challenges that had arisen, and it is likely that this level of care will be sufficient for many of these patients. However, the possibility that patients do need shared or complex care during their recovery cannot be ruled out based in the findings of these studies alone.

Thoracotomy In contrast to participants who had undergone VATS, most participants who had undergone thoracotomy and received standard care were not satisfied with the course of their recovery. They reported feeling that they had not been given a correct picture of what occurred during surgery and what to expect during recovery, and felt that standard care had not been sufficient to meet their ongoing care needs. Some expressed that they had felt abandoned by the health care system. Many participants who had received standard care felt that they needed additional supportive care services, and felt that a rehabilitation programme would help with recovery. The potential benefit of a rehabilitation programme in terms of participant experience of recovery was confirmed by the experiences of those who had enrolled in the ROC programme. In general, these patients spoke positively about their recovery, and the rehabilitation programme content and format was praised by participants. Indeed, these participants did feel that they had benefited from participating in the programme in a variety of different ways that had aided their recovery.

A detailed understanding of differences in the satisfaction with recovery between participants who received standard care and those enrolled in the ROC programme, and satisfaction with the level of care, would be best gained by analysing how participants chose to communicate about these issues during the interview (i.e. choice of words, tone of voice, hesitancy or confidence for example) given that participants could not compare these conditions themselves. Analysis of this type falls into the methodological approach of discourse analysis, and is outside the scope of the analysis performed in this thesis. However, in general, compared with participants who had received standard care, those who participated in the ROC programme were less concerned about the health challenges they had faced during recovery, particularly breathlessness, and used language which suggested that they felt more in control of their recovery. For example, a characteristic that emerged from the accounts of all participants in this study was of high levels of motivation to aid their own recovery, particularly to improve their physical fitness and breathing. Most participants recounted some form of 'rehabilitation programme' that they had constructed for themselves to improve their fitness and to measure the improvement. Many spoke of building regular exercise into their day (normally walking), and noted how

their breathlessness improved. However, those who had enrolled in the ROC programme spoke about their own personal programmes with enthusiasm and found direction/support from the ROC programme invaluable in helping them to continue improving their fitness on their own. In contrast, those who had received standard care, and in particular those who had undergone thoracotomy and had been moderately/severely affected by health challenges, spoke about their routines with an air of anxiety and struggle for survival. Taken together, the findings indicate that shared or complex care may be most suitable for many patients after thoracotomy, based on patient reported experience and views.

4.1.4 Content and format of a tailored rehabilitation programme (interview aim/main topics 1, 2, 3 and 4)

The detailed exploration of health and health behaviour (i.e. smoking) presented in the first and second main topics of analysis (see section 3.4 and 3.5), combined with attitudes towards recovery and supportive care preferences expressed by participants as reported in the second, third and fourth main topics of analysis (see section 3.5, 3.6 and 3.7) create a detailed picture of participants' additional supportive care needs. The purpose of this section is to integrate these findings and considerations, and suggest important components of a rehabilitation programme tailored to the needs of surgical lung cancer patients. The findings of this study, along with other considerations of this thesis, will then be discussed in the context of the lung cancer stratified pathways as defined by the NCSI, in association with NHS Improvement, and mapped onto the pathway in the final discussion (see chapter 7). It should be noted that most of the detail has been provided by participants who had undergone thoracotomy, as it was this group that were experiencing ongoing needs that were unmet by current services.

Participants in standard care found it difficult to describe specific preferences for the content and format of a rehabilitation programme. However, five did express preferences and interestingly they involved many features that are currently delivered as part of a pulmonary rehabilitation programme for COPD (e.g. structured and supervised exercise, enhanced information giving and disease education), and hence also the ROC programme.[3] Three of these patients had undergone surgical treatment before the ROC programme had begun (PID4, PID10, PID11), and therefore did not know about it, and the principles or possibilities of pulmonary rehabilitation were not introduced during the interview by myself. The remaining two patients (PID16, PID20) received standard care whilst the ROC programme was running, as they were referred for surgery from a non-participating hospital. It is possible that these patients had heard about the programme, and it was for this reason that they made suggestions that involved similar elements. However, neither of these patients explicitly referred to a programme that had been available to some, but not to them.

Based on the point of view of participants who had received standard care, pulmonary rehabilitation represents a promising template to build an intervention that is tailored to the needs of surgical lung cancer patients. The potential of pulmonary rehabilitation to improve outcomes has also been recognised by NICE who recommended further research to evaluate the benefits of pulmonary rehabilitation for surgical lung cancer patients.[46] Previous studies have piloted this approach with promising results,[191–193] although participants' views on this type of programme and suggestions for change have not been explored (see section 1.8.3). The ROC programme pilot running at the time of this study provided an ideal opportunity to explore if patients who had received a programme based on pulmonary rehabilitation found this to be helpful, as those who had received standard care suggested that it would be, and to assess from the participants point of view if any changes were needed to improve the fit of the programme to their specific needs.

As was described in section 3.7, the ROC programme was well received. Those who participated in the ROC programme articulated aspects of the programme that they particularly valued, but again did not have ideas for changes necessary to improve the programme. In particular, participants were happy with the group format, with the opportunity to exercise at their own pace and also receive one-to-one support if necessary. Participants were happy to return around 4 weeks after surgery and felt that taking part in the programme improved their health and motivation to exercise. In addition, participants felt that the ROC programme gave sufficient opportunity for dissemination of information that was useful to them. This confirms the potential of using pulmonary rehabilitation as a starting point, or a template from which to build a tailored intervention.

Although not raised by participants as specific ideas for change, some challenges identified by participants in the first main topic of analysis were not covered by the programme indicating areas which require improved tailoring. First, both participants who had received standard care and those enrolled on the ROC programme expressed the view that there was a lack of information regarding the cause of pain and the expected length of time that pain experiences

would continue. They indicated difficultly in managing pain, including getting help. In addition, participants indicated that they did not know how to differentiate 'normal' from 'cause from concern', and that they were anxious regarding the significance of pain that they experienced. As part of the enhanced information given in the ROC programme, participants were told that they might experience pain and to go to a GP if it persists for longer than a few weeks or becomes unbearable. However, this did not seem to filter through to the patients. This indicated that this aspect of the programme needs to be augmented.

Second, the possibility that participants may benefit from a respiratory assessment and prescription of appropriate pharmacotherapy was highlighted by this study. Little research has been carried out regarding post-surgical breathlessness, and the cause is largely unknown (see section 1.5.2.1). Although most participants experienced respiratory symptoms after surgery, and this has also been reported in other studies of lung cancer patients (see section 1.5.2.1), current UK guidelines do not advocate referring symptomatic patients to respiratory care for an assessment and treatment. Thus these patients 'fall through the cracks' and are not gaining access to already well developed pathways of care for patients with other respiratory diseases. A few participants in this study reported that they had been prescribed bronchodilator and steroid inhalers to help manage their breathless by their GP and that they felt that this pharmacological intervention had relieved their symptoms. This indicates that for some patients breathlessness may be reversible. Further investigation of the causes of breathlessness and potential benefits of pharmacological treatments such as corticosteroid and bronchodilator therapy is warranted. It is possible that respiratory assessment and care in addition to the benefits of participating in pulmonary rehabilitation may further improve patient experience and health.

Third, there was evidence that some participants may be in need of an occupational health assessment at home. This is especially important if patients are living on their own with no carers to help. The worst affected of participants felt vulnerable when they were discharged and were severely compromised in their ability to carry out essential day to day functioning. In addition, some participants indicated that they would have benefited from having access to

mobility aids, and also practical help to prevent bed sores.

In summary, consistent with previous studies, this study has found that surgical lung cancer patients have ongoing healthcare needs after discharge that are not currently met by standard care. This is particularly the case after thoracotomy. Pharmacological and non-pharmacological treatments that are routinely made available to patients with other conditions for respiratory and pain management may prove to be effective in improving surgical lung cancer patients' quality of life after surgery, although this remains to be formally tested. Rehabilitation programmes based on pulmonary rehabilitation have shown promise as a useful and relevant template on which to build specifically tailored support. Table 4.2 summarises the design features of a tailored rehabilitation programme that were identified as important, based on participants' expressed needs and preferences, building on the structure of the ROC programme.

Table 4.1: Final content and format priorities and considerations for a rehabilitation programme for surgical lung cancer patients

Identified needs to be addressed	Health challenges - Breathlessness, pain, appetite and sleep disturbance, weight loss and fatigue Support - Informational, emotional, mobility, dietary and smoking cessation
Proposed content	(1) Spirometric and other respiratory function assessment to ascertain the underlying cause of breathlessness (2) Management of breathlessness with appropriate pharmacotherapy (3) Exercises to improve lung and general strength, deal with acute breathlessness, and aid chest clearance - participants valued following an individual programme that they can tailor to their ability and are able to take at their own pace. (4) Pain assessment - referral to pain management clinic for those who continue to be affected by pain (5) Dietary assessment - participants who had lost more than 10% of their body weight should be referred to a Macmillan dietician (6) Smoking assessment - participants were not offended by being asked their smoking status or an offer of support. Support needs to be proactively offered by NHS rather than relying on patients to contact their general practitioner (7) Mobility assessment - some participants felt vulnerable after discharge home and felt that they needed mobility aids such as wheelchair, walking frames and also preventative care for pressure sores (8) Enhance information regarding the nature of the surgical procedure, what to expect/ how to deal with health challenges during recovery and to understand the boundary between 'normal' and indication of something wrong
Delivered by	Health professionals who know about previous care and are able to answer questions specific to the impact of lung surgery
Timing	Smoking cessation support - as soon as possible after diagnosis Exercise and information - restart 1-2 months after surgery
Group or individual	Support from group members who are in a similar position is valued by participants
Potential challenges	Some participants may find it difficult to travel to rehabilitation sessions due to ill health or lack of funds for travel/parking Some participants may find it unsettling to be placed in a group with other patients who are seriously ill Some participants may not understand why they are exercising before the surgery and need further explanation

Table 4.2: Suggested design features of a tailored rehabilitation programme for surgical lung cancer patient building on the design of the ROC programme, with relevant findings/considerations/preferences expressed by participants

Content of ROC programme	Relevant findings/considerations from study findings, including suggestions for change
First clinic appointment after patient identified as eligible at MDT	
(1) Assessment of smoking status, BMI and nutritional status. Referral to stop smoking service and Macmillan dietician if necessary	(1) Participants felt that it was the place of health professionals to ask them their smoking status and offer help. They were willing for this to happen as soon as possible in the cancer care pathway and expressed a preference for continued support after discharge. (2) Specific preferences for pharmacotherapy were not expressed but participants were open to trying treatments that they had tried before. (3) There was evidence that some smokers may feel guilty about their smoking and find it difficult to be honest about their smoking status. This underlines the importance of a proactive, sensitive approach to smoking by health professionals. (4) Research evidence suggests that quitting 4 weeks or more before surgery reduces risk of pulmonary complications and therefore participants should be advised to quit as soon as possible before surgery. There is no evidence that quitting immediately before surgery increases the risk of complications, and NICE guidance recommends that surgery is not delayed to allow patients to quit smoking.

Table 4.2: cont.

Content of ROC programme	Relevant findings/considerations from study findings, including suggestions for change
(2) Lung CNS delivers educational element including: a. What to expect before, during and after surgery b. Details of the surgical procedure c. Physical side effects of surgery and pain management in hospital d. Lifestyle advice	(1) Participants preferred and valued access to health professionals who knew about their cancer care and were able to answer specific questions about lung surgery. (2) Participants who had received standard care felt they needed enhance information regarding the nature of the surgical procedure, what to expect/ how to deal with health challenges during recovery and to understand the boundary between 'normal' and indication of something wrong. This confirms the usefulness of this session. (3) Both participants enrolled in the ROC programme and those who received standard care did not feel prepared for the amount of pain that they experienced after discharge. Information regarding what to expect and how to manage pain needs to be augmented, and may be best delivered by a lung CNS
(3) Arrangement for attendance at next pulmonary rehabilitation class	(1) Cost of travelling and parking was highlighted as a potential difficulty associated with participating in the programme. This could potentially be overcome by having community based services as well as services based at the hospital.
Pulmonary rehabilitation before surgery	
(1) Patient arrives 1hr early for one to one educational session with physiotherapist including: a. Assessment of activity/fitness/limitations b. Assessment of health behaviours c. Explanation of lung physiology	(1) Participants found this session helpful, and valued one to one time with a health professional.

Table 4.2: cont.

Content of ROC programme	Relevant findings/considerations from study findings, including suggestions for change
(2) Participate in pulmonary rehabilitation classes twice a week until surgery including: a. 1st hr exercise session - Lower and upper body exercises (see section 2.3.4.1) b. 2nd hr education session - Lifestyle advice and benefits of exercise, how to deal with breathlessness, chest clearance, COPD and co-morbidities	(1) Participants valued following an individual programme that they could tailor to their ability and were able to take at their own pace. (2) Some participants felt well before surgery and did not understand why they needed to exercise before the surgery. Further explanation of the value and purpose of pre-surgical sessions may be necessary. (3) Some participants found it unsettling to be placed in a group with other patients who are seriously ill, whereas support from group members who are in a similar position was valued by other participants
Support on discharge	
The ROC programme did not included assessment of support needed on discharge	(1) Some participants felt vulnerable after discharge and felt that they needed mobility aids such as wheelchair, walking frames and also preventative care for pressure sores. Although no extra support was given to patients as part of the ROC programme until they restarted pulmonary rehabilitation after surgery, some patients may benefit from an occupational health assessment and referral for/access to additional support on discharge if necessary.
Pulmonary rehabilitation after surgery	

Table 4.2: cont.

Content of ROC programme	Relevant findings/considerations from study findings, including suggestions for change
(1) Patient returns 4 weeks after surgery for 6 weekly sessions including: a. 1st hr exercise session - Lower and upper body exercises. b. 2nd hr education session - Lifestyle advice and benefits of exercise, how to deal with breathlessness, chest clearance, COPD and co-mobidities.	(1) Most participants felt that they would be ready to restart the rehabilitation programme 1-2 months after surgery. However, some were not well enough. A flexible re-start date after surgery was offered to participants enrolled in the ROC programme and this is appropriate. (2) Additional elements suggested by patient needs after surgery: a. Pain assessment - referral to pain management clinic for those who continue to be affected by pain. b. Spirometric and other respiratory function assessment to ascertain the underlying cause of breathlessness. c. Management of breathlessness with appropriate pharmacotherapy.
Outcomes	

Table 4.2: cont.

Content of ROC programme	Relevant findings/considerations from study findings, including suggestions for change
The ROC programme pilot measured the following outcomes: (1) Post-surgical pulmonary complication rate (primary outcome) (2) Hospital length of stay (LOS) (3) HDU LOS (4) ICU admissions (5) Re-admission rate (6) Smoking status (7) 6 minute walk test (8) Quality of life measured using EORTC questionnaires	The following were identified as potentially important outcomes based on findings from participants interviewed in this study: (1) Receive additional support in following domains: informational, emotional, mobility, dealing with symptoms, dietary, smoking cessation. (2) Improvements in: breathlessness, pain, appetite and weight loss, sleep disturbance and fatigue, general functioning In addition, NICE guidelines recommend that the effectiveness of pulmonary rehabilitation should be tested against the following outcomes: (1) Mortality (2) Pulmonary complications (3) Pulmonary function (4) Quality of life (including assessment by EQ-5D).

4.2 Strengths and weaknesses of the study and reflections on the process

This is the first known qualitative study to have been undertaken with post-surgical lung cancer patients that has aimed to describe the health and explore supportive care preferences. Investigation of these issues is timely as national developments are under way to improve current services for cancer survivors who, until recently, have received care that does not fully address their needs.[177] The following sections discuss the strengths and weaknesses of the study, including personal reflections on conducting specific aspects of the study and scrutiny of the risk of investigator bias. Many have argued that quality standards of quantitative methods, for example internal validity, external validity, reliability and objectivity, are not appropriate for qualitative inquiry.[199, 268, 269] Guba and Lincoln [270] offered alternative quality criteria to these, of credibility (the results accurately represent the experiences of participants, and are sufficiently supported with evidence from the underlying data), transferability (sampling that represents diversity of participant characteristics, with sufficient information given for others to determine if the results are transferable to other settings), dependability (the researcher gives a detailed account of the methods so that the study could be repeated, and these methods include efforts to ensure internal validity) and confirmability (the role of investigator bias is fully disclosed), respectively. The strengths and weaknesses of this study will be considered in light of these criteria.

General reflections: use of qualitative inquiry and role of personal bias within data collection and analysis Before this study, I had been involved in one other qualitative project seven years ago. My role in this project was small and, therefore, constitutes minimal experience with qualitative inquiry. As such, whilst conducting this project I had a steep learning curve. Most of my previous training has been in quantitative methods within epidemiology, although before embarking on this project I completed a total of three days training with the National Centre

for Social Research on in-depth interviewing and data analysis using Framework Approach. It became clear to me, particularly as I started both the interview and the analysis process, that although I understood that the emphasis of qualitative research is different to quantitative research, I still found myself trying to fulfil the quantitative mindset regarding research quality and felt uncomfortable departing from it. Some particular examples of this are given in subsequent sections.

Reflecting on the possibility of the influence of personal bias on the construction of the coding framework and presentation of the data, I feel that there is low risk. Before this study, I have not had experience with this group of patients, either in a research, clinical or personal capacity. I had read and summarised findings of QOL studies, but until I conducted the interviews with patients I had not realised the extent to which many experience difficulties during recovery or are affected in their day-to-day functioning. In addition, although QOL studies had identified that some groups of patients continue to experience breathlessness and pain, I did not anticipate how these challenges would dominate their recovery experience. In this way, although I had some indication as to the challenges that participants may experience, I was largely able to build a picture of patients recovery from their descriptions rather than fitting them to a strong vision of what I expected, aiding impartiality and an unbiased interpretation of the data. This impartial view of the data is a strength of this study.

Sampling This qualitative study was carried out on a large group of purposefully sampled patients to represent a broad range of demographic and clinical characteristics. Purposeful sampling is commonly used within the discipline of qualitative research.[200] Rather than recruiting a large random sample of participants that will allow for assessment of statistical differences between groups, the goal of sampling is to reflect diversity.[219, 271] For this study in particular, high diversity within the sample was achieved allowing the exploration of experiences and attitudes demonstrated within and between different sub-groups of post-surgical lung cancer patients, with wide representation from groups based on primary incision procedure (thoracotomy or VATS), extent of lung resection (wedge resection, lobectomy, pneumonectomy), demograph-

ics (age, gender) and the level of care that they received (standard care or ROC programme participant) during their first year after surgery. Although smoking behaviour was not a criteria for sampling, the sample represented a broad range of behaviours including non-smokers, ex-smokers and those who were smoking at diagnosis that either quit, attempted to quit and relapsed or continued to smoke. The diversity of the final sample of participants represents a main strength of this study.

Although the sample was represented by patients belonging to each of these sub-groups above, the sample included participants of white British ethnicity only. Participants were recruited in batches, and the diversity of the sample in terms of sub-group representation was assessed on an ongoing basis, with this process informing the characteristics of patients that were invited to be interviewed in future recruitment batches. Participants' clinical and demographic characteristics were recorded confidentially in a spreadsheet. I realised late in the process that no patients from ethnic minorities had been recruited, possibly because I had prioritised ensuring sufficient sampling of clinical sub-groups over this demographic sub-group. To rectify this, I attempted to interview some patients who belonged to this demographic group. However, I was unable to find a patient fulfilling this criterion that was available and willing to be interviewed within the time frame that remained for conducting interviews.

To avoid this in the future, rather than listing details of recruited patients on a spreadsheet, mixed with other administrative details, I will ensure that a separate spreadsheet is constructed for a tally to be made of participants who have been recruited that represent the sub-groups of interest to the project. This will more readily identify patient sub-groups that are under represented by the sample. Despite this omission, there is no reason to believe that the health challenges faced by participants after surgery would greatly differ based on ethnic background, if these challenges are largely biologically determined. However, the attitudes towards recovery, smoking cessation and additional supportive care needs may not be generalisable to those from different ethnic or cultural backgrounds. To fully explore the impact of health challenges on recovery, the attitudes towards recovery and needs of patients from different cultural background, future

studies need to include these groups to understand how they differ and how supportive care can be further tailored to the needs of these populations.

Whilst considering the transferability (i.e. representativeness[270]) of the findings, i t should also be noted that participants in this study were recruited from one hospital only. Although this hospital is a tertiary referral centre for thoracic surgery, and therefore the catchment area for patients is large, there may be regional variations in the amount of supportive care offered to patients. However, at the time of interview, this hospital was the only known place in the country to be piloting a programme aimed at rehabilitation. In addition, according to the 2011 National Lung Cancer Audit report [48], 91.7% of patients within this hospital trust were seen by a Clinical Nurse Specialist which was above the national average of 75%. It is likely, therefore that participants in this study received the same or better supportive care than others in the country.

An additional consideration regarding transferability of the findings is of the potential for sampling bias. Given the qualitative methododology used, random sampling is not necessary.[219] The purposeful nature of sampling involves non-random selection of patients in order to represent diversity. However, these sampling decisions, as outline above, should be based on predetermined patient characteristics. Bias would occur if inclusion of participants in the final sampling was based either on recruiter knowledge of patient experiences/views or if participants are more or less likely to participate based on their knowledge of the project.[200]

It is possible that bias may have been introduced by the research nurse/physiotherapist who initially contacted patients. Patients that fulfilled the inclusion criteria for the study were sampled from a list of all patients who had received surgery for lung cancer at Heartlands Hospital during the course of recruitment. Although I informed the research nurse/physiotherapist of the inclusion criteria, and of the characteristics to be purposefully sampled, due to ethical constraints I was not involved in the decision process regarding which patients would be contacted.

The research nurse/physiotherapist were not involved in the care of patients who received standard care; however, they were involved in the day-to-day running of the ROC programme (i.e.

recruitment and collection of research measures). This meant that they had prior knowledge of the patients who were enrolled on this programme. It is possible that participants who had been particularly difficult or expressed issues with the programme may have not been given the opportunity to participate, or vice versa. Data regarding eligible patients who were not contacted by the research nurse/physiotherapist was not available to myself due to ethical constraints. Therefore, it is not possible to tell if the selection of these patients was biased. This is a potential limitation of the findings that the ROC programme was well received by participants, and there may have been additional issues with the programme to those that were identified. To avoid this in future qualitative studies that I run, I will include explicit instructions to guard against this type of bias.

There is also potential for bias to have been introduced through non-participation. By choosing to recruit patients throughout 3-12 months after surgery rather than all at 12 months, the risk of non-participation due to death (i.e. survival bias) was reduced. However, there may have been patients who died within the first three months after surgery who were not interviewed. Survival to one year after surgery is high at 80%,[216–218] and is likely to be higher to 3 months. Therefore, the potential for survival bias to have affected the findings is regarded as minimal. In addition, given this thesis focuses on the experiences and care needs of survivors (rather than patients eligible for palliative treatment), the experiences of those who die within 3 months are not as relevant.

Although influence of survival bias was deemed to be low, there is a possibility of selection bias due to non-participation for other reasons. Ten of the patients who were identified as eligible did not participate. Various reasons for non-participation were given, including not interested, not the right time or they didn't answer their phone. It is possible that for some the underlying reason was that they felt too unwell to be interviewed. If the sample was biased in this way, the findings would have underestimated the extent to which patients are affected after surgery. Another underlying reason for non-participation may have been that patients were not comfortable to talk about the proposed interview topics. In general, this is particularly

problematic for discussion of sensitive issues. Of all the topics discussion at interview, patients' smoking behaviour and attitudes were thought to be the most sensitive. During the initial phone contact by the research nurse/physiotherapist, patients were given a broad description of what the interview was about and smoking was not specifically identified. When I called patients who were willing to participate, I gave a more detailed description of the aims of the interview, which included smoking. Many of the patients would begin to start telling me about their smoking during this conversation, and were not apparently uncomfortable talking about it. This was also my experience during interviews. Although some patients may not have participated because they felt uncomfortable about their smoking, the experience of consent and talking to patients makes me concluded that the findings regarding smoking are likely to be transferable (i.e. representative).

The interview Using a semi-structured one-to-one interview format, I was able to obtain rich descriptions of participants' experiences and attitudes, and the meaning and impact attributed to experiences by individual participants. As noted by Barbour [208], semi-structured interviewing *"allows for the ordering of questions to be employed flexibly to take account of the priority accorded each topic by the interviewee."* A strength of using this approach is that participants are able to indicate which topics were of the most importance to them, meaning that issues raised by the participants in this study were those that were 'at the forefront of their minds' and, therefore, of priority. Encouraging participants to 'tell their story' as they had experienced it, allowed participants to initiate the discussion of topics of importance to them and gave participants the freedom to define issues and express their views in relation to their care needs in their own way. It is possible that there were topics that may have also been priority but were not initially raised because participants found them difficult to discuss. To take account of this, after having built rapport with participants, I asked if there had been 'anything else' that they had struggled with. A few participants proceeded to disclose difficulties that they had not mentioned at first, but generally, given the opportunity, participants did not feel that there were any topics that were left unraised.

A challenging aspect in the design of this study was the ability to accurately capture participants' health experiences, which evolved during recovery, through the first year after surgery. It would have been preferable to conduct serial interviews with participants throughout the first 12 months to see how their experience evolved. However, due to time and budget restraints, participants were interviewed once only. Instead of interviewing all participants at 12 months and asking them to describe how there health experiences had evolved since surgery, participants were interviewed at different time points between 3-12 months after their surgery. As has already been described, the strengths of this chosen method were considered to be minimisation of the potential for recall and survival bias. Although, in general, participants health improved, a weakness of recruiting people at different time points is that it is not possible to be sure of the full trajectory of all patients. As all participants were interviewed at least 3 months after surgery, a full account was given by all participants of this period; however, in effect, cross sections of experiences were elicited throughout the time period between 3 and 12 months through different sub sets of participants. However, if sampling was relatively unbiased at each time point and, considering the low death rate, then it is likely that the findings will be representative of the range of experiences that patients may report throughout this period.

Although it was useful to interview patients contemporanously about experience during 3-12 months after surgery, an additional limitation of the study design was that there would be varying degrees of recall bias between participants' accounts of how experience evolved. For example, those who were interviewed at 3 months would likely recall their experiences during these first 3 months after surgery more precisely than participants who were interviewed at 12 months. Collecting data on the evolution of experiences also posed challenges, as often participants would skip between past and present, particularly if they were still experiencing the health challenge. This lead to some confusion, particularly in the earlier interviews, regarding the time point that the participant had experienced the health challenge that they were describing. As I proceeded to complete more interviews, I became more adept at explaining to participants that I was wanting to understand how their experience had evolved over time and at keeping them on track with that pursuit. In earlier interviews I found myself asking leading questions to clarify

timing in participants' accounts, such as *"so the breathlessness started straight after surgery, did it?"* for example. However, I learned to turn this type of prompt into a non-leading open question of clarification such as *"so when did you first notice that you were breathless?"*

Although I was able to gain in-depth understanding regarding the recovery experiences of patients over the full course of the first year within one interview, as previously mentioned, an alternative approach to the method taken in this study would be to conduct serial interviews with each participant at different time points. This would give greater precision as to how the experience evolves over time, and direct comparisons between all interviewees at each time point could be made to understand different experiences. This approach has previously been advocated for gaining an understanding of dynamic health experiences.[272] In addition, serial interviews can enable the development of a relationship between the participant and researcher which may facilitate the discussion of personal and sensitive issues. Conducting multiple interviews with the number of participants recruited in this study was outside the scope and constraints on time of this study. However, in order to gain a clearer view of the evolution of participants' health experiences and care needs over time, this method may be more appropriate for future research of a similar nature.

In addition to capturing evolution of experiences over time, exploring participants' attitudes towards post-surgical supportive care and discussion of their ideas for the content and format of a rehabilitation programme posed some challenges. This was particularly the case for those who had received standard care. There were a few possible reasons why this was difficult. First, although it was explained to participants at the beginning of the interview, and sometimes reiterated during interview, that highlighting unmet needs would not be taken as a bad reflection on the hospital staff, there was sometimes a feeling that participants did not speak candidly about their attitudes towards gaps in the present service and future supportive care. When being asked to evaluate their experience of care, some participants did not move beyond explaining that the health professionals involved in their care had done their best. It is possible that this participant group found the interview particularly difficult because their generation are not as

familiar with the concept of patient involvement in service development as maybe people from younger generations. Participants' use of language often represented themselves as grateful users of a service which was administered by experts, and they may have felt uncomfortable offering constructive criticism.

Second, even if participants felt comfortable highlighting areas of unmet need, often they were not able to specifically imagine or articulate what kind of service they felt they needed in the absence of that service. It was possible that a single one-to-one interview was not the best method of facilitating this kind of discussion with participants, particularly when the interviews had also focused on a number of other topics. It is possible that participants would be in a position to fully reflect on their attitudes towards services if this was the single subject of an interview, and also if they were presented with a range of options to stimulate discussion and help understanding of what might be possible. For those who had participated in the ROC programme, discussion regarding their attitudes towards care and the design of a rehabilitation programme were easier, although again participants did not provide an in-depth critique of the programme and did not offer specific ideas for improvement, although they had indicated needs that remained unmet in earlier discussion within the interview. In future work, this may be overcome by conducting more that one interview thus giving the time to focus on this aspect of discussion in more depth, and by providing options for design change with visual prompts within the interview to stimulate discussion.

Reflecting on my experience of conducting the interview, I found the process a little unnerving, particularly for the initial interviews. In summary, this came down to two reasons. First, as noted by Barbour [208], qualitative interviewing is somewhat a rarefied version of normal human interaction. Although I knew this in theory before conducting the interviews, I found this uncomfortable at the beginning and had to adjust to the mindset of an impartial researcher. After some of the earliest interviews, I realised that I had fallen into the trap of trying to help the interviewee feel that I was 'on their side'. I was conscious of raising participants' awareness of their situation, asking them what help they felt they needed and then not being able

to address these concerns. In the initial interviews, I often finished participants' sentences in what I quickly recognised was an unnecessary attempt to show that I had understood and 'back them up'. I realised that this may also have the undesirable effect of leading participants, and participants may not have felt able to challenge my interruptions if I had not fully understood what had been explained. After I realised that I was doing this, I made a conscious effort to stop this practice and allow the participant to explain their thoughts without interference. As I became more experienced at interviewing, I was more able to distance myself emotionally and empathetically from interviewees, and act as a non-leading prompt, guiding participants to discuss issues of relevance to the interview aims.

Second, I found interviewing challenging initially because I was concerned about a lack of rigour. This is an example of an uncomfortable departure from quantitative approaches. This is a common experience according to Barbour[208], who also goes on to explain that *"There is a bit of an art to asking questions that departs very markedly from the approach favoured in fixed-choice formats"*. Whilst interviewing participants, I was also conscious of the recommendation given during my training, and by a number of experts in this area, to anticipate the analysis while generating data, and to ensure that you have sufficiently probed an area during interview.[199, 200, 208] Combining these two elements, I found I had to adjust to participants describing phenomena in different ways, in different orders and from different perspectives, and that, as is necessary with semi-structured interviews, I was using questions that were often phrased differently, depending on how the interview evolved. In earlier interviews, I found myself trying to re-cover ground that had already been covered in order to ensure that when I got to the analysis I would not have missed out probing on important areas and in an attempt to ensure that participants' accounts were directly comparable. As mentioned before, often participants did not give strictly chronological accounts, and I also found myself interrupting the flow of their accounts trying to bring participants back to points in the story where they had jumped. This often had the effect of participants restarting the story at that point but then veering off on other tangents before providing the clarification I had sought. It took a few interviews to strike the balance between understanding where clarification of points and chronology were important,

and where clarification was not needed and would just lengthen the period of time spent on issues that were not important. In addition, as I gained more experience, I found myself being able to be more direct with participants regarding what was of interest and what was a tangent (such as their views on the food and nursing care that they received whilst an inpatient).

The analysis A strength of the analytical method used for this study (framework approach) is that it allows themes to be ordered under pre-existing headings. This allowed me to analyse the data from the perspective of the pre-defined interview aims, whilst remaining grounded in the data and also exploring unanticipated themes emerging within each aim. As outlined by Richie and Lewis [200], analysis of the data was an iterative process, and a coding tree was constructed and modified as the process of interviewing and analysis continued. At the time that I began this, a new version of NVivo (version 9.2) was released that merged the functionality of this widely used and well developed package for qualitative analysis with functions that had been available previously using FrameWork software. Using NVivo 9.2 allowed me to be able to code data and build framework matrices within the same package. This helped me to keep track of the data through the analysis trail, from interview transcript, through to coding and summarising the data, ensuring the analysis remained grounded or in other words that fidelity to the underlying data was maintained in the summaries making the analysis credible.[199]

Iterative analysis also allowed me to assess whether 'saturation of themes' had been reached within participant sub-groups and for the different study aims. The material covered in the interviews was complex, and although I was confident saturation of themes had occurred for the majority of themes, some sub-themes within participant sub-groups may not have been explored to exhaustion. For example, although there were only six participants that had undergone a VATS procedure, I am confident that saturation of themes was reached in terms of the first and third aim of the project, as interviews with both participants who had undergone thoracotomy and those who had undergone VATS were not generating any new themes for these aims. It is likely that a smaller number of participants who had undergone VATS were needed because this surgical procedure did not impact participants to the same degree as thoracotomy, and their

experiences were less complex. However, within the group of participants that had undergone VATS, there was only one who had participated in the rehabilitation intervention pilot and one who was a smoker. It is therefore likely that saturation of themes within the VATS surgical sub-group was not reached for interview aims two and four. It is possible that participants' attitudes to smoking may differ in those who have undergone thoracotomy compared with those who had undergone VATS, due to the higher impact of the former on health and functioning. Those who had undergone VATS did not report needing extra supportive care and are likely to represent those who would benefit least from a rehabilitation programme. However, this could not be ruled out given the small number of patients interviewed.

Dependability (i.e internal validity [270]) of the analysis is subject to rigorous identification of themes and coding of interviews, and elimination of investigator bias or error.[270] Investigator bias or error may manifest as an incorrect definition of emerging themes/sub-themes, as assigning data to themes/sub-themes to which they did not belong or by missing relevant data for coding altogether. The potential for these biases/errors in identification of themes and in coding of data were minimised using two methods. First, my supervisor independently coded five interviews throughout the series of interviews (PID1, PID4, PID9, PID12, PID17) in order to compare our indexing decisions on the evolving coding structure. My supervisor coded data blind to my coding assignments, using the coding structure that I had created (inter-rater reliability[205]). It was deemed appropriate for my supervisor to use the created coding structure as it was largely defined by the interview aims, although the appropriateness of emerging themes and sub-themes were also double checked. Our decisions regarding assignment of data to main themes were largely the same. However, coding decisions regarding sub-themes were not an exact replica. Differences were mainly of three main types: 1) assigning a different amount of contextual data around a quote, 2) failure to code data under all of the themes which it was relevant to, 3) differences in the language used to define emerging themes, each of which were resolved through discussion.

Checking inter-rater reliability whilst the coding structure evolved minimised the potential for

investigator bias to affect the coding structure (and therefore identification of emerging themes). However, it was possible that data within unchecked interviews had been missed, especially when they were relevant to more than one theme. To overcome this, a second method was used to minimise investigator bias/error. Specifically, this involved running queries in NVivo to retrieve portions of the interview script that referred to key words that identified main topics and themes (see appendix A.17). Queries were carried out to identify data relevant to the themes of breathlessness, pain, fatigue and sleep, appetite and weight loss and smoking. However, due to a lack of common key words that could identify data relevant to the themes of attitudes towards recovery, supportive care received or preferences for a rehabilitation programme, queries were not for these themes. Running queries minimised the potential for missing relevant data for coding. All conscious effort was made to objectively assess the relevance of data to themes and sub-themes, which was done in the context of understanding derived from a non-clinical background. Overall, it was considered that the potential of the findings of the study to be affected by investigator bias were reduced to a minimum.

4.3 Conclusion

This study has investigated the health and supportive care needs of surgical lung cancer patients during the first year after surgery. Participants were found to experience a number of ongoing health challenges to varying extents, which often limited function. For many, health challenges had been a source of emotional distress. Health and functioning was compromised to the greatest extent after thoracotomy. Although there were some participants who were satisfied with the level of support they received in standard care, there were many whose needs were not met and they were unsatisfied with standard care. It is possible that treatments and services that are widely available to other patients may be beneficial to surgical lung cancer patients. In particular, breathlessness and pain emerged as dominant challenges during recovery, and pulmonary rehabilitation was found to be a promising template on which to build a tailored rehabilitation intervention. Participants who had access to inhaled corticosteroids and

bronchodilators reported that this helped them manage breathlessness, and in addition access to specialist pain management was highly valued. There is a strong rationale for the integration of smoking cessation support into standard care, and participants in this study felt that it was the place of health professionals involved in their care to ask them about their smoking and were open to offers of support. On the foundation of the ROC programme design, which was based on COPD rehabilitation, design components identified as important for a tailored rehabilitation programme based on the expressed needs and preferences of participants have been suggested (see table 4.2). Future work is needed to assess the acceptability of the proposals to clinicians and patients, before a final design of the programme can be taken forward and tested for effectiveness.

4.3.1 Identified research priorities

The following is a list of research questions that have been identified based on the findings of this study:

1. What is the best method to measure breathlessness after surgery and to what extent can breathlessness after surgery be attributed to physiological and psychological factors?
2. What are the most suitable and effective pharmacological and non-pharmacological treatments for post-surgical breathlessness?
3. What are the most suitable and effective identification tools and treatment protocols for lung cancer patients experiencing enduring post-surgical pain?
4. Assess the acceptability of the proposed components for a tailored rehabilitation programme to health professionals and patients and design a final programme for testing.
4. What is the effectiveness of a tailored rehabilitation programme based on pulmonary rehabilitation in improving symptoms that have been identified as important by participants in this study (breathlessness and pain, and secondarily appetite, sleep disturbance and fatigue), QOL measures, respiratory function, respiratory complication rates and survival.

CHAPTER

FIVE

INVESTIGATION OF THE ASSOCIATION BETWEEN SMOKING HISTORY AND LUNG CANCER PROGNOSIS: SYSTEMATIC REVIEW WITH META-ANALYSIS AND META-REGRESSION

5.1 Review questions

1. Main question: What is the association between smoking history (in terms of presence of a smoking history, recency of smoking history or intensity of smoking history) and the risk of all cause mortality, cancer specific mortality, development of a second primary tumour or tumour recurrence in lung cancer patients?
2. If an increased risk is found, can this be explained by reduced eligibility for curative surgical treatment?
3. If risk is not totally explained by eligibility for curative surgical treatment, is increased risk in surgical patients explained by histology, stage at diagnosis or presence of co-morbidity?

5.2 Introduction

The causal role of smoking in the development of lung cancer has previously been discussed in detail (see section 1.3.2). In brief, smokers aged 55 years and over have around a 26 fold age-adjusted increased risk of dying of lung cancer compared to those who never smoke.[23] Around 40% of patients are current smokers at the time of diagnosis, and most patients have a history of smoking.[144] Past literature has focused on the role of smoking in developing lung cancer.[23, 31] However, the influence of smoking history on prognosis has received less attention. Although various studies have been published in this area, this evidence has not been systematically reviewed and there is no consensus on the prognostic significance of smoking history in lung cancer.

Understanding the prognostic significance of smoking history is important for a number of reasons. First, it has been recognised that the current system of follow up care for cancer patients is not sustainable as the number of patients requiring follow up in the future is predicted to rise (see section 1.7.2).[177] Currently, all cancer patients receive regular specialist follow up appointments with the primary aim of checking for tumour recurrence.[47] In the future, surveillance is likely to be prioritised based on risk and therefore understanding the prognostic significance of smoking history may be important for risk stratification.[182] Second, improvements in prediction of prognosis may aid patient counselling, and help in clinical decision making. For example, improved prognostic information is of potential importance for patients of borderline fitness for surgery and may help the clinician or patient to decide on a most appropriate course of action.[273] Third, investigation of the prognostic significance of smoking history using both all cause mortality and cancer progression related outcomes may shed further light on the the mechanism by which smoking history may affect prognosis, and the role of co-morbidity in the prognosis of lung cancer patients.[274] Fourth, smoking history is not generally used as a stratification factor in clinical trials. However, if smoking history independently predicts prognosis, this should be taken into account in future trials.[273]

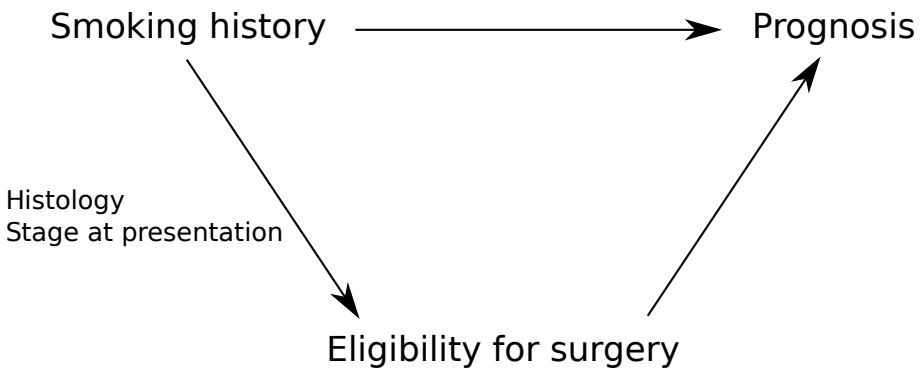


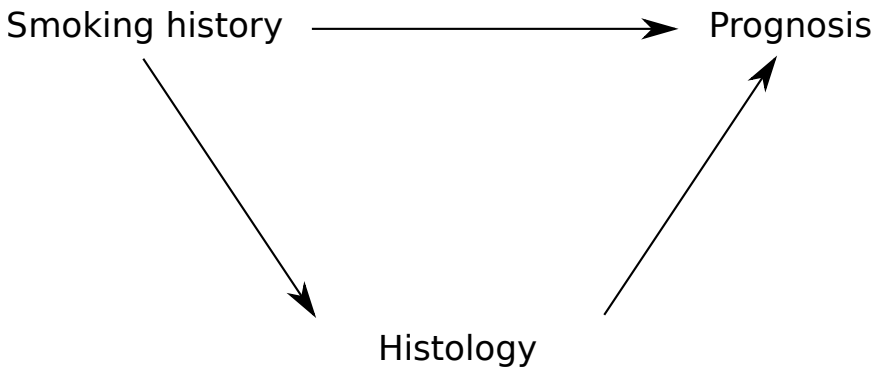
Figure 5.1: Hypothesis 1: smoking history is associated with an increased risk of death as it decreases eligibility for surgery. If this is true, smoking history would not be associated with risk when sub-grouping studies based on treatment.

There are a number of different pathways through which smoking history could influence the prognosis of patients with lung cancer. In addition to investigating the association between smoking history and prognois, these pathways have also been investigated and for clarity are outlined in figure 5.1 and 5.2. It is possible that having a history of smoking reduces eligibility for curative surgical treatment (hypothesis 1 - see figure 5.1).[1] The decision to proceed with surgical treatment is largely dependent on disease stage at presentation and also patient fitness,[47] and receipt of surgery greatly improves prognosis.[57] Smoking is more strongly associated with factors that reduce eligibility for surgery i.e. the development of more aggressive tumour histologies, later presentation and compromised cardiorespiratory function due to smoking related diseases. [31, 39, 275] If smoking history influenced prognosis by reducing the chance of being selected for surgery, it would be expected that in a stratified analysis based on receipt of surgical treatment no association would be found in each stratum. In this case, smoking history would not be a prognostic factor for patients treated with surgery.

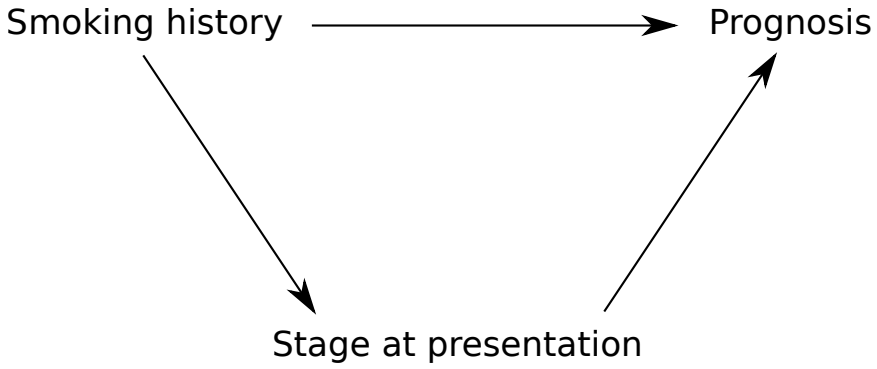
However, it is also possible that smoking history does hold prognostic significance for surgical patients. I have hypothesised that in surgically treated patients, smoking history may be associated with a worse prognosis due to reasons related to cancer (hypothesis 2-3, see figure 5.2)

[1]This is because surgery is a curative treatment, which significantly improves prognosis. Although either surgery or radiotherapy can be administered with curative intent,[47] the mainstay of curative treatment is surgery. Studies in this review did not include any patients that had been treated with radical radiotherapy. Therefore, only mediation by surgical treatment for curative intent was investigated. Exploration of the relationship between smoking history and prognosis was subsequently confined to curatively treated surgical patients only (hypothesis 2-4), as this patient group is the focus of this thesis.

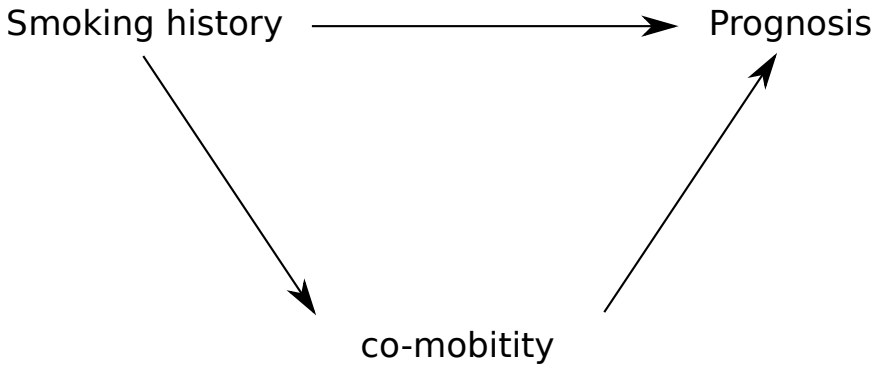
or that are unrelated to cancer (hypothesis 4, see figure 5.2). Tumour histology and stage of at diagnosis[41, 276] have both been shown to be independent prognostic markers in surgical patients. This means that these cancer-related factors can increase risk of death in additional ways than indicating treatment, although the mechanisms by which this may happen are a matter of ongoing research and not fully understood. It may be that even though surgery was apparently successful, patients with a smoking history are still at a greater risk of dying because they are more likely to have been diagnosed in a later stage (i.e Stage IIIa instead of Stage Ia for example, both are eligible for surgery) or with a more aggressive tumour (i.e. squamous cell carcinoma rather than adenocarcinoma). Alternatively, co-morbid disease has also been shown to be an independent prognostic factor for surgical patients.[60, 277] As patients with a smoking history are more likely to have co-morbid disease, this factor which is unrelated to cancer may explain an increased risk of death associated with smoking history in this group.



(a) Hypothesis 2



(b) Hypothesis 3



(c) Hypothesis 4

Figure 5.2: Hypothesis 2–4: These are tested in surgical patients only. Smoking history may cause increased risk due to a more aggressive tumour histology (hypothesis 2) or later stage at diagnosis (hypothesis 3) which leads to a greater chance of the cancer recurring. If this is true, risk of both all cause and cancer-related mortality would be raised. Alternatively, patients with a smoking history may have an elevated risk of dying due to other co-morbid diseases (hypothesis 4). If this is true, risk of all-cause mortality would be raised only.

The relationship between smoking history and prognosis, and these hypothetical pathways through which a relationship might operate were investigated by systematically reviewing observational longitudinal studies. In addition to comparing patients with smoking history (ever smokers) with those without a smoking history (never smokers), the importance of recency (current, former, never smokers) or heaviness of smoking history (pack years) was also investigated.

5.2.1 Theoretical and methodological considerations

It has previously been acknowledged that systematic reviews of observational prognostic studies pose a number of challenges.[273] The following section outlines these challenges and also describes the rationale for the methodological approaches that have been taken.

Study design and confounding Randomised clinical trials are the most robust study design to determine the size of an association between two variables from primary data, normally healthcare treatment and treatment outcome. This is because randomisation ensures equal distribution of potential confounding factors between randomisation groups. Assuming results are not influenced by post-randomisation bias, a statistically significant difference between groups is considered evidence of treatment being causally related to the outcome.[278] It is not possible to randomise people to a level of smoking history, making randomised controlled trials an unsuitable study design to investigate the questions posed by this review.[279] Therefore, data from longitudinal observational (cohort) studies have been used.

Cohort studies are the second most robust study design in the hierarchy of evidence,[280] and are the only suitable observational study design to consider prognostic outcomes using time to event data, as this type of data necessitates a follow up period. For meta-analysis of observational data, combination of individual patient data is most favourable.[273] This is because in studies that employ an observational design, it is possible that confounding variables are not balanced between exposure groups, obscuring the true effect. Although groups may not be balanced at the start, the use of individual level patient data enables modeling of the data in a

uniform way and confounding factors can be adjusted for and moderation/mediation explored in the same way as if all data had originated from the same study.[273]

In the absence of individual patient data, association between two variables can also be explored using study level estimates as has been done in this review. However, this method does pose some challenges with regards to control of confounding.[281] [2] Prognostic studies may present study level estimates that are adjusted and/or unadjusted for confounders As exposure groups are not randomised, the unadjusted model may be subject to uncontrolled confounding. Baseline characteristics may be presented for the study group as a whole, or by the exposure of main interest for that particular study. However, if baseline characteristics are not presented by the exposure of interest to the review, it is not possible to assess if potential confounders are unbalanced. Although 'best fit' adjusted models may be chosen for use within systematic reviews of prognostic studies to over come this difficulty, often studies use different adjusted models which can create difficulties for interpretation if pooled.[273]

[2]Confounding factors are associated with the exposure and also the outcome, but do not lie on the causal pathway between the exposure and outcome (see figure 5.3)

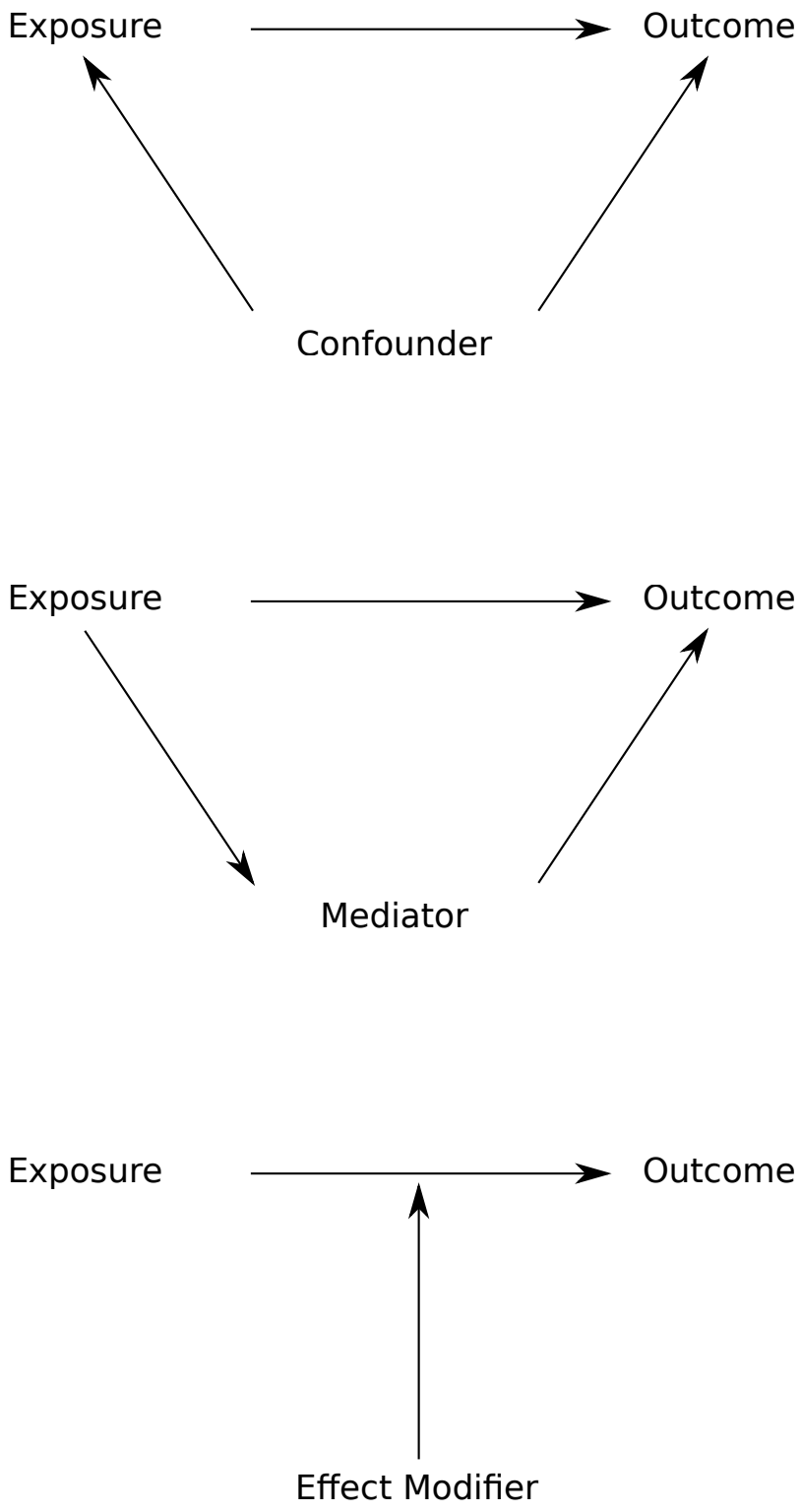


Figure 5.3: Diagramatic reprentations of confounding, mediation and effect modification

For this review, it was decided that unadjusted estimates would be used as a basis for the analysis. This decision was taken due to the difficulty in interpreting a combined estimate of models adjusted for different factors. Interpretation was considered to be particularly challenging for this review, as from scoping searches it was clear that many studies presented models adjusted for both potential confounders and also modifiers and/or mediators [3] e.g. tumour histology, stage, treatment and co-morbidity. When mediators are controlled for in a regression analysis, the association between the exposure and outcome partially or completely disappears, depending on whether the association is partially or completely mediated through the third variable of interest.[282] Therefore, it would not be possible to assess the effect of smoking history itself on prognosis using an estimate adjusted for mediators. Using an estimate controlled for a modifier would give an average estimate of the association between smoking history and prognosis across different strata, and the size of association would be better explored within individual strata of the modifier.[281]

For these reasons, it was considered that unadjusted estimates should be used. In order to assess the potential for uncontrolled confounding that would arise due to using unadjusted estimates, baseline characteristics by smoking history exposure group were extracted where presented. Both age and gender predict smoking behaviour,[283] and these factors have also been shown to be independent prognostic factors in lung cancer.[284–287] These factors were considered to be the main possible confounders. A full consideration of the potential for uncontrolled confounding to influence the results is given in the discussion section of this chapter.

Due to many of the difficulties outlined above, some have argued against meta-analysis of observational studies using study level estimates.[288, 289] However, others have argued that the inherent difficulties do not preclude meta-analysis, but that the emphasis should be on exploration of heterogeneity rather than quantifying the magnitude of the true effect.[273, 290] This latter approach has been taken for this review.

[3] A modifying factor is a third variable that, when present, alters the size of the association between exposure and outcome. In contrast, a mediating factor is a third variable that lies on the causal pathway between the exposure and outcome (see figure 5.3).

Heterogeneity and investigating effect modification Statistical heterogeneity indicates that studies in a meta-analysis are estimating different underlying values of effect size. There are two main sources of heterogeneity, clinical characteristics of study participants and methodological difference between studies.[291] Methodological heterogeneity is present when study design or outcome measures lead to measurement of different quantities. For example, in this review, it is possible that differences in the way that smoking exposure is measured (e.g. retrospectively from case notes or prospectively with biochemical validation) may lead to differences in effect size. In this case, the underlying 'true' effect size may be the same, but studies are not measuring exactly the same aspect of the effect. Clinical heterogeneity is present when the 'true' underlying effect size differs between clinical populations. The factor that defines the clinical population is said to be an effect modifier (see figure 5.3).[282, 291] For example, I have hypothesised that risk of death associated with smoking history may be modified by receipt of curative treatment.

Modification was investigated using sub-group analysis, and study sub-groups were formed based on participant characteristics within each study. If the size, or direction, of the association was found to be different between two sub-groups this was interpreted as modification by the factor that defined the sub-group.[281] In addition, the effect of sub-grouping on heterogeneity was noted using I^2 statistic which gives the percentage of variability due to heterogeneity of the underlying effect sizes rather than chance. Heterogeneity of above 50% is considered to be high, and indicates that there is more than one underlying 'true' effect.[291] If a particular clinical characteristic (e.g. receipt of surgical treatment) was acting as a modifier, then sub-grouped analyses based on the presence or absence of the characteristic should reduce the heterogeneity observed compared with when all studies are combined. However, it is widely recognised that the power of this measure to detect heterogeneity is low, and it is possible that heterogeneity exists even if not detected.[292]

It should be noted that in addition to the possibility of unbalanced confounding within studies, characteristics of patients between studies may also differ in important ways other than the

sub-grouping factor as patients are not randomised to the study that they participate in.[292] Therefore, sub-analyses must be considered exploratory, and the focus of the analysis be on observing *changes* in the magnitude or direction of the association and in the amount of heterogeneity after sub-grouping, rather than estimating the magnitude and direction *per se*.

Meta-analytic combination of study estimates can be done using fixed effects or random effects models.[293] A fixed effect model assumes that all combined studies are estimating a common effect size, and that any variability between the studies is due to chance. In other words, if each study had an infinitely large sample size, a fixed effects model assumes that they would all find the same effect size. Based on this assumption, the 95%CI are calculated using a measure of *within* study variation only (the standard error), as it is not necessary to take into account non-random variation *between* studies. In this review, pooling of study estimates was done using a random effects meta-analysis model rather than fixed effects for all meta-analyses. Random effects models assume that studies are estimating different underlying effect sizes (i.e. there is heterogeneity between study estimates and infinitely large studies would find different effect sizes).[294] Based on this assumption, calculation of the 95% CI for a random effects meta-regression includes both a measure of the variability within studies (represented by study SE) and between studies (represented by tau).[291] Random effects modeling was chosen because it was considered that there were many potential sources of both clinical and methodological heterogeneity within individual meta-analyses conducted for this review.

The interpretation of combined summary estimates generated by a random effects meta-analysis model differs from the interpretation of a fixed effects model. This is because of differences in the underlying assumptions of each model, and the way in which 95% CI are calculated. For a fixed effects model, the summary estimate gives the 'best' estimate of the single underlying effect size, and the confidence intervals depict the range in which the single effect size may fall with 95% confidence. In contrast, as a random effects model assumes that studies are measuring different underlying effect sizes, the summary estimate represents the *mean* of these different effect sizes and the confidence intervals depict the range in which the mean effect size may fall.

Thus, the 95% CI intervals do not include the full range of values that an individual underlying effect size may take.[294]

In order to estimate the full range of values an individual effect size may take, it is necessary to calculate a 'prediction interval'.[294] A prediction interval is calculated by adding the within study variance (se-squared) to the between study variance (tau-squared). This is then squared rooted, and multiplied by the 100(1- alpha/2) percentile of the t-distribution with the number of studies in meta-analysis (k) minus two degrees of freedom. Given k-2 degrees of freedom, at least 3 studies have to be included in a meta-analysis in order for the calculation to be made.[294] It was decided that the 95%CI would be reported in the text, as the focus of this review is to understand if clinical or methodological factors change the size or magnitude of the summary effect size. However, prediction intervals are also presented on forest plots in order to indicate the full range of possible underlying values.

In an exploratory analysis, the difference between sub-group estimates were tested using a random effects meta-regression. As with simple regression, meta-regression tests if independent variable(s) predict the outcome of interest, which in this case is prognosis. However, instead of using individual level data, meta-regression uses study level data. Studies are sub grouped based on a their characteristics (e.g. participant characteristics, methodological characteristic) and this sub-grouping is entered as an explanatory variable into the meta-regression model in order to assess if the outcome is predicted by these study features.[291] If the co-efficient for the sub-group term entered into the meta-regression model is significant, this indicates that the mean of the underlying true effects is different between sub-groups. In general, the more studies included in a meta-regression, the more reliable the findings, including the estimate of between study variance (tau-squared). Meta-regression is not suitable when there are fewer than 10 studies in a meta-analysis,[291] and if this was the case, sub-group differences were not tested.

Mediation Baron and Kenny proposed four steps necessary for establishing that a factor mediates the relationship between an exposure (in this case smoking history) and outcome (in

this case prognosis).[295] First, a relationship between exposure and outcome must be demonstrated. Second, the exposure must be associated with the mediating factor. Thirdly, the mediating factor must affect the outcome variable. Fourth, in order to demonstrate complete mediation by the mediating factor, controlling for the factor must abolish the relationship between the exposure and the outcome. Based on this framework, this review has attempted to explore mediation by receipt of surgical treatment, and in surgical patients only by stage at diagnosis, tumour histology and presence of a co-morbid disease.

In line with the first aim of this review, and as described earlier, the first step in this mediation model will be examined by combining all unadjusted estimates. It is known from previous studies that the hypothesised mediators are all associated with smoking history, and that they all independently predict prognosis (see section 5.2) thus establishing the second and third step outlined above.[31, 39, 41, 57, 60, 275–277] In order to establish the fourth step, it is necessary to demonstrate that controlling for the mediating factor leads to a reduction in magnitude of the association between smoking history and prognosis.

In addition to indicating modification of risk, findings from sub-group analyses could also fulfil the fourth step of the mediation analysis . Sub-grouping by the presence or absence of a mediating factor is, in effect, controlling for that factor. If sub-grouping for surgical treatment resulted in an abolishing of the risk between those with a smoking history and those without that was found when both levels of this factor were combined (i.e. surgical and non-surgical treated patient studies combined), this would indicate that the risk associated with smoking history was mediated through reduced eligibility for surgical treatment. In this case, smoking history would not be of prognostic significance after treatment, and there would not be value in further investigating the prognostic role of smoking for surgical patients. However, if surgical patients with a smoking history remained at an increased risk, it was hypothesised that this risk may be mediated through pathways that were either related to (i.e. later stage at presentation, more aggressive histology of primary tumour) or not related to (i.e co-morbidity) cancer.

A second way of investigating mediation is to investigate the effect of adjustment on the size of

association. If available, the best way to test this would be to compare unadjusted estimates to those individually adjusted for potential mediating factors within a single study. For example, smoking may causes poorer prognosis because smokers present at a later stage in their disease course. If this is true, and in the absence of confounding, studies that examine the association between smoking history and prognosis will have a unadjusted hazard ratio greater than one. On adjustment for stage, this will decrease to one.[281] Thus, all other things being equal, a meta-analysis of unadjusted study estimates will show an elevated hazard ratio and a meta-analysis of study estimates adjusted for stage will show a hazard ratio around one. Although this is an appealing idea, in practice both estimates are subject to sampling variation and residual confounding. Also, often intermediate adjusted models are not presented, and only a fully adjusted model given. Therefore, depending on what evidence is available, it may not be possible to tease out the effect of adjustment for individual potential modifiers using this method.

A third way to test for mediation is the effect of adjustment across studies. This has been done by comparing studies that adjusted for each of these variables with studies that had not adjusted for them using a dummy variable defining adjustment as an explanatory variable in a meta-regression model. The justification for this analysis is the same as for testing for modifying factors, except instead of participants or clinical characteristics being used to subgroup studies, adjustment/or no adjustment for either stage, histology or co morbidity were the sub grouping factors. Again, as with comparing estimates from within study adjustment, the ability to tease out the effect of controlling for individual potential mediators will be dependent on what multivariable models are presented within included studies.

Outside of the four step model for investigating mediation, an additional indicator that risk is mediated through pathways that are either related to or not related to cancer is the association between smoking history and different prognostic outcomes. If mediated through the first, an increased risk in both all cause mortality and also cancer related prognostic outcomes would be expected in patients with a smoking history. However, if risk is mediated through the latter, only an increase in all cause mortality would be expected.

5.3 Methods

5.3.1 Database searches

After scoping the literature to check that no relevant systematic review had previously been published, search strategies were constructed based on study inclusion criteria (see table 5.1). I searched CINAHL (from 1981), EMBASE (from 1980), MEDLINE (from 1966), Web of science (from 1966) and CENTRAL (from 1977)[4] to December 2008 (search strategies can be found in appendix B.1 - B.5). Search strategies included exploded MeSH terms and also text words relating to smoking and lung cancer. At the time of conducting the search, there was no widely accepted search strategy to identify prognostic studies.[273] However, due to the large volume of studies identified using only disease and smoking related terms, search returns were filtered in EMBASE and MEDLINE using 'prognosis-specificity' database specific filters, and in Web of Science using text words relating to the study design. All searches were combined in a reference manager database and duplicates removed. I also searched the reference lists of included studies for additional studies that may contain relevant data that had not been identified in the search.

5.3.2 Inclusion criteria

The inclusion criteria were broad in order to capture all relevant data (see table 5.1). Longitudinal studies were chosen for inclusion as this study methodology represents the most robust design available. No exclusions were made on the basis of clinical or demographic characteristics of the study population (e.g. tumour histology, tumour stage, co-morbidities, treatment) so that all possible sub-groups could be explored, if data allowed. Studies that presented any data regarding the association between smoking and prognostic outcome were included regardless of description and method of calculation.

[4]This systematic search was also used to identify studies for the review reported in chapter 6. Data relevant to this second review could potentially be generated by an RCT, therefore CENTRAL was also searched

Table 5.1: Inclusion criteria - systematic review of the association between smoking history and lung cancer prognosis

Study design	Observational cohort study (prospective or retrospective)
Population	Patients diagnosed with a lung tumour
Exposure	Presence of smoking history (ever, never) Recency of smoking history (current, former, former/never, never) or Heaviness of smoking history (Pack/years)
Outcome	All cause mortality Cancer specific mortality Development of second primary Development of recurrence

5.3.3 Data extraction

Studies were identified for inclusion by applying the inclusion criteria to the title, abstract and full text article. This was performed by myself in parallel with one other reviewer. Any differences were resolved through discussion. Data were dual extracted and cross checked for inaccuracies. Papers in languages other than English were translated. Study authors were contacted to request data if estimates could not be extracted or calculated from presented data. Studies were excluded if data were not provided upon request. Data were extracted regarding:

1. Number of participants included in the study;
2. Details of study design (prospective/retrospective, length of follow up, country of study);
3. Baseline characteristics of study participants (age, gender, histology, stage, treatment, co-morbidity);
4. Definition of smoking exposure groups and number of participants in each group; and
5. Prognostic outcomes (all cause mortality, cancer specific mortality, development of second primary, recurrence) for smoking exposure comparisons.

Adjusted and unadjusted estimates of the association between smoking exposure and prognostic outcomes were extracted as a hazard ratio (HRs) with 95% confidence intervals (CI) where

available. If studies had given more than one adjusted model, these were extracted. When HR and 95% CIs were not presented, I followed methods described by Parmar to calculate them from Kaplan Meier (KM) curves, p values, or percentage survival (e.g. five-year survival).[296] Most studies compared risk between ever, current or former smokers and never smokers. In order to assess if risk reduced over time of quitting before diagnosis, the risk in current smokers was compared to former using indirect comparison.

An indirect comparison compares the risk in two groups which have both been independently compared to a common comparator. Methods outlined by Bucher were used to calculate the indirect comparisons.[297] In order to calculate the indirect hazard ratio, one hazard ratio is divided by the other. For example, to compare the risk associated with current smokers to that of former smokers, the current/never smoker hazard ratio would be divided by the former/never hazard ratio. The variance of this is the sum of the variances of each hazard ratio that are being indirectly compared. This is calculated in the log scale. Data were also extracted regarding the risk of prognostic outcomes for categories or continuous measures of pack years. Where pack year data were presented as a continuous variable, risk estimates were converted into a per 10 pack year unit as an arbitrary amount using the log values of the HR and confidence intervals.

5.3.4 Assessment of study quality

Appraisal of the quality of studies in a systematic review is needed to assess risk of bias, and to check that findings are valid.[298] There is scant empirical evidence demonstrating which aspects of prognostic studies affect validity, and there is not a general consensus regarding how best to rate quality.[299] However, Altman proposed a framework for assessing quality of prognostic studies based on indirect evidence of factors that have the potential to introduce bias, and this has been used to assess quality for studies in this review.[300] Studies could score a maximum of 22 points based on description of the cohort and study methodology. Studies scored highly if the inclusion/exclusion criteria were well defined, if the characteristics of the patient sample were described including distribution of important confounders and prognostic factors

between smoking exposure groups, if treatment and smoking status were clearly described and if patients were followed prospectively for more than five years. The details of scoring is summarised in table 5.2.

5.3.5 Exploration of the association between smoking history and prognosis

5.3.5.1 Risk of all-cause mortality

Clinical heterogeneity Unadjusted hazard ratios comparing the risk of all cause mortality between ever smokers and never smokers were combined using a random effects inverse variance meta-analysis model. This was performed in STATA10, using the 'metan' command suite. Statistical heterogeneity was measured using the I^2 statistic.[291] It was hypothesised that significant heterogeneity would be detected between study estimates, and that in particular risk would be modified by curative treatment. To investigate this, unadjusted estimates from studies in which all received surgical treatment were compared to estimates from studies that included patients that had received non-surgical treatment. Differences between sub-groups were tested using random effects meta-regression.

Methodological heterogeneity and publication bias Using sub-group analysis, estimates that were presented as HR (95%CI) were compared with those that were calculated from data provided such as survival curves or percentage survival. In addition, sensitivity analyses were conducted to investigate if association between smoking history and prognosis was affected by the exclusion of low quality studies. The median score (8/22) for quality was determined for all studies included in the review. Studies that scored lower than the median score were considered to be of low quality. Funnel plots were constructed and visually inspected for evidence of publication bias. Plots were constructed using all available unadjusted estimates and for sub-groups based on findings of clinical and methodological heterogeneity.

Table 5.2: Criteria for assessment of study quality

Study feature	Scoring Method	Total Score
Definition of study sample		
Inclusion criteria	0 = not stated 1 = some definition but not clear 2 = clearly stated date range, inclusion and exclusion criteria, recruited at diagnosis	2
Baseline characteristics: gender, age, co-morbidity, histology, stage	0 = not described 1 = described for whole study population 2 = described by smoking exposure group	10
Treatment received	0 = not described 1 = described for whole study population 2 = described by smoking exposure	2
Study characteristics		
Exposure measurement	0 = not described 1 = obtained from medical records 2 = obtained from questionnaire/interview at time of study	2
Exposure categories	1 = 2 categories only 2 = split into more than 2 categories	2
Follow up	0 = not described 1 = $\leq$ 5 years 2 = more than 5 years	2
Study design	1 = retrospective cohort 2 = prospective cohort	2
		22

Mediation by histology, stage and co-morbidity In order to investigate mediation of risk associated with smoking history in surgical patients, three approaches were taken using data from studies that included surgical patients only. First, where possible, sub-group analyses were conducted based on histology and stage characteristics of patients in each study, using unadjusted estimates only. Second, using both unadjusted and adjusted estimates, three binary dummy variables were created that defined whether an estimate did (defined as 1) or did not (defined as 0) control for either histology, stage or co-morbidity. Studies that provided both an unadjusted estimate and an adjusted estimate for one of these potential mediators were identified. Adjusted and unadjusted estimates were combined separately, and the effect of adjustment on the HR was observed. Third, in order to use all available data, one estimate was used from each study, with preference given to an adjusted estimate if studies provided both unadjusted and adjusted estimates. Dummy variables defining adjustment for histology, stage or co-morbidity were added separately and then together into a random effects meta-regression model in order to explore the effect on the size of association.

Other analyses In order to investigate if recency of smoking at diagnosis was important in determining the association between smoking history and prognosis, the above analyses were repeated comparing current or former smokers with never smokers, current with former smokers and also current with former/never smokers. Some studies also presented estimates for smoking exposure measured in pack years, indicating the importance of heaviness of smoking history in determining risk. Most studies compared two or more pack year categories, and cut-offs varied between most studies. Where possible, meta analyses were performed for both recency and heaviness of smoking comparisons. If this was not possible, estimates were presented individually in tabular form.

5.3.5.2 Risk of cancer-related prognostic outcomes

To investigate if smoking history was associated with prognosis by increasing the risk of cancer progression, all of the above analyses were repeated to estimate the risk of developing a second

primary tumour, recurrence or cancer related mortality. Again, if there was sufficient data, estimates were combined, otherwise they were presented individually in tabulated form.

5.4 Results

Searches of bibliographic databases returned 6466 potentially relevant study titles for screening. Full text articles were obtained for 268 papers and 78 individual studies were identified for inclusion in the review (figure 5.4).

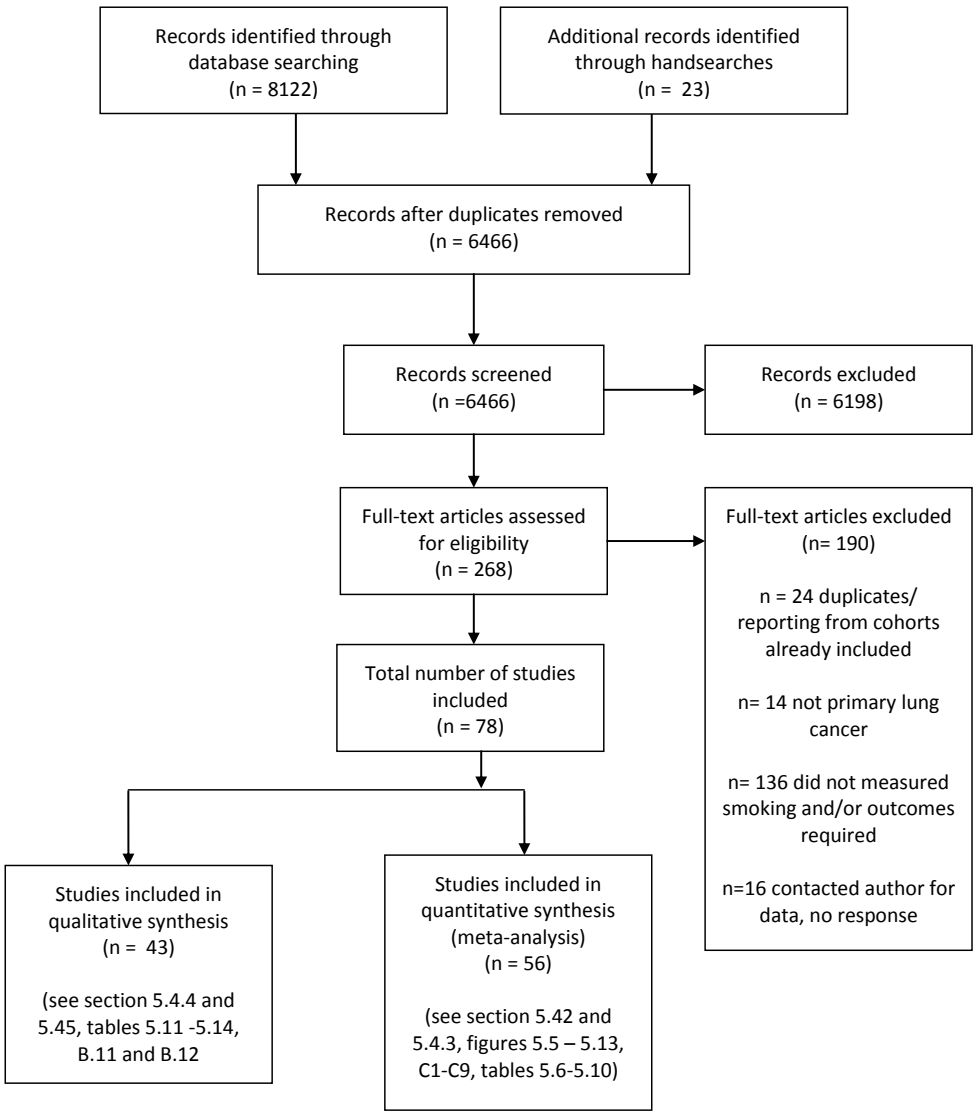


Figure 5.4: PRISMA flow diagram of study selection and use. [301] (N.B. Twenty-one studies contributed to both qualitative and quantitative syntheses [62, 137, 302–320])

5.4.1 Characteristics of included studies

Study design characteristics Most included studies focused on prognostic factors other than smoking, but had included data on smoking to assess potential confounding. Twenty two studies prospectively followed participants, and the remaining 56 studies retrospectively extracted data from hospital records at the time that the study was conducted. The earliest year that cohort studies began was 1952, and latest 2002. The median year of cohort inception was 1987. Seventy five studies reported maximum follow up which ranged from 2-24 years (median 10yrs). Twenty nine studies reported median follow up which ranged from 1-9 years (median 4.6yrs). Most studies (55%) were conducted in Asia, with the remaining studies originating from Europe, North and South America. A summary of the study characteristics of all included studies is presented in appendix B.6.

The majority of studies estimated the association between smoking history and risk of all cause mortality (74 studies), and a minority of studies reported risk of cancer specific mortality (11 studies), second primary (5 studies) or recurrence (12 studies). Some studies compared a number of different smoking exposure categories, and for different outcomes. However, the majority of studies presented estimates of the risk of all cause mortality in ever smokers compared to never smokers.

Table 5.4 reports a breakdown of the number of unadjusted and adjusted estimates available, as well as the number of studies presenting within study adjustments, by smoking exposure comparison and outcome. Adjusted estimates were extracted from 57 studies. No studies presented intermediate models of adjustment, but only the final 'best fit' adjusted model. Most studies adjusted for both confounders and more than one mediator and a summary of these adjusted models is provided in table 5.3.

Table 5.3: All adjusted model estimates extracted from included studies (1 = adjusted for, 0 = not adjusted for).

Author	Age	Gender	Ethnicity	Histology	Stage	Treatment	PS[1]	Com[2]	Other
Ademuyiua, 2007	1	1	1	0	0	0	1	0	FEV1, BMI, Hb level, PET scan
Birim, 2003	1	1	0	1	0	1	0	1	FEV % $\leq$70
Bryant, 2007	0	1	0	0	1	1	0	0	
Chatkin, 2004	1	1	0	1	1	1	0	1	FEV, post-surgical complications
Fujisawa, 1999	1	1	0	1	0	0	0	0	
Goodman, 1990	1	0	0	0	0	0	0	0	
Haga, 2003	1	1	0	0	1	0	0	0	Ki-67 LI
Hanagiri, 2008	1	1	0	1	1	0	0	0	
Hendricks, 1996	1	1	0	1	1	1	1	0	
Hinds, 1982	1	0	0	1	1	1	0	0	
Holli,1999	0	0	0	1	0	0	0	0	
Hotta, 2009	1	0	0	0	1	1	1	0	
Hung, 2007	1	0	0	0	1	0	0	0	
Isobe, 1994	0	0	0	0	1	0	0	0	ras, p53
Iyoda, 2006	1	1	0	1	1	0	0	0	
Kato, 1990	1	1	0	0	1	1	0	0	
Kawaguchi, 2006	0	1	0	1	0	0	0	0	
Kawahara, 1998	1	1	0	0	0	0	1	0	

[1]PS = performance status
[2]Com = co-morbidity

Table 5.3: (cont.)

Author	Age	Gender	Ethnicity	Histology	Stage	Treatment	PS	Com	Other
Kawai, 2005	0	0	0	0	1	0	0	0	
Kim, 2005	1	0	0	0	1	1	0	0	neuron specific enolase level
Kobayashi, 2007	1	1	0	1	1	0	0	0	CEA
Kosaka, 2009	0	1	0	0	1	0	0	0	KRAS, TP53, EGFR
Liang, 2003	0	1	0	0	1	0	0	0	cyclin D1, VEGF
Maeda, 2006	1	0	0	1	1	1	0	0	
Marsit, 2005	1	0	0	1	1	0	0	0	TP53, 9p13
Matsugama, 2008	1	1	0	1	1	0	0	0	CEA
Moro-Sibilot, 2005	1	0	0	1	1	0	0	0	
Mulligan, 2006	1	1	1	0	1	0	0	1	
Myrdal, 2002	1	0	0	0	1	0	0	0	
Nakamura, 2008	0	1	0	1	1	0	0	0	
Nia, 2005	1	1	0	1	1	1	0	1	
Nordqui, 2004	0	1	0	0	1	0	0	0	
Okada, 2004	1	1	0	1	0	0	0	0	CEA
Ramnath, 2007	0	0	0	1	0	0	1	0	tumour location
Rice, 2003	0	0	0	1	1	1	0	0	
Rui, 2006	0	0	0	0	1	0	0	0	p21, p53, p-glycosidoprotein, CD44
Sakao, 2008	0	0	0	1	0	0	0	0	CEA> 3mg/ml
Sawabata, 2006	1	1	0	1	0	0	0	0	%FEV 1.0 (<=50)

Table 5.3: (cont.)

Author	Age	Gender	Ethnicity	Histology	Stage	Treatment	PS	Com	Other
Sekine, 1997	1	1	0	1	1	0	0	0	period of operation
Shiba, 2000	1	0	0	0	1	0	0	0	Ki-67 LI
Sioris, 2000	1	1	0	0	1	0	0	0	p53, asbestos exposure
Sobue, 1991	1	1	0	0	1	0	0	0	year of op
Sun, 2006	1	1	0	1	1	1	0	0	
Takeshita, 2008	1	1	0	1	1	0	0	0	Aurora-A, CHFR
Tammemagi, 2000	0	0	0	1	1	0	0	0	p53 status
Tammemagi, 2004	1	1	0	1	1	1	0	1	illicit drug use, adverse symptoms
Tan, 2003	1	0	0	1	1	0	0	0	
Tang, 2006	0	0	0	0	1	0	0	0	P-Akt, PTEN
Toh, 2004	0	0	0	0	1	1	1	0	weight loss
Tsai, 2006	1	1	0	1	1	1	0	0	serum CEA, tumour location
Videtic, 2003	1	1	0	0	1	0	0	0	
Wolf, 1991	1	1	0	0	1	0	1	0	weight loss
Wu, 2003	0	0	0	1	1	0	0	0	
Yoshino, 2006	0	1	0	1	1	0	0	0	
Zhang, 2008	0	0	0	0	1	1	1	0	
Zhou, 2006	1	1	0	0	1	0	0	0	
Total ($n = 56$)	37	33	2	30	45	16	8	5	

Table 5.4: Number of unadjusted, adjusted and within study adjustments available by smoking exposure comparison groups and outcome

	ACM (study $n = 74$)			CSM (study $n = 11$)			SP (study $n = 5$)			REC (study $n = 11$)		
Smoking exposure categories	Unadj	Adj	Within	Unadj	adj	Within	Unadj	Adj	Within	Unadj	Adj	Within
Presence of smoking history												
ever v never smoker	17	21	8	1	1	1	0	0	0	0	2	0
Recency of smoking at diagnosis												
current v never smoker	11	8	2	1	0	0	1	1	1	3	3	2
current v former smoker	8	8	2	1	1	1	2	1	1	2	2	1
current v former or never smoker	4	6	1	0	0	0	0	0	0	2	0	0
former v never smoker	8	6	2	0	0	0	1	1	1	2	1	1
Intensity of smoking history												
categorical pack years	16	11		5	5		1	2		0	0	
continuous pack years	3	3		1	2		0	0		1	3	

[4]ACM = All cause mortality, CSM = Cancer specific mortality, SP = development of a second primary, REC = development of a recurrence, Unadj = unadjusted estimates available, Adj = adjusted estimates available, Within = within study adjustment available

Characteristics of all participants in included studies Gender was reported in all but two studies.[315, 321] Studies were conducted in a mixture of male and female participants, apart from two that solely recruited female participants.[322, 323] Of the mixed gender studies, a range of 28-93% of participants were male, with a median of 77%. Age was reported in all but 6 studies.[307, 308, 315, 321, 324, 325] Average age ranged from 60-70 years in 64 studies, was over 70 in three studies [304, 326, 327] and below 60 in five studies.[309, 328–331]

Five studies were conducted on participants diagnosed with SCLC only (all included patients received non-surgical treatment), [331–335] 12 studies were conducted on a mixture of participants with NSCLC and SCLC (SCLC = 3-21% of participant sample) [274, 322, 323, 325, 336–343] and the remaining studies were conducted on participants with NSCLC only. Of the NSCLC studies, 51/62 reported the proportion of patients diagnosed at stage I-IIIa which ranged from 19-100% with a median of 95%. Of the SCLC studies, 4/5 reported the proportion of patients diagnosed with limited stage which ranged from 38-100% with a median of 79%.

Treatment regimes varied between studies. In 51 studies, all participants had undergone surgery and some had received adjuvant therapy, patients received either surgery or chemoradiotherapy in 11 studies,[302, 303, 309, 322, 327, 339, 341, 344–347] and eight studies included no patients that had received surgical treatment.[304, 331–335, 348, 349] In 8 studies, treatment was not reported.[312, 323, 338, 340, 343, 350–352] However, these studies all included patients diagnosed at a range of stages that were both eligible (Stage 1-3a) and ineligible (stage 3b-4) for surgery so it was assumed that patients would have received either surgery or chemoradiotherapy. Studies in which some or all patients did not receive surgery were compared to studies in which all patients received surgery or surgery with adjuvant treatment to investigate moderation by surgical treatment. These will be referred to as 'surgical' and 'non-surgical' studies, respectively. A summary of participant characteristics for all included studies is presented in appendix B.6.

Characteristics of participants by smoking exposure group Sixteen studies [137, 304, 305, 307, 311, 314, 315, 320, 328, 340, 343, 351–355] described baseline characteristics by smoking

status. Balance of age and gender was assessed due to the confounding potential of these factors (see table 5.5). In all studies, a greater proportion of smoking exposure groups were male, and most 'never smokers' were female. Most studies found a significant difference in mean age at diagnosis between smoking and non-smoking groups. However, the difference was not more that 5 years, and this is unlikely to be clinically significant. Three studies reported detail of ethnicity by smoking exposure, but grouped in different ways, and no pattern emerged. No study reported socio-economic status.

Study quality Scores for study quality ranged from five to 11 out of a possible total of 22 points, with a median score of 8. Most studies lost points due to a retrospective study design, a poor description of inclusion criteria and lack of description of participant baseline characteristics by exposure group. Five of the 78 included studies described co-morbidity at baseline, and it was not possible to tell if participants in other studies did not have co-morbid disease or if it had simply not been measured. Smoking exposure was most often assigned based on retrospective assessment of clinical notes, and was split into two groups. Ever smokers and former smokers were poorly described in terms of the distribution of current smoking and of years of quitting before diagnosis. Finally, treatment and length of follow up was not described in eight and five studies respectively resulting in further losses of quality points.

5.4.2 Risk of all cause mortality associated with presence of a smoking history

Ever smokers were at a 41% increased risk of death compared to never smokers but as was expected, there was significant heterogeneity (unadjusted HR 1.41 (95% CI 1.12, 1.63), 17 studies, $I^2 = 77\%$; figure 5.5; table 5.6). When studies were combined based on surgical treatment subgroup, the findings suggested that treatment modified risk rather than mediated it. Risk was higher for patients that had received curative surgical treatment and was reduced when combining studies that included non-surgically treated patients (surgical HR 1.69 (95% CI 1.29,

Table 5.5: Distribution of age and gender by smoking categories for included studies giving baseline characteristics for smoking exposure groups

Study	Country	Date of cohort	Smoking category	Age (mean/median)[1]	Age *p*-value[1]	Gender(% male)[1]	Gender *p*-value[1]
Hanagari, 2008	Japan	1994 – 2005	≥20 PY v >20PY	n/r	n/r	90 v 29	n/r
Fujisawa, 1999	Japan	1981 – 1993	≥30 PY v >30PY	64 v 59	< 0.01	95 v 38	< 0.001
Shiba, 2000	Japan	1989 – 1992	≥30 PY v >30PY	64 v 60	> 0.05	59 v 13	< 0.0001
Kawai, 2005	Japan	1982 – 1997	≥40 PY v >40PY	63 v 67	< 0.0001	75 v 40	< 0.0001
Bryant, 2007	USA	1999 – 2005	Ever v never	66 v 53	0.04	79 v 41	< 0.001
Fox, 2004	USA	1991 – 2001	Ever v never	54 v 54	n/r	n/r	n/r
Haga, 2003	Japan	1988 – 1993	Ever v never	n/r	n/r	93 v 9	n/r
Sakao, 2008	Japan	1996 – 2006	Ever v never	64 v 63	0.89	76 v 16	< 0.001
Toh, 2004	Singapore	1999 – 2002	Ever v never	65 v 57	< 0.001	89 v 26	< 0.001
Goodman, 1990	USA	1979 – 1983	Current v former v never	n/r	n/r	72 v 76 v 32	n/r
Nakamura, 2008	Japan	1980 – 2003	Current v former v never	64 v 68 v 63	> 0.05	94 v 94 v 17	< 0.0001
Nia, 2005	Belgium	1991 – 2001	Current v former v never	63 v 67 v 65	n/r	89 v 90 v 68	n/r
Sawabata, 2006	Japan	2000 – 2000	Current v former v never	65 v 66 v 64	0.5	81 v 75 v 12	< 0.0001
Tammemagi, 2004	USA	1995 – 1998	Current v former v never	n/r	n/r	51 v 42 v 5	n/r
Zhou, 2006	USA	1992 – 2002	Current v former v never	67 v 71 v 73	$P< 0.01$	54 v 54 v 31	0.04
Holli, 1999	Finland	1983 – 1987	Heavy v moderate v light	68 v 64 v 65	0.003	99 v 92 v 72	< 0.001

[1] n/r = Not reported

2.22), 13 studies, $I^2 = 80\%$; non-surgical HR 1.12 (95% CI 1.06, 1.18), 5 studies, $I^2 = 0\%$; figure 5.5). This difference in risk approached statistical significance when tested using meta-regression ($p = 0.09$). Heterogeneity remained high for surgical patients but was not detected between estimates from studies including non-surgically treated patients.

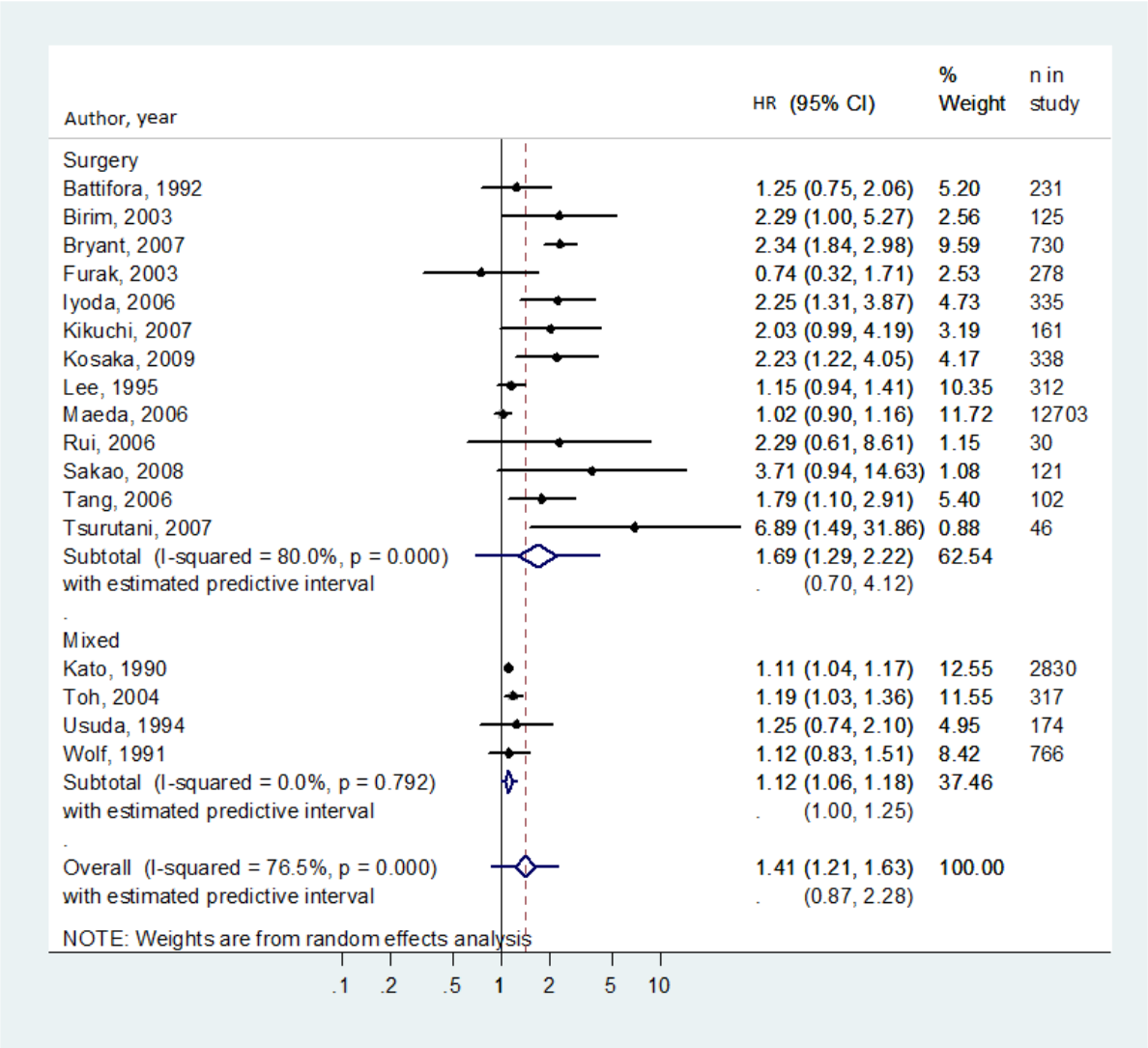


Figure 5.5: Risk of all cause mortality in ever compared to never smokers: sub-group analysis by treatment (all received surgery v none or some received surgery only)

Sensitivity analysis based on methodological characteristics of studies in surgically treated patients The robustness of the finding that risk of death is elevated for surgical patients with a smoking history compared to patients without a smoking history was investigated through sub-group analysis based on methodological characteristics. Estimates that were calculated from

Table 5.6: Characteristics of studies comparing the association between ever and never smoking and all cause mortality

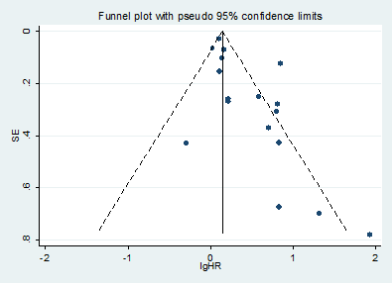
Author	Unadjusted HR (95% CI)	Male (%)	Squamous (%)	Adeno (%)	SCLC (%)	Stage 1-3a (%)	Quality Score	Study Design	Smoking exposure measurement
Surgical (all included patients received surgical treatment)									
Battifora, 1992	1.25 (0.75, 2.06)	74	56	28	4	N/R	7	Retrospective	N/R
Birim, 2003	2.29 (1.00, 5.27)	81	47	30	0	95	9	Retrospective	Medical notes
Bryant, 2007	2.34 (1.84, 2.98)	69	40	40	0	93	8	Retrospective	Medical notes
Furak, 2003	0.74 (0.32, 1.71)	55	0	100 BAC	0	88	7	Retrospective	N/R
Iyoda, 2006	2.25 (1.31, 3.87)	56	19	77	3	100	8	Retrospective	Medical notes
Kikuchi, 2006	2.03 (0.99, 4.19)	68	42	52	0	N/R	6	Retrospective	N/R
Kosaka, 2009	2.23 (1.22, 4.05)	51	0	100	0	97	7	Retrospective	N/R
Lee, 1995	1.15 (0.94, 1.41)	72	5	36	4	79	6	Retrospective	N/R
Maeda, 2006	1.02 (0.90, 1.16)	71	39	53	0	96	7	Retrospective	N/R
Rui, 2006	2.29 (0.61, 8.61)	67	37	40	20	100	7	Retrospective	Medical notes
Sakao, 2008	3.71 (0.94, 14.63)	49	0	100	0	N/R	7	Retrospective	Medical notes
Tang, 2006	1.79 (1.10, 2.91)	72	50	50	0	87	8	Prospective	N/R
Tsurutani, 2007	6.89 (1.49, 31.86)	37	0	100 BAC	0	76	8	Retrospective	Medical notes
Non-surgical (no patients in the study or only some received surgical treatment)									
Kato, 1990	1.11 (1.04, 1.17)	74	24	44	9	37	5	Retrospective	N/R
Toh, 2004	1.19 (1.03, 1.36)	66	22	55	0	19	8	Retrospective	Medical notes
Usuda, 1994	1.25 (0.74, 2.10)	71	39	49	4	71	8	Prospective	N/R
Wolf, 1991	1.12 (1.06, 1.18)	85	0	0	100	38	8	Prospective	N/R

data provided (i.e survival curves, percentage survival etc.) were found to be smaller than presented HR (95% CI) (presented HR 2.14 (95%CI 1.64, 2.79), 6 studies, $I^2 = 0\%$; calculated HR 1.38 (95%CI 0.98, 1.95), 7 studies, $I^2 = 85\%$; see figure C.1 in appendix B). Heterogeneity was high for calculated estimates. In contrast, no heterogeneity was detected between presented estimates. Difference between groups approached significance when tested using meta-regression ($p = 0.07$) and the prediction interval did not include 1 for presented estimates, but ranged from 0.49 to 3.94 for calculated estimates. This gives some evidence that larger and more precise estimates were more likely to be presented as HR (95% CI), whereas less certain estimates were generally present in other ways e.g. survival curve, percentage survival.

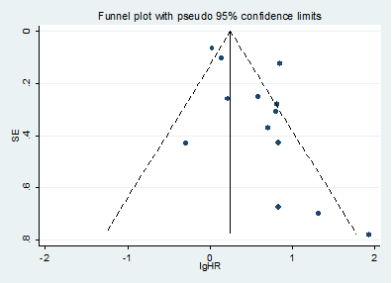
All other study characteristics that may increase the risk of bias were incorporated into the quality assessment. When confining the analysis to high quality studies only, the size of the associated risk was strengthened and there was no heterogeneity detected (surgical patients HR 2.27 (95% CI 1.87, 2.75), 5 studies, $I^2 = 0\%$; see figure C.2 in appendix B). However, it should be noted that four out of five high quality estimates from surgical studies were presented as HRs, whereas five out of seven estimates from low quality studies were calculated from other data.

Publication bias It is possible that large or significant estimates of risk associated with smoking history were more likely to be published or reported in adjusted models. To test for publication bias, funnel plots were constructed and visually inspected. As previous analyses indicated that treatment, mode of estimate presentation and study quality moderated risk, these groups were assessed separately. Funnel plots of estimates demonstrated an asymmetrical pattern, with a greater number of estimates congregating on the right hand side of the summary effect line (figure 5.6a). This remained when considering only those studies conducted in surgical patients (figure 5.6b). However, little asymmetry was detected when considering sub-groups based on mode of presentation or study quality (figure 5.6d - 5.6f). These findings suggest that publication bias may be affecting the results of the meta-analyses for clinical sub-groups. However, although the size and precision of estimate appeared to influence the way in which estimates

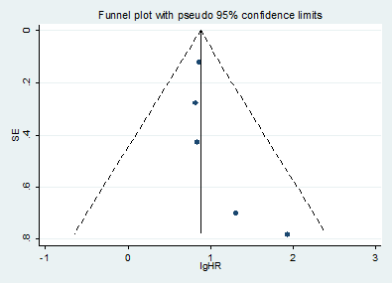
were presented, there was no publication bias within mode of presentation.



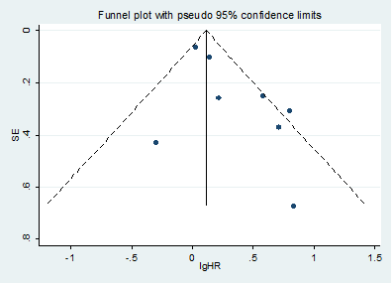
(a) All estimates



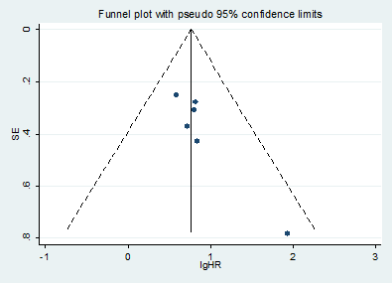
(b) Surgery only



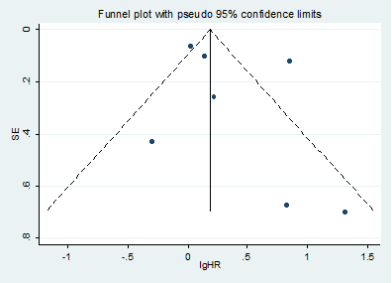
(c) High quality studies



(d) Low quality studies



(e) Presented estimates



(f) Calculated estimates

Figure 5.6: Exploration of publication bias in studies with surgical patients: funnel plots of ever compared to never smoking estimates

5.4.2.1 Exploration of mediation by histology, stage and co-morbidity in surgically treated patents

Method 1: sub-group analysis Data allowed sub-grouping of studies based on histology only, as all studies included a mixture of stages and co-morbidity was not reliably reported. Two sub-group analyses were conducted by histology. First, studies including both SCLC and NSCLC patients were compared to studies that included only NSCLC. Second, studies in adenocarcinoma patients were compared with studies that included a number of different NSCLC

histotypes. No evidence of difference was found in the size of associated risk for ever smokers compared to never smokers for either of these analyses (see table 5.7). Forest plots are found in appendices C.3 and C.4.)

Table 5.7: Risk of all cause mortality in ever smokers compared to never smokers: sub-group analyses

	HR (95%CI)	Prediction interval	number of studies	I^2	p
All estimates	1.41 (1.12, 1.63)	0.87, 2.28	17	77	n/a
Surgical treatment	1.69 (1.29, 2.22)	0.70, 4.12	13	80	
Non surgical treatment	1.12 (1.06, 1.18)	1.00, 4.12	5	0	0.09
Surgery only:					
NSCLC only	1.86 (1.24, 2.79)	0.51, 6.74	9	85	
NSCLC and SCLC	1.43 (1.01, 2.02)	0.39, 5.19	4	49	0.52
Adenocarcinoma	1.86 (0.99, 3.51)	0.26, 13.41	5	58	
mixed NSCLC	1.76 (1.07, 2.88)	0.61, 4.61	5	91	0.83

Method 2: within study adjustment Eight studies provided within study adjustments. These estimates are presented in table 5.8 stratified by adjustment for histology, stage and/or co-morbidity. Other factors that were included in these adjusted models are also presented. The findings of these analyses need to be interpreted with caution as the study quality varied but more importantly, adjusted models varied. Some models included gender and age, which were considered key confounding factors. However, others did not. The effect of adjusting for biological or genetic markers is unknown. However, assuming that adjustment for these other factors does not affect the estimate, there was some evidence that adjustment for histology decreased the size of associated risk, adjustment for stage made no difference, and adjustment for co-morbidity strengthened the estimated risk (see table 5.8).

Method 3: between study adjustment Finally, dummy variables that coded for adjustment for histology or comorbidity between studies showed similar results to within study adjustment when added to a random effects meta regression model. However, the co-efficients were non-significant (histology unadjusted HR 1.79, adjusted HR 1.28, $p = 0.18$; co-morbidity unadjusted

Table 5.8: Within study adjustment in studies conducted on surgical patients only

Study	Ever v never comparisons		Study quality	Other Adjustment
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)		
Adjusted for histology, stage and co-morbidity				
Birim, 2003	2.29 (1.00, 5.27)	2.61 (1.10, 6.17)	high	Age, gender, treatment, FEV % $\leq$ 70
Adjusted for histology and stage only				
Iyoda, 2006	2.25 (1.31, 3.87)	1.25 (0.53, 2.93)	high	Age, gender, site of tumour
Maeda, 2006	1.02 (0.90, 1.16)	1.02 (0.95, 1.10)	low	Age, gender, treatment
Combined	*1.45 (0.67, 3.12)*	*1.02 (0.95, 1.10)*		
Adjusted for stage only				
Bryant, 2007	2.34 (1.84, 2.98)	1.21 (0.98, 1.49)	high	Gender, treatment
Kosaka, 2009	2.23 (1.22, 4.05)	3.46 (1.12, 10.71)	low	Age, differentiation, EGFR status, KRAS status, TP53 status
Rui, 2006	2.29 (0.61, 8.61)	7.46 (2.67, 20.87)	low	CD44, differentiation, p21, p53, p-glycosidoprotein, size of tumour
Tang, 2006	1.79 (1.10, 2.91)	1.90 (1.30, 2.76)	high	p-Akt expression, PTEN expression
Combined	*2.22 (1.82, 2.71)*	*2.28 (1.24, 4.18)*		
Adjusted for histology only				
Sakao, 2008	3.71 (0.94, 14.63)	1.99 (0.40, 9.97)	low	Gender, CEA> 3mg/ml

HR 1.49, adjusted HR 2.01, $p = 0.59$). Unlike after adjustment within study, a non-significant increase was observed after adjusting for stage (unadjusted HR 1.36, adjusted HR 1.60, $p = 0.57$). The co-efficient for adding all three variables simultaneously was not significant ($p = 0.5$).

5.4.3 Risk of all cause mortality associated with recency of smoking history

Risk of all cause mortality was compared between current, former, former/never and never smokers in order to investigate if risk of death was lower in people who stopped smoking before diagnosis. When combining studies, regardless of patient treatment, current and former smokers were at a 54% and 56% increased risk of death compared to never smokers, respectively (current v never HR 1.54 (95% CI 1.21, 1.94), 11 studies, $I^2 = 73\%$; former v never HR 1.56 (95% 1.12, 2.18), 8 studies, $I^2 = 53\%$; figure 5.7). Comparing current and former smokers indirectly confirmed a similar magnitude of risk in these two groups (current v former HR 1.04 (95% 0.79, 1.28), 8 studies, $I^2 = 0\%$; figure 5.8). Four studies compared current smokers to a group of both former and never smokers. The risk in this comparison fell between that seen for current smokers when compared to former smokers and when compared to never smokers (current v former/never HR 1.31 (95% CI 1.17, 1.46), 4 studies, $I^2 = 0\%$; figure 5.8). Again, this is consistent with the finding that both current and former smokers were at increased risk compared with never smokers. No heterogeneity was detected between studies comparing current with former or former/never smokers. However, heterogeneity was high between estimates of both current and former smokers compared with never smokers. For characteristics of the patients included in the studies in these analyses see appendices B.11 and B.12.

As with ever compared with never smokers, there was evidence that risk was modified by treatment. Risk was strengthened when combining studies in surgical patients only for both current and former smokers compared to never smokers, and heterogeneity was reduced (surgical current v never HR 2.03 (95% CI 1.56, 2.64), 7 studies, $I^2 = 11\%$; surgical former v never HR 1.80

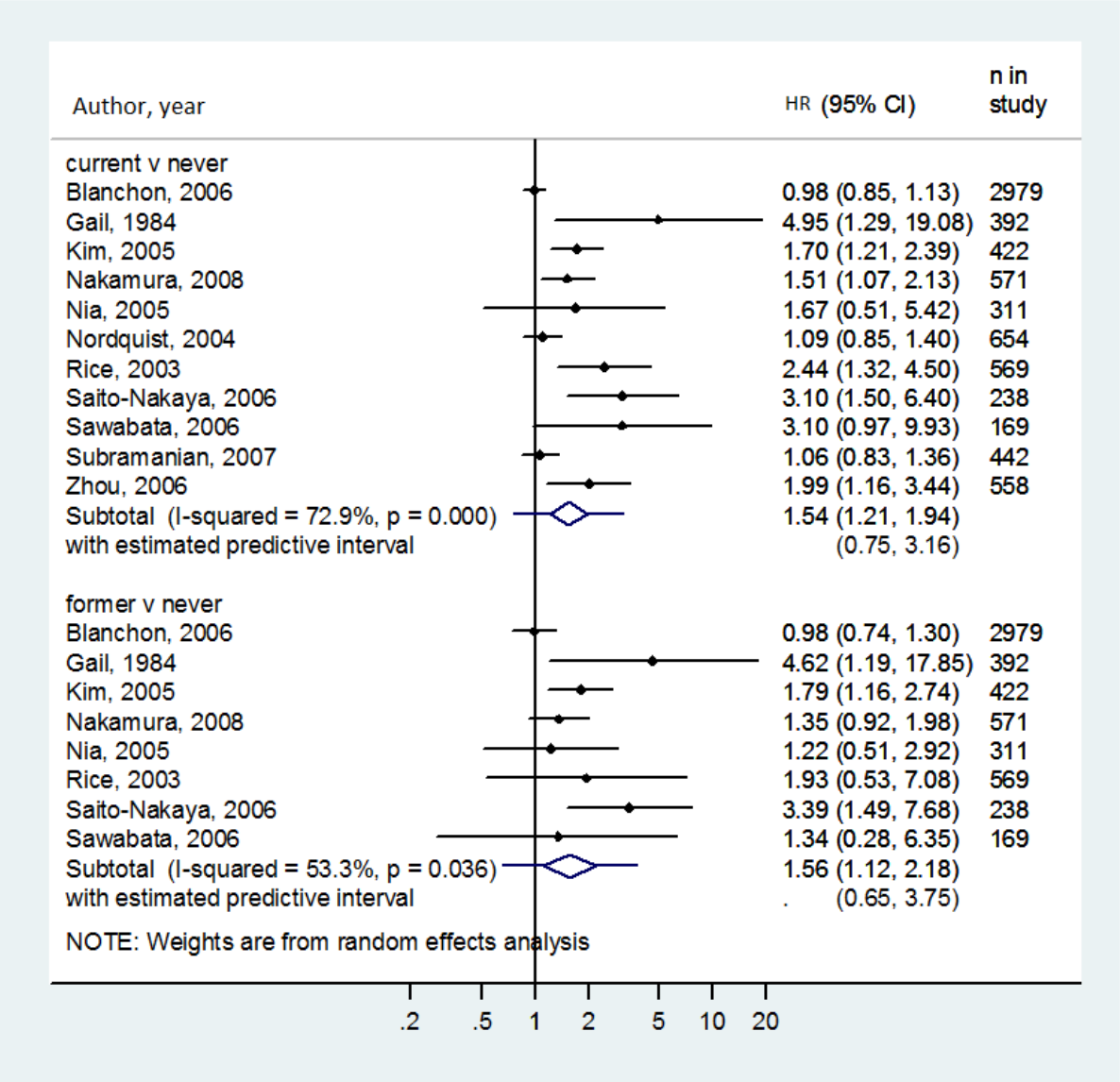


Figure 5.7: Unadjusted risk estimate of all cause mortality comparing different categories of smoking history

(95% CI 1.18, 2.73), 6 studies, $I^2 = 27\%$ figure 5.9). Conversely, risk was reduced for current and former smokers who had not received surgical treatment (non surgical current v never HR 1.13 (95% CI 0.93, 1.38), 4 studies, $I^2 = 65\%$; non surgical former v never HR 1.29 (95% CI 0.72, 2.32), 2 studies, $I^2 = 81\%$; figure 5.9).

Risk significantly differed between treatment sub-groups for current smokers, but not former smokers, compared with never smokers (current v never $p = 0.002$, former v never $p = 0.36$). Also, prediction intervals were significant for current smokers treated surgically compared to

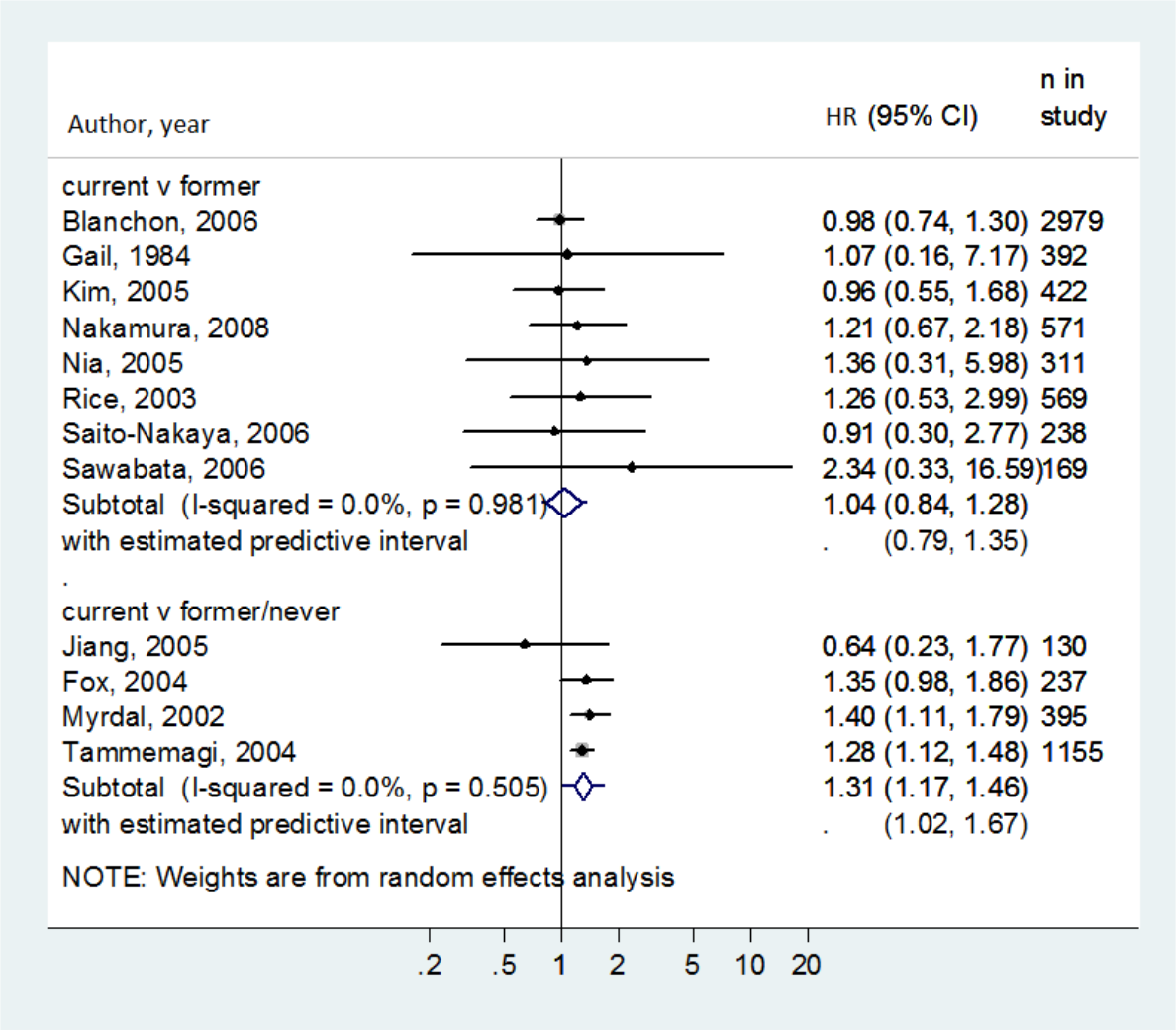


Figure 5.8: Unadjusted risk estimate of all cause mortality comparing different categories of smoking history

never smokers, but were non-significant for surgically treated former smokers. This indicates that for surgical patients, current smoking at diagnosis may be a stronger prognostic factor, and that risk may decrease over time. For both surgical patients and non surgical patients, there was no significant difference in risk detected between current and former smokers. However, although not significant, risk estimates indicated that currently smoking surgical patients may have an increased risk of death compared to former smokers (surgical current v former HR 1.21 (95% CI 0.81, 1.82), 6 studies, $I^2 = 0\%$; non surgical current v former HR 0.98 (95% CI 0.76, 1.25), 2 studies, $I^2 = 0\%$; figure 5.10). Risk was similar for current compared with former/never smokers (surgical only current v former/never HR 1.11 (95% 0.55, 2.26), 2 studies,

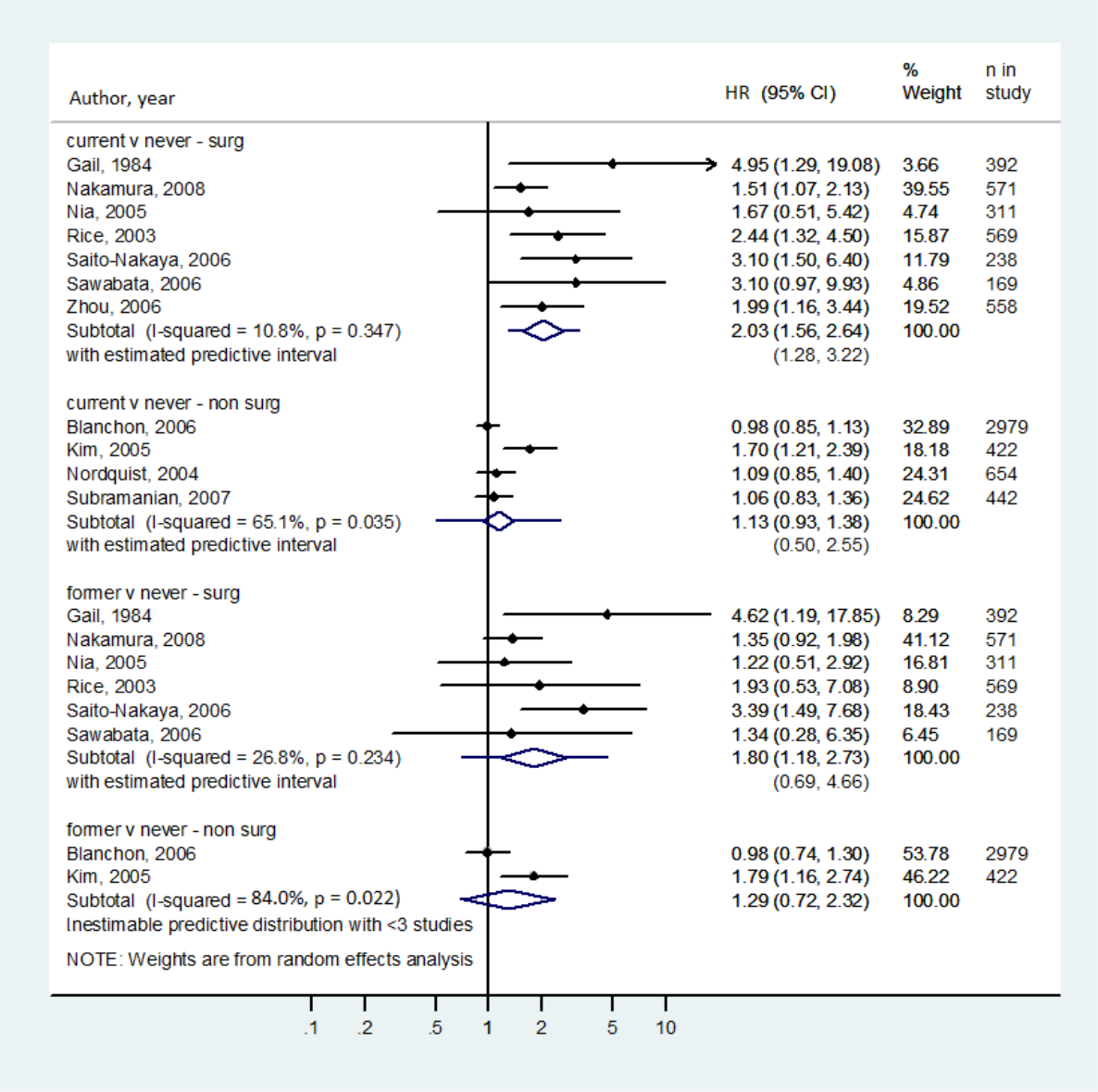


Figure 5.9: Unadjusted risk estimate of all cause mortality comparing current or former smokers with never smokers: sub-group analysis by treatment (surgical patients only v non surgical patients)

54% $I^2 = 54\%$; non surgical current v former/never HR 1.29 (95% 1.14, 1.47), 2 studies, 0%; figure 5.10).

Sensitivity analysis based on methodological characteristics of studies in surgically treated patients The robustness of the finding that risk of death is elevated for current and possibly also former smokers treated with surgery compared with never smokers was investigated through sub-group analysis based on methodological characteristics. There was some indica-

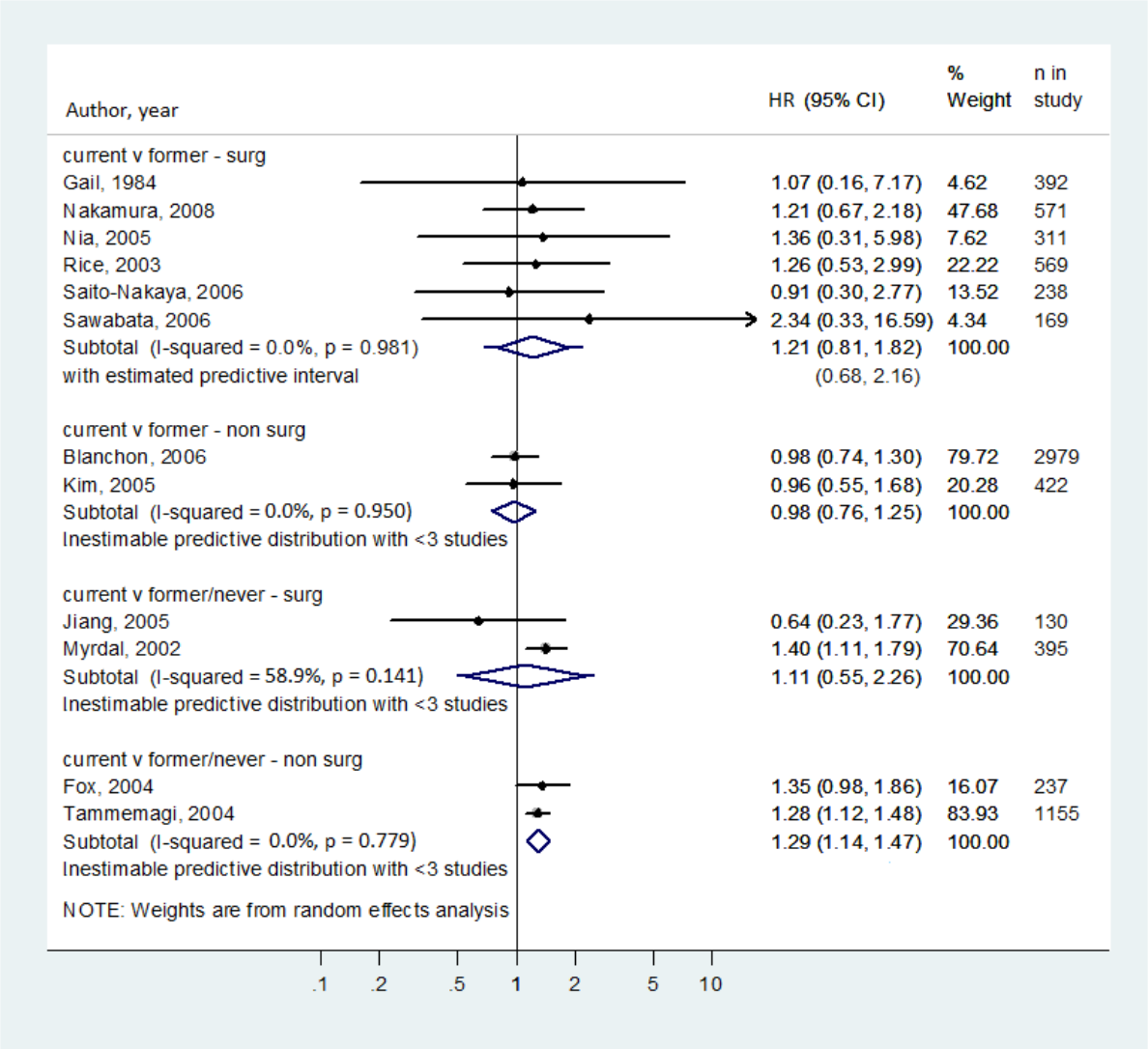


Figure 5.10: Unadjusted risk estimate of all cause mortality comparing current with former or former/never smokers: sub-group analysis by treatment (surgical patients only v non surgical patients)

tion that presented estimates were larger and more precise than those that were calculated from other data (e.g. survival curves, % survival) when comparing current or former smokers with never smokers (current v never presented HR 2.37 (95% CI 1.66, 3.38), 3 studies, $I^2 = 0\%$; current v never calculated HR 1.93 (95% CI 1.20, 3.12), 4 studies, $I^2 = 23\%$; former v never presented HR 2.39 (95% CI 1.40, 4.07), 2 studies, $I^2 = 13\%$; former v never calculated 1.44 (95% CI 1.01, 2.06), 4 studies, $I^2 = 4\%$; see figure C.5 in appendix B). Presented estimates were also larger than calculated estimates when comparing current smokers to former/never smokers, although there was only one study in each of these sub-groups. All current compared with for-

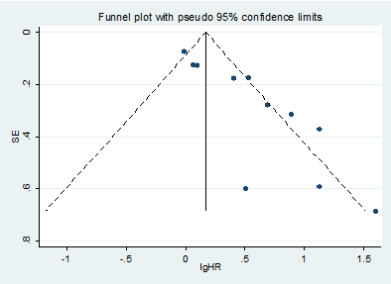
mer estimates were calculated and so it was not possible to investigate differences within this comparison.

The risk of all cause mortality for both current and former smokers compared with never smokers strengthened after removal of low quality studies. Current smokers were at over two and a half fold increased risk of death compared with never smokers, and the risk was more than two fold for former smokers (current v never high quality HR 2.53 (95% CI 1.82, 3.52), 5 studies, $I^2 = 0\%$; former v never high quality 2.12 (95% CI 1.38, 3.26), $I^2 = 11\%$; see figure C.6 in appendix B). Estimates from all studies of low quality were calculated, whereas both presented and calculated HRs were extracted from high quality studies. Removing low quality studies from the comparison of current with former or with former/never smokers did not change the findings for these groups (see figure C.7 in appendix B).

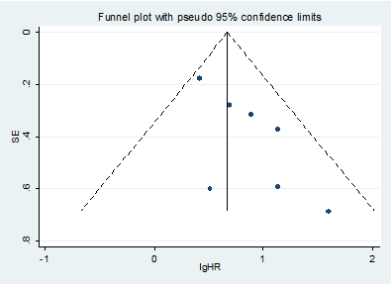
Publication bias There was evidence of publication bias of estimates comparing current or former with never smokers. Funnel plots showed an asymmetrical pattern when all estimates were included and only those from studies of surgical patients (figure 5.11a to 5.11d). However, no asymmetry was detected for current compared with former/never smokers (figure 5.11e and 5.11e).

5.4.3.1 Exploration of mediation by histology, stage and co-morbidity in surgically treated patents

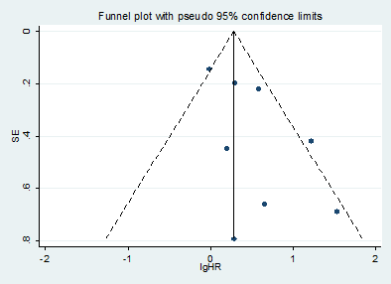
Method 1: sub-group analysis Data allowed comparison between surgically treated patients with stage I disease and those diagnosed in a mixture of stages. Risk was greater in current and former smokers compared to never smokers diagnosed in stage I and heterogeneity was eliminated (current v never stage I HR 2.81 (95% CI 1.70, 4.66), 3 studies, $I^2 = 0\%$; current v never mixed stage HR 1.90 (95% CI 1.30, 2.78), 3 studies, $I^2 = 39\%$; former v never stage 1 HR 2.12 (95% CI 1.25, 3.58), 3 studies, $I^2 = 0\%$; former v never mixed stage HR 1.69 (95% CI 0.96, 2.97), 3 studies, $I^2 = 53\%$; see table 5.9 and figure C.8 in appendix B). No significant



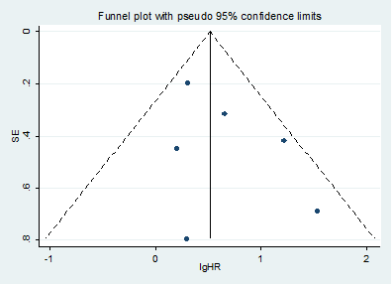
(a) CvN all estimates



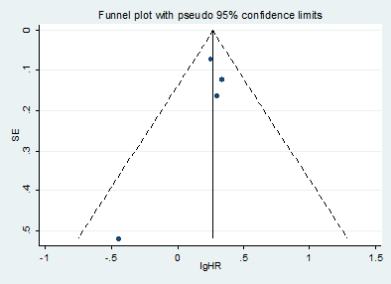
(b) CvN surgery only



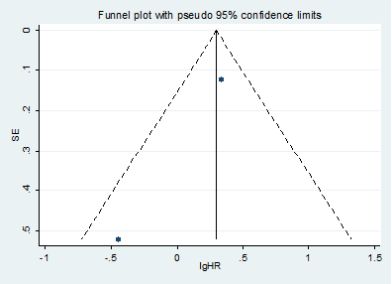
(c) FvN all estimates



(d) FvN surgery only



(e) CvFN all estimates



(f) CvFN surgery only

Figure 5.11: Exploration of publication bias in studies with surgical patients: funnel plots of ever compared to never smoking estimates

difference was detected between risk in current and former smokers in each stage sub-group (current v former stage I HR 1.34 (95% CI 0.65, 2.78, 3 studies, $I^2 = 0\%$; current v former mixed stage 1.14 (95% CI 0.65, 1.92), 2 studies, $I^2 = 54\%$; see table 5.9 and figure C.8 in appendix B). All studies estimating risk for current compared with former/never smokers were conducted in patients of mixed stage and therefore no sub-group analysis could be carried out for this comparison.

It was not possible to conduct sub-group analyses by histology or co-morbidity. All studies included a mixture of different types of NSCLC, and co-morbidity was not reliably reported. Table 5.9 summarises the risk of all cause mortality between current, former, never and for-

mer/never smokers from sub-group analyses.

Table 5.9: Summary of findings for all studies and sub-groups based on surgery and stage

	HR (95%CI)	Prediction interval	number of studies	heterogeneity	*p*
Current v never					
All estimates	1.54 (1.21, 1.94)	0.75, 3.16	11	73	n/a
Surgical treatment	2.03 (1.56, 2.64)	1.28, 3.22	7	11	0.002
Non surgical treatment	1.13 (0.93, 1.38)	0.50, 2.55	4	65	
Surgery only:					
Stage 1 only	2.81 (1.70, 4.66)	0.11, 73, 83	3	0	n/a
Mixed stage	1.81 (1.36, 2.42)	0.84, 3.88	4	0	
Former v never					
All estimates	1.56 (1.12, 2.18)	0.65, 3.75	8	53	n/a
Surgical treatment	1.80 (1.18, 2.73)	0.69, 4.66	6	27	0.36
Non surgical treatment	1.29 (0.72, 2.32)	n/a	2	81	
Surgery only:					
Stage only 1	2.12 (1.25, 3.58)	0.07, 64.10	3	0	n/a
Mixed stage	1.69 (0.96, 2.97)	0.00, 649.90	3	53	
Current v former					
All estimates	1.04 (0.84, 1.28)	0.79, 1.35	8	0	n/a
Surgical treatment	1.21 (0.81, 1.82)	0.68, 2.16	6	0	n/a
Non surgical treatment	0.98 (0.76, 1.25	n/a	2	0	
Surgery only:					
Stage 1 only	1.34 (0.65, 2.78)	0.01, 153.24	3	0	n/a
Mixed stage	1.16 (0.65, 2.78)	0.01, 28.16	3	0	
Current v former/never					
All estimates	1.31 (1.17, 1.46)	1.02, 1.67	4	0	n/a
Surgical treatment	1.11 (0.55, 2.26)	n/a	2	54	n/a
Non surgical treatment	1.29 (1.14, 1.47)	n/a	2	0	
Surgery only:					
Mixed stage	1.11 (0.55, 2.26)	n/a	2	54	n/a

Method 2: within study adjustment Two studies provided estimates before and after adjustment for both histology and stage in surgical patients, comparing risk between current, former and never smokers. One study was conducted in stage 1 patients and also adjusted for treatment, the other was conducted in a mixture of patients with stage 1-3a disease and also adjusted for gender. Combined risk estimates were similar before and after adjustment (see figure 5.12). One additional study[356] provided within study adjustment for current smokers compared with former/never smokers. The adjustment model included stage in addition to age, and adjustment had no effect on the size of risk (current v former/never unadjusted HR 1.28 (95% 1.12, 1.48),

1 study; current v former/never adjusted CvFN HR 1.25 (95% 1.08, 1.46), 1 study).

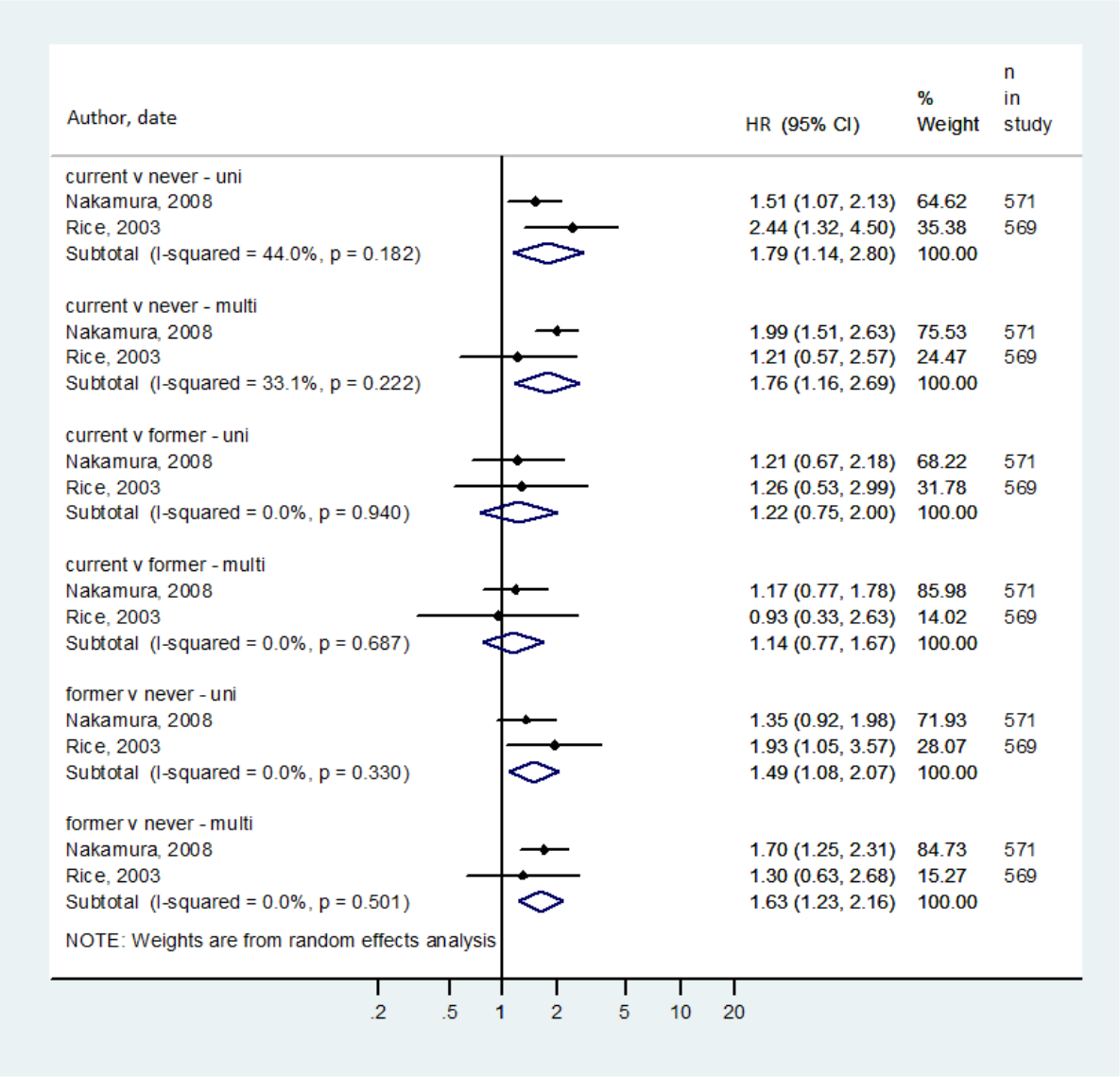


Figure 5.12: Risk of all cause mortality and recency of smoking in surgical patients only: adjustment within study for histology

Method 3: between study adjustment When using all available estimates to compare risk before and after adjustment between studies, the size of risk reduced after adjustment for histology although the change was not significant. Similar non-significant reductions were observed after adjustment for stage, apart from when comparing current smokers to former/never smokers when risk increased after adjustment. One study adjusted for co-morbidity, and compared risk in current to former/never smokers only. Adjusting for this factor non significantly increased

the risk of all cause mortality (see table 5.10).

Table 5.10: Risk of all cause mortality and recency of quitting: adjustment for histology, stage and co-morbidity using meta regression

	Histology		
	Unadjusted HR	Adjusted HR	*p*-value
Current v never	1.80	1.52	0.59
Current v former	1.16	1.01	0.72
Current v former/never	1.55	1.40	0.90
Former v never	2.05	1.68	0.42
	Stage		
	Unadjusted HR	Adjusted HR	*p*-value
Current v never	1.93	1.62	0.58
Current v former	1.13	1.01	0.81
Current v former/never	0.64	1.58	0.37
Former v never	2.12	1.72	0.42
	Co-morbidity		
	Unadjusted HR	Adjusted HR	*p*-value
Current v never	N/R	N/R	N/R
Current v former	N/R	N/R	N/R
Current v former/never	1.36	1.88	0.73
Former v never	N/R	N/R	N/R
	All factors		
	Unadjusted	Adjusted	*p*-value for adding all terms
Current v never	2.01	1.51	0.77
Current v former	3.32	2.97	0.92
Current v former/never	0.64	0.00	0.79
Former v never	2.12	1.68	0.68

5.4.4 Risk of all cause mortality associated with heaviness of smoking

Three studies provided unadjusted estimates of the risk of all cause mortality associated with a unit increase change in pack years.[62, 339, 357] Each of these studies were conducted in surgical patients only. When converted to represent the risk associated with ten pack years of smoking, no difference was found (per 10 yr increase in pack year HR 1.03 (95% CI 1.00, 1.05), 3 studies, $I^2 = 89.3\%$).

Twenty three studies compared 2 or more categories of pack year history in mixed NSCLC, adenocarcinoma or SCLC patients (table 5.11 and 5.12).[302, 303, 305, 307, 309, 314–316,

318, 319, 331, 344–347, 353, 354, 358–363] Three studies [307, 316, 318] compared surgical patients with under 20 pack year history to those who had 20 or more years and a fourth study [303] compared less than 19 pack years to 19 or more pack years in surgical patients. Combining these estimates showed a non-significant increased risk for patients with a heavier pack year history (<20 PY v $\geq$20 PY HR 1.26 (95% CI 0.76, 2.07), 4 studies, $I^2 = 70\%$; see figure C.9 in appendix B). Two studies conducted in surgical patients compared risk in patients with a pack year history greater than 30 to those less than 30. Those with a heavier pack year history showed a significant increase in risk (<30 PY v $\geq$30 PY HR 1.44 (95% CI 1.12, 1.84), 2 studies, $I^2 = 0\%$; see figure C.9 in appendix B). It was not possible to combine any other estimates to explore if risk was associated with heaviness of smoking history due to the differences in exposure category classification. In general, a greater pack year history was associated with a higher risk of all cause mortality. However, no discernible trend was observed in risk with pack year history when comparing individual estimates. In addition, the effect of adjustment did not have a consistent effect across studies, with some showing an increase in risk whilst in other studies adjustment lead to a decrease in risk (see tables 5.11 and 5.12).

Table 5.11: Pack year (PY) data comparing 2 or 3 categories: All available estimates of all cause mortality for mixed NSCLC or squamous cell only

Author	PY comparisons	unadjusted HR (95% CI)	adjusted HR (95% CI)	study *n*	Male (%)	Squamous (%)	Stage 1-3A (%)	Treatment
2 categories of PY history								
Rades, 2008	≥50 v <50	1.12 (0.75, 1.67)	N/R	181	78	0	100	Mixed
Marsit, 2005	≥40 v <40	N/R	0.80 (0.40, 1.60	85	60	44	78	Surgery
Kawai, 2005	≥40 v <40	1.34 (1.24, 1.44)	1.13 (0.95, 1.34)	3217	61	27	100	Surgery
Sioris, 2000	≥38 v <38	N/R	1.90 (0.80, 4.51)	101	83	58	91	Surgery
Shiba, 2000	≥30 v <30	1.39 (0.79, 2.45)	2.00 (0.80, 5.00)	156	72	55	100	Surgery
Sawabata, 2006	≥30 v <30	N/R	1.67 (0.58, 4.81)	169	89	100	100 Stage 1	Surgery
Takeshita, 2008	≥20 v <20	3.90 (1.35, 11.27)	1.00 (0.99, 1.01)	157	64	26	99	Surgery
Wu, 2003	≥20 v <20	1.45 (1.20, 1.75)	1.61 (1.22, 2.12)	321	85.7	49	100	Surgery
Buccheri, 1993	≥19 v <19	0.68 (0.36, 1.28)	N/R	360	93	100	50	Mixed
Suzuki, 1999	≥5 v < 5	2.05 (1.11, 3.79)	N/R	836	63	26	90	Mixed
Hendrick, 1996	high v low	N/R	1.02 (1.01, 1.03)	100	86	52	47	Surgery
Liang, 2003	high v low	N/R	1.27 (0.73, 2.20)	55	78	33	47	Mixed
3 categories of PY history								
Blanchon, 2006	>60 v ≤20	1.06 (0.85, 1.32)	N/R	2979	84	47	54	Mixed
Blanchon, 2006	41–60 v ≤20	1.04 (0.86, 1.26)	N/R	2979	84	47	54	Mixed
Blanchon, 2006	21–40 v ≤20	1.00 (0.84, 1.19)	N/R	2979	84	47	54	Mixed
Mulligan, 2006	>60 v <40	N/R	1.00 (0.72, 1.39)	97	62	31	50	Mixed
Mulligan, 2006	40–60 v <40	N/R	1.11 (0.79, 1.56)	97	62	31	50	Mixed

Table 5.11: cont.

Author	PY comparisons	unadjusted HR (95% CI)	adjusted HR (95% CI)	study *n*	Male (%)	Squamous (%)	Stage 1-3A (%)	Treatment
Martins, 1999	≥45 v 1-44	1.08 (1.02, 1.14)	N/R	1635	76	51	33	Mixed
Martins, 1999	>45 v 0	1.04 (0.97, 1.12)	N/R	1635	76	51	33	Mixed
Martins, 1999	1–45 v 0	1.21 (1.08, 1.35)	N/R	1635	76	51	33	Mixed
Mitsudomi, 1989	>40 v 1-40	0.7 (0.45, 1.09)	N/R	492	73	35	85	Surgical
Mitsudomi, 1989	1-40 v 0	1.61 (1.16, 2.22)	N/R	492	73	35	85	Surgical
Fujisawa, 1999	≥30 v 1-29	2.36 (1.26, 4.42)	N/R	369	66	38	100	Surgery
Fujisawa, 1999	≥30 v 0	3.35 (2.42, 4.65)	N/R	369	66	38	100	Surgery
Fujisawa, 1999	1–29 v 0	1.42 (0.83, 2.43)	N/R	369	66	38	100	Surgery
Hanagiri, 2008	≥20 v 1-20	0.98 (0.55, 1.75)	N/R	770	86.5	28	85	Surgery
Hanagiri, 2008	>20 v never	1.32 (0.97, 1.80)	N/R	770	86.5	28	85	Surgery
Hanagiri, 2008	<20 v never	1.35 (0.84, 2.17)	N/R	770	86.5	28	85	Surgery

Table 5.12: Pack year (PY) data estimates of all cause mortality : Adenocarcinoma or SCLC only

Author	PY comparisons	unadjusted HR (95% CI)	adjusted HR (95% CI)	study n	Male (%)	Stage 1-3a or limited (%)	Treatment	Quality score
Adenocarcinoma								
Haga, 2003	≥50 v non	7.81 (2.22, 27.45)	N/R	187	64	100	Surgery	8
Haga, 2003	<50-30 v non	7.18 (2.01, 25.54)	N/R	187	64	100	Surgery	8
Haga, 2003	≥50 v <50 - 30	1.09 (0.18, 6.48)	N/R	187	64	100	Surgery	8
Kim, 2005	<35 v never	1.70 (1.20, 2.41)	N/R	422	58.5	61	Mixed	6
Kim, 2005	≥35 v never	2.26 (1.62. 3.15)	N/R	422	58.5	61	Mixed	6
Kim, 2005	≥35 v 1-34	1.33 (0.82, 2.15)	N/R	422	58.5	61	Mixed	6
Maeshima, 2008	≥25 v <25	N/R	1.50 (0.79, 2.85)	236	61	89	Surgery	8
Yoshino, 2006	≥50 v never	1.70 (1.51, 1.92)	N/R	999	N/R	N/R	Surgery	5
Yoshino, 2006	<50-20 v never	1.53 (1.37, 1.71)	N/R	999	N/R	N/R	Surgery	5
Yoshino, 2006	≥50 v <50-20	1.11 (0.94, 1.32)	N/R	999	N/R	N/R	Surgery	5
Small cell carcinoma								
Song, 2004	≥5020 v <20	0.75 (0.37, 1.50)	N/R	60	71.7	45	Non surgery	4

5.4.5 Risk of disease progression and cancer-related death associated with smoking history

Twenty four studies reported on cancer specific outcomes. [62, 137, 304–308, 310, 312–314, 317, 318, 320, 323, 333, 335, 343, 349, 353, 359, 364–366] Due to low numbers of studies in each comparison of smoking exposure, no meta-analyses were possible for cancer specific mortality or risk of second primary. These data are presented in table 5.13. One study [323] reported a significantly increased risk of cancer specific mortality in ever smokers compared to never smokers. Adjustment for age, stage and histology reduced the risk and it became non-significant. A second study [312] found no difference in risk when comparing current and never smokers. Both of these studies included patients that had received either surgical or non-curative treatment. A third study [314] found an increased risk of cancer specific mortality associated with current smoking at diagnosis compared to being a former smoker. However, confidence intervals were very wide. Seven studies report the risk of cancer specific mortality associated with different categories of pack year history, and two studies reported the risk of pack year history as a continuous variable. In general, a greater pack year history was associated with a higher risk of cancer specific mortality, although it was not possible to discern if there was a linear trend. Similarly, it was not possible to unpick the effect of adjustment on risk (see table 5.13).

Risk of developing a second primary was reported by five studies (see table 5.13). [313, 333–335, 367] Similar to observations with all cause mortality outcomes, unadjusted estimates suggested an increased risk of similar size for current and former smokers compared to never smokers in surgical patients. However, estimates were not significant. Adjustment for treatment, stage, histology and treatment by smoking status changed the magnitude of the risk in opposite directions, but remained non-significant.[313] One additional study [334] conducted in SCLC patients who received non-surgical firstline treatment found no difference in risk of developing a second primary for current smokers at diagnosis compared with former smokers (table 5.13). Three studies found there was no significant association between pack year history and risk of

second primary.[333, 335, 367]

A more coherent pattern emerged regarding the risk of developing tumour recurrence. Three studies provided unadjusted estimates that compared current or former smokers to never smokers, and current to former smokers.[306, 313, 320] All of these studies were conducted in NSCLC patients who had received surgical treatment, and two studies included stage 1 patients only. Similar to the observations for all cause mortality and risk of second primary, when combining estimates there was an indication that both current and former smokers were associated with increased risk of a similar size compared with never smokers (current v never unadjusted HR 1.75 (95%CI 0.98, 3.12), 3 studies, $I^2 = 52\%$; former v never unadjusted HR 1.86 (95%CI 0.52, 6.67), 2 studies, $I^2 = 70\%$; figure 5.13), whereas there was no difference between current and former smokers (CvF unadjusted HR 1.04 (95%CI 0.51, 2.08), 2 studies, $I^2 = 0\%$; figure 5.13). In addition, three studies found a significant increase in risk of recurrence per pack year increase of smoking history (see table 5.14). Adjustment appeared to effect the estimate of risk of recurrence in most studies. However, it is difficult to interpret the meaning of this finding as adjusted models varied (table 5.13).

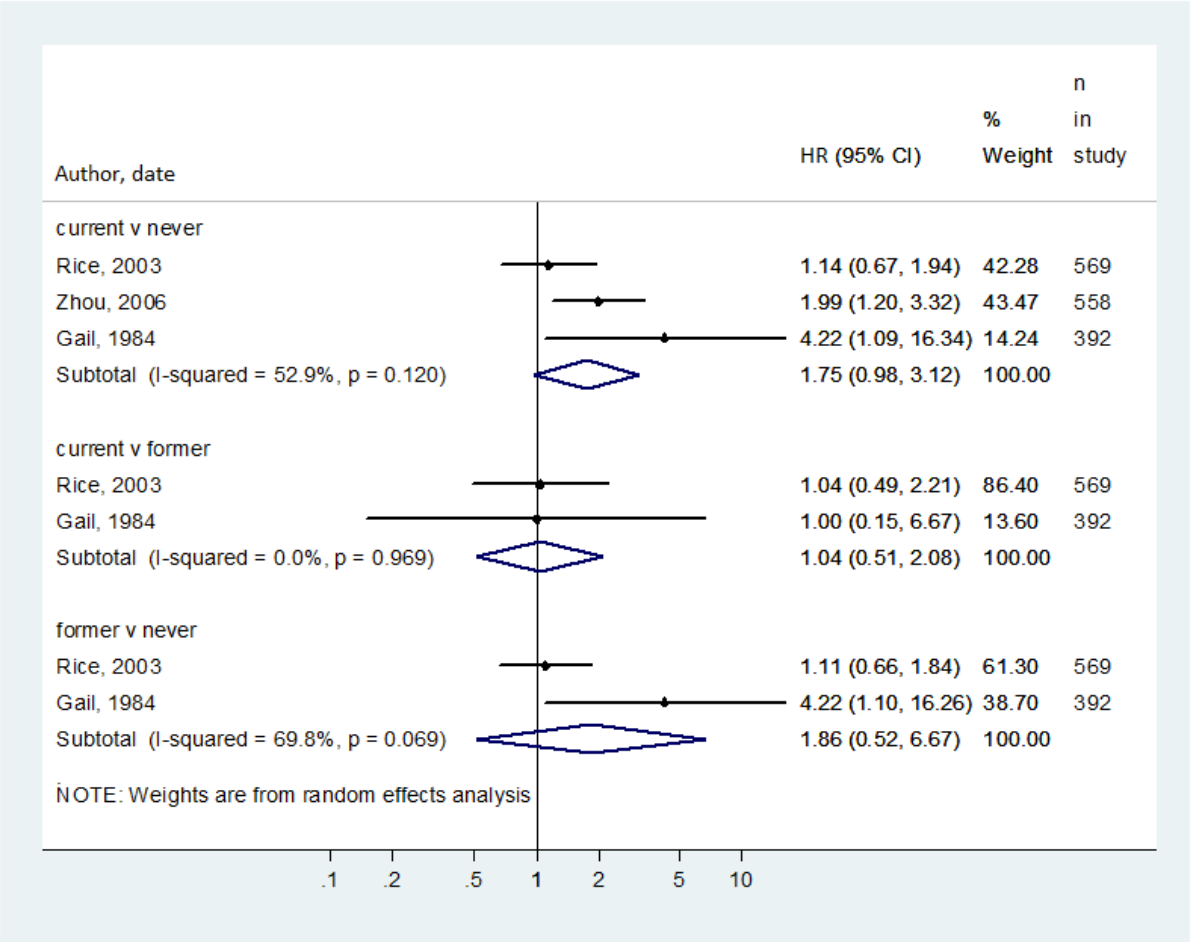


Figure 5.13: Risk of developing tumour recurrence associated with recency of smoking at diagnosis

Table 5.13: Risk of cancer specific mortality or second primary: all available data (E = ever smoker, N = never smoker, C = current smoker, F = former smoker, PY = pack years, N/R = not reported, n = number in the study, SCLC = small cell lung cancer)

Author	Group	unadjusted HR (95% CI)	adjusted HR (95% CI)	Study *n*	Treatment	SCLC %	Stage %	Controlled for in analysis
Cancer specific mortality								
Tan, 2003	EvN	1.70 (1.30, 2.22)	1.30 (1.00, 1.69)	326	Mixed	7.7	45.7	Age, stage, histology
Nordquist, 2004	CvN	1.08 (0.83, 1.41)	N/R	654	Mixed	0	44	
Sawabata, 2006	CvF	6.69 (0.58, 76.88)	8.41 (1.04, 67.96)	169	Surgery	0	100 stage 1	Age, sex, stage, histotype, FEV,PY or smoking history
Harpole, 1995	>50PY v 1-50PY	1.16 (0.75, 1.79)	N/R	289	Surgery	0	100	
Harpole, 1995	≥50PY v never	1.05 (0.44, 2.15)	N/R	289	Surgery	0	100	
Harpole, 1995	1-50PY v never	0.90 (0.39, 2.08)	N/R	289	Surgery	0	100	
Kawai, 2005	≥40PY v <40PY	1.42 (1.28, 1.58)	1.22 (0.98, 1.52)	3217	Surgery	0	100	Histology
Sioris, 2000	<38PY v ≥38PY	N/R	1.70 (0.8, 3.61)	101	Surgery	0	91	Age, gender, stage, p53, asbestos exposure

Author	Group	unadjusted HR (95% CI)	adjusted HR (95% CI)	Study *n*	Treatment	SCLC %	Stage %	Controlled for in analysis
Sawabata, 2006	<30PY v ≥30PY	N/R	4.67 (1.54, 14.16)	169	Surgery	0	100 Stage 1	Age, gender, histology, FEV1
Fujisawa, 1999	≥30PT v <30PY	2.63 (1.84, 3.76)	1.39 (0.67, 2.88)	369	Surgery	0	100	Age, sex, histology, grade
Hanagiri, 2008	>20PY v 1-20PY	1.08 (0.52, 2.24)	N/R	770	Surgery	0	85	
Hanagiri, 2008	≥20PY v never	1.02 (0.55, 1.89)	N/R	770	Surgery	0	85	
Hanagiri, 2008	1-20PY v never	1.10 (0.75, 1.61)	N/R	770	Surgery	0	85	
Wu, 2003	>20PY v ≤20PY	1.64 (1.29, 2.08)	2.14 (1.42, 3.23)	321	Surgery	0	100 Stage 1	Stage, histology
Holli, 1999	Per 10PY	0.94 (0.68, 1.30)	1.13 (0.77, 1.66)	290	Mixed	21	N/R	Histology
Tammemagi, 2000	Per 1PY	N/R	1.03 (1.01, 1.05)	199	Surgery	0	100	Age, gender, histology, tumour size, stage, differentiation
Second Primary								
Rice, 2003	CvN	1.51 (0.72, 3.16)	2.72 (0.64, 11.55)	569	Surgery	0	100 Stage 1	Treatment, stage, histology, treatment-by-smoking status

Author	Group	unadjusted HR (95% CI)	adjusted HR (95% CI)	Study *n*	Treatment	SCLC %	Stage %	Controlled for in analysis
Rice, 2003	CvF	0.97 (0.34, 2.77)	0.88 (0.12, 6.44)	569	Surgery	0	100 Stage 1	Treatment, stage, histology, treatment-by-smoking status
Tucker, 1997	CvF	1.05 (0.44, 2.51)	N/R	611	Non-surgical	100	79 limited	
Rice, 2003	FvN	1.55 (0.76, 3.19)	3.10 (0.75, 12.80)	569	Surgery	N/R	100 Stage 1	Treatment, stage, histology, treatment-by-smoking status
Kawahara, 1998	>45PY v ≤45PY	N/R	0.90 (0.2, 4.05)	70	Non-surgical	100	N/R	Gender, age, performance status, etoposide, radiotherapy
Kawaguchi, 2006	≥40PY v <40PY	N/R	1.40 (0.2, 9.80)	67	Surgery	0	100	Histology, gender
Yoshida, 1996	≥20PY v <20PY	0.66 (0.03, 14.52)	N/D	569	Non-surgical	100	85	

Table 5.14: Risk of recurrence: all available data

Author	grp	unadjusted HR (95% CI)	adjusted HR (95% CI)	Study *n*	Treatment	SCLC %	Stage %	study quality	Controlled for in analysis
Kobayashi, 2007	EvN	N/D	4.01 (0.45, 35.86)	163	surgery	0	Stage 1a	4	age, sex, serum CEA level, pathologic tumor size, histologic subtype, histologic grade, visceral pleural invasion
Tsai, 2006	EvN	N/D	1.48 (1.17, 1.87)	236	surgery	0	Stage 1a	3	age, gender, symptoms, cell type, location, procedure, tumour volume, tumour length, Resected LNs, serum CEA
Nia, 2005	CvN	N/D	1.51 (0.79, 2.88)	311	surgery	0	92.1	7	age, sex, type of op, histology, post-op radiotherapy, N-status, T status, previous malignancies
Rice, 2003	CvN	1.14 (0.67, 1.94)	0.73 (0.37, 1.45)	569	surgery	0	Stage 1	8	treatment, stage, histology, treatment-by-smoking status
Zhou, 2006	CvN	1.99 (1.20, 3.32)	1.82 (1.03, 3.22)	558	surgery	0	Stage 1-3a	6	age, gender, stage, cpd
Gail, 1984	CvN	4.22 (1.09, 16.34)	N/D	392	surgery	0	Stage 1	8	

Table 5.14: cont.

Author	grp	unadjusted HR (95% CI)	adjusted HR (95% CI)	Study *n*	Treatment	SCLC %	Stage %	study quality	Controlled for in analysis
Nia, 2005	CvF	N/D	1.90 (1.19, 3.01)	311	surgery	0	92.1	7	age, sex, type of op, histology, post-op radiotherapy, N-status, T status, previous malignancies
Rice, 2003	CvF	1.04 (0.49, 2.21)	0.84 (0.33, 2.15)	569	surgery	0	Stage 1	8	treatment, stage, histology, treatment-by-smoking status
Gail, 1984	CvF	1.00 (0.15, 6.67)	N/D	392	surgery	0	Stage 1	8	
Rice, 2003	FvN	1.11 (0.66, 1.84)	0.87 (0.46, 1.64)	569	surgery	0	Stage 1	8	treatment, stage, histology, treatment-by-smoking status
Gail, 1984	FvN	4.22 (1.10, 16.26)	N/D	392	surgery	0	Stage 1	8	
Fox, 2004	CvFN	1.03 (0.72, 1.47)	N/D	237	Non surgical treatment	54	8		
Jiang, 2005	CvFN	2.69 (0.37, 19.56)	N/D	130	Surgery	100	6		

Table 5.14: cont.

Author	grp	unadjusted HR (95% CI)	adjusted HR (95% CI)	Study *n*	Treatment	SCLC %	Stage %	study quality	Controlled for in analysis
Hung, 2007	Per 1PY	1.01 (1.003, 1.02)	1.01 (1.004, 1.02)	445	Surgery	0	100 Stage 1	8	Age, tumour size, no. of lymph nodes dissected
Hotta, 2009	Per 1PY	N/D	1.01 (1.003, 1.02)	260	Non surgical treatment	0	40	7	Age, stage, prior chemotherapy, performance status
Tammemagi, 2000	Per 1PY	N/D	1.03 (1.01, 1.05)	119	Surgery	0	100	8	Histology, Stage, p53 status

5.5 Discussion

The purpose of this discussion is to consolidate and interpret findings of the review in the context of past literature. This will first include a discussion of findings regarding the association between smoking history and all cause mortality, including the evidence that smoking history has prognostic significance for surgically treated patients. Second, the potential pathways through which smoking history may influence prognosis in surgical patients will be discussed, along with the evidence found from this review regarding these pathways. Next, the strengths and weaknesses of the data are discussed, including the risk that findings may be a reflection of bias or confounding. Finally, the implications of the findings and recommendations for future research are summarised.

5.5.1 Risk of all cause mortality associated with smoking history and prognostic significance for surgically treated patients

This review has found consistent evidence of an association between smoking history and prognosis in lung cancer. Risk of all cause mortality was increased by around 50% in current, former or ever smokers when compared with patients that had never smoked. When conducting sub-group analyses based on treatment, risk was strengthened for patients treated surgically whereas the size of risk was smaller for patients treated non-surgically. If risk of death had been completely explained (or mediated) by receipt of curative treatment, no difference in risk between patients with a smoking history and those without would be detected when confining analysis to surgical patients only. This supports the hypothesis that curative surgical treatment modifies rather than mediates risk, and that smoking history is of prognostic significance for surgical patients. Contrary to the initial hypothesis, there was some evidence from sub-group analysis in current and former smokers compared with never smokers that stage also modifies risk. In high quality studies, risk strengthened to a 2-3 fold increase in current, former or ever smokers treated with surgery for stage I NSCLC compared with never smokers (see table 5.9).

This indicates that the prognostic significance of smoking history is strongest for patients who have greatest survival advantage. In other words, for those who have a poor prognosis, the risk associated with smoking history does not have a sufficient time window to operate. However, for those with surgically removed early stage tumours, the time window is greater for the prognostic disadvantage of smoking history to emerge.

Recency of smoking history Taking together the findings of relevant analyses, there was an indication that more recent smoking at diagnosis was associated with a higher risk of all cause mortality. There was a largely consistent pattern of higher risk associated with current smokers than with former smokers when compared to never smokers. In surgical stage I NSCLC patients, current smokers were associated with more than a two and a half fold increased risk whereas former smokers were at a two fold increased risk when combining high quality studies. In addition, prediction intervals did not include 1 for current smokers, but did for patients who had quit before diagnosis. Although this suggests that risk may be different in these two groups, the best method to test difference in risk is to directly compare these two group. Most studies did not provide this comparison, so current and former smokers were indirectly compared using methods described by Song.[368] No difference was observed between current and former smokers using this method. However, in clinical sub-groups for which smoking history was a stronger prognosticator, the estimate suggested that current smoking carried greater risk.

Most studies did not describe how they defined former smoking. It is possible that former smokers included a mixture of patients who had quit within a year before diagnosis with patients who had quit decades before diagnosis. If a risk reduction is seen only after a number of years, including those who had quit shortly before diagnosis would limit the ability to detect a difference between current and former smokers. One study [320] only in surgical patients that was included in this review described the length of quitting before diagnosis in former smokers. Patients were recruited consecutively and were not selected on the basis of their smoking history, therefore it is likely that the distribution in time since quitting would be comparable to other random samples. These authors reported that a third of former smokers quit within

9 years of diagnosis, a further third quit between 9 and 17 years and the remaining third quit 18 or more years before diagnosis. A significant reduction in risk was found for each period of recent quitting compared to current smokers, further indicating that risk may be reduced in former smokers and that it reduces over a number of many years.

Intensity of smoking history Evidence regarding the importance of pack year history was difficult to interpret as studies often categorised this exposure differently. Individual estimates did not reveal a discernible pattern of risk. However, where it was possible to combine estimates, there was an indication that a heavier smoking history may be associated with greater risk. There was an significant increase in risk for those with a greater than 30 pack year history, compared to those with less than 30 pack year history, and risk was also raised when 20 pack years was used to dichotomise groups, but non-significantly. A small non-significant increase per 10 pack years was also observed.

Pack year history is calculated by multiplying the number of years smoked by the number of cigarette packs containing 20 cigarettes smoked per day. Thus, a patient that smoked 20 cigarettes per day (cpd) for 20 years will have a 20 pack year history, whereas a smoker of 40/cpd for 20 years will have a 40 pack year history. As most people begin smoking between ages 18-25, and based on the assumption that the number of cigarettes smoked per day by most lung cancer patients is similar, it is likely that a greater pack year history reflects more recent smoking at the time of diagnosis. If these assumptions are correct, this would lend further weight to the interpretation that greater risk is associated with more recent smoking. However, it is also possible that increased risk is due to a higher dose of toxins due to a larger number of cigarettes smoked each day.

It was not possible to tell with the data available in this review if there was a true association between pack years and risk of death, and whether any increased risk associated with pack years was due to recency or dose. Understanding the influence of recency or dose on risk is important not only for patient counseling, but also for risk stratification in health care and clinical trials.[273] More studies are needed which examine the risk associated with length

of quitting in detail, and the risk associated with pack years adjusted for years of quitting, to confirm or refute the gradual reduction in risk with increasing years of quitting before diagnosis and the significance of dose.

5.5.2 Possible mechanisms of increased risk associated with smoking history in surgical lung cancer patients

Assuming the relationship found between smoking history and all cause mortality in surgical lung cancer patients is causal, this may be mediated through pathways that are related or unrelated to cancer. Risk of cancer related outcomes, and mediation by tumour histology, stage or co-morbidity were investigated in this review in order to understand mediation of risk through these pathways. I will now discuss these two potential pathways in turn, considering relevant findings from this review in addition to other published studies.

5.5.2.1 Cancer related mechanisms of increased risk of death in patients with a smoking history

It is possible that smoking exposure leads to increased risk of disease progression and cancer related death in surgical patients. Unfortunately, this review found limited data to investigate this. Most studies reported risk of all cause mortality rather than cancer specific outcomes, and within study adjustments for stage and histology were not always available. In surgical patients, risk of cancer specific mortality or development of a second primary tumour was non-significantly elevated for both current or former smokers compared with never smokers, and risk did not differ when comparing current and former smokers directly. These findings were based on data from two studies.[313, 314] Within study adjustment for stage and histology generally increased the size of the estimate and differences remained non-significant, apart from in one study where confidence intervals were very wide.[314]

Surgical stage I-IIIa NSCLC current and former smokers were both at a non-significant in-

creased risk of recurrence compared with never smokers, based on unadjusted estimates from three studies.[306, 313, 320] Again, when comparing the risk in current smokers with formers smokers, the estimate was close to 1 and not significant. Within study adjustment for histology and stage appeared to reduce the risk associated with current and former smokers, but did not completely abolish it. Two studies gave adjusted estimates only for risk of recurrence, comparing ever smokers with never smokers. Both studies were conducted in stage I NSCLC surgical patients and found that risk was elevated in patients with a smoking history independent of age, gender, histology and stage. Increased risk was statistically significant in one of these studies. Although estimates often did not reach statistical significance, the size of summary estimates indicate that smoking history does increase the risk of second primary, recurrence, and cancer-related death and that the risk is greater for current smokers than former smokers. In addition, adjustment for stage and histology gave no reliable indication of mediation by these factors. However, the evidence is very weak and further studies are needed to assess cancer related mediation pathways and risk associated with smoking history.

Potential mechanisms If it is true that a smoking history increases the risk of cancer-related death there are a few potential mechanisms by which this could occur. The goal of curative surgical treatment is complete resection of the tumour. The International Association for the Study of Lung Cancer (IASLC) Staging Committee published a definition of complete resection in 2005.[369] Resection is considered to be complete when resected tumour margins are found to be free from cancer cells after microscopic investigation. In addition, there should be systematic resection of local lymph nodes, and the highest mediastinal lymph node to be removed should be negative, including no extracapsular extension of tumour cells. However, even after apparent complete resection, solid tumours recur locally in up to two third of cases in the absence of adjuvant treatment.[370, 371] Adjuvant therapy may reduce the risk of recurrence and development of second primaries, but this still occurs in lung cancer[372–377] and other tumours. [378–383]

The reasons for the development of second primary and recurrent tumours after complete re-

section are not fully understood, but a few possible mechanisms have been cited.[370] One possibility is 'field cancerisation', a concept that was first described over 50 years ago in the context of oral cancer.[384] Field cancerisation is present when multiple genetic and phenotypic alterations are present within an area that has been exposed to the same carcinogen (e.g. smoking, asbestos, human papillomavirus). These pre-neoplastic lesions are not apparent on microscopic investigation, but can be detected with molecular analysis.[384] The existence of field cancerisation has been described for a number of tumours,[370, 385, 386], and multiple alterations have been found throughout the lungs of smokers and patients with both NSCLC and SCLC.[387–390] It is possible that these changes would also been detected in other regions of the body exposed to carcinogens from cigarette smoke. Therefore, exposure to smoking may increase risk of recurrence or second primary due to increased burden of pre-neoplastic lesions which remain after complete lung tumour resection and go on to develop into new tumours.[370] Although lung cancer risk reduces after smoking cessation, it never returns to baseline.[388] If risk is operating through this pathway, it is likely that a decrease in risk would be seen for those who have quit smoking years before diagnosis but that risk would still be elevated. In addition, there would be little evidence of mediation through tumour stage or histology as risk would not be conferred by the nature of the primary tumour but the burden of mutation and phenotypic changes. The findings of this review are consistent with this mechanism of increased risk. However, given the limitation of the data regarding reduction in risk over time, cancer related outcome and mediation by stage and histology, it is not possible to conclude that risk may be mediated through this pathway with any certainty.

A second possible mechanism by which progression of cancer may occur is dissemination of occult primary tumour cells, or micro-metastasis.[370] In addition to spread of cancer cells into the lymphatic system and bone marrow,[391] haematogenous tumour cell dissemination, or 'seeding' of cells from the primary tumour into the blood stream, has been demonstrated in both mice and humans.[370, 392, 393] Circulating tumour cells have been detected in lung cancer patients.[394, 395] Traditionally, cancer progression is divided into initial phases where the tumour grows and later phases in which cancer cells acquire the ability to disseminate and

colonise new environments (see section 1.2).[396] However, recent research has shown that dissemination may start early in tumour development[391, 397–400].

In addition, it has been demonstrated that surgical resection via either thoracotomy or video assisted thoracic surgery (VATS) can promote haematogenous dissemination of lung cancer cells.[371, 401] Detection of cancer cells in the blood after resection has been associated with poorer prognosis in a number of tumours, including lung cancer.[371, 402–404] Many tumour recurrences occur at the site of the surgical wound,[405] and it has been hypothesised that circulating tumour cells may be responsible.[370] Surgical wounding precipitates an inflammatory response to aid cellular repair and angiogenesis,[406, 407] and biological markers of inflammation are increased after thoracotomy[408] and to a lesser degree after VATS for lung resection.[232] Inflammation creates a micro-environment that is tumour promoting,[409–412] and infiltration of inflammatory cells into a tumour micro-environment is correlated with poorer prognosis.[413–415] Such an environment may promote the development of unresected micro-metatases in the location of the primary tumour, or reinfiltration and development of circulating tumour cells.[370, 397]

It is possible that risk of re-infiltration and development of disseminated cells is higher in later stages due to a higher burden of circulating cells. If increased risk associated with smoking was operating through these mechanisms, evidence of mediation through tumour histology and stage would be expected. Recency of smoking would influence risk in as much as it was associated with development of more aggressive tumours and presentation at later stages. There was little evidence of mediation by stage and histology in this review. However, it is not possible to rule this mechanism out given the limitations in the data. Further research is needed to investigate if smoking history increased the risk of cancer progression, and through which pathway this operates.

An additional point to consider is that smoking itself increases expression of inflammatory cytokines in lung and other tissue. [319] It is possible that a number of current smokers at diagnosis continue to smoke, and that increased risk of cancer development is due to smoking

induced inflammation in continuing smoking. Association of risk with continued smoking after diagnosis has not been assessed in this review, but is the subject of the second review of this thesis which can be found in chapter 6.

5.5.2.2 Non-cancer related mechanisms of increased risk of death in patients with a smoking history

Within cancer literature there has been little attention paid to co-morbid conditions in terms of prevalence, impact on care needs or influence on prognosis.[127, 416] Indeed, if co-morbidities are acknowledged, it is normally as an exclusion criterion for clinical trials.[417] Given the association of lung cancer with both smoking and older age,[14, 21, 39] it is likely that prevalence of smoking related disease is high in this patient group. Some studies have reported that the prevalence of co-morbid cardiovascular or respiratory disease may be as high as 50% in lung cancer populations (see section 1.5.3). Although presence of co-morbidity may reduce a persons chance of receiving curative treatment, patients with co-morbid disease may still undergo surgery, and it is possible that difference in survival rates in surgical patients are partly explained by co-morbid disease. One previous study in surgically treated stage I NSCLC found co-morbidity to be an independent predictor of prognosis as measured by the Kaplan-Feinstein Index.[60] This measure classifies co-morbidity as absent, mild, moderate or severe based on the number of individual diseases present and the extent to which the disease is advanced. After adjustment for age, sex, tumour stage and tumour histology those with moderate or severe co-morbidity were at a significantly increased risk of death compared to patients in whom co-morbid disease was absent.

Although co-morbid disease may contribute to the increased risk of death of surgical lung cancer patients as a whole, it is unknown if patients with a smoking history are at a greater risk of death due to co-morbid disease compared to those with no smoking history. No known study has looked at the distribution of co-morbid conditions between surgical patients based on smoking history. In the studies included in this review, co-morbidity was often not described. In studies

that did describe this patient characteristic, it was given for all patients in the study rather than by smoking history. One study included co-morbidity in a multivariable regression analysis which considered the risk of all cause mortality in ever smokers compared with never smokers.[326] Co-morbidity was measured using the Charlston Comorbidity Index (CCI), which gives a score based on the presence or absence of 19 conditions, weighted by relative mortality risk.[418] If an increased risk of death was operating through this mechanism only, controlling for co-morbidity should abolish the association between smoking history and prognosis. However, risk was found to increase after adjustment rather than decrease.

Based on this study alone it is not possible to dismiss the possibility that association between smoking history and prognosis is mediated through co-morbidity. Caution should be taken in interpretation as the adjusted model also included both histology, stage and other factors. Future studies are needed to more adequately describe the prevalence of co-morbidities on surgical lung cancer patients, and to ascertain if smoking history increases risk of death after surgery due to co-morbid disease.

5.5.3 The relationship between smoking history and prognosis in other tumours

Decreased survival in patients with a smoking history has been reported for a number of other solid tumours, including breast,[419–421] colorectal,[422, 423] head and neck,[424, 425] kidney,[426–429] and prostate tumours.[421, 430–434] However, other studies have also found no significant association between smoking and survival for these tumours.[435–438] As was found in this review, studies have generally compared risk in current, former or ever smokers with never smokers, and the length of time since quitting in the ever and former smokers groups is poorly described.

A systematic review has previously been conducted in breast and bladder cancer only.[419, 439] Aveyard[439] identified fifteen studies that investigated the relationship between smoking and

prognosis in patients with bladder cancer. All included studies used a longitudinal cohort design and most included patients with superficial tumours. No study found an increased risk of all cause mortality associated with smoking history. However, most studies included both incident and prevalent cases of bladder cancer and were of a low quality which limited the ability to draw conclusions from the data, and data were not pooled. Braithwaite[419] reviewed eight longitudinal cohort studies conducted in breast cancer patients. All patients had received surgery in addition to either chemotherapy and/or radiotherapy. There was evidence that smoking history was associated with an increased risk of all cause mortality, and risk of death was increased in current and former smokers when compared to never smokers. However, the definition of both current and former smokers was not described.

Concurrent to investigations of this thesis, I have been leading a systematic review examining the association between smoking history and prognosis in head and neck cancer. Searches found 50 observational studies with data on overall survival, cancer specific survival and recurrence/second primaries in relation to smoking history. Briefly, studies provided 75 estimates comparing risk of all cause mortality between various smoking exposures. Exposure was associated with an increased risk of death in 69 out of the 75 estimates, 27 were statistically significant and the median HR was 1.59. A further 43 estimates of risk of cancer progression or cancer specific mortality were extracted. Forty three showed an increase in risk associated with smoking, 12 were statistically significant and the median HR was 1.5. Although a thorough analysis of these data are yet to be completed, this brief analysis indicates that findings in head and neck cancer may be consistent with the findings of this review; that smoking history is associated with a less favourable prognosis.

5.5.4 Strengths and limitations

An important strength of this review is the exhaustive search for relevant studies. In addition, broad inclusion criteria were applied and if possible, data not presented in the form of HR (95% CI) were used to calculate this measure. This enabled all relevant and available data

to be captured and used, increasing the power of sub-group analysis. However, as data were observational, it is not possible to conclude that associations were causal, which is an important limitation. Unadjusted estimates were used as adjusted estimates were considered to have intractable difficulties in terms of interpretation, as many studies controlled for both potential mediators/modifiers in addition to potential confounders . Non-randomised, unadjusted estimates may be subject to confounding, and this is a possible interpretation of the findings of this review.

By definition, for a variable to act as a confounder within the context of this review, it would need to predict the risk of a person smoking and therefore 'pre-date' the smoking behaviour of a patient, and also independently predict prognosis. Age and gender are the two main candidate factors that may act as confounders. It is known from national population statistics that smoking prevalence differs within sub-groups of these demographics.[283] Smoking prevalence has also changed over time.[283] Most of the studies in this review were conducted in past decades, and samples are likely to reflect underlying population demographic structures of smoking prevalence at the time of the study. Many of the included studies were also conducted in Asia where the 'smoking epidemic' is in an earlier stage than seen in the western world.[32] Even so, in these countries, certain demographic sub-groups are at a higher risk of smoking.

In terms of gender, it was considered that males were more likely to have a smoking history than females. In Asia, smoking prevalence is higher in men.[32] Even though in the western world the prevalence of smoking has decreased more rapidly in men over the past years, in the time frame that included studies were conducted, men were more likely to smoke.[283] In all 15 studies included in this review that reported gender by smoking exposure group, ever, current and former smokers had a higher proportion of men than never smokers, and a higher proportion of men were in heavier compared to lighter pack year history groups (see table 5.5). Gender differences in lung cancer survival rates have also been reported in a number of previous studies.[284, 285] In particular, women have been found to have higher survival rates than men, regardless of stage. This has recently been demonstrated in the US, based on analysis of the

SEER database[286], a large cohort from the Mayo Clinic[440] and in a Japanese study with stage I-IIIa NSCLC treated with surgery.[441] However, these past studies have generally found that the survival benefit of female gender can be explained by higher rates of adenocarcinoma, earlier stage at presentation and low rates of co-morbid disease. Therefore, it is highly likely that males have a worse prognosis because of a higher rate of smoking, which leads to increased risk of death via the cancer dependent or cancer independent pathways considered in this review. If this is the case, gender would not be acting as a confounder, but would rather be an antecedent factor on the causal pathway between smoking and prognosis.

Although some of the 12 studies that described age by exposure group found a significant difference at baseline, no difference was greater than 5 years (see table 5.5). There have been mixed reports of the prognostic significance of age for surgical lung cancer patients. One previous study compared patients who were younger than 50 to those who were older than 50 at diagnosis. Younger patients were more likely to be diagnosed with adenocarcinoma, but there was no difference in stage at presentation between the two group or in rates of survival.[442] A second study compared patients diagnosed younger than 45 to those diagnosed older than 45 and found that survival was worse for younger patients. The authors concluded that this was likely to be because younger patients delayed seeking treatment.[328] A third study compared patients diagnosed before age 65 with those who were 65 or older at diagnosis and found that older age was an independent predictor of risk of disease recurrence and all cause mortality.[287] Even if age does predict a worse prognostic outcome, it is unlikely that this would be an important confounder if on average non-smokers are diagnosed roughly 5 years younger than those with a smoking history. Thus, overall, it was considered unlikely that the findings of this review could be attributed to confounding.

In addition to potential confounding, there are a few other considerations that should taken into account when interpreting these data. First, sub-groups were formed within the constraints of available data, and compromises had to be made. For example, treatment varied both between studies and between individuals within a study. Although there were studies in which

all received surgery or all did not receive surgery, treatment was not uniform within groups. Also, often studies did not explicitly confirm that resection was complete. However, there is no reason to assume that this would be systematically more likely for those with a smoking history compared to those without. Including patients with incomplete resection would likely reduce the size of association between smoking history and prognosis to a similar size as patients treated non-curatively. There were other studies that included both patients that had been treated with curative intent and those that had not. This third group was combined with the studies of patients treated non-surgically in order not to 'dilute' the surgical group. However, this would have underestimated the difference in prognostic significance between patients who were treated with surgery and those who were treated non-surgically.

Second, quality was assessed based on criteria proposed by Altman,[300] and studies were found to be of low to moderate quality gaining between 23 and 50% of the total score. It is therefore possible that the findings are subject to bias addressed by this score. In particular, smoking exposure was mostly obtained in retrospect and poorly defined. If smokers were systematically more likely to be assigned as non-smokers, or vice versa, this would create assignment bias. However, when analyses were restricted to high quality studies only, the strength of the estimate increased, indicating the bias was obscuring the true effect size. It is worthy of note that there was methodological heterogeneity based on mode of estimate extraction (i.e. hazard ratios that were presented compared with those that were calculated from other data such as percentage survival or Kaplan-Meier plots). Presented estimates were larger and more precise than those calculated from other data, and more likely to be the chosen mode of presentation in high quality studies. As has been found by others reviewing prognostic studies,[300] this review also found strong evidence of publication bias. Studies were missing from the lower left quadrant of funnel plots, and this asymmetry remained when confining these analyses to sub-groups. This suggests that small, negative estimates have not been published which may lead to an over-estimation of the risk. It is possible that bias was introduced in low quality studies or due to publication bias. However, study quality and publication bias affected the estimate in opposite ways, with low quality studies (high risk of methodological bias) obscuring

the association and publication bias falsely inflating it.

5.6 Conclusion

This review has found consistent evidence that smoking history is associated with increased risk of all cause mortality in lung cancer patients. Findings suggested that risk was not explained by reducing eligibility for surgery, as surgery modified the risk. Risk appeared to be elevated for both surgical patients who were smokers at diagnosis and those who had quit before diagnosis, and there was an indication that risk decreased with increased time since quitting. This is an important finding as although a minority of patients are currently smoking when diagnosed, most have a history of smoking.

Lack of data prevented strong conclusions to be drawn regarding mediation pathways. Few studies reported cancer specific prognostic outcomes. In addition, no models adjusted for individual potential mediators were available, and it was difficult to interpret the effect of adjustment for multiple factors. Most studies that reported risk of developing a second primary, recurrence or of cancer specific death found an increased risk although often this was not statistically significant and it was often not possible to combine data. However, this indicates that risk may be operating through cancer related mechanisms, although mediation through co-morbidity cannot be ruled out. It is biologically plausible that smoking history may affect prognosis through cancer related risk, even after surgery has completely removed the tumour. A prevailing hypothesis that fits with tentative conclusions of this review is that of field cancerisation; in other words, multiple pre-neoplastic lesions remaining after successful surgery are responsible for development of second primaries and increased risk of death. However, further work is needed to confirm this as data were limited and it is not possible to rule out bias or confounding as an explanation for the findings.

Taken together, this review indicates that smoking history may be an important prognostic factor in surgical patients. Currently, little attention is paid to smoking history either in clinical

practice or in cancer clinical trials. If it was confirmed that smoking history is an independent prognostic factor, more careful detailing of a patients' smoking history would need to be taken at diagnosis as this would have implications for identifying those are greater risk of disease progression. In addition, future prognostic studies would need to address this as a potential confounding factor.[300] Despite the limited ability to draw a strong conclusion regarding the prognostic significance of smoking history for surgical patients, this constitutes moderate evidence of an association and warrants further investigation. Given the difficulties encountered using study level estimates, it is most likely that investigation of these questions will be best answered using individual patient data.

5.6.1 Identified research priorities

The following is a list of research questions that have been identified based on the findings of this study:

1. What is the prevalence of current and former smoking at diagnosis in lung cancer surgical patients.
2. What is the distribution of length of time of quitting before diagnosis in former smokers treated with surgery.
3. Using propensity score matched individual level surgical lung cancer patient data, the following questions need to be investigated:
   (a) Is there evidence of a causal relationship between presence of a smoking history and all cause mortality, development of a second primary, tumour recurrence or cancer specific mortality and what is the size of risk, controlling for the effect of continuing smoking after diagnosis and key confounders.
   (b) Is the relationship mediated by surgical stage, histology, pre-neoplastic lesion burden, inflammatory markers or co-morbidity
   (c) Does the magnitude of risk decrease with increasing time since quitting.
   (d) Does intensity of smoking history predict risk after controlling for recency of smoking.

CHAPTER

SIX

INVESTIGATION OF THE ASSOCIATION BETWEEN CONTINUED SMOKING AFTER LUNG CANCER DIAGNOSIS AND PROGNOSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

6.1 Review question

1. What is the association between continued smoking after a diagnosis of lung cancer and the risk of all cause mortality, cancer specific mortality, development of a second primary tumour or tumour recurrence in lung cancer patients?

6.2 Introduction

This chapter reports a second systematic review that investigates the association between smoking and prognosis, in particular focusing on the prognostic significance of continued smoking after a lung cancer diagnosis. This review has been published by the BMJ, and a copy of the full text publication can be found in appendix C. For clarity, the review presented in chapter 5 will be referred to as the smoking history review and the review presented in this chapter will be referred to as the post-diagnosis smoking review.

Past studies have estimated that a significant minority of patients are current smokers at diagnosis, and many continue to smoke (see section 1.6.1). As with smoking history, it was hypothesised that continued smoking may affect prognosis either through pathways that are related or unrelated to cancer. Patients who continue to smoke and those who quit smoking are likely to have a similar smoking history, as both groups are current smokers at diagnosis. Therefore, any increased risk of disease progression and cancer related death is not likely to operate through the same mechanisms hypothesised for smoking history e.g. later stage at diagnosis, more aggressive tumour histology or presence of pre-malignant lesions (see section 5.5.2). However, there are other possible mechanisms by which continued smoking may increase the risk of disease progression and cancer related death. It is possible that carcinogens in cigarette smoke not only act as genetic inducers of tumour development but exposure to tobacco smoke may also promote progression of the disease.[319, 443] For example, inflammation has been shown to create a micro-environment that supports tumour development,[409, 410, 412] and smoking causes inflammation.[444–446] As well as potentially increasing the risk of cancer related morbidity and mortality, continued at diagnosis may also increase overall mortality by increasing risk of death from co-morbid disease.[31, 447]

It is possible that the difficulty and discomfort of smoking cessation would mean that many patients with advanced lung cancer choose to continue to smoke.[138] However, curative treatment has good survival ratings, with up to 78% of patients surviving for 5 years after diagno-

sis,[41] and it is possible that smoking cessation may be worthwhile in this group. Patients who are still smoking at diagnosis may be given brief advice to stop but delivery of or signposting to specialist smoking cessation support is not a standard component of cancer care. A recent survey of 1 500 lung cancer clinicians who were members of the International Association for the Study of Lung Cancer (IASLC) showed that although more than 90% believed that smoking cessation support should be a routine part of care, only 39% routinely offered assistance with quitting smoking.[248]

The Cancer Reform Strategy highlighted the need for development of tailored services to support cancer patients after diagnosis and treatment, and new care pathways are being developed and tested (see section 1.7.2). In the future, these services for lung cancer patients may include smoking cessation interventions.[186, 448] The qualitative interview study that was presented in chapters 2 - 4 of this thesis found that most surgical lung cancer patients who were smoking at diagnosis had a desire to be a non-smoker, and were open to offers of support to quit. Adoption of smoking cessation support into standard care should be based on robust evidence that quitting smoking improves outcomes. A systematic search of the literature was performed to assess if there was evidence that continued smoking after diagnosis is associated with prognosis in lung cancer patients, and to understand if risk is elevated through pathways that are related or unrelated to cancer.

6.2.1 Methodological considerations

The question posed by this review could possibly be answered using a randomised controlled trial (RCT) design. However, no RCTs testing smoking cessation interventions and reporting both smoking cessation and prognostic outcomes were found from searches of the literature. Therefore, this review is based on study level data from observational cohort studies. The methodological considerations of using this type of data have been discussed at length in chapter 5. The most important consideration for this review is the possibility of uncontrolled confounding. As smoking cessation would occur after diagnosis with a tumour and development

of co-morbid disease, it is not possible for these factors to act as mediators of the relationship between quitting and prognosis. In order to investigate confounding, comparison between unadjusted and adjusted estimates were used as a basis of this review. This review found an equal number of studies conducted in NSCLC and SCLC patients. Given the difference in disease course and treatment approach, studies in non-small cell lung cancer were considered separately to small cell lung cancer.

6.3 Methods

Relevant studies were identified from the same search conducted for the smoking history review (for search methods see section 5.3.1). Inclusion criteria were also similar, but differed for the exposure and also study design (see table 6.1). Studies were included if they estimated the difference in risk for those who continued smoking after diagnosis compared with patients who quit smoking. As it was possible that data may be derived from RCTs, this study design was also included in the criteria.

Table 6.1: Inclusion criteria – systematic review of the association between smoking cessation after diagnosis and lung cancer prognosis

Study design	RCTs Observational cohort study (prospective or retrospective)
Population	Patients diagnosed with a lung tumour regardless of stage, histology and treatment
Exposure	Continued smoking after diagnosis compared with quitting at diagnosis
Outcome	All cause mortality Cancer specific mortality Development of second primary Development of recurrence

6.3.1 Data extraction and study quality

Data were extracted using the same methods reported for the smoking history review (see section 5.3.3). Unadjusted and adjusted estimates were extracted as a hazard ratio (HR) with 95% confidence interval (CI) and methods described by Parmar were used to calculate HR (se) from Kaplan Meier curves, p values or percentage survival when this was not presented.[296] In some studies, observed risk was presented as a proportion of expected risk calculated using Poisson regression modelling with general population data. In these cases, the HR was calculated by indirect comparison.[368]

Study quality was assessed using the same scoring system as used for the smoking history review which was based on a framework proposed by Altman for the assessment of prognostic studies.[273] Studies could score a maximum of 22 points based on description of the cohort and study methodology. Studies scored highly if the inclusion/exclusion criteria were well defined, if the characteristics of the patient sample were described including distribution of important confounders and prognostic factors between smoking exposure groups, if treatment and smoking status were clearly described and if patients were followed prospectively for more than five years. The scoring system is summarised in table 5.2 in chapter 5.

6.3.2 Exploration of the association between smoking cessation and prognosis

Extracted HRs were combined using a random effects inverse variance model in STATA10, as clinical and methodological heterogeneity was high. It was decided to report the results for non-small cell lung cancer and small cell lung cancer studies separately given the difference in disease course and treatment of these histological types. Statistical heterogeneity was assessed using the I^2 test. Where possible, sub-group analysis was conducted by receipt of surgical treatment, and publication bias was assessed using funnel plots.

Assuming the findings of the review reflected a causal relationship between smoking cessation and risk of all cause mortality, I further investigated the data by constructing life tables for a hypothetical group of one hundred 65 year old early stage lung cancer patients to estimate how many deaths would be prevented by smoking cessation within the NSCLC and SCLC population during five years. The number of patients who continued to smoke after diagnosis that would survive for 5 years was estimated using the average risk of death reported for continuing smoking from two high quality studies included in this review.[137, 449] Five year survival in quitters at diagnosis was estimated by applying the continuing smoker death rate multiplied by the reciprocal of the adjusted HR for risk all cause mortality presented in this review.

To investigate if reduction in risk associated with quitting smoking could be explained by a reduced risk in death due to other smoking related diseases, I estimated the expected number of cardiovascular and respiratory (CR) diseases that would be prevented due to smoking cessation in the general population using life tables as above. The number of 65-69 year olds and number that died of cardiorespiratory causes were estimated from ONS data from 2009, thus giving the risk of cardiorespiratory death for this age group.[450] It was assumed this mortality rate was approximately that of the non-smoking population because around 12% of this age group smoke.[246] This rate was multiplied by the relative risk of death from CR causes in lifelong smokers to estimate the number of deaths that would be expected over 5 years from CR causes in the smoking 65 year old general population.[31] The risk reduction from cessation was then applied to estimate the number of deaths that would be prevented, which was then compared to the risk reduction from cessation in NSCLC and SCLC populations estimated in this review.[31]

6.4 Results

Full text articles were obtained for 268 papers from which 10 individual cohort studies [137, 315, 333, 335, 366, 367, 449, 451–453] were included in the review (figure 6.1).

6.4.1 Characteristics of included studies

Five included studies estimated the association of smoking cessation with all cause mortality (4 NSCLC, 2 SCLC), four studies with the development of second primaries (1 NSCLC, 3 SCLC) and two studies with recurrence of the primary tumour (1 NSCLC, 1 SCLC). In eight studies that reported gender, most participants were male, ranging from 55-86%. Stage of disease was reported in all studies. Nine of the studies were conducted on a patient sample with over 75% presenting with early stage disease (stage 1-3a NSCLC or with limited stage SCLC). In three studies in NSCLC, all patients received surgery and in the remaining two studies patients were included that received surgery or chemo/radiotherapy. For studies in SCLC, all patients receive radiotherapy and/or chemotherapy.

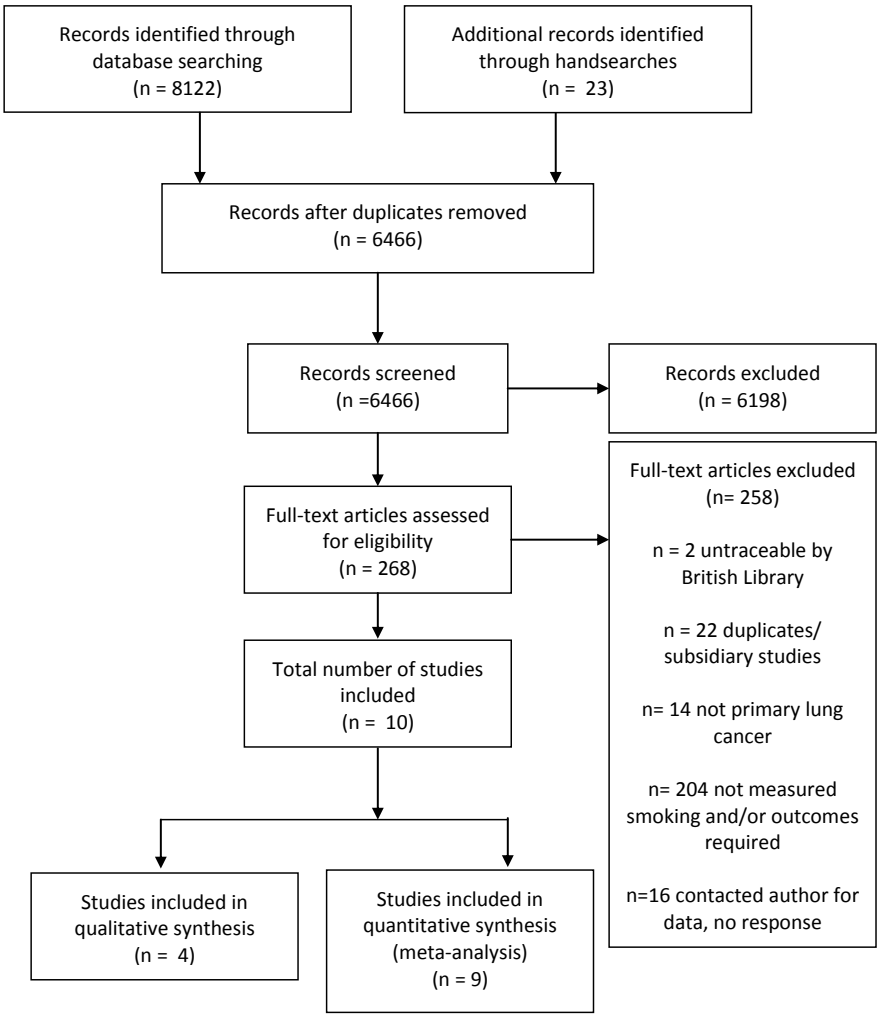


Figure 6.1: PRISMA flow diagram of study selection and use. [301] (N.B. Three studies contributed to both qualitative and quantitative syntheses [137, 333, 453])

Table 6.2: Participant characteristics of included studies

Author (year)	no. in study[1]	no. of continuing smokers[2]	no. quitters[2]	continuing smokers[3] (%)	Males (%)	Squamous (%)	SCLC (%)	Stage 1-3A/ limited (%)	Treatment
NSCLC studies									
Baser (2006)	93	47	46	51	49	n/r	0	90	Mixed
Kawaguchi (2006)	62	16	19	46	81	48	0	100	Mixed
Nia (2005)	311	169	35	83	86	47	0	92.1	Surgery
Saito-Nakaya (2006)	238	6	92	6	60.9	21	0	81	Surgery
Shiba (2000)	156	8	61	12	72	59	0	100	Surgery
SCLC studies									
Johnstone-Early (1980)	112	57	35	62	n/r	0	100	29	Chemo/radiotherapy
Kawahara (1988)	70	33	31	52	60	0	100	100	Chemo/radiotherapy
Tucker (1997)	611	214	181	54	55	0	100	79	Chemo/radiotherapy
Videtic (2003)	215	79	107	42	60	0	100	100	Chemo/radiotherapy
Yoshida (1996)	61	26	33	44	80.3	0	100	85	Chemo/radiotherapy

Table 6.3: Methodological characteristics of included studies and quality score

Author (year)	Prospective(1)/ Retrospective(2)	Exposure f/u[1] (max)	Method of outcome measurement	Outcome f/u[1] (yrs max)	Outcomes measured[3]	Study quality score
NSCLC studies						
Baser (2006)	1	1 year	Self report, case notes	5+	ACM	15
Kawaguchi (2006)	2	3 years	Self report, questionnaire[2]	12.2	SP	14
Nia (2005)	2	Unclear	Self report, questionnaire	11.25	ACM, REC	18
Saito-Nakaya (2006)	1	1 month	Self report, case notes	7.6	ACM	13
Shiba (2000)	1	Unclear	Self report, case notes	5+	ACM	17
SCLC studies						
Johnstone-Early (1980)	Unclear	After treatment	Self report, verbal	4	ACM	13
Kawahara (1988)	2	2 years	Self report, verbal[2]	10+	SP	13
Tucker (1997)	2	2 years	Self report, case notes	10+	SP	13
Videtic (2003)	2	Start of treatment	Self report, case notes	7	ACM, REC	16
Yoshida (1996)	1	2 years	Self report, case notes/verbal[2]	10+	SP	16

Overall study quality scores ranged from 13 to 18 points out of a maximum of 22 points. Four studies reported the distribution of potential confounding factors by smoking exposure group (see table 6.4). Quitting status was based on follow up 6 months or greater in five studies, [333, 335, 366, 367, 449] but smoking was only measured at the time of treatment in four [137, 451–453]. Follow up was not defined in one study.[315] Reporting of smoking exposure varied between studies. The best evidence for smoking status would be a prospectively collected measure with biochemical verification.[146] However, often there was ambiguity in the reporting of the method used to obtain smoking status, or else it was not described. Two studies defined quitting as continuous abstinence within six months of treatment initiation to longest follow up[333, 367] and one study defined quitting as continuous abstinence during and subsequent to treatment.[451] The remaining studies did not give a definition of quitting. In three studies,[333, 335, 366] patients were included in the analysis if they had survived two years disease free and one study [367] only included patients that had been disease free for three years (Table 6.3).

Table 6.4: Balance of potential confounders between quitters and continuers

		Gender	Age	Histology	Stage
Baser, 2006	NSCLC	Balanced	Balanced	N/R	Balanced
Nia, 2005	NSCLC	Balanced	Balanced	Balanced	Balanced
Johnstone-Early, 1980	SCLC	N/R	N/R	Balanced	Unbalanced
Videtic, 2003	SCLC	Unbalanced	Balanced	Balanced	Balanced

6.4.2 The association between continued smoking after diagnosis and prognostic outcomes

Non-small cell lung cancer - All cause mortality, occurrence of second primary and recurrence Four studies reported estimates of the association between continued smoking with all cause mortality, one study with occurrence of a second primary, and one study with recurrence in non-small cell lung cancer (figure 6.2). Estimates were derived from patient samples where at least 80% were diagnosed with a stage 1-3a tumour. Three studies were conducted in surgical patients, and one study[449] included patients who had not received surgery. Unadjusted

estimates suggested that continued smoking was associated with a non-significant increased risk of all cause mortality of 19% when compared to quitters. When considering only surgical patients, a strengthening of risk to 71% increase was observed although this remained non-significant (surgical patients HR 1.71 (95% CI 0.75, 3.93). On adjustment for potential confounding variables there was an almost three fold increase in risk of all cause mortality for continuing smokers compared to quitters (unadjusted HR 1.19 (95% CI 0.91, 1.54), 4 studies, $I^2 = 0\%$; adjusted HR 2.94, (95% CI 1.15, 7.54), 1 study; 6.2).

There was no significant increase in the occurrence of second primaries before or after adjustment although confidence intervals were wide (unadjusted HR 0.35, (95% CI 0.06, 2.06), 1 study; adjusted HR 2.29 (95% CI 0.50, 10.58, 1 study; figure 6.2). One study reported an almost two fold increase in unadjusted risk for continuing smokers of tumour recurrence (adjusted HR 1.86 (95% CI 1.01-3.41), 1 study; figure 6.2). Given the small number of studies, it was not possible to conduct sensitivity analyses by study quality and the ability to assess publication bias was limited. Unadjusted estimates of all cause mortality showed no evidence of funnel plot asymmetry.

Small cell lung cancer - All cause mortality, occurrence of second primary and recurrence

All cause mortality in continuing smokers with small cell lung cancer was significantly increased before and after adjustment, with adjustment strengthening the association (unadjusted HR 1.18 (95% CI 1.03-1.36), 2 studies, $I^2 = 0\%$; adjusted HR 1.86 (95% CI 1.33-2.59), 1 study; figure 6.3). In each of these studies, patients were treated with either radiotherapy and/or chemotherapy. Estimates were derived from patient populations where at least 79% were diagnosed with limited stage disease apart from one study where 29% of patients presented with limited stage disease.[451] There was no heterogeneity between unadjusted scores despite there being a marked difference between the patient populations in terms of stage at presentation.

Unadjusted estimates suggested an 86% increase in risk of developing a second primary, which was strengthened to a fourfold increase in risk after adjustment for continuing smokers compared to those who quit at diagnosis (unadjusted HR 1.86 (95% CI 0.96, 3.60), 3 studies,

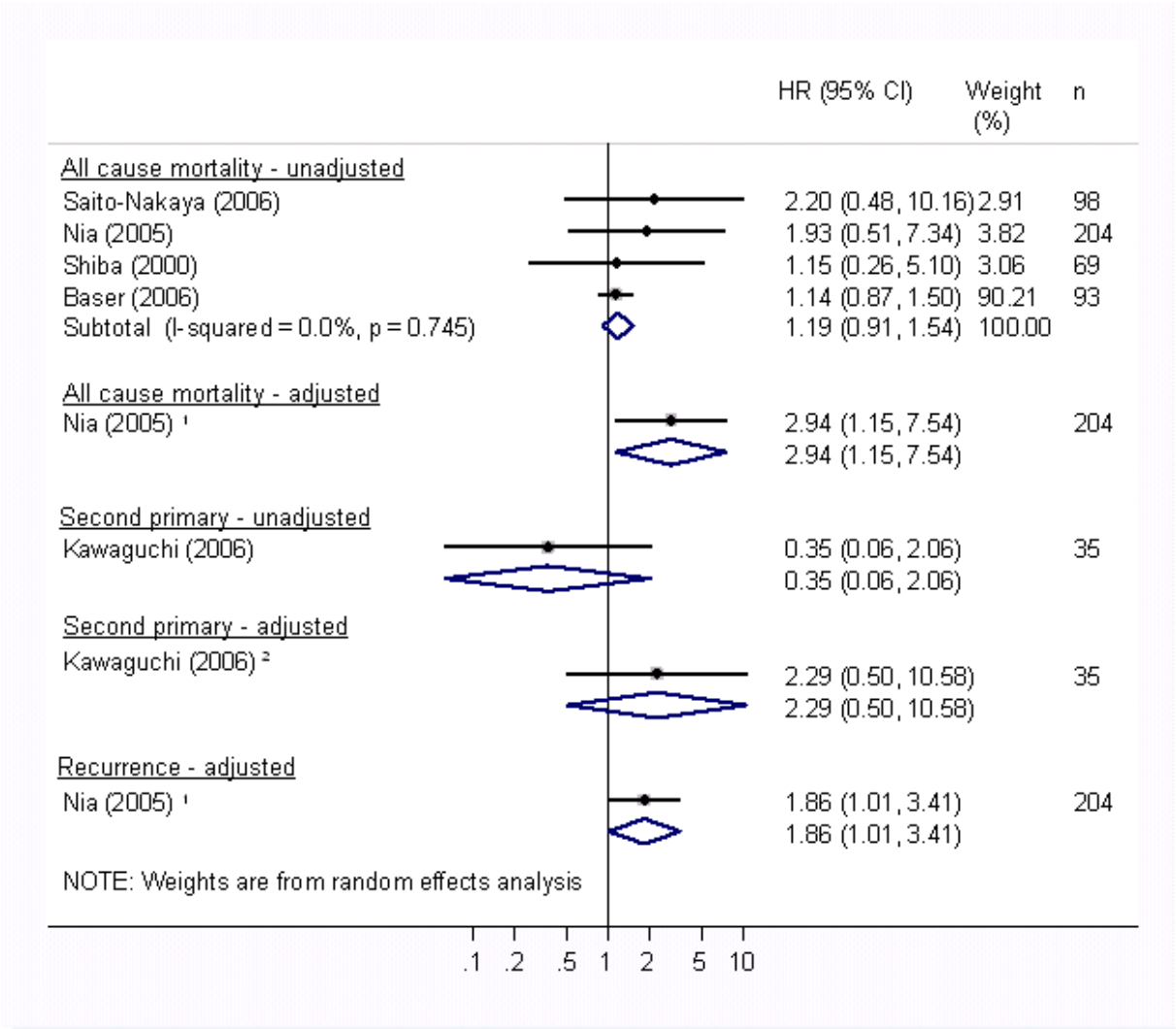


Figure 6.2: The association of continued smoking in early stage non-small cell with risk of all cause mortality, second primary and recurrence compared with quitting at diagnosis

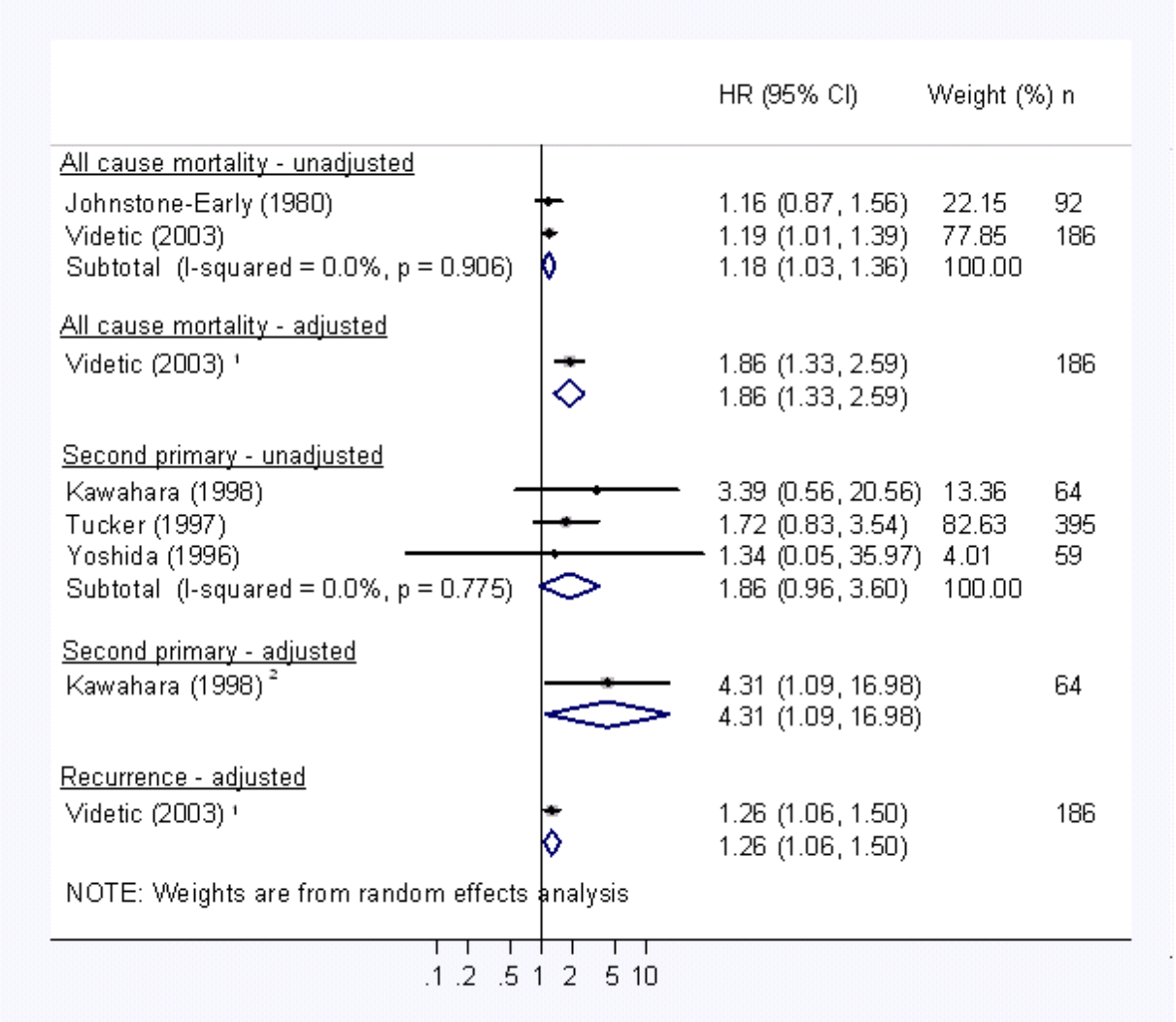


Figure 6.3: The association of continued smoking in small cell lung cancer with all cause mortality, development of a second primary or recurrence compared to in quitting at diagnosis

$I^2 = 0\%$; adjusted HR 4.31 (95% CI 1.09-16.98), 1 study; figure 6.3) although confidence intervals were wide. One study reported an unadjusted estimate for the association between continued smoking on recurrence that was statistically significant (unadjusted HR 1.26 (95% CI 1.06-1.50)). Given the small number of studies, it was not possible to conduct sensitivity analyses by study quality or assess publication bias.

6.4.3 Contribution of cardiovascular and respiratory mortality to reduced mortality rates in lung cancer patients who quit.

The life table analysis was based on a notional cohort of 65 year old smokers diagnosed with early stage NSCLC or limited stage SCLC. Assuming a causal relationship between smoking cessation and all cause mortality, the estimated five year survival rates were 41% in continuing smokers and 75% in quitters for NSCLC and 36% in continuing smokers and 68% in quitters for SCLC. In life table analyses based on general population data, five year survival from cardiorespiratory deaths was estimated at 91% in smokers and 94% in quitters.

6.5 Discussion

This review included 10 observational studies, all of which showed some evidence that continued smoking after a diagnosis of early stage lung cancer is associated with elevated risk of recurrence, second primary, or all-cause mortality compared to quitting at the time of diagnosis. Although unadjusted estimates suggest that the associated risk of continuing (or the benefits of cessation) may be modest, within study adjustment for key confounders suggested a doubling of risk of mortality for SCLC and tripling of the risk for NSCLC. Across study assessment of the effect of adjustment also suggested a strengthening in the risk of mortality, and this remained when limiting the analysis to patients who had been treated with surgery.

Potential mechanisms of increased risk Assuming that the association between smoking cessation and risk of all cause mortality represents a causal relationship and is not due to bias or confounding, two possible explanations were hypothesised. Firstly, continued smoking may increase the risk of death due to other smoking related causes such as cardiorespiratory diseases. If this was the case, it would be expected that continued smoking would be associated with an increased risk of all cause mortality, but no increase in cancer specific prognostic outcomes would be found. Secondly, it is possible that continued smoking may increase the risk of

disease progression and cancer death. In both early stage NSCLC and limited stage SCLC, this study found evidence of a significant association between continued smoking and recurrence of the primary tumour. There was additional evidence in limited stage SCLC of a significant elevation in the incidence of a second primary tumour. Adjustment within study and across studies strengthened the association between continued smoking and these cancer outcomes. Thus, although data were limited, it indicated that continued smoking increased risk through cancer related mechanisms.

Life table modelling estimated that smoking cessation in the general population would lead to increased five year survival by 3% in absolute terms due to reduction in cardiorespiratory deaths, whereas smoking cessation after diagnosis of early stage NSCLC and limited stage SCLC increased five year survival by 34% and 32% respectively. This exercise was based on assumptions that are likely to underestimate the possible mortality benefit from smoking cessation. For the 65-69 year old general population, the baseline cardiorespiratory death rate estimate was based on an assumption that the population were non-smokers. However, although the prevalence of smoking is only around 12% many will be ex-smokers, conferring a greater baseline risk for cardiovascular death than a completely non-smoking population. On the other hand, the higher prevalence of pre-existing cardiorespiratory disease in lung cancer patients means the absolute mortality gains seen in a general population are probably lower than in lung cancer patients. Neither assumption seems sufficiently inaccurate to challenge the data suggesting the major benefit from smoking cessation would be conferred by a reduction in cancer-specific risk, if the reduced risk seen in this review was caused by smoking cessation, but no studies reported cancer specific mortality rates to confirm this.

It is known that the risk of cardiovascular related illness and death decreases after smoking cessation in patients with coronary heart disease,[454] reducing dramatically over the first three years.[455] However, it generally takes longer for the risk of developing lung cancer to reduce after smoking cessation,[31, 455, 456] It is noteworthy that this review has found evidence that after lung cancer has been diagnosed, reductions in risk of developing a second primary or

recurrence were associated with quitting within at least four years of follow up, suggesting that the mechanism of increased risk acts in the short term and, even at diagnosis, it may be possible to improve the prognostic outlook by smoking cessation.

There are a few potential mechanisms by which continued smoking may increase the risk of disease progression and cancer death, acting in the short term. It is possible that continued smoking may reduce the effectiveness of adjuvant treatment.[457, 458] Although little has been done to assess the interaction between smoking and treatment on outcome, some studies in other tumours have indicated that smoking during radiotherapy may effect the outcome. For example, one study in 115 head and neck cancer patients reported that response rate was significantly lower (45% vs 74%, p=0.008) and also 2 year survival was significantly lower (39% vs 66%, p=0.005) in patients that continued to smoke during treatment compared to those who quit at diagnosis or before.[459] Two case-control studies conducted in breast cancer patients found that radiation to the chest in combination with smoking was a risk factor for developing a second primary tumour in the lung. In one of these studies, radiotherapy alone was not found to increase risk and in the second study radiotherapy and smoking were found to be a multiplicative risk.[460, 461]

Smoking may also affect response to chemotherapy as it is a potent inducer of the cytochrome P450 enzymes which is responsible for metabolism of a number of difference drugs in the liver.[462] Several chemotherapeutic agents are metabolised by this enzyme system, and therefore smoking could potentially increase the rate of metabolism, leading to lower levels in the blood and tissues.[457] No studies have investigated the effect of continued smoking on response to chemotherapy, but one study showed that clearance of erlotinib (a epidermal growth factor receptor tyrosine kinase inhibitor monoclonal antibody used to treat patients with advanced disease) to be 24% higher in patients who smoked compared to non-smokers.[463]

In addition to leading to worse treatment outcomes, constituents of tobacco smoke may also alter the biological behaviour of lung cancer or aid processes that support tumour progression.[319, 457, 458] Smoking causes inflammation and, particularly over the past 10-15 years,

evidence has been mounting for the critical role of 'smouldering inflammation' for both the development and progression of tumours.[6, 410, 412] The mechanisms by which smoking, inflammation and lung cancer are linked are complex and not completely understood. However, inflammatory cells and mediators have been found to be highly expressed in the lung tissue of smokers, in precursor lung lesions and in established lung tumours.[446] Cigarettes smoke contains many potential irritants and is a strong inflammatory stimulus, inducing pro-inflammatory cytokines such as IL-6 and TNF$\propto$. In addition, COPD, for which smoking is an important risk factor,[464] is characterised by deregulated inflammation.[465] Chronic exposure to tobacco smoke is associated with mutations that lead to the loss of p53 tumour suppressor gene function and mutation of the KRAS oncogene, and presence of these mutations has also been linked to increased inflammation, cell proliferation and angiogenesis.[446]

In addition to the potential tumour-promoting effects of smoking-induced inflammation, nicotine itself has also been shown to suppress apoptosis, stimulate cell proliferation and promote angiogenesis *in vivo*.[466, 467] Thus, although the details of mediating pathways are yet to be confirmed, evidence is mounting of plausible biological mechanisms by which continued smoking after surgery may help create an environment that stimulates and support growth of unresected pre-neoplastic lesions or unresected tumour cells.

Strengths and limitations An important strength of this review is the exhaustive search for relevant studies. Five of the ten studies were ostensibly about the relationship of other potential prognostic variables with outcome, but happened to present data on smoking status as a potential confounder of those associations. Such a strategy mitigates concern about publication bias because the decision to publish was unrelated to the findings on smoking status and cancer outcome. However, it is still possible that reporting of factors included in an adjusted model may be biased towards those that were statistically significant. No asymmetry was detected in funnel plots to suggest such reporting bias, but it is possible that bias was not detected given the small number of studies.

An important limitation of the data in this review is that it is derived from observation studies,

and therefore no causal inferences can be made. A major challenge with systematic reviews of observational studies is the possibility of uncontrolled confounding.[273] It was considered that in the context of this review, the main potential confounders were age, gender, tumour histology, tumour stage at diagnosis and co-morbidity. If, in general, potential confounding variables were not associated with quitting status, the ratio of unadjusted to adjusted HRs within studies should be randomly distributed about one. For those studies that presented unadjusted and adjusted HRs, these ratios were lower than one, with adjustment revealing a strengthening of the association.[137, 333, 453] This suggests that smokers with unfavourable prognostic factors were the most likely to give up smoking and therefore unadjusted estimates underestimated the benefits of quitting. Four out of the ten included studies presented data on the baseline distribution of potential confounders split by quitting status.[137, 449, 451, 453] One study[453] reported a significantly higher proportion of men in the quitter than continuer smoking group, and a further study reported that more patients with extensive stage SCLC quit smoking than continued to smoke through treatment.[451] Both male gender and more advanced stage have been demonstrated as independent predictors of a worse prognosis. None of these studies measured co-morbidity and therefore it was not possible to assess if this factor was unevenly distributed between continuers and quitters.

Quality was assessed based on criteria proposed by Altman,[300] and studies were found to be of moderate quality gaining between 59 and 81% of the total score. Generally, smoking abstinence definitions were poor and only five of the 10 studies assigned patients to smoking categories based on smoking status recorded at 6 months or greater after diagnosis. As a result, the proportion of current smokers at diagnosis who continued to smoke based on the definitions used for included studies ranged from 6-83%. There are conflicting reports in the literature of the proportion of lung cancer patients who continue to smoke after diagnosis, with estimates ranging from 13-60%,[132, 254, 468] There may be true variation in prevalence of continued smoking based on differences in the clinical characteristics of study populations or course of treatment for instance.[469] However, it is likely that much of the variation seen in included studies resulted from heterogeneity in the classification of continued smoking. This may have

led to a mixing of true exposure status. However, this is likely to have underestimated the benefits of cessation as it is more likely that those who were counted as quitters went on to relapse than vice versa.[258] Future studies in this area need to use accepted standards for measurement of smoking abstinence in order for gain a more accurate estimate of the relationship between continued smoking and prognosis.[146]

6.6 Conclusion

This study has found evidence that continued smoking after a diagnosis of early stage non-small cell or small cell lung cancer is associated with a worse prognosis. Life table modelling indicated that risk of continued smoking (or benefit of smoking cessation) was much larger than would have been expected due to cardiovascular deaths only. Coupled with evidence that risk of recurrence or development of a second primary was significantly elevated, this supports the hypothesis that continue smoking increases risk through cancer-related pathways. Given the limitations of the data, these findings must be considered preliminary. However, they are of sufficient strength to warrant further investigation, including a randomised trial of a smoking cessation intervention to examine questions of effect on smoking behaviour, health outcomes and cost-effectiveness. Establishing the role of cigarette smoke in cancer progression will not only produce the necessary evidence for implementing smoking cessation interventions, but may also help to further understanding of the biological behaviour of lung cancer.

6.6.1 Identified research priorities

The following is a list of research questions that have been identified based on the findings of this study:

1. What is the prevalence of continued smoking in surgical lung cancer patients?
2. What is the effectiveness of a smoking cessation programme for lung cancer patients in terms of smoking abstinence and also prognostic outcomes.

CHAPTER

SEVEN

OVERARCHING CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER RESEARCH

The research presented in this thesis aimed to investigate key health and supportive care issues for surgical lung cancer patients in order to increase the evidence base for future developments in supportive care for this patient group. Each individual research study, documented in chapters 2 - 6, contains a detailed discussion of the findings in the context of past published research, considers the strengths and limitations of the study, draws conclusions from the findings and makes specific recommendations for further research. Important design components of a tailored rehabilitation programme for surgical lung cancer patients to take forward for testing are described in section 4.1.4. The main findings from each individual study of this thesis, as discussed within relevant chapters, along with identified research priorities are summarised in table 7.1. The purpose of this final chapter is to summarise the overarching conclusions to be drawn from this doctoral study and indicate their relevance to the ongoing developments within cancer research and care.

Table 7.1: Main findings and research priorities for each study of this thesis

Qualitative interview study
Main findings: • Breathlessness and pain were the most dominant health challenges reported during the first 12 months after surgery. Other health challenges reported included loss of appetite, weight loss, altered sleep, fatigue and psychological distress. • There was a range in the extent to which participants were affected by these health challenges from not being affected to being severely affected. Participants who were mildly affected were able to manage their own recovery and felt the level of supportive care that they received had met their needs. However, most participants were moderately or severely affected affected . These participants felt they needed additional support and often felt abandoned after discharge • Participants were noticeably less affected by health challenges after VATS than after thoracotomy • No other pattern of experience was seen for other sub-groups including extent of resection, presence of co-morbidity, smoking behaviour or participation in the ROC programme. • Most participants had a smoking history and some were current smokers at diagnosis. • Of the current smokers, most found it easy to remain abstinent whilst in hospital. • After discharge, some participants continued to smoke, some tried to remain abstinent but relapse and other remained abstinent until interview • Most participants reported that they were not asked about their smoking or offered help to quit. • All participants had a desire to be a non-smoker, but some expressed conflicting beliefs that supported continued smoking behaviour including lack of will power to quit, reflecting on smoking with fondness, maintenance of mood and concerns regarding health consequences of quitting. • Despite attitudes regarding smoking and smoking cessation, all participants felt that it was the place of the health professional to ask about their smoking behaviour and some wanted help to quit • Participants found it difficult to articulate specific preferences for the content and format of a rehabilitation programme, but for those who did pulmonary rehabilitation proved to be a promising template. • Participants needs and preferences for a rehabilitation programme are summarised in table 4.2

Table 7.1: cont.

Research priorities:

- Investigation of the causes of breathlessness after surgery
- Identification of appropriate measures/identification tools and investigation of the effectiveness of pharmacological (e.g. inhaled bronchodilators and cortiosteroids, analgesics, varenicline, NRT) and non-pharmacological (e.g. exercise, relaxation, cognitive behavioural therapy) treatments for breathlessness, pain and smoking cessation.
- Assess the acceptability to patients and clinicians of the proposed tailored rehabilitation programme
- Test the effectiveness of the tailored rehabilitation programme: outcomes include QOL, respiratory function, post-surgical pulmonary complication rate and survival.

Systematic review: association between smoking history and prognosis

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Main findings:

- There was consistent evidence of an association of increased risk of death for ever, current and former smoking compared with never smokers.
- Increased risk of death was not explained by reducing eligibility for curative treatment, and smoking history remained significantly associated with increased risk of death in surgical patients.
- Findings indicated that risk remained high for former smokers, although was possibly reduced compared to current smokers. Additionally, there was an indication that smoking history increased risk through cancer related mechanisms, although the role of co-morbidity could not be ruled out.
- Study quality was found to be poor and limitations of the data prevent drawing of strong conclusions. However, the data were sufficiently strong to warrant further investigation.

Research priorities:

- The review questions need to be addressed using individual patient data. Using such data will improve the ability to investigate mediating pathways. Potential mediating pathways to investigate are: stage, histology, co-morbidty, inflammatory markers, burden of pre-neoplastic lesions.
- Investigate if risk associated with smoking history decreases with time since quitting and evaluate importance of dose.

Table 7.1: cont.

Systematic review: association between continued smoking after diagnosis and prognosis
Main findings: • There was preliminary evidence that continued smoking was associated with an increased risk of developing a second primary, recurrence and of death. • Lifetable modeling indicated that the risk of death associated with continued smoking was much larger than would be expected due to increased risk of cardiovascular death. **Research priorities:** • What is the prevalence of current smoking and continued smoking during and after treatment in surgical lung cancer patients • What is the effectiveness of a smoking cessation intervention for surgical lung cancer patients in terms of smoking abstience, QOL and prognostic outcomes
Other identified priorities for future research (see section 7.4)
• Is smoking correlated with COX-2 expression in young, healthy smokers and in surgical lung cancer patients. • Using an epidemiological study design, investigate the association between long term use of anti-inflammatory medication and prognostic outcome in surgical lung cancer patients.

7.1 Many lung cancer patients experience a difficult and protracted recovery after surgery, and their needs are not being met

During the lifetime of this doctoral study, the NCSI has developed a new model of follow up care for cancer patients. This features a risk stratified approach which is based on ongoing assessment of patients' needs. Patients who are largely well after treatment will be given the tools they need to self-manage, whereas other patients may need additional support from secondary and/or primary care and will be managed using the 'shared care' model. Finally, those who have complex ongoing health care needs will receive consultant-led care (complex care). The NCSI estimated that 15%, 60% and 25% of lung cancer patients will require self-management, shared care or complex care, respectively.[181] This estimate is for lung cancer patients as a whole rather than being specific for surgical lung cancer patients.

Qualitative investigations conducted as part of this doctoral study found that most participants were affected by health challenges as a results of their treatment, although to different extents. Most participants had improved over time but many were not yet back to normal at the time of interview and were limited in their normal daily activities due to health challenges. In the most extreme cases, participants continued to find activities of daily living difficult and were largely housebound due to their health. Whilst some participants felt prepared for what to expect with regards to surgery and recovery, many participants who underwent thoracotomy expressed concern that they had not realised the extent to which they would be affected by health challenges as a consequence of surgery.

Participants who were mildly affected by health challenges reported being able to manage their health without additional support from primary or secondary care. Participants that demonstrated this had generally undergone VATS, although a minority of participants who had undergone thoracotomy felt their needs had been met and were satisfied with standard care. In con-

trast, most participants who underwent thoracotomy were moderately or severely affected by health challenges, felt abandoned at discharge and expressed the need for additional supportive care. Interviews took place with a purposeful sample of patients, and therefore the proportions of patients that reported being mildly, moderately or severely affected by health challenges during recovery may not reflect surgical lung cancer patients as a whole. However, QOL studies in random samples of surgical patients also indicate that many continue to experience health challenges and limitations in function for at least 3 months, and often up to 12 months. Taken together, these data show that although some patients may be able to manage their recovery after surgery without additional support, many are in need of additional supportive care i.e. either shared care or complex care.

7.2 Well developed treatments and services that are widely available to other patients may potentially improve quality of life and health outcomes after lung cancer surgery

Breathlessness and pain were reported to be dominant health challenges during the first year after surgery, and in addition some participants reported loss of appetite and weight, disturbed sleep and general fatigue. There is a danger that poor overall survival rates for lung cancer and the lack of research funding or studies for this tumour group may mean that the needs of surgical patients (for whom survival rates are much improved) may continue to get overlooked.[261] Although lung cancer patients were included in the considerations of earlier phases of the work carried out by the NCSI, testing and implementing improved survivorship care pathways is now focusing on breast, prostate and colorectal cancer patients only.[182] A recent announcement of a new research alliance for lung cancer, uniting the expertise of leading research hospitals and academic institutes in London, promises to increase funding available and research attention on

lung cancer.[470] However, it is not clear whether supportive care needs will be prioritised.

This doctoral study concludes that the needs of lung cancer patients after surgery could be met by accessing services and treatments (both pharmacological and non-pharmacological) that are already available to other patients, and are well established. In particular, there is a strong rationale for testing the benefit of pharmacological treatment of reversible breathlessness and also pulmonary rehabilitation for this patient group. Participants that had enrolled on a COPD rehabilitation-based programme being piloted at the time of the interview study were highly satisfied with the level of supportive care they received, and this seems a promising template on which to base additional supportive care for lung cancer patients after surgery. Based on needs and preferences expressed by participants, and building on this rehabilitation programme, important components of a tailored rehabilitation programme have been identified (see section 4.1.4). Assessment and referral for support to manage pain, nutrition, anxiety/depression, smoking cessation and mobility were also identified as potentially relevant to this patient group. These findings support and extend the stratified pathway of care developed for lung cancer patients that was developed by the NCSI (see figure 7.1). In addition to the clinical support services that are identified by this pathways as relevant to this patient group, investigations of this thesis highlight that pain management and smoking cessation support are also important. Further research to assess the effectiveness of these treatment and services for improving quality of life and health outcomes is warranted.

7.3 Measurement of smoking behaviour and support for smoking cessation should take a more central role within research and health care for surgical lung cancer patients

Despite wide recognition of the causal role of smoking in the development of lung cancer, the potential for smoking behaviour to determine cancer outcomes is largely overlooked in cancer care and research. This is a cyclical problem. Without evidence that smoking is an independent prognostic factor, past or present smoking behaviour is not adequately recorded in patients' clinical notes but inadequate recording also undermines studies investigating the relationship between smoking behaviour with prognostic outcome. Few studies have overcome this problem by recruiting patients at the time of diagnosis and obtaining a detailed description of smoking behaviour for study purposes. Most studies identified by the systematic reviews reported in this thesis were of poor quality, and due to limitations in the data conclusions are preliminary. However, there was consistent evidence of an association between both smoking history and continued smoking after diagnosis with prognosis. It is biologically plausible that smoking history or smoking after diagnosis may increase the risk of cancer progression, and although a limited number of studies reported cancer-specific prognostic outcomes there was some indication that smoking was associated with an elevated cancer-specific risk.

There are a few commonly cited barriers to routinely offering smoking cessation support to patients with cancer.[254, 256, 257] A particular concern has been that patients will not be receptive to intervention, and that tackling smoking cessation at such a difficult time may be unwelcome. However, there was no evidence that this was the case when patients' attitudes towards smoking and smoking cessation were explored in the qualitative study reported in this thesis. On the contrary, many participants expressed a strong desire to be offered help. An expressed caveat to this desire was that health professional approached the subject with a

non-judgemental attitude, demonstrating an understanding of the difficulty of quitting smoking. Previously published studies suggest that continued smoking may be associated with worse short term outcome (e.g. elevated pain, increased risk of post-surgical complication, reduced QOL)[134–136] and there is evidence that smoking cessation at least 4 weeks before surgery leads to reduced risk of post-surgical complications.[169] Evidence indicating that health outcomes may be improved, coupled with the finding that patients would prefer to receive support to quit, constitutes a strong rationale for incorporating smoking cessation into standard care for this patients group. Indeed, this has been advocated by leaders in the field for a number of years.[143, 254, 457, 471–474] Taken together, findings of this thesis highlight the importance of routine recording of smoking behaviour in clinical practice and indicate that further investigation of the prognostic significance of smoking history is warranted. On the basis of patient preference and gathering evidence for the short and long term health benefits of quitting, smoking cessation support should be embedded within lung cancer care pathways. However, further investigations to test the optimum intervention and length of support, and to confirm prognostic benefits are needed.

7.4 Cancer-related inflammation: a unifying feature that may underpin quality of life and prognostic outcome for surgical lung cancer patients

This thesis began by outlining six hallmarks of cancer proposed by Hanahan and Weiberg in 2000, which are critical capabilities a tumour must develop in order to survive, develop and invade new tissue (see section 1.2).[8] Over the past 10-15 years, the role of the environment in which tumour formation is initiated, develops and gains the ability to metastasise has come under increasing attention. New understandings have revealed that in addition to changes that occur within cancer cells themselves, non-cancerous stromal cells forming the so called 'tumour micro-environment' play a critical role in the neoplastic process.[410] In particular, excit-

ing new developments have shown how cells of the innate immune system such as macrophages and neutrophils may have an integral role in cancer,[409, 475–477] and in 2009 Colotta and colleagues proposed that 'cancer-related inflammation' should be regarded as a seventh hallmark of cancer.[6]

The first known link between inflammation and cancer was made in 1863 by Virchow, a German polymath, who noted leukocytes to be present in neoplastic tissue.[412] He hypothesised that 'lymphoreticular infiltrate' was responsible for the development of cancer at sites of chronic inflammation.[412] The developments of the past 10-15 years represent a renaissance of the idea that cancer and inflammation are linked, and several lines of scientific enquiry are supporting Virchow's original hypothesis.[409, 412, 478] The risk of cancer is known to be increased at sites of chronic inflammation, such as that caused by disease (e.g. inflammatory bowel disease, COPD),[479, 480] by chronic infection (e.g. HPV, hepatitis, Helicobacter pilori)[481–483] and by chronic irritation (e.g. cigarette smoke, asbestos).[15, 27, 31] This has been referred to as 'smouldering inflammation' which represent extrinsic causes of cancer-related inflammation (CRI). It has also been established that CRI can arise from intrinsic pathways within cancer cells, where mutations in oncogenes and tumour suppressor genes activate expression of inflammatory programmes which further build the inflammatory tumour micro-environment.[409, 477]

A common overarching theme that repeatedly emerged during this doctoral study was the potential for presence of pulmonary inflammation in surgically treated lung cancer patients. Throughout this thesis, evidence from previous studies has been discussed showing that inflammation is triggered in response to cigarette smoking, surgical wounding and also in the presence of pre-neoplastic lesions. Prevalence of co-morbid inflammatory conditions, particularly COPD, is high in this patient group.[465] It is known that many cases of mild COPD remain undiagnosed, and it is possible that the prevalence of this 'smouldering inflammation' is higher than studies have shown.[484] Breathlessness and pain, the health challenges that dominated the experience of patients during the first months after surgery, are both symptoms of inflam-

mation.[228, 231, 485] Breathlessness and pain have other non-inflammatory causes and the cause of these symptoms in surgical lung cancer patients are yet to be fully understood.[102, 111] However, if inflammation is involved due to some of the reasons above, it is possible that anti-inflammatory treatment may partially or substantially reverse these symptoms leading to an improvement in quality of life. In addition, given the evolving evidence base that inflammation is critical to the neoplastic process, it is plausible that anti-inflammatory treatment may also effect prognostic outcome in these patients.

Inflammation is a term that refers to a complex cascade of inter-related pathways that may be mediated by a number of difference cells and a myriad chemicals.[486] One inflammatory mediator that has received much attention is the cyclooxygenase-2 (COX-2) enzyme,[487] which catalyses the rate-limiting step for the production of prostaglandins and thromboxanes from arachidonic acid.[487] COX-2 enzymes are inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen, in addition to more recently developed drugs such as celecoxib which is indicated for osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.[488] There are several reasons why this inflammatory mediator may have an important role to play in CRI in surgical lung cancer patients. Oncogenic *K-ras* and EGFR signalling has been demonstrated to correlate with COX-2 expression,[487, 489–491] and it is possible that this signal remains after tumour resection due to the presence of unresected pre-neoplastic lesions or 'field cancerisation'. Post-surgical pain can also be successfully treated using NSAID and COX-2 specific inhibitors, suggesting that COX-2 has a role to play in surgery-related inflammation.[119, 485] Prostaglandin E2 (PGE2), which is produced in the presence of COX-2, is a pro-inflammatory mediator and has been implicated in roles crucial to development and progression of a tumour, including resistance to apoptosis, angiogenesis, enhanced invasion, metastasis and suppression of anti-tumour immunity.[487, 492, 493] A number of studies have demonstrated a chemopreventative effect of long term low dose aspirin and other NSAIDS in both colorectal cancer [494–497] and in lung cancer.[498] In line with this, COX-2 overexpression has also been associated with a decreased survival in lung cancer[499, 500] and other tumours.[493, 501–503] Treatment of inflammation using COX-2 inhibitors (NSAIDs)

has previously been highlighted for use as a potential chemopreventative and treatment drug in lung cancer.[487]

This doctoral study has shown that many lung cancer patients have ongoing needs after surgery, including management of breathlessness, pain and smoking cessation. In addition to the further research that has already been suggested throughout this thesis, the presence and role of pulmonary inflammation warrants further investigation. Further epidemiological studies are needed to confirm the link between anti-inflammatory treatment and prognosis, and to test the effectiveness of treatment on quality of life and prognostic outcomes.

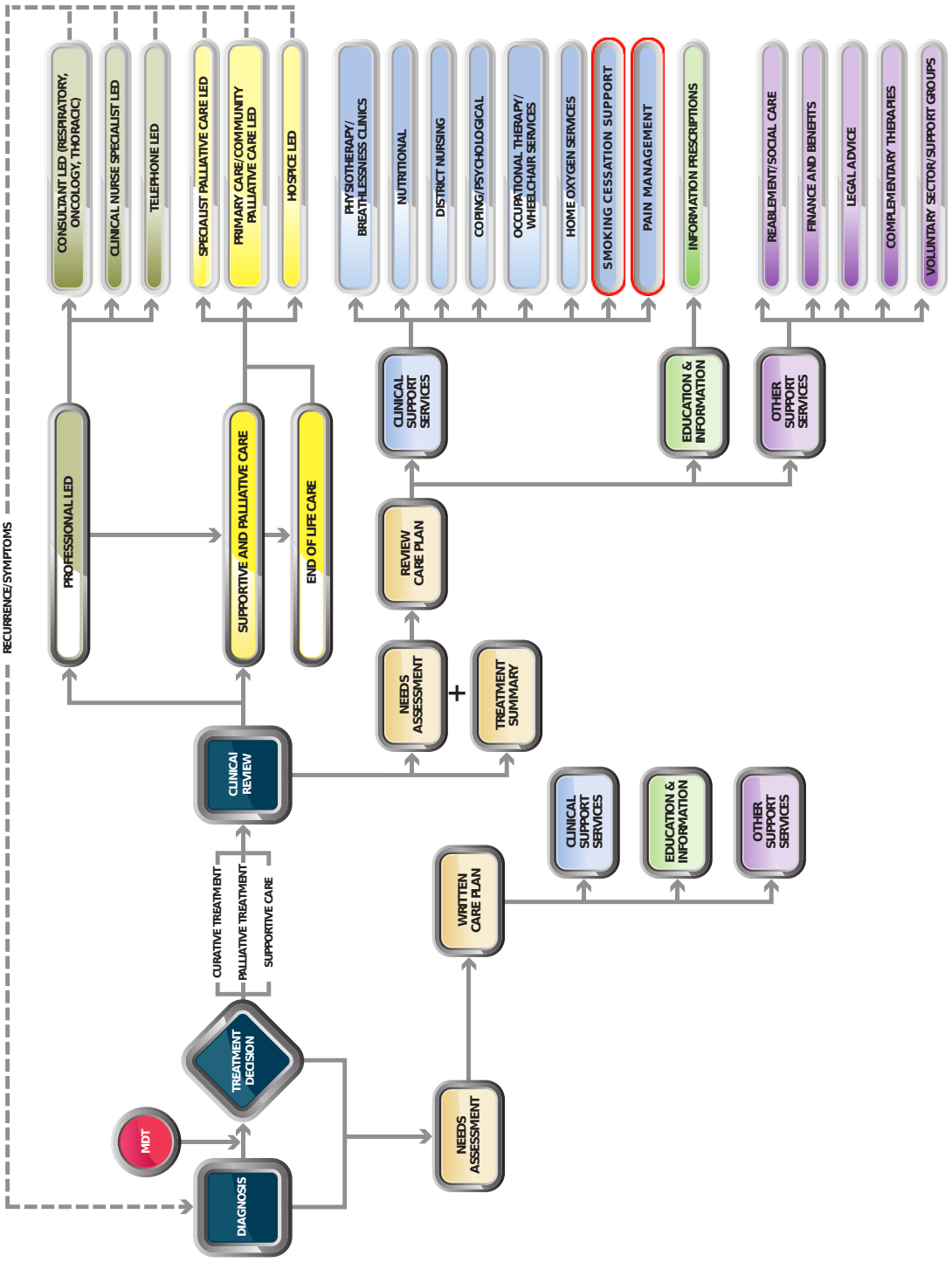


Figure 7.1: NCSI Lung Stratified Pathway of Care with additional clinical support services identified as important from this doctoral study for surgical patients (highlighted in red). [Source: NHS Improvement Cancer/NCSI, http://www.improvement.nhs.uk/documents/survivorship/Lung_Pathway.pdf]

APPENDIX

A

SUPPLEMENTARY MATERIAL FOR THE QUALITATIVE INTERVIEW STUDY (CHAPTERS 2–4)

Figure A.17: Nvivo queries

Figure A.1: McGill Pain Questionnaire

The McGill Pain Questionnaire

Overview: The McGill Pain Questionnaire can be used to evaluate a person experiencing significant pain. It can be used to monitor the pain over time and to determine the effectiveness of any intervention. It was developed at by Dr. Melzack at McGill University in Montreal Canada and has been translated into several languages.

Sections:

(1) What Does Your Pain Feel Like?

(2) How Does Your Pain Change with Time?

(3) How Strong is Your Pain?

What Does Your Pain Feel Like?

Statement: Some of the following words below describe your present pain. Circle ONLY those words that best describe it. Leave out any category that is not suitable. Use only a single word in each appropriate category - the one that applies best.

Group	Descriptor	Points
1 (temporal)	flickering	1
	quivering	2
	pulsing	3
	throbbing	4
	beating	5
	pounding	6
2 (spatial)	jumping	1
	flashing	2
	shooting	3
3 (punctate pressure)	pricking	1
	boring	2
	drilling	3
	stabbing	4
	lancinating	5
4 (incisive pressure)	sharp	1
	cutting	2
	lacerating	3

5 (constrictive pressure)	pinching	1
	pressing	2
	gnawing	3
	cramping	4
	crushing	5
6 (traction pressure)	tugging	1
	pulling	2
	wrenching	3
7 (thermal)	hot	1
	boring	2
	scalding	3
	searing	4
8 (brightness)	tingling	1
	itchy	2
	smarting	3
	stinging	4
9 (dullness)	dull	1
	sore	2
	hurting	3
	aching	4
	heavy	5
10 (sensory miscellaneous)	tender	1
	taut	2
	rasping	3
	splitting	4
11 (tension)	tiring	1
	exhausting	2
12 (autonomic)	sickening	1

	suffocating	2
13 (fear)	fearful	1
	frightful	2
	terrifying	3
14 (pinishment)	punishing	1
	gruelling	2
	cruel	3
	vicious	4
	killing	5
15 (affective-evaluative-sensory: miscellaneous)	wretched	1
	blinding	2
16 (evaluative)	annoying	1
	troublesome	2
	miserable	3
	intense	4
	unbearable	5
17 (sensory: miscellaneous)	spreading	1
	radiating	2
	penetrating	3
	piercing	4
18 (sensory: miscellaneous)	tight	1
	numb	2
	drawing	3
	squeezing	4
	tearing	5
19 (sensory)	cool	1
	cold	2
	freezing	3

20 (affective-evaluative: miscellaneous)	nagging	1
	nauseating	2
	agonizing	3
	dreadful	4
	torturing	5

pain score = SUM(points for applicable descriptors)

How Does Your Pain Change with Time?

Question	Response	Points
Which word or words would you use to describe the pattern of your pain?	continuous steady constant	1
	rhythmic periodic intermittent	2
	brief momentary transient	3

Do the following items increase or decrease your pain?

(1) liquor

(2) stimulants such as coffee

(3) eating

(4) heat

(5) cold

(6) damp

(7) weather changes

(8) massage or use of a vibrator

(9) pressure

(10) no movement

(11) movement

(12) sleep or rest

(13) lying down

(14) distraction (TV reading etc.)

(15) urination or defecation

(16) tension

(17) bright lights

(18) loud noises

(19) going to work

(20) intercourse

(21) mild exercise

(22) fatigue

How Strong is Your Pain?

Statement: People agree that the following 5 words (mild discomforting distressing horrible excruciating) represent pain of increasing intensity. To answer each question below write the number of the most appropriate word in the space beside the question.

Question	Response	Points
Which word describes your pain right now?	mild	1
	discomforting	2
	distressing	3
	horrible	4
	excruciating	5
Which word describes it at its worst?	mild	1
	discomforting	2
	distressing	3
	horrible	4
	excruciating	5
Which word describes it when it is least?	mild	1
	discomforting	2
	distressing	3
	horrible	4
	excruciating	5

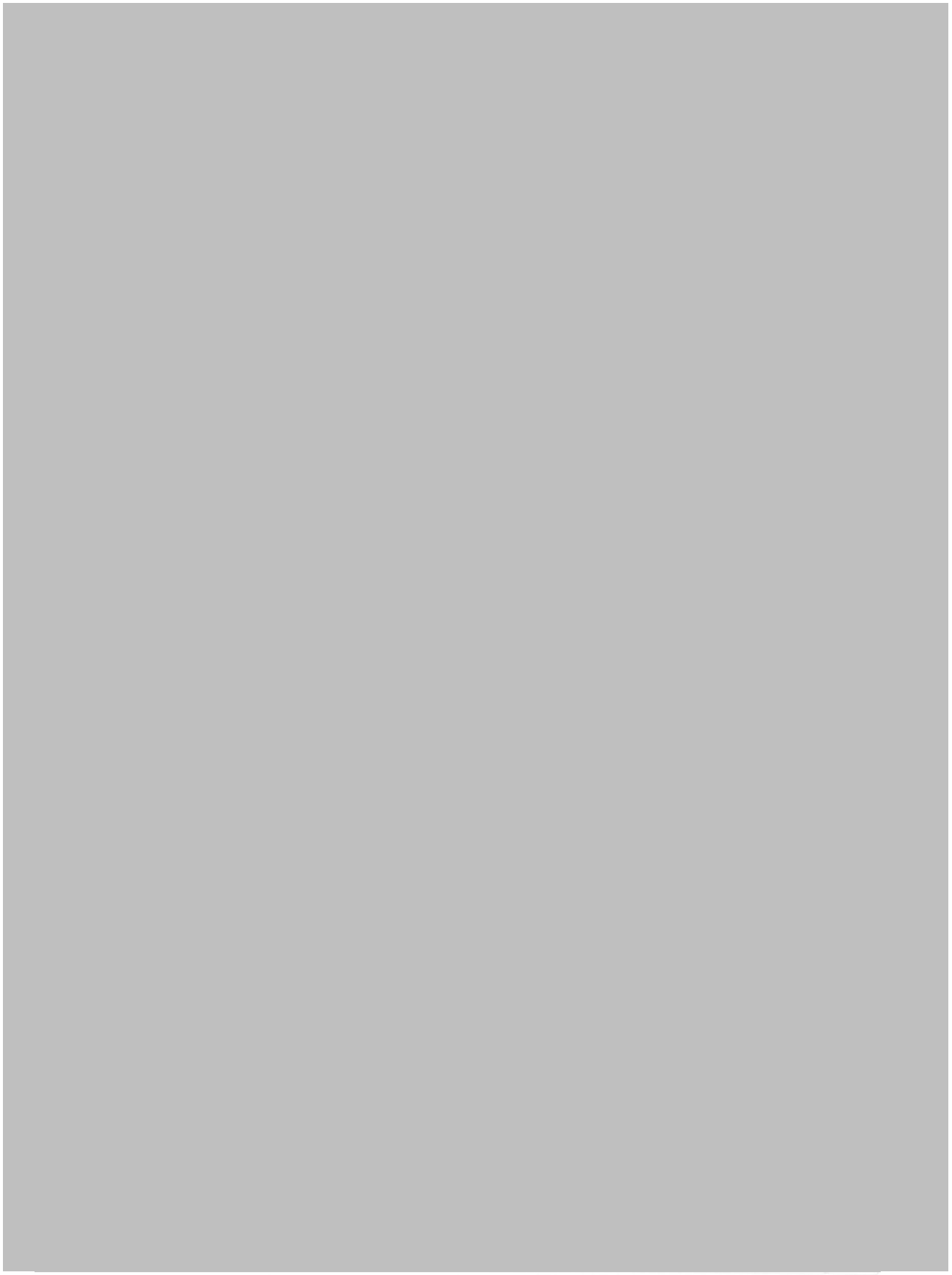
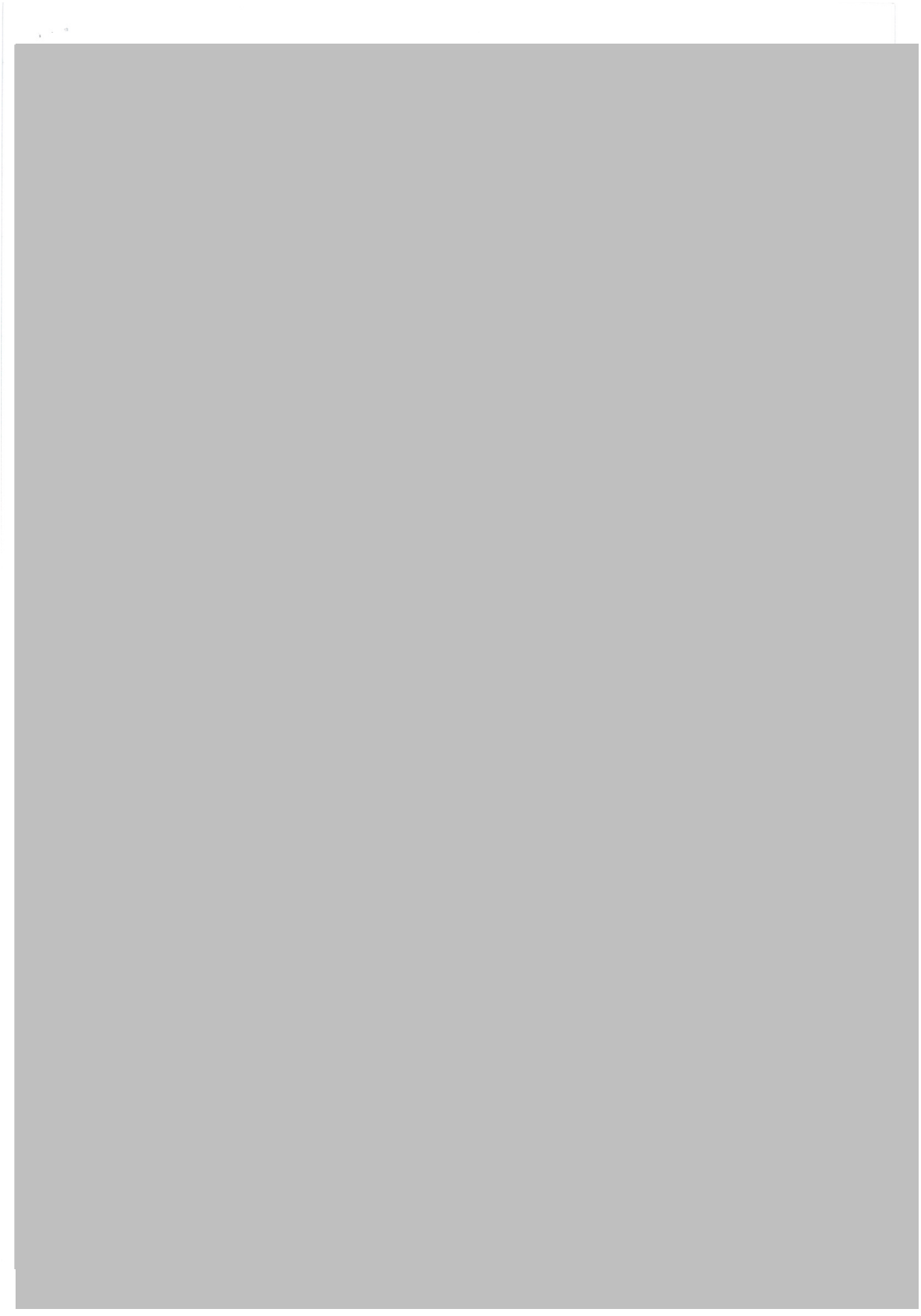


Figure A.3: University of Birmingham to act as sponsor



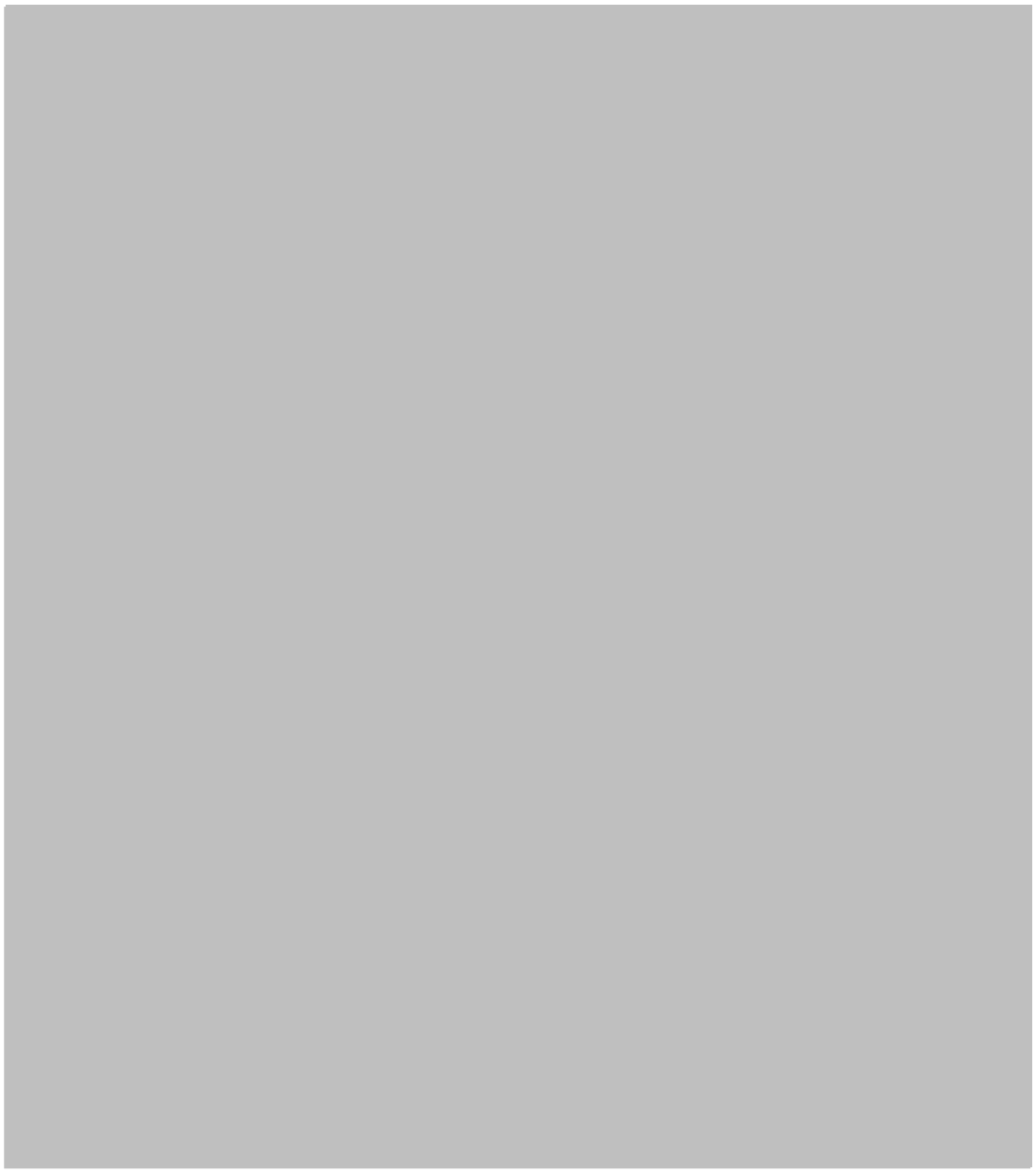
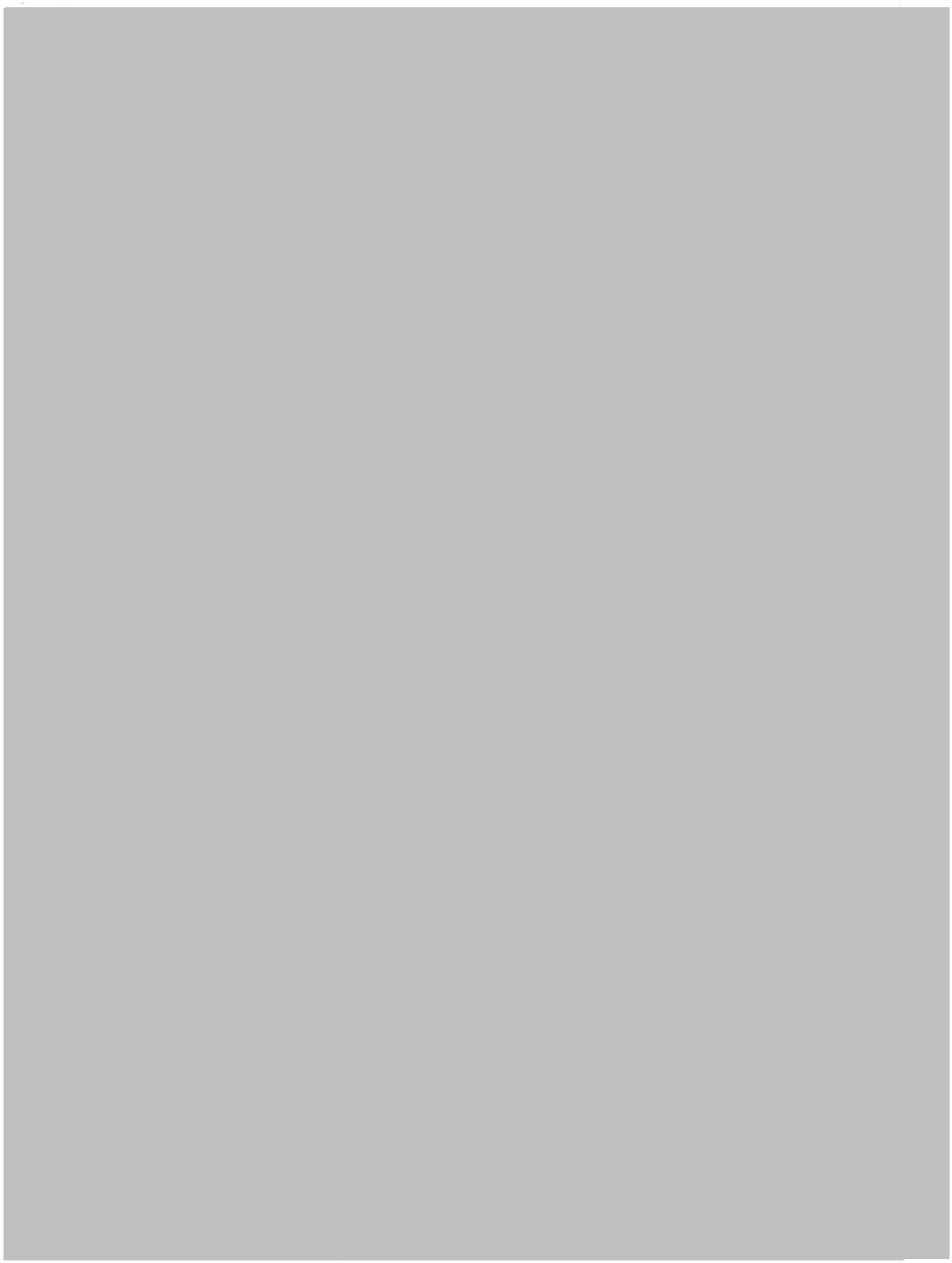


Figure A.4: Ethical approval for interview study (11th March, 2009)



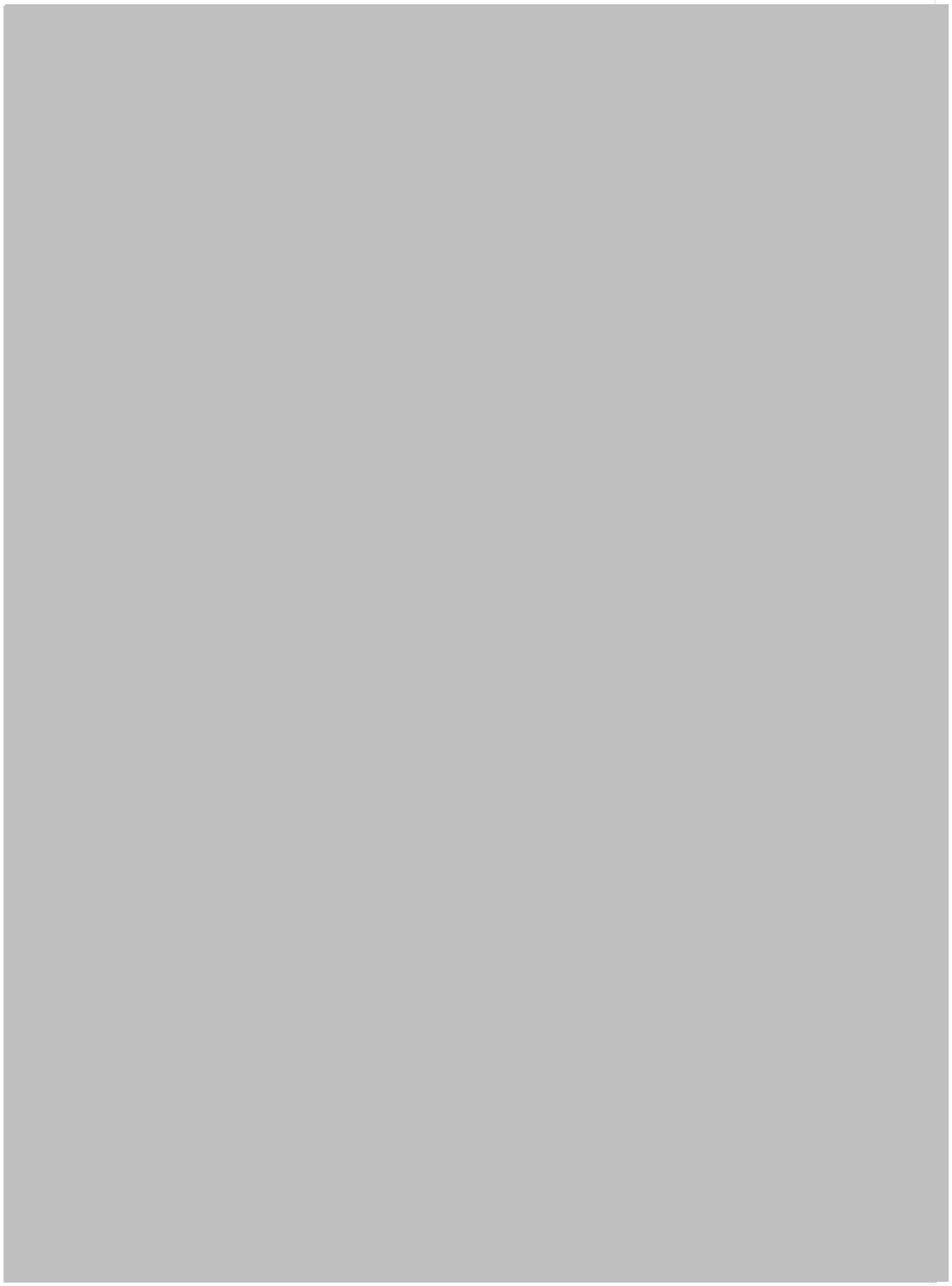
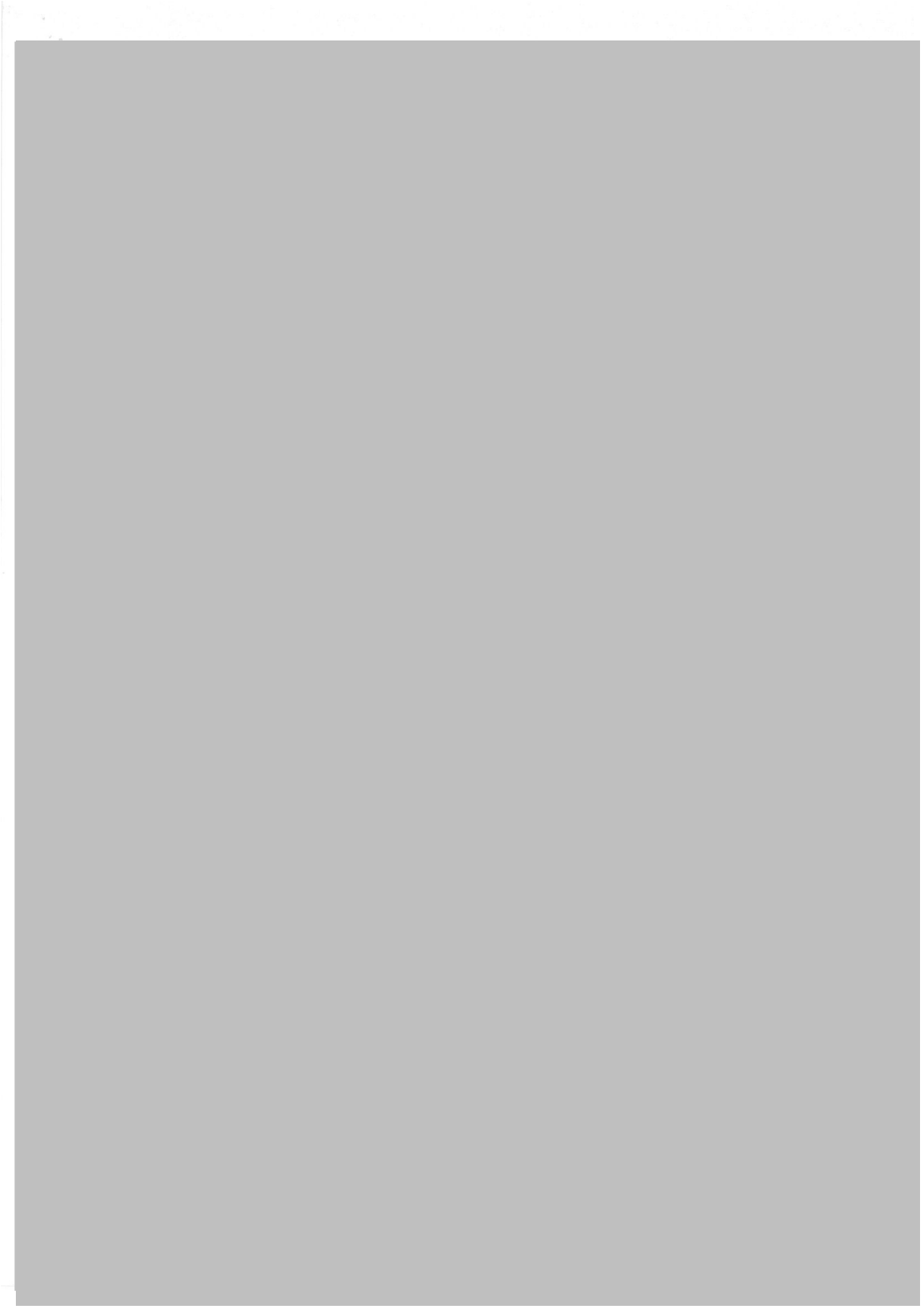


Figure A.5: Ethical approval for interview study - substantial amendment 1 (21th Sept, 2009)



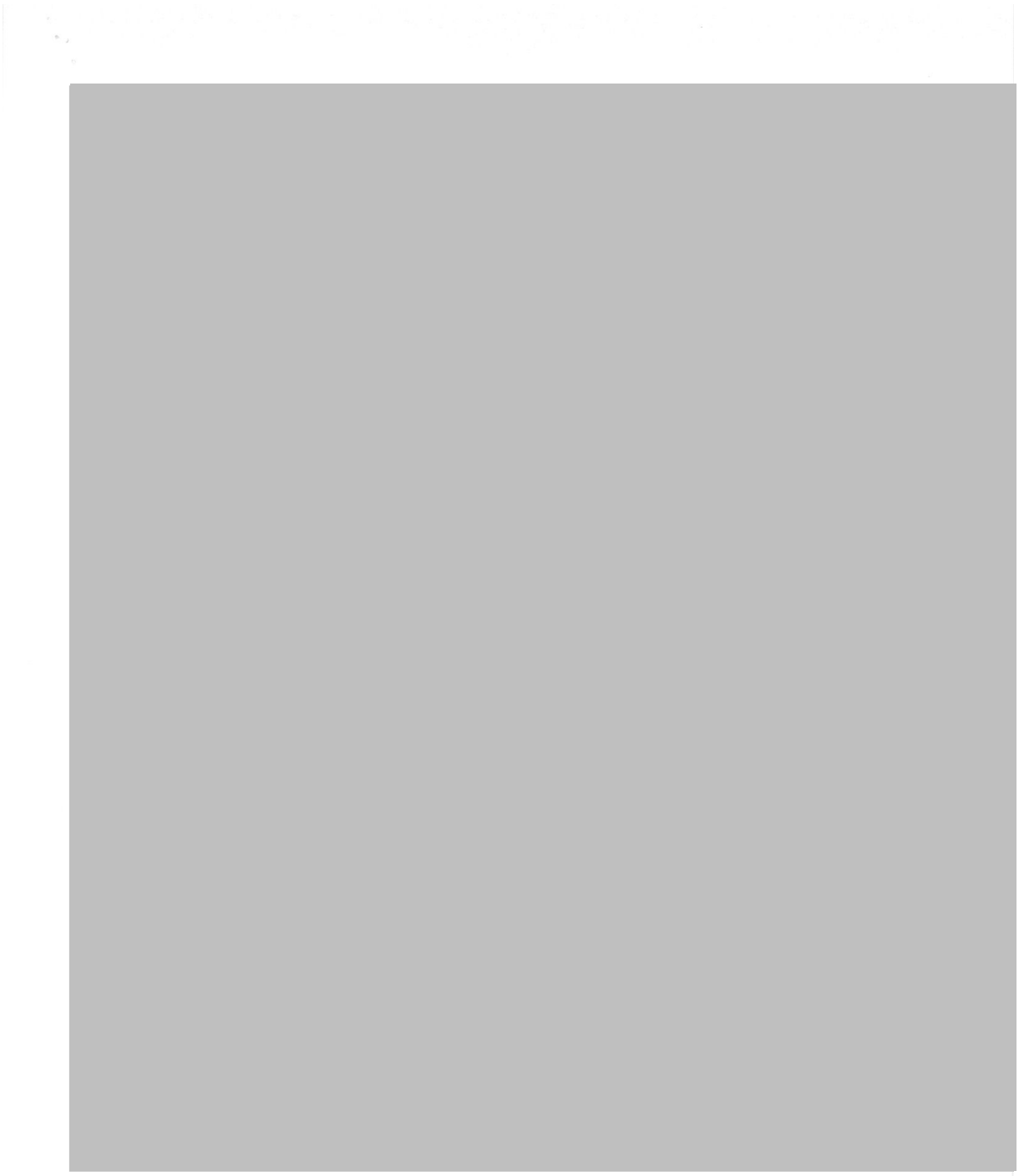
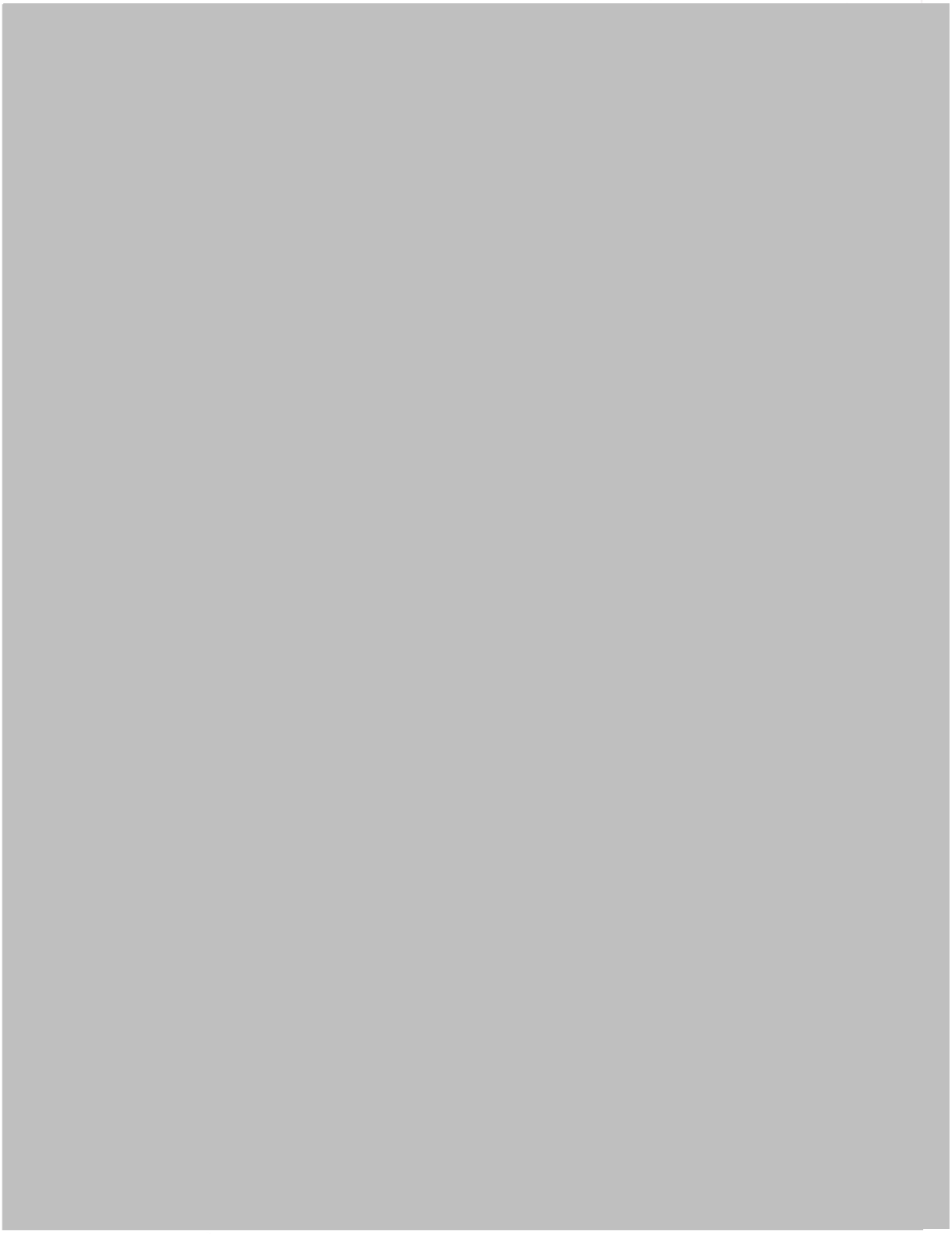


Figure A.6: Ethical approval for interview study - substantial amendment 2 (16th May, 2011)



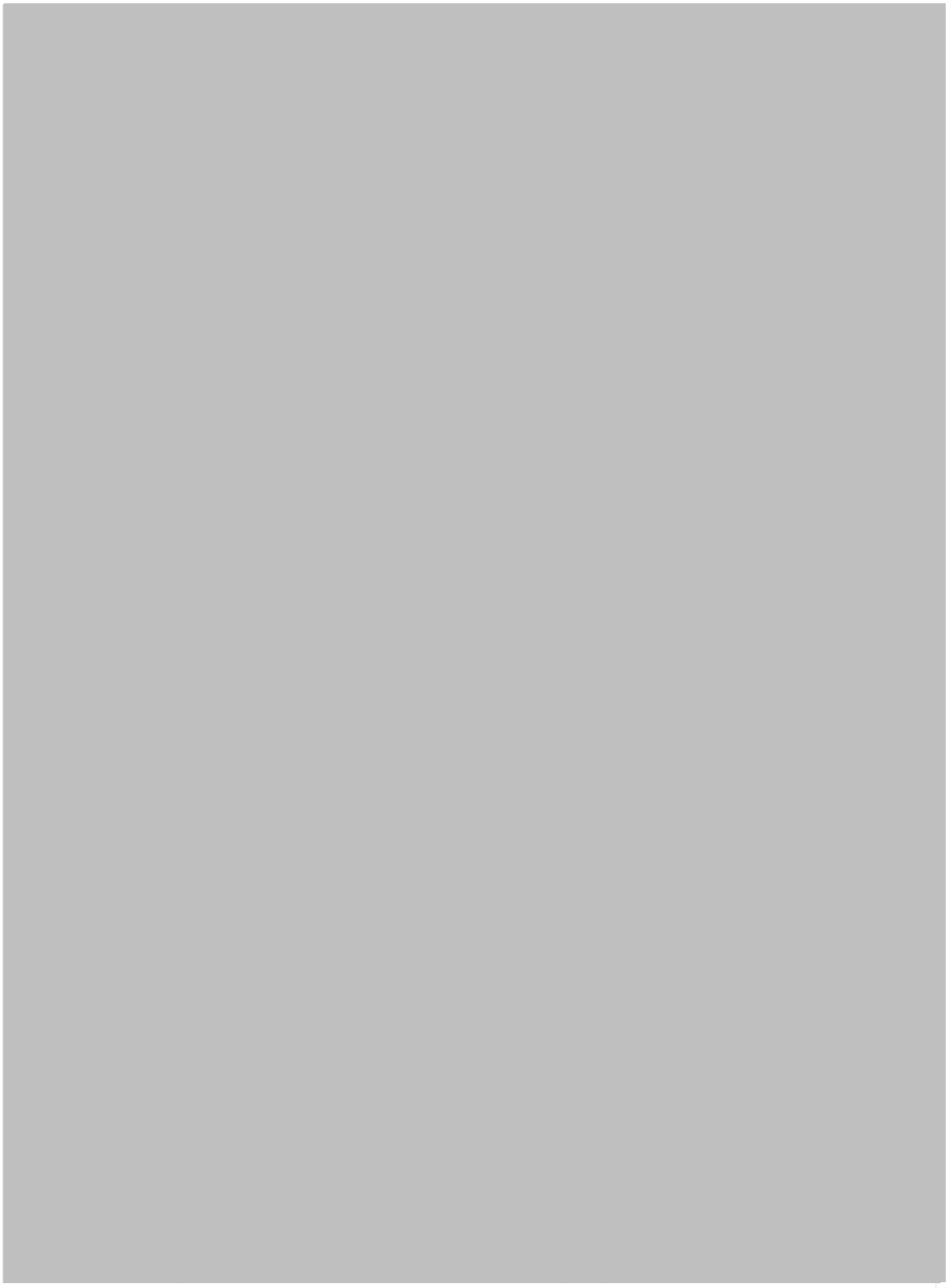


Figure A.7: Letter of access to Birmingham Heartlands Hospital

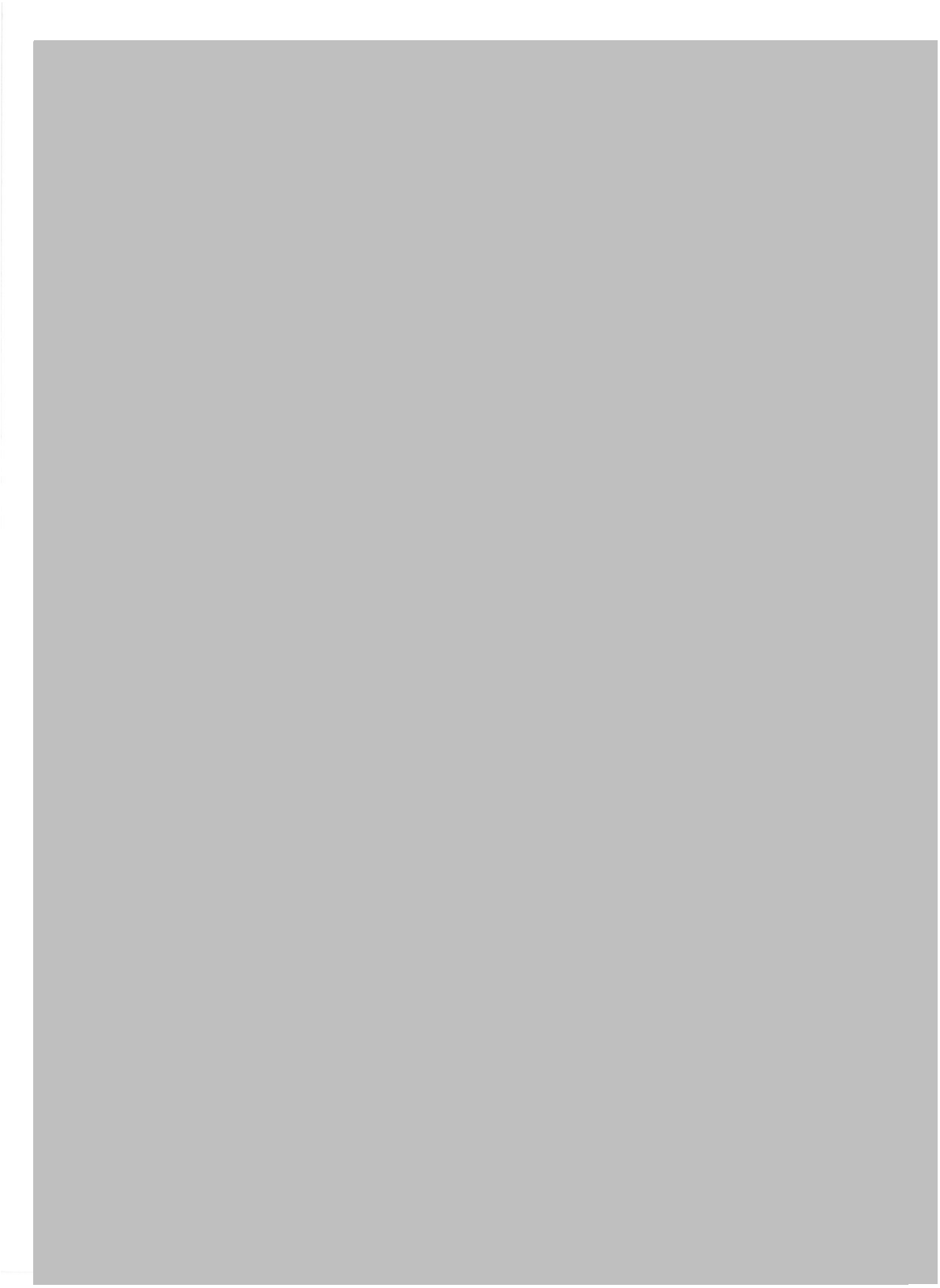


Figure A.8: Letter of access to University Hospital Birmingham

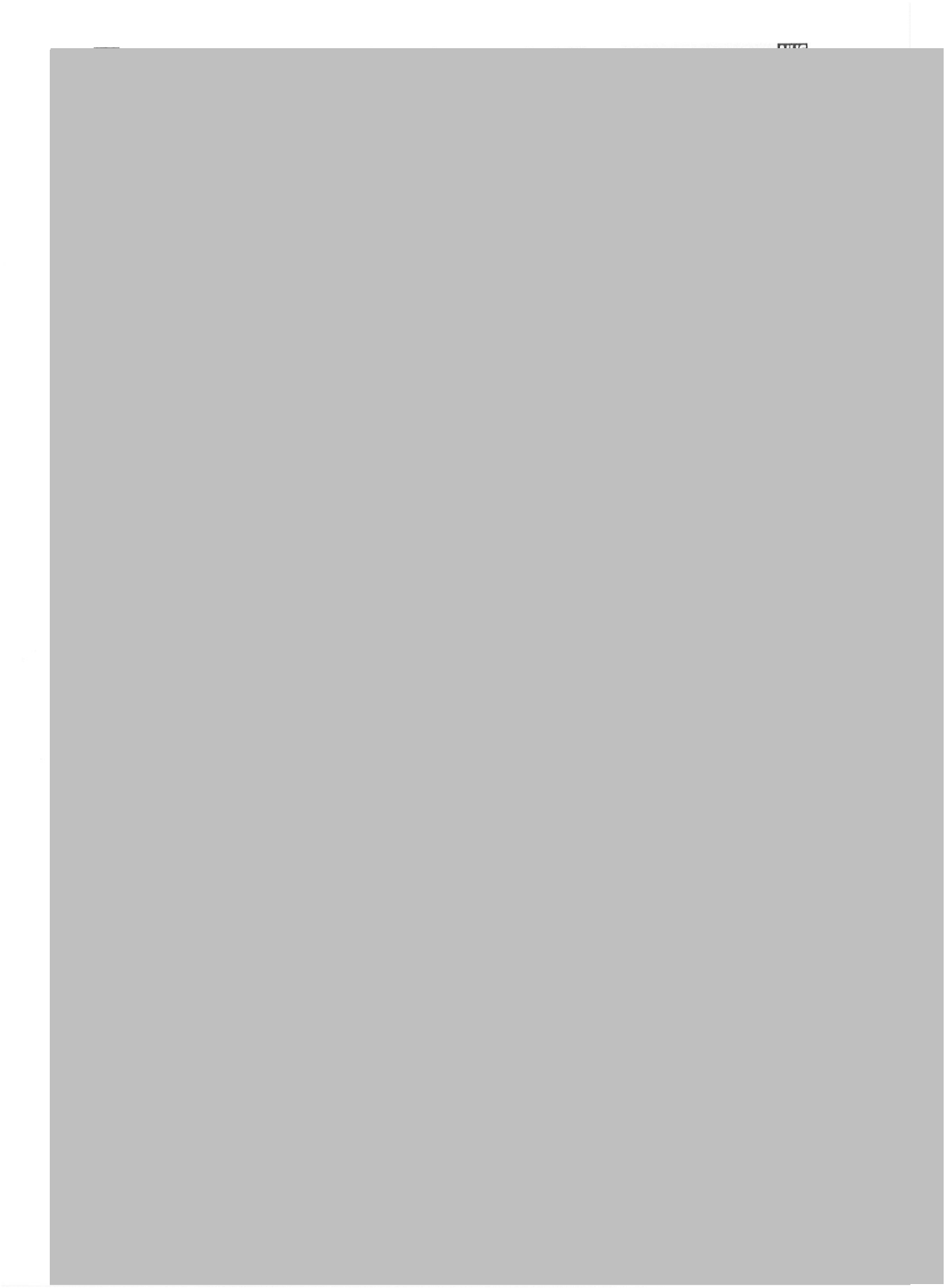


Figure A.9: Consent form for interview study

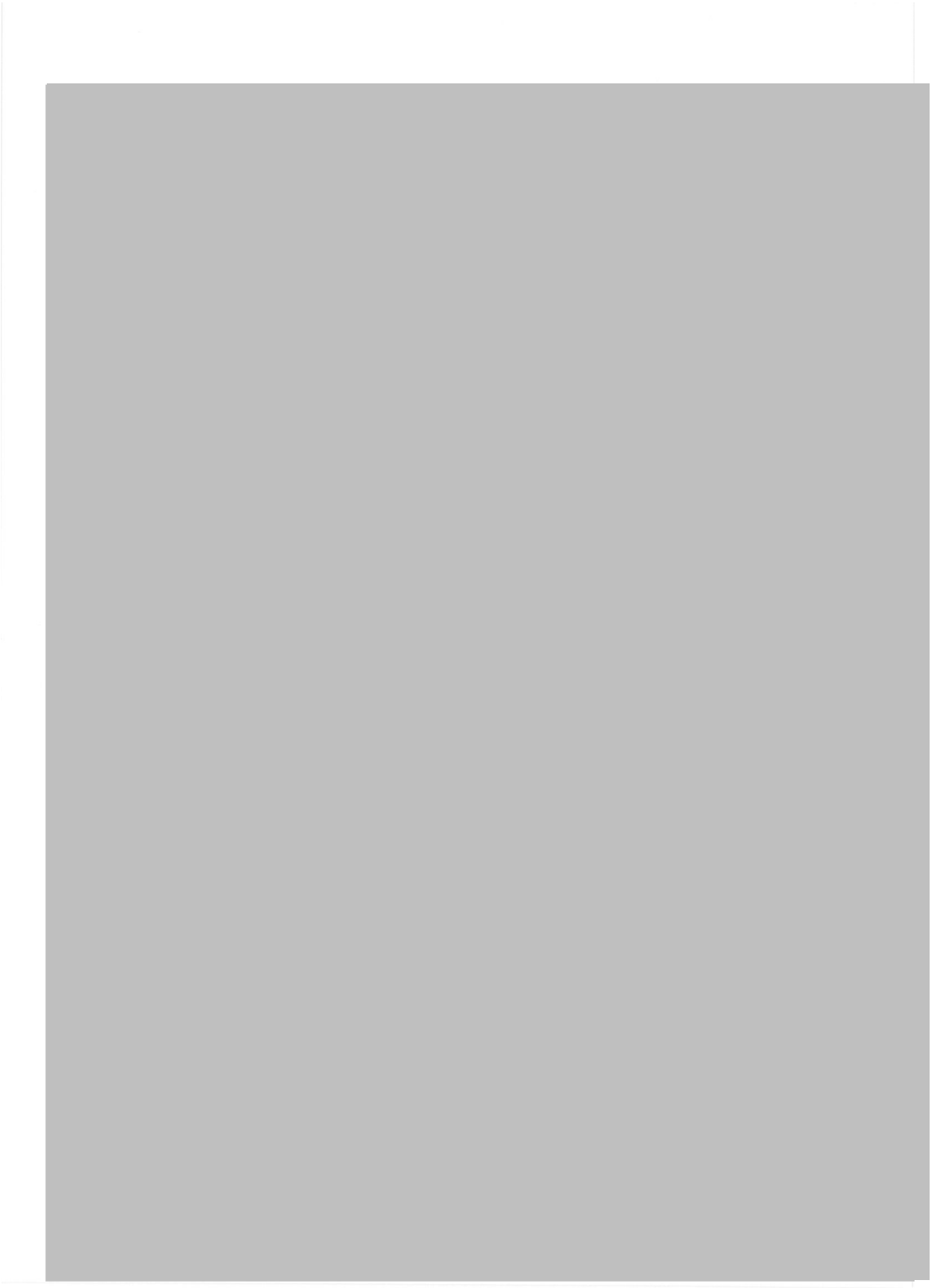
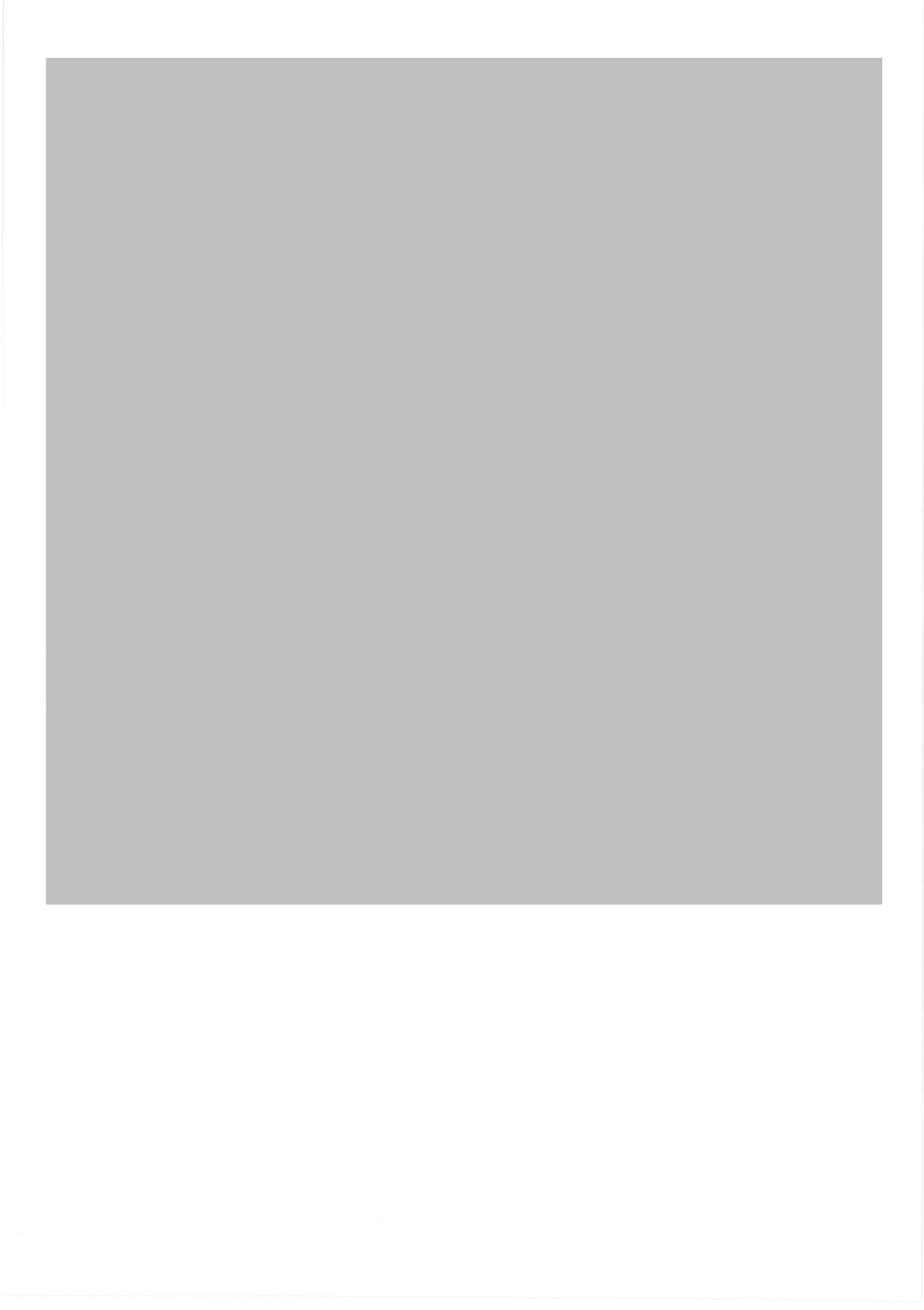


Figure A.10: Patient information sheet for interview study



What is the purpose of the study?

The purpose of this study is to talk to you about your experiences as somebody who has been diagnosed and treated for lung cancer. We know that after treatment has ended people can find they have been left with difficulties in different areas of their lives and we want to talk to you about how being a patient with lung cancer has affected your physical and psychological health. Advances in medicine mean that more people are combating this disease, and cancer services now not only want to treat cancer but also provide support and help for people to rehabilitate and be as healthy as possible once treatment has ended. One of the most valuable tools we have to know exactly what patients' health needs are and how best to help them is to talk to patients themselves. We would be very interested to talk to you about your views about how the health service could support you to rehabilitate from cancer.

Why have I been chosen?

These interviews are part of a research study that is being conducted by a research team at the University of Birmingham, which aims to develop a programme for lung cancer patients who have been treated by surgery to help them rehabilitate after treatment. The information that we find out during the interviews will be use to inform the development of the programme. We anticipate interviewing about 30 people, and you have been chosen by your consultant as a patient that would be suitable to participate.

Do I have to take part?

It is up to you to decide if you would like to take part or not. Below is a more detailed description of what you can expect to happen during the interview. If you decide to participate then we will ask you to sign a consent form, however *at any time* you are free to withdraw from the study and this would not affect the standard of care you receive. Although you have been chosen as someone who can participate in this study, you are not obliged to take part in any way.

What will happen at the interview?

A researcher from The University of Birmingham will be conducting the interview. The interview will take no longer than 1 and a half hours and with your permission can take place in your home or at the hospital. During the interview, you will be asked questions on the following topics:

(1) Background information about your diagnosis of cancer and treatment.
(2) The main ways in which you feel healthy or unhealthy (physically or psychologically) on a day-to-day basis as a result of cancer.
(3) Measures you have taken to try to improve your health or difficulties you have found when doing things to try and improve your health e.g. giving up smoking, changing your diet, doing more exercise.

(4) What you think about the health service providing help for cancer patients to rehabilitate e.g. is it needed, what sort of things do patients need help with, how long should the help last for, what format should the help be in?

How will what I say in the interview be used?

With your consent, we would like to record what is said during the interview. This is so that we can a have an accurate record, which will be transcribed into written form. What you tell us during the interview will be collected together with transcripts from other interviews so that we can get a picture of the needs and views of lung cancer patients in relation to their health and help needed from the health service to rehabilitate. We will follow ethical and legal practice and the recordings will be kept strictly confidential and you will not be identifiable from the transcribed recordings.

Benefits of taking part in the study

This is a good opportunity for you to share your experiences as somebody who has been diagnosed and treated with cancer, and take part in improving the services that the NHS provide for people with lung cancer.

Who is conducting and funding the research?

This research is being conducted by a team based at the University of Birmingham, College of Medicine and Dentistry. The team is part of the UK Centre of Tobacco Control Studies (UKCTCS) and this study is funded by the National Institute of Health Research (NIHR), an NHS organisation that funds health related research. The UK Centre of Tobacco Control Studies is a strategic partnership of seven UK universities that carries out research work to help in the efforts to control the effects of tobacco. It is not afflicated with any tobacco companies. Although this team is part of research work in the area of smoking, we are equally interested in talking to patients who both have a history of smoking and those who do not. All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. The study has successfully complied with both The University of Birmingham regulatory procedures and has been approved by the NHS Research Ethics Committee.

NIHR website: http://www.nihr.ac.uk/Pages/default.aspx
UKCTCS website: http://www.ukctcs.org/

Who do I contact if I have any questions?

If you have any questions that you would like answered before the researcher comes to interview you, please call the researcher leading the study:
Amanda Parsons on 0121 414 8611.

Should you have any concerns about the research project or the manner in which you are treated by research staff you can call the Patient Advice and Liaison Service at UHB Queen Elizabeth hospital who are independent of this work

PALS office **0121 371 3280 (office hours 09:00 – 17:00)**

Figure A.11: Information given to participants after interview to signpost information and support

Information available for lung cancer patients
(v4 12/11/2010)

There are a few different organisations that provide information and support to people who have had cancer, and some specialise in lung cancer. Most organisations also offer help to carers.

Cancer support

(1) The Roy Castle Foundation
http://www.roycastle.org/index.php

Specific information to support people who have had lung cancer can be found by clicking on "About Lung Cancer" at the top of the menu on the left hand side of the page, and then clicking on "Living With Lung Cancer". Amongst other things you can find information here about coping with breathlessness and also financial help that is available. Also, if you click on "Get Support" further down the menu on the left hand side of the page this lists avenues of support that are available to you, including a free phone helpline manned by lung cancer nurse specialists. The number is **0800 358 7200** and is open Mon-Fri 9am-5pm

(2) Cancer Research UK
http://www.cancerresearchuk.org/

There is a lot of information about cancer on this website. To get information specifically for lung cancer click on "patients information" at the top of the homepage and then select "lung cancer" in the box titled "your cancer type" at the top left. The bottom right hand box "coping with cancer" also provides helpful support for coping physically, emotionally and practically. This charity also runs a helpline that is manned by nurses. The number is **0808 800 4040** and is open Mon-Fri 9am-5pm. The number is free to call from landlines however some mobile network providers may charge for this call and it is best to check with them before making the call.

(3) Macmillan
http://www.macmillan.org.uk/Home.aspx

Cancerbackup and Macmillan have merged into one organisation that provide information and services for cancer patients. They have a helpline number **0808 808 00 00** that is open 9-5pm Monday to Friday. Clicking on the tab "Cancer information" running across the page near the top of their homepage leads to lots of information about cancer, which you can access by clicking on one of the links on the menu listed down the left hand side of the page. One of these links is "Living with and after cancer" which give lots of useful information and support about the longer term impacts of receiving a cancer diagnosis and treatment.
http://www.macmillan.org.uk/Cancerinformation/Livingwithandaftercancer/Livingwithandaftercancer.aspx

Help giving up smoking

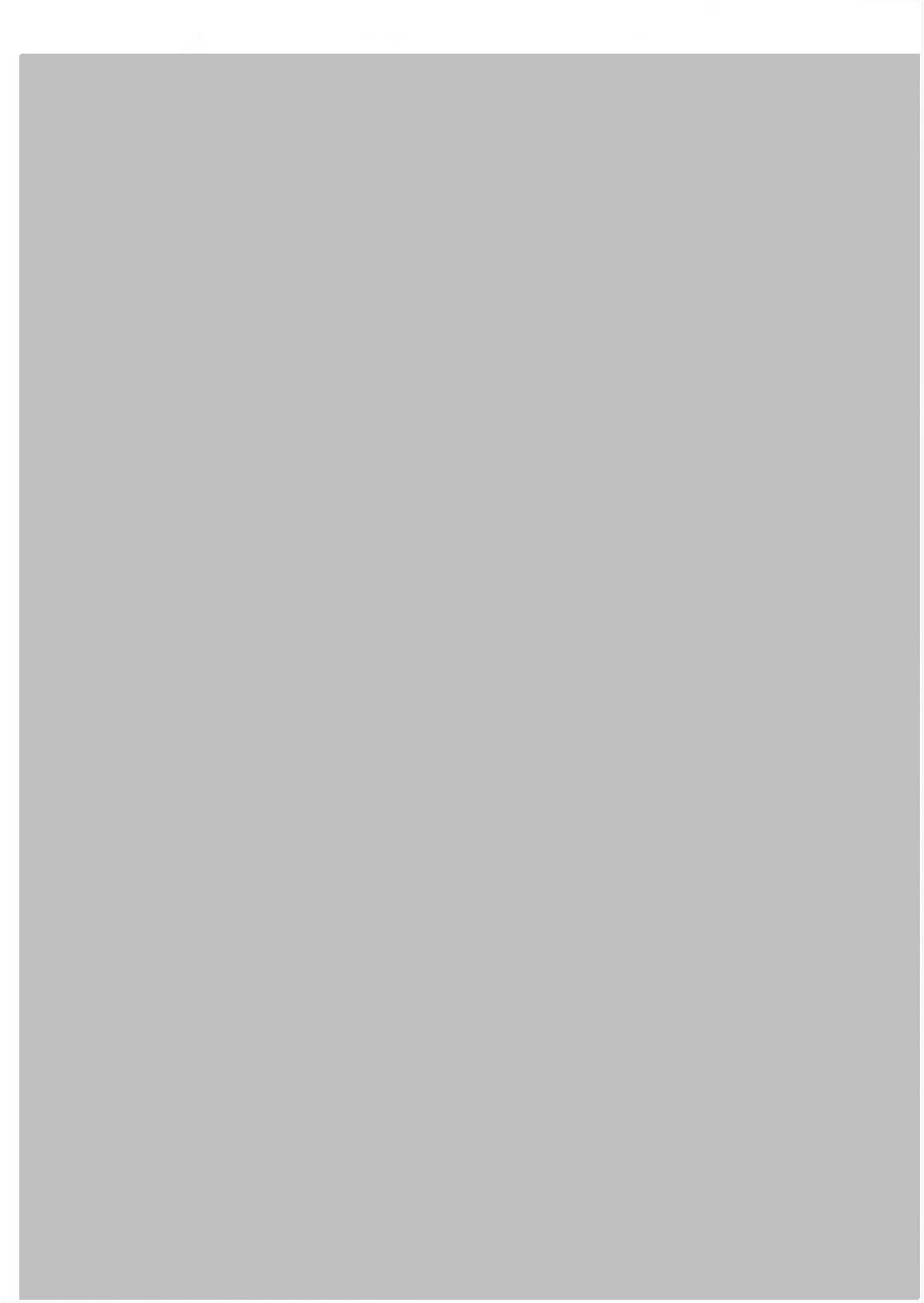
(1) Go smoke free
http://smokefree.nhs.uk/

This is the NHS stop smoking website which gives information about giving up smoking and helpline for booking in to your local stop smoking clinic **0800 022 4 332**

(2) Quitline
http://www.quit.org.uk/

This is a charity that gives information about smoking and how to give up and also has a helpline number **0800 00 22 00**

Figure A.12: Ethical approval for healthtalkonline interviews



4. The researcher was asked whether Social Services or the Police would be alerted if it is suspected a young person has been abused. It was explained that this has never occurred. When the research was extended in 2003 to include 16-18 year olds the REC that gave approval required a procedure to be in place if abuse was identified and this same procedure remains.

5. The researcher was asked whether participants may have mental health problems and it was explained that they would like to complete studies on Dementia and Alzheimer's patients but they have not received funding for this yet. The Committee recommend that if the researcher wanted to include these patients they should make themselves familiar with the Mental Capacity Act (MCA) Regulations. The researcher was informed that under the MCA research cannot take place on a person who lacks capacity to consent if it can be carried out on a person with capacity. This was noted.

6. The Committee questioned whether the research would be used towards the academic qualification of the student involved. It was agreed the Information Sheets could be amended to explain the researcher is part of an educational qualification.

7. The researcher was asked to clarify what the wording 'optional depends on funding' referred to in the Information Sheet. It was explained that participants may be interviewed in their home and they will be asked to tell their story. If they are willing, then the interview will be recorded. They will write a transcript and send this to the participant to approve. The participant can then choose to give permission for video or audio recordings to be used on the website. If they prefer to be completely anonymous they can have a written version of the transcript on the website or have an actor speak their words. Some studies may have funding for the use of actors, but this will not be available for all studies.

8. The researcher was asked how the analysis will be validated. It was explained that the researchers will send a transcript of the interview to the participants to validate for accuracy. Each study has a researcher who is responsible for carrying this out. The researchers will use thematic and discourse analysis. For the website, the researchers will carry out thematic analysis of about twenty-five different topics. They will be different for each illness. The analysis will then be checked by a research buddy and then by an advisory panel, which is made up of members of the public and Clinicians.

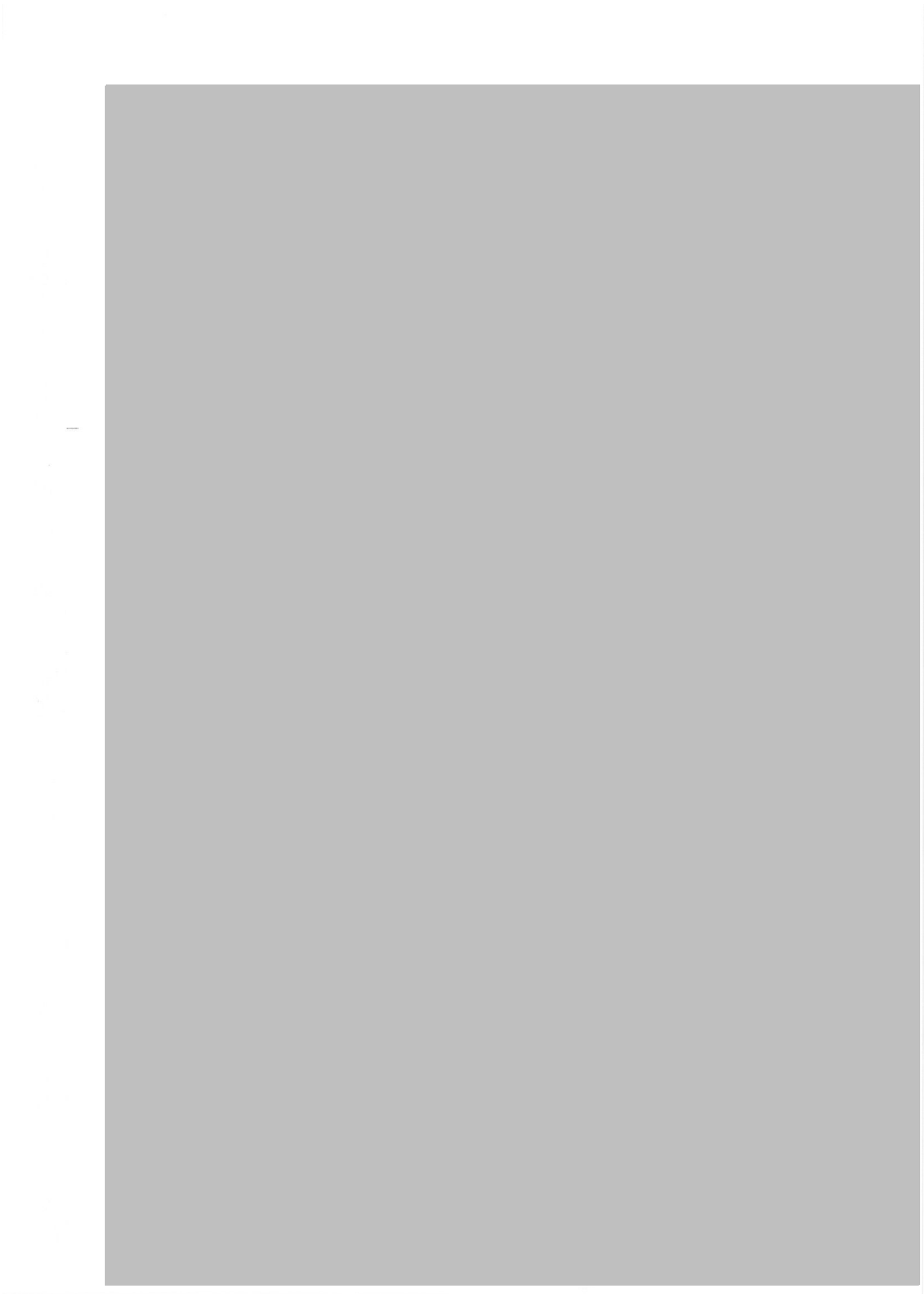
9. The Committee questioned what would happen if the content of the interview contained factually incorrect information. The researcher confirmed that they select clips to put on the website. They select ten clips, which then go to the specialist on the advisory panel to check the information is factually correct. The researcher confirmed that this is to ensure that only factually correct information is available on the website.

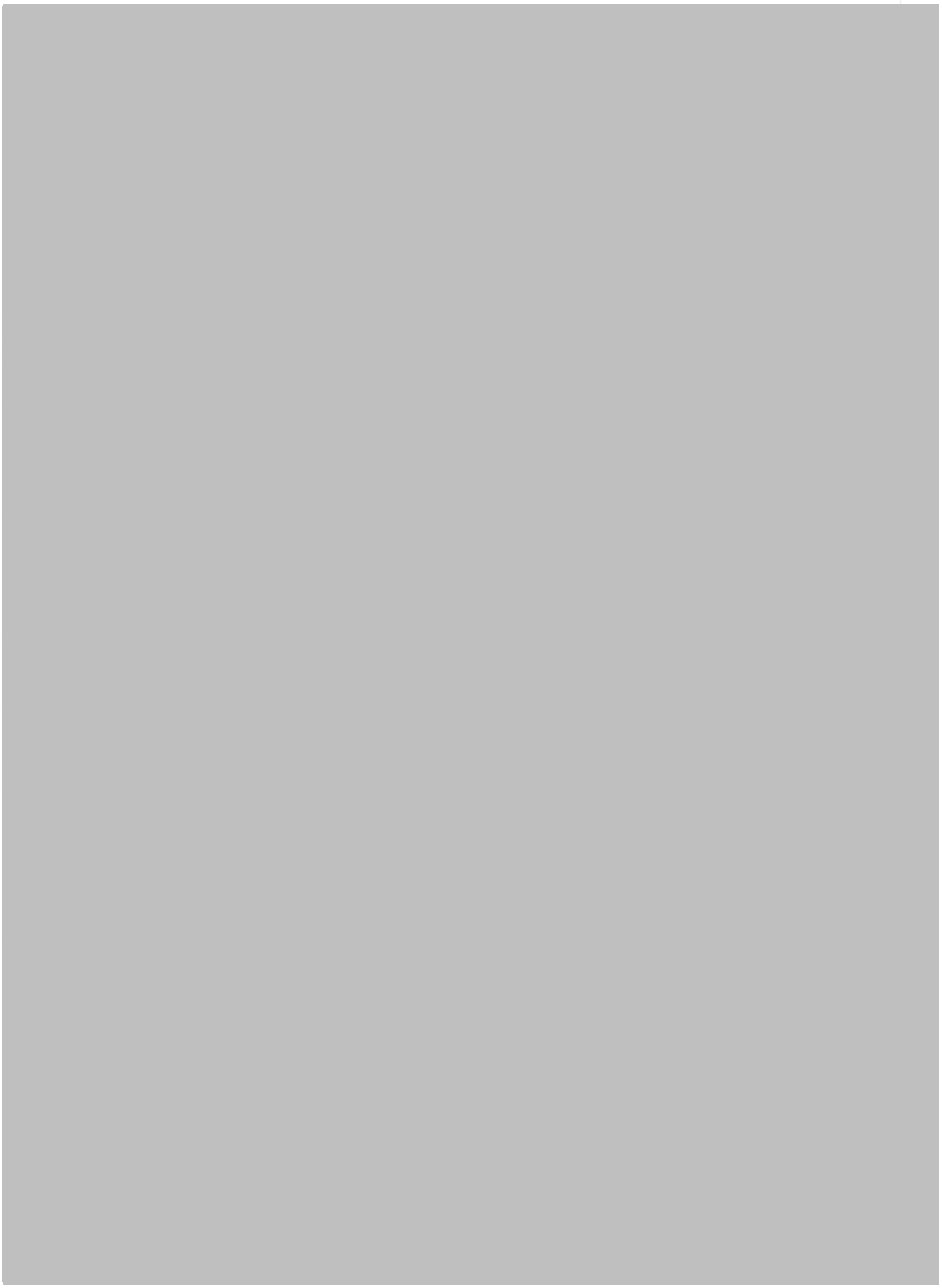
The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England





APPENDIX A. SUPPLEMENTARY MATERIAL FOR THE QUALITATIVE INTERVIEW STUDY (CHAPTERS 2–4)

This Research Ethics Committee is an advisory committee to South Central Strategic Health Authority

The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

Figure A.13: Letter of access to Birmingham Heartlands Hospital for healthtalkonline interviews

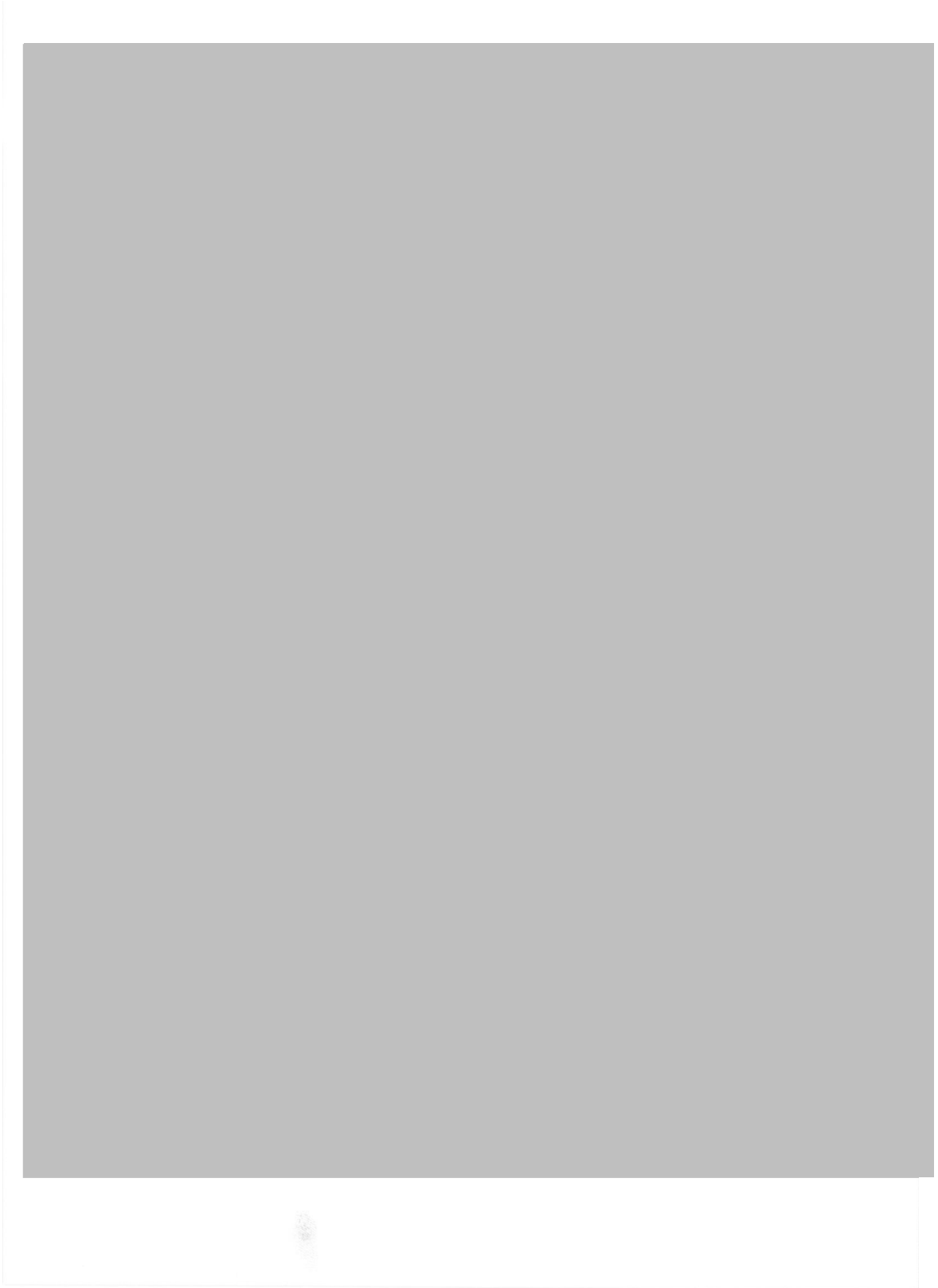


Figure A.14: Consent form for healthtalkonline interviews

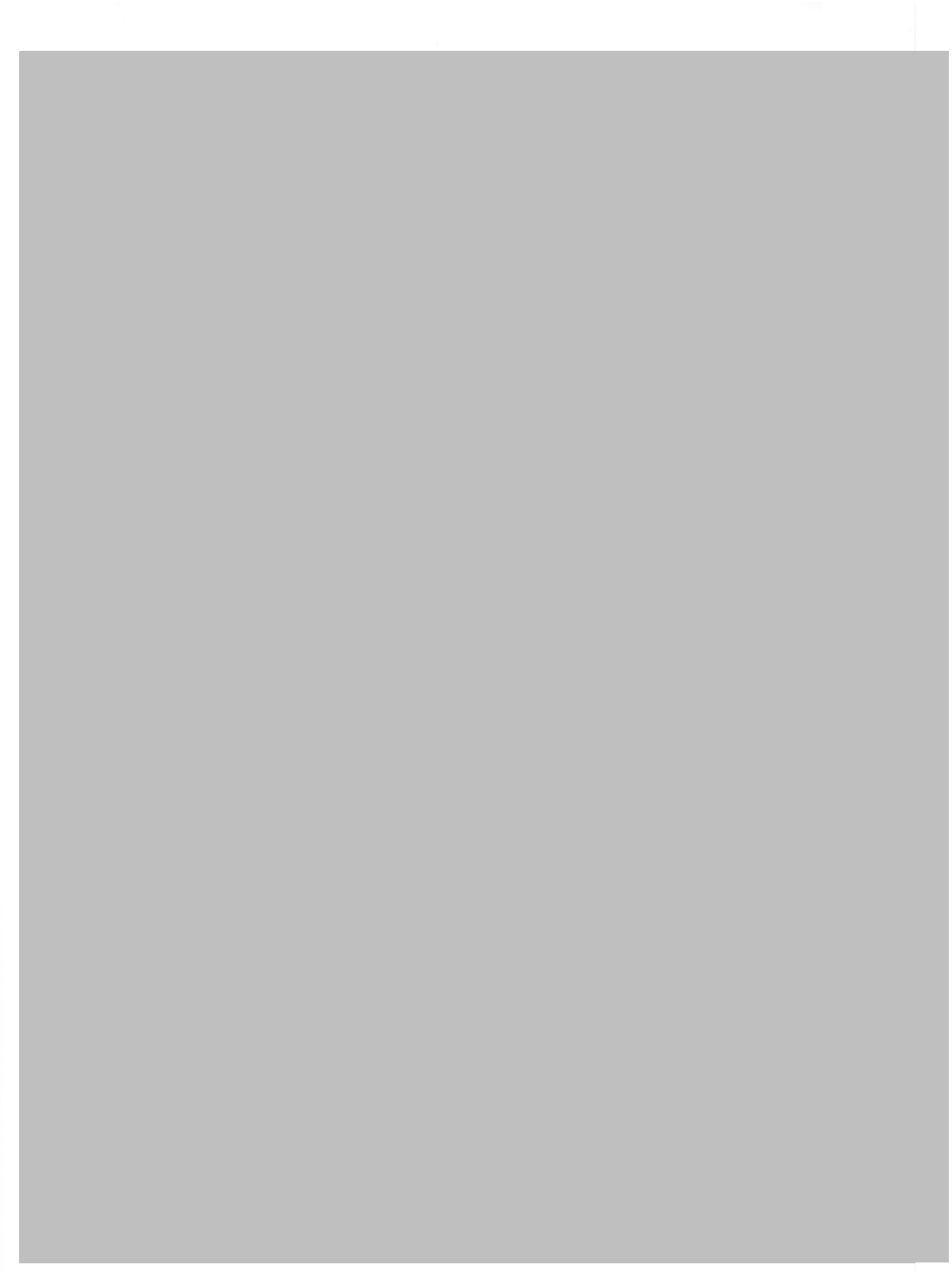


Figure A.15: Patient information sheet for healthtalkonline interviews

healthtalkonline.org
youthhealthtalk.org

Tel : 01865 289328
Fax : 01865 289287
www.healthtalkonline.org
Email :
francie.smee@phc.ox.ac.uk

Health Experiences Research Group
Dept of Primary Health Care, University of Oxford, Old Road Campus
Oxford OX3 7LF

PARTICIPANT INFORMATION SHEET

TAKING PART IN RESEARCH - A STUDY OF EXPERIENCES OF LUNG CANCER

Hello

My name is Amanda Parsons. I am a researcher working with the Health Experiences Research Group at the University of Oxford. I am asking you to take part in research. Before you decide if you want to take part or not, I want to tell you why the research is being done, and what you can expect if you do take part. Please read what I have to say carefully. Talk about it with friends, relatives and your GP if you wish. Ask me if you have any other questions. Please take as much time as you like to decide. This research is being carried out as part of an educational qualification.

Thanks for reading this.

What is the purpose of the study?

The aim of our research programme is to improve understanding of people's experiences of health and illness, and provide resources to support people living with a wide variety of health conditions, their families, friends and the health professionals involved in their care. We collect video, audio and written interviews, which may be used in several ways:

- to find out what is important to people faced with different health issues

Contact for further information

I hope that this information sheet about has told you what you need to know before deciding whether or not to take part. If you have any queries at all about the project or wish to make a complaint please telephone Amanda Parsons on 0121 4148611 or Sue Ziebland, Manager of the Health Experiences Research team on 01865 289302.

Notes:

- I am a professional researcher and am paid for my work.
- The study has been approved by **Berkshire Research Ethics Committee for health research**

Given the nature of this study, it is highly unlikely that you will suffer harm by taking part, however if you are harmed by participation in the study, you may have grounds for legal action for compensation against the University of Oxford.

Many thanks for reading this information sheet.

The Healthtalkonline site is run by DIPEx, which is a registered charity number 1087019 and a company limited by guarantee, company number 04178865, whose registered office is at P O Box 428 Witney Oxfordshire OX28 9EU.

Participation Information sheet May 2009 v3 - Generic

- to contribute to the www.healthtalkonline.org website which is run by the DIPEx charity
- to develop other support and information resources for people
- to train health and social care professionals
- to write research papers

www.healthtalkonline.org is a website that has:

- people's stories of health and illness
- information about tests and treatments,
- details about support groups & other resources (e.g. self-help books)
- a teaching and learning area for health and social care staff.

The idea is that Healthtalkonline will help people to:

- understand & cope with health problems and issues
- know what really matters to people when they are ill or are facing health issues; and
- answer common questions and provide information.

People who are faced with difficult choices (e.g. which tests or treatment to choose) will be able to go to the Healthtalkonline website to find out how others have made their decisions. Health professionals who want to understand what it is like for people to have an illness or face health choices can also visit the website.

Anyone who has access to the Internet would be able to use Healthtalkonline.

Can I choose how my interview will appear?

You will have a choice about whether a video, audio or written version of your interview is included. If you want to be anonymous, you will be invited to use an alias for yourself and others, and you can keep out of the interview anything which might identify you.

You may wish to discuss this with members of your family, since they might possibly be connected to your appearance on the screen.

If you are recognised on a website or a DVD, this would be a little like appearing on the TV. The material on the website is protected by copyright and people are not allowed to copy or record what they find there but it is possible that they could. If you have any doubts about how you want the interview to be included, talk to me, or I could find an independent adviser for you to talk to if you prefer.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct by the Berkshire Research Ethics Committee.

Who is organising and funding the research?

The Health Experiences Research Group is based at the Department of Primary Health Care, University of Oxford. The project for lung cancer is being funded by The National School of Primary Care Research.

I will send you a copy of the interview transcript to help you decide whether you want your interview to be made available to use for our research, including on Healthtalkonline and other audio-visual resources. A copy of the interview tape can also be provided if requested. You would be asked to read or listen to the interview and consider if there was anything you would like to change or remove, to keep anything secret or hide your identity, or to delete or change some of your interview. We can remove any sections that you do not want us to use. You can take as long as you need to do this. You can also choose how your interview will appear in any resources we produce (see below).

How would the researcher use the interview tape and transcript?

You will be asked to sign a form '**Further use of my interview**'. If you sign this form, you give copyright of the interview to the University of Oxford. It is very important that you take time to think about and discuss the copyright form before you sign it. You will be given a copy of this form to keep.

If you do decide to allow your interview to be used for the study, it would be used along with interviews of other people who have experiences of lung cancer. A summary of these interviews would be prepared for the healthtalkonline website. People who use the site would be able to see the summaries of the interviews as well as read extracts from the interviews and view the video clips of people who agree to this kind of use of their interviews. All data use is strictly within the terms of the Data Protection Act (DPA 1998). The study data may be looked at by individuals from the University of Oxford, for the purpose of audit and monitoring.

The interviews we collect contribute to the information presented on the site, and extracts from many of them will be used to show what it is like for people facing illness or health issues. The interviews will not be used for profit or commercial gain.

As well as the website, we may use interviews to help create other information and support resources, such as DVDs or short films. These may for example be shown to people by health professionals as part of their care or they may appear on other websites approved by the University of Oxford

Interviews may also be used to develop training materials for health and social care professionals, so they can learn from people's experiences and improve the care they provide. Again, these training materials may be presented on the teaching and learning area of the www.healthtalkonline.org website, on other approved websites, and on DVDs.

All the interviews we collect are included in our analysis for preparing research articles and papers.

Why have I been chosen?

You have been contacted because I want to interview people who have had experience of health issues and decisions such as yours. I will be interviewing a range of people who have had such experiences.

While people sometimes find it helpful to talk about their story to researchers this research is not the same thing as counselling. However, I can give you a list of useful contacts which can be used to get more help if you want.

Do I have to take part?
No. It is entirely up to you to decide whether or not you want to take part. If you decide to take part, you will be given this information sheet to keep. You will also be asked to sign a 'consent form'. If you decide to take part, you are still free to stop at any time without giving a reason. No questions will be asked if you stop. Deciding whether or not to take part in the study will not affect the standard of medical care you receive.

What will happen if I take part?
If you complete and send back the enclosed 'reply slip', I will contact you to arrange an interview at a time and place that suits you. If this place is not your home, you will be paid for the cost of your travel. I will try to answer any questions you may have about the interview or the Healthtalkonline project.
Before the interview I can show you the Healthtalkonline website on a portable computer. You can see how clips from other people's interviews look in video, audio and written formats.

What would the interview be like?
I will ask you if you are willing to have the interview video or audio tape recorded. You will be given the 'consent form'. You only sign this form if you agree to take part in the interview. You will be given a copy of the consent form to keep.
The interview will be a little like a conversation, in which I will help you talk about yourself in your own words. I will ask you to talk about your experiences of lung cancer. I will ask questions about what happened to you, what your thoughts and feelings have been at different stages, how you have got information, what you have done, and what have been the good and bad parts of the experience.

How long would the interview take?
The time it takes for an interview varies, depending on how much you have to say, but most interviews last at least an hour. If you would prefer, I can interview you on two different occasions. Remember, if you want to stop the interview at any time, you can do so without giving any reason at all.

What if I decide to withdraw after the interview has taken place?
You are free to leave the study at any time. If you decide to leave after an interview has taken place, all video, tapes, transcripts and typing of your interview would be destroyed. If you decide to leave after the website or other audio-visual resources have been finished, we would remove your contribution from all later versions, but we would not be able to destroy existing material, which other people could already have seen or copied.

What would happen after the interview?
I will label the interview tape with a code number and give it to a typist who will type out everything you said in the interview. The typist has signed an agreement to keep everything you say in the interview secret. The tape and the typed up record (transcript), identified only by the code number, would be kept in a secure place at the University of Oxford.

Figure A.16: Interview script, version 1

- Thank the participant for allowing us to interview him/her.
- Reiterate the purpose of the interview:

> *"The purpose of this interview is to talk to you about your experiences as somebody who has been diagnosed and treated with lung cancer. We know that after treatment has ended people can find they have been left with difficulties in many different areas of their lives and we particularly want to talk to you about how being a patient with lung cancer has affected your physical and psychological health. Some ways to help your health and hopefully improve your quality of life might be to exercise and eat well as well as not smoke. We are looking at how best to help you with these things. In order for us to improve the services offered to cancer patients we want to talk to patients themselves to find out what you think and what your experiences have been. During this interview I'm going to ask you questions about your health, what things you may already be doing yourself to be healthy and we are going to talk about what you think about some ways in which the health service can help you to be as well as possible."*

- Reiterate what the participant can expect to happen during the interview
  - will last no longer than 1.5 hrs
  - ask if it is ok to record
  - explain that the interviewer will ask questions but they are permitted to decline to answer
  - information recorded will be kept confidentially and not traceable to them personally.
  - Can completely withdraw at any time. If they do withdraw we will ask participant at that point if they are happy for us to use the data we have already collected.
- Gain written consent

Background information (10mins)

- Background information about diagnosis and treatment
  - To start off with, can you tell me when you first realised there was something wrong and went to see the doctor?
  - What happened after that?
  - What were you told was wrong with you?
  - What happened after that? What treatments did you get?
  - How long has it been since you finished treatment?

Day to day post operative physical and mental health (10 mins)

- Briefly find out about their current day to day physical and mental health as related to the long term impacts of cancer
  - How healthy do you feel on a day to day basis?
  - What are the main ways you feel healthy?
  - What are the main ways that you feel unhealthy?
  - What are some of the worries that you feel you have been left with as a result of having cancer?
  - Do you think that people need help with their health after being treated with cancer? What help would you want? Why? What about depression? What about anxiety? What about smoking? What about diet?

Attitudes towards effects of health behaviours on health (10 mins)

- Have a general discussion about patients attitudes towards improving health behaviours (it may be that this section needs to be integrated into the in depth section below). "A rehabilitation programme might include things like an exercise programme to help your lungs recover and general fitness, or eating healthily and/or support to give up smoking."
  - Has having cancer changed the way you think about smoking, your diet or exercise?
  - Do you feel that changing you diet, doing more exercise or cutting out smoking could help your health on a day to day basis or to reduce the risk of the cancer

coming back?

Attitudes towards and experiences of health behaviour management (30 mins)

- More in depth discussion about health behaviours and management
  - If you were planning a rehabilitation programme for lung cancer patients, what do you think would be the main things you would address? (investigate topic areas raised by the patients, in particular probe as below)

For patients with smoking history only:

- First of all I want to talk to you a bit about your smoking. When did you start smoking?
- Have you ever tried to give up smoking? When was that? What made you decide to try to give up smoking then? How did you find it?
- Did the doctors or nurses that you saw speak to you about your smoking and about giving up? What did they say?
- How did you feel about the advice to give up/the prospect of giving up?
- CURRENT SMOKER
  - Did you try to give up? What happened?
  - Was it difficult to talk to the doctors and nurses about your smoking?
  - How do you feel about smoking now? What are the good things about it and what are the bad things?
  - Would you like to be able to give up smoking?
- QUIT AT DIAGNOSIS
  - When did you quit smoking?
  - Did you get any help?
  - What was it like? Do you think that it helped or hindered you physically/mentally whilst going through the treatment or now?
  - Was it easier/harder in comparison to other quit attempts you may have made earlier in your life? Why?
  - Do you feel healthier for giving up smoking?

  - Would you have liked some support?
- RELAPSED FROM FORMER SMOKER/QUIT AT DIAGNOSIS
  - When did you start smoking again?
  - What led you to start smoking again?
  - How did you feel about your smoking? How do you feel now? What are the good things and what are the bad things?
  - Did you receive any help to stop smoking?

For all interviewees

- Have you tried to do anything to improve your health (other than giving up smoking for smokers)? What have you done? What was helpful? What was unhelpful?
- Were you advised by doctors or nurses to change your diet or increase the amount of exercise that you do?
- Do you think it would be hard or easy to change you diet and increase exercise..?
- Do you think that changing your diet or exercise would be helpful? Why?
- Is there anything else that you think might help?

Attitudes towards health service intervention to help improve health behaviours and views about delivery (20 mins)

- Views on services available to help people give up smoking
  - PATIENTS WITH SMOKING HISTORY ONLY - When do you think is the best time to give up smoking, before or after treatment? (We need to probe a bit here because suppose they say after, we could and should perhaps bring up the idea that it would help their recovery from surgery, reduce the chance of them getting wound infections or chest infections and does that change their mind? Why do they suggest that.)
  - Do you think it would be good to cut out cigarettes all at once or gradually?
  - Would you like to take medications that we know help people to give up? Do you think that taking nicotine replacement for a long time would help you?

  - ALL PATIENTS - Would you be interested in enrolling in a programme that not only helps you with your smoking but also gives you an exercise programme tailored to your needs and encouragement to do more exercise and improve your diet?
  - When do you think is the best time to address these things?
  - How would other types of rehabilitation discussed in this interview best be delivered?
  - Would you like help in the form of a group or individually?
  - Would you prefer to go to the normal services i.e. NHS stop smoking services, for treatment or to see someone who knows about your cancer and the treatment that you have received for that?
  - How long do you think it would be helpful to have support?
  - How often would you like to attend such a programme, once a week/month..?
- Any other interesting topics raised during the interview (10 mins)

Figure A.17: Nvivo queries

The following queries were used to identify interview text that was potentially relevant to the themes in bold:

Breathlessness

```
breath*
```

Pain

```
pain* OR sore* OR heal* OR wound* OR numb*
```

Appetite or weight loss

```
diet OR appetite OR weigh* OR eat* OR food
```

Fatigue and sleep

```
tired* OR sleep* OR exhaust* OR fatigue OR
energy OR weak* OR weary OR effort
```

Smoking

```
smok* OR quit*
```

APPENDIX

B

SUPPLEMENTARY TABLES FOR THE SMOKING HISTORY SYSTEMATIC REVIEW (CHAPTER 5)

Table B.1: Medline search strategy

1	lung neoplasms/
2	carcinoma, non-small-cell lung/
3	adenocarcinoma/
4	carcinoma, squamous cell/
5	lung.mp.
6	**3** and **5**
7	**4** and **5**
8	(lung adj2 (cancer or carcinoma$ or neoplasm$)).mp.
9	**1** or **2** or **6** or **7** or **8**
10	smoking/
11	smoking cessation/
12	tobacco/
13	(smoking or smoke or smoker$ or tobacco or cigarette).mp.
14	**10** or **11** or **12** or **13**
15	**9** and **14**
16	limit **15** to "prognosis (specificity)"
17	limit **15** to "etiology (specificity)"
18	**16** or **17**
19	Clinical Trials/
20	**15** and **20**
21	**18** or **20**

Table B.2: Embase search strategy

1	exp lung tumor/
2	(lung adj**2** (cancer or carcinoma$ or neoplasm$)).mp.
3	**1** or **2**
4	smoking/
5	smoking cessation/
6	tobacco/
7	Tobacco Smoke/
8	TOBACCO DEPENDENCE/
9	(smoking or smoke or smoker$ or tobacco or cigarette).mp.
10	**4** or **5** or **6** or **7** or **8** or **9**
11	**3** and **10**
12	limit **11** to "prognosis (specificity)"
13	limit **11** to "causation-etiology (specificity)"
14	**12** or **13**
15	Clinical Trials/
16	**11** and **15**
17	**14** or **16**

Table B.3: Web of science search strategy

#1	TS=(lung SAME neoplasm*)
#2	TS=(lung SAME cancer)
#3	TS=(non SAME small SAME cell SAME lung SAME cancer)
#4	TS=(adenocarcinoma AND lung)
#5	TS=(squamous cell AND lung)
#6	TS=((small SAME cell) AND lung)
#7	**#6** OR **#5** OR **#4** OR **#3** OR **#2** OR **#1**
#8	TS=(smoking)
#9	TS=(smoking cessation)
#10	TS=(tobacco)
#11	TS=(cigarette*)
#12	**#11** OR **#10** OR **#9** OR **#8**
#13	**#12** AND **#7**
#14	TS=((cohort OR prognos* OR (relative SAME risk) OR surviv*))
#15	**#13** AND **#14**
#16	TS=(control* SAME trial)
#17	**#13** AND **#16**
#18	**#15** or **#17**

Table B.4: CINAHL search strategy

1	lung neoplasms/
2	carcinoma, non-small-cell lung/
3	adenocarcinoma/
4	carcinoma, squamous cell/
5	lung.mp.
6	**3** and **5**
7	**4** and **5**
8	(lung adj**2** (cancer or carcinoma$ or neoplasm$)).mp.
9	**1** or **2** or **6** or **7** or **8**
10	exp smoking/
11	tobacco/
12	(smoking or smoke or smoker$ or tobacco or cigarette).mp.
13	**10** or **11** or **12**
14	**9** and **13**

Table B.5: COCHRANE search strategy (CENTRAL)

#1	lung neoplasms
#2	non small cell lung cancer
#3	adenocarcinoma
#4	squamous cell carcinoma
#5	lung
#6	**#3** AND **#5**
#7	**#4** AND **#5**
#8	**#1** OR **#2** OR **#6** OR **#7**
#9	smoking
#10	smoking cessation
#11	tobacco
#12	**#9** OR **#10** OR **#11**
#13	**#8** AND **#12**

Table B.6: Study characteristics of included studies

Author	*n* in study	Cohort years	Study design[1]	Min fu	Max fu	Med fu	Exposure	Treatment	Country	Continent
Ademuyiua, 2007	203	2002–2006	1	<1	4.3	2.13	N/R	Non surgical only	USA	N America
Battifora, 1992	231	1982–1987	1	<1	8	N/R	N/R	Surgical only	Denmark	Europe
Birim, 2003	125	1989–2001	2	<1	12	N/R	Medical records	Surgical only	Netherlands	Europe
Blanchon, 2006	2979	2000–2000	1	<1	5	N/R	Medical records	Mixed surgical or non-surgical	France	Europe
Bryant, 2007	730	1999–2005	2	N/R	6	N/R	Medical records	Surgical only	USA	N America
Buccheri, 1993	360	1984–1990	1	<1	7	N/R	N/R	Mixed surgical or non-surgical	Italy	Europe
Chatkin, 2004	109	1900–2000	2	<1	13	N/R	Medical records	Surgical only	Brazil	S America
Demeter, 2003	611	1998–1998	2	<1	2	N/R	Medical records	Mixed surgical or non-surgical	Canada	N America
Fox, 2004	237	1991–2001	2	0.08	8.6	1	Medical records	Non surgical only	USA	N America
Fujisawa, 1999	369	1981–1983	2	>1	14	N/R	Medical records	Surgical only	Japan	Asia
Furak, 2003	278	1992–2001	2	<1	10	N/R	N/R	Surgical only	Hungary	Europe
Gail, 1984	392	1977–1980	1	<1	5	N/R	N/R	Surgical only	USA	N America
Goodman, 1990	675	1979–1985	1	<1	9	N/R	Interview	N/R	USA	N America
Haga, 2003	187	1988–1993	1	<1	14	N/R	N/R	Surgical only	Japan	Asia
Hanagiri, 2008	770	1994–2005	2	N/R	11	5.3	Medical records	Surgical only	Japan	Asia
Harpole, 1995	289	1980 -1988	1	2	16	5.2	Medical records	Surgical only	USA	N America

Table B.6: cont.

Author	*n* in study	Cohort years	Study design[2]	Min fu	Max fu	Med fu	Exposure	Treatment	Country	Continent
Hendricks, 1996	100	1992–1994	2	<1	3	N/R	N/R	Surgical only	Belgium	Europe
Hinds, 1982	223	1968–1978	2	<1	11	N/R	Medical records	Mixed surgical or non-surgical	Japan	Asia
Holli, 1999	290	1983–1987	2	>1	10	N/R	Medical records	N/R	Finland	Europe
Hotta, 2009	260	2000–2003	2	<1	5.2	1.13	N/R	Non surgical only	Japan	Asia
Hung, 2007	445	1980–2000	2	<1	24.84	5.86	N/R	Surgical only	Taiwan	Asia
Isobue, 1994	30	1978–1990	2	<1	5	N/R	N/R	Surgical only	Japan	Asia
Iyoda, 2006	335	1988–2003	2	1	17	N/R	Medical records	Surgical only	Japan	Asia
Jiang, 2005	130	1986–1996	2	<1	17	N/R	N/R	Surgical only	USA	N America
Kato , 1990	2830	1983–1986	2	<1	5	N/R	N/R	N/R	Japan	Asia
Kawaguchi, 2006	62	1985–1995	2	3	13	N/R	Interview	Surgical only	Japan	Asia
Kawahara, 1998	70	1978–1992	2	2.1	15.1	6.7	Questionnaire	Non surgical only	Japan	Asia
Kawai, 2005	3217	1982–1997	2	<1	15	3.9	Medical records	Surgical only	Japan	Asia
Kikuchi, 2006 [504]	161	1982–1994	2	<1	24	9.2	N/R	Surgical only	Japan	Asia
Kim, 2005	422	1994–2004	2	<1	10	N/R	Medical records	Mixed surgical or non-surgical	Korea	Asia
Kobayashi, 2007	163	1995–2002	2	N/R	10	N/R	N/R	Surgical only	Japan	Asia
Kosaka, 2009	338	2000–2005	2	>1	6.3	2.7	N/R	Surgical only	Japan	Asia
Lee, 1995	312	1981–1990	2	<1	13	N/R	N/R	Surgical only	Taiwan	Asia

Table B.6: cont.

Author	*n* in study	Cohort years	Study design[2]	Min fu	Max fu	Med fu	Exposure	Treatment	Country	Continent
Liang, 2003	55	N/r	2	<1	>6.6	N/R	Medical records	Mixed surgical or non-surgical	China	Asia
Maeda, 2006	12703	1975–1997	2	N/R	N/R	N/R	N/R	Surgical only	Japan	Asia
Maeshima, 2008	236	1984–1990	2	<1	17	7	Medical records	Surgical only	Japan	Asia
Marsit, 2005	85	1992–1996	1	<1	10	N/R	Interview	Surgical only	USA	N America
Martins, 1999	1635	1990–1996	2	N/R	N/R	1.25	N/R	Mixed surgical or non-surgical	Brazil	S America
Matsugama, 2008	455	1986–2003	1	2.5	19	7.5	N/R	Surgical only	Japan	Asia
Mitsudomi, 1989	492	1974–1988	2	<1	14	N/R	N/R	Surgical only	Japan	Asia
Moro-Sibilot, 2005	588	1979–2003	2	<1	13	N/R	N/R	Surgical only	France	Europe
Mulligan, 2006	97	1990–2000	2	1	12	N/R	Medical records	Mixed surgical or non-surgical	USA	N America
Myrdal, 2002	395	1987–1999	2	0.3	13	3.8	Medical records	Surgical only	Sweden	Europe
Nakamura, 2008	571	1980–2003	2	2	22	N/R	N/R	Surgical only	Japan	Asia
Nia, 2005	311	1991–2001	2	0.16	11.25	2.75	Medical records	Surgical only	Belgium	Europe
Nordquist, 2004	654	1985–2000	1	<1	16	N/R	Questionnaire	N/R	USA	N America
Okada, 2004	954	1985–2002	2	0.75	18.75	5.1	N/R	Surgical only	Japan	Asia
Rades, 2008	181	2000–2005	2	1	5.3	1.42	N/R	Mixed surgical or non-surgical	Germany	Europe

Table B.6: cont.

Author	*n* in study	Cohort years	Study design[2]	Min fu	Max fu	Med fu	Exposure	Treatment	Country	Continent
Ramnath, 2007	155	1986–2002	2	< 1	19	1.56	N/R	Surgical only	USA	N America
Rice, 2003	569	1992–1997	1	<1	10	5.9	N/R	Surgical only	USA	N America
Rui, 2006	30	1998–1998	2	4.3	5	N/R	N/R	Surgical only	China	Asia
Saito-Nakaya, 2006	238	1996–1999	1	0.1	7.6	5.9	N/R	Surgical only	Japan	Asia
Sakao, 2008	121	1996–1999	2	< 1	9	3.33	Medical records	Surgical only	Japan	Asia
Sawabata, 2006	169	2000–2000	2	<1	5	N/R	Medical records	Surgical only	Japan	Asia
Sekine, 1997	970	1992–1995	2	0	12	2.3	Medical records	Surgical only	Japan	Asia
Shiba, 2000	156	1989–1992	2	<1	11	5.7	Medical records	Surgical only	Japan	Asia
Sioris, 2000	101	1988–1993	2	>1	10	N/R	Interview	Surgical only	Finland	Europe
Sobue, 1991	267	1978–1987	1	<1	11	N/R	Interview	Surgical only	Japan	Asia
Song, 2004	60	1997–1999	1	<1	3	N/R	N/R	Non surgical only	China	Asia
Subramanian, 2007	442	1992–2002	2	5	15	8	Medical records	N/R	USA	N America
Sun, 2006	5018	1997–2003	1	<1	8	N/R	Medical records	Surgical only	USA	N America
Suzuki, 1999	836	1987–1997	2	>1	12	N/R	N/R	Surgical only	Japan	Asia
Takeshita, 2008	157	1997–2001	2	< 1	8.83	4.6	N/R	Surgical only	Japan	Asia
Tammemagi, 2000	119	1988–1996	2	N/R	N/R	3.4	Medical records	Surgical only	Canada	N America
Tammemagi, 2004	1155	1995–1998	2	<1	8	N/R	Medical records	N/R	USA	N America
Tan, 2004	326	1996–1998	1	<1	4	N/R	Interview	N/R	Singapore	Asia
Tang, 2006	102	1997–1998	1	<1	7	N/R	N/R	Surgical only	China	Asia

Table B.6: cont.

Author	*n* in study	Cohort years	Study design[2]	Min fu	Max fu	Med fu	Exposure	Treatment	Country	Continent
Toh, 2004	317	1999–2002	2	<1	5	N/R	Medical records	N/R	Singapore	Asia
Tsai, 2006	236	1991–2001	2	2.275	13.5	4.63	N/R	Surgical only	China	Asia
Tsurutani, 2007	46	1959–2004	2	N/R	23	N/R	Medical records	Surgical only	Iceland	Europe
Tucker, 1997	611	1973–1990	2	2	N/R	5.2	Medical records	Non surgical only	Canada	N America
Usuda, 1994	174	1985–1986	1	<1	5	N/R	N/R	Mixed surgical or non-surgical	Japan	Asia
Wolf, 1991	766	1981–1986	1	3	8	N/R	N/R	Non surgical only	Germany	Europe
Wu, 2003	321	1980–1990	2	<1	21	N/R	N/R	Surgical only	Taiwan	Asia
Yoshida, 1996	61	1977–1991	1s	2	12	N/R	Interview	Non surgical only	Japan	Asia
Yoshino, 2006	999	N/r	2	<1	10	N/R	Medical records	Surgical only	Japan	Asia
Zhang, 2008	148	1990–2006	2	<1 yr	14	N/R	N/R	Mixed surgical or non-surgical	China	Asia
Zhou, 2006	558	1992–2002	1	<1	11.6	4.75	Questionnaire	Surgical with adjuvant treatment	USA	N America

Table B.7: Participant characteristics of included studies: stage 1 surgical patients (** = 100% NSCLC).

Author	Male (%)	Average age mean (SD or range)	Squamous (%)	SCLC (%)	Stage	Co-morbidity
Chatkin, 2004	70	62.9 (9.3)	46	0	1	N/R
Gail, 1984	73	62	48	0	1	N/R
Haga, 2003	64	62	65	0	1	N/R
Hung, 2007	76.2	65.5 (9.4)	32.6	0	1	N/R
Isobue, 1994	43	62 (45-73)	0	0	1	N/R
Iyoda, 2006	55.5	63 (36-83)	19.4	3.3	1a	N/R
Kobayashi, 2007	55	64 (30-84)	16	0	1a	N/R
Matsugama, 2008	61.3	65 (35- 85)	25	0	1	N/R
Rice, 2003	57	63.4	N/R	0	1	N/R
Sawabata, 2006	89	65.5 (10)	100**	0	1	N/R
Tsai, 2006	69.1	65.13 (24-86)	20.8	0	1a	N/R
Wu, 2003	85.7	63 (8)	49.2	0	1	N/R

Table B.8: Participant characteristics of included studies: mixed stage surgical patients. (* = stage 1–3. ** = 100% NSCLC. *** = 100% adenocarinoma)

Author	Male (%)	Average age mean (SD or range)	Squamous (%)	SCLC (%)	Stage 1-3a Limited (%)	Co-morbidity
Battifora, 1992	74	62	56	4	N/R	N/R
Birim, 2003	81	70+	47	0	95	80
Bryant, 2007	69	59.9 (21-85)	40	0	93*	N/R
Fujisawa, 1999	66	62.2 (34-87)	38	0	100	N/R
Furak, 2003	55	60.5 (41-79)	0	0	88	N/R
Hanagiri, 2008	86.5	N/R	28	0	85	N/R
Harpole, 1995	63	63 (8)	34	0	100	N/R
Hendricks, 1996	86	62.5 (8)	52	0	95	N/R
Jiang, 2005	52.3	N/R	45.4	0	100	N/R
Kawaguchi	81	61 (34-80)	48	0	100	N/R
Kawai, 2005	61	63 (10.2)	27	0	100	N/R
Kikuchi, 2006 [504]	68	N/R	42	0	n/r	N/R
Kosaka, 2009	51	64 (29-89)	0	0	97	N/R
Lee, 1995	72	N/R	36	4	79	N/R
Maeda, 2006	70.7	64.0 +- 9.7	39	0	95	N/R
Maeshima, 2008	61	60 (26-84)	100***	0	89*	N/R

Table B.8: cont

Author	Male (%)	Average age mean (SD or range)	Squamous (%)	SCLC (%)	Stage 1-3a Limited (%)	Co-morbidity
Marsit, 2005	60	64-70	44	0	78	N/R
Mitsudomi, 1989	73	61-62	35	0	85.4	N/R
Moro-Sibilot, 2005	89	62.7 (33-86)	62	0	100	53
Myrdal, 2002	65	60-69	46	0	100	N/R
Nakamura, 2008	64	64.8 (35-81)	29	0	100	N/R
Nia, 2005	86	65	47	0	92.1	N/R
Okada, 2004	64	64.6 +/- 9.9	27	0	89	N/R
Ramnath, 2007	64.5	57.1(11.2)	54	0	85	N/R
Rui, 2006	67	63 (52- 84)	36.7	20	100*	N/R
Saito-Nakaya, 2006	60.9	62.4 (10.4)	21	0	81	40
Sakao, 2008	49	64 (35-82)	100**	0	n/r	N/R
Sekine, 1997	68	60-69	64	0	86	N/R
Shiba, 2000	72	62.4 (8.8)	59	0	100	N/R
Sioris, 2000	83	median 65	58	0	91	N/R
Sobue, 1991	66	60-69	0	0	90	N/R
Sun, 2006	58	66	28	0	64	N/R
Suzuki	63	64 (23-85)	26	0	90	N/R
Takeshita, 2008	64	67 (41-84)	26	0	99	N/R
Tammemagi, 2000	44	68 (9.5)	39	0	100	N/R
Tang, 2006	72	59 (30-78)	50	0	87	N/R
Tsurutani, 2007	37	65 (38-84)	100***	0	76*	N/R
Yoshino, 2006	N/R	N/R	40	0	N/R	N/R
Zhou, 2006	51	67 (31-89)	29	0	100	N/R

Table B.9: Participant characteristics of included studies: non-surgical patients (* = stage 1–3. ** = 100% NSCLC. *** = 100% adenocarinoma)

Author	Male (%)	Average age mean (SD or range)	Squamous (%)	SCLC (%)	Stage 1-3a Limited (%)	Co-morbidity
Ademuyiua, 2007	66	median 60-70	100**	0	39.4	N/R
Blanchon, 2006	84	64.1 (11.5)	47	0	54	N/R
Buccheri, 1993	93	64 (38-88)	100	0	50	N/R
Demeter, 2003	55	66.5 (11)	23	17	28	N/R
Fox, 2004	56	70	37	0	54	N/R
Goodman, 1990	69	64	28	14	64	N/R
Hinds, 1982	0	50-64	17	16	55	N/R
Holli,1999	88	65 (9)	59	21	n/r	N/R
Hotta, 2009	60	63 (29-85)	0	0	40	N/R
Kato, 1990	74	60-69	24	9	N/R	N/R
Kawahara	N/R	N/R	0	100	N/R	N/R
Kim, 2005	58.5	59.8	100***	0	61.3	N/R
Liang, 2003	78.2	60 (33-77)	32.7	0	47.3	N/R
Martins, 1999	76	60-70	51	0	33	N/R
Mulligan, 2006	62	median 66	31	0	50	N/R
Nordquist, 2004	41	56-65	0	0	44	N/R
Rades, 2008	78	median 65	55	0	100*	N/R
Song, 2004	71.7	58 (22-76)	0	100	45	N/R
Subramanian, 2007	28	median 70	8.8	0	60.9	N/R
Tammemagi, 2004	59	67 (10.6)	26	12	63	61
Tan, 2003	0	65 (23-93)	16.6	7.7	45.7	N/R
Toh, 2004	66	62.4 (11.8)	22	0	19	52
Tucker, 1997	55	61	0	100	79	N/R
Usuda, 1994	70.7	67 (33-86)	38.5	4	90.8	N/R
Wolf, 1991	85	50-60	0	100	38	N/R
Yoshida, 1996	80.3	61 (37-79)	0	100	85	N/R
Zhang, 2008	81.1	77 (70-94)	38.5	0	49	N/R

Table B.10: Quality scores for included studies

Author	Inc[1]	M/F[2]	Age[2]	Histol[2]	Stage[2]	Co-morbidity[2]	Treatment[2]	Exposure measure-ment[3]	Exposure description[4]	Follow up[5]	Pros/ retro[6]	total
Ademuyiua, 2007	2	1	1	1	1	0	1	0	1	1	2	8
Battifora, 1992	1	1	1	1	0	0	1	0	1	0	2	7
Birim, 2003	1	1	1	1	1	1	1	1	1	2	1	9
Blanchon, 2006	2	1	1	1	1	0	1	1	2	1	2	10
Bryant, 2007	2	1	1	1	1	0	1	1	1	2	1	8
Buccheri, 1993	1	1	1	1	1	0	1	0	1	0	2	8
Chatkin, 2004	2	1	1	1	1	0	1	1	1	2	1	8
Demeter, 2003	1	1	1	1	1	0	1	1	2	1	1	9
Fox, 2004	1	1	1	1	1	0	1	1	1	2	1	8
Fujisawa, 1999	2	1	1	1	1	0	1	1	1	0	1	8
Furak, 2003	1	1	1	1	1	0	1	0	1	2	1	7
Gail, 1984	0	1	1	1	1	0	1	0	1	1	2	8
Goodman, 1990	1	1	1	1	1	0	0	2	1	0	2	9
Haga, 2003	2	1	1	1	1	0	1	0	2	2	2	9
Hanagiri, 2008	1	1	0	1	1	0	1	1	1	2	1	7
Harpole, 1995	2	1	1	1	1	0	1	1	1	2	2	9
Hendricks, 1996	1	1	1	1	1	0	1	0	1	1	1	7
Hinds, 1982	2	0	1	1	1	0	1	1	1	2	1	7

[1] 0 = Inclusion criteria not described, 1 = some description, 2 = clear description
[2] 0 = Not described, 1 = described for whole group, 2 = described by smoking status
[3] 0 = Method not described, 1 = case notes, 2 = interview/questionnaire
[4] 0 = Not described, 1 = retrospective measurement, 2 = prospective measurement
[5] 0 = Not described, 1 = less than 5 years, 2 = 5 years or more
[6] 1 = Retrospective, 2 = prospective

Table B.10: cont.

Author	Inc[1]	M/F[2]	Age[2]	Histol[2]	Stage[2]	Co-morbidity[2]	Treatment[2]	Exposure measure-ment[3]	Exposure description[4]	Follow up[5]	Pros/ retro[6]	total
Holli, 1999	2	1	1	1	0	0	0	1	1	0	1	6
Hotta, 2009	1	1	1	1	1	0	1	0	1	2	1	7
Hung, 2007	2	1	1	1	1	0	1	0	2	2	1	8
Isobue, 1994	0	1	1	1	1	0	1	0	1	1	1	7
Iyoda, 2006	2	1	1	1	1	0	1	1	1	2	1	8
Jiang, 2005	1	1	0	1	1	0	1	0	1	0	1	6
Kato , 1990	1	1	1	1	0	0	0	0	1	1	1	5
Kawaguchi, 2006	2	1	1	1	1	0	1	2	1	0	1	9
Kawahara, 1998	2	0	0	1	0	0	1	2	1	2	1	6
Kawai, 2005	1	1	1	1	1	0	1	1	1	2	1	8
Kikuchi, 2006 [504]	0	1	1	1	0	0	1	0	1	2	1	6
Kim, 2005	1	1	1	1	1	0	1	1	1	2	1	8
Kobayashi, 2007	2	1	1	1	1	0	1	0	1	2	1	7
Kosaka, 2009	2	1	1	1	1	0	1	0	1	2	1	7
Lee, 1995	2	1	0	1	1	0	1	0	1	2	1	6
Liang, 2003	1	1	1	1	1	0	1	1	1	2	1	8
Maeda, 2006	1	1	1	1	1	0	1	0	1	1	1	7
Maeshima, 2008	2	1	1	1	1	0	1	1	1	0	1	8
Marsit, 2005	1	1	1	1	1	0	1	2	1	2	2	10
Martins, 1999	2	1	1	1	1	0	1	0	1	0	1	7
Matsugama, 2008	2	1	1	1	1	0	1	0	1	2	2	8
Mitsudomi, 1989	1	1	1	1	1	0	1	0	1	2	1	7
Moro-Sibilot, 2005	0	1	1	1	1	1	1	0	1	2	1	8

Table B.10: cont.

Author	Inc[1]	M/F[2]	Age[2]	Histol[2]	Stage[2]	Co-morbidity[2]	Treatment[2]	Exposure measure-ment[3]	Exposure description[4]	Follow up[5]	Pros/ retro[6]	total
Mulligan, 2006	1	1	1	1	1	0	1	1	2	2	1	9
Myrdal, 2002	2	1	1	1	1	0	1	1	1	2	1	8
Nakamura, 2008	1	1	1	1	1	0	1	0	1	0	1	7
Nia, 2005	2	1	1	1	1	0	1	1	2	2	1	9
Nordquist, 2004	2	1	1	1	1	0	0	2	1	2	2	9
Okada, 2004	2	1	1	1	1	0	1	0	1	2	1	7
Rades, 2008	1	1	1	1	1	0	1	0	1	2	1	7
Ramnath, 2007	2	1	1	1	1	0	1	0	1	2	1	7
Rice, 2003	2	1	1	1	1	0	1	0	1	2	2	8
Rui, 2006	1	1	1	1	1	0	1	0	1	1	1	7
Saito-Nakaya, 2006	2	1	1	1	1	1	1	0	1	0	2	9
Sakao, 2008	2	1	1	1	0	0	1	1	1	2	1	7
Sawabata, 2006	2	1	1	1	1	0	1	1	1	1	1	8
Sekine, 1997	2	1	1	1	1	0	1	1	2	2	1	9
Shiba, 2000	2	1	1	1	1	0	1	1	1	2	1	8
Sioris, 2000	2	1	1	1	1	0	1	2	1	0	1	9
Sobue, 1991	1	1	1	1	1	0	1	2	1	2	2	10
Song, 2004	2	1	1	1	1	0	1	0	1	1	2	8
Subramanian, 2007	2	1	1	1	1	0	0	1	1	2	1	7
Sun, 2006	2	1	1	1	1	0	1	1	2	0	2	10
Suzuki, 1999	2	1	1	1	1	0	1	0	1	0	1	7
Takeshita, 2008	1	1	1	1	1	0	1	0	1	n/r	1	7
Tammemagi, 2000	1	1	1	1	1	0	1	1	1	0	1	8

Table B.10: cont.

Author	Inc[1]	M/F[2]	Age[2]	Histol[2]	Stage[2]	Co-morbidity[2]	Treatment[2]	Exposure measure-ment[3]	Exposure description[4]	Follow up[5]	Pros/ retro[6]	total
Tammemagi, 2004	2	1	1	1	1	1	0	1	1	2	1	8
Tan, 2004	2	1	1	1	1	0	0	2	1	1	2	9
Tang, 2006	1	1	1	1	1	0	1	0	1	0	2	8
Toh, 2004	1	1	1	1	1	1	0	1	1	1	1	8
Tsai, 2006	2	1	1	1	1	0	1	0	1	1	1	7
Tsurutani, 2007	2	1	1	1	1	0	1	1	1	2	1	8
Tucker, 1997	2	1	1	1	1	0	1	1	1	2	1	8
Usuda, 1994	2	1	1	1	1	0	1	0	1	1	2	8
Wolf, 1991	2	1	1	1	1	0	1	0	1	2	2	8
Wu, 2003	2	1	1	1	1	0	1	0	1	2	1	7
Yoshida, 1996	2	1	1	1	1	0	1	2	1	2	2	10
Yoshino, 2006	0	0	1	1	0	0	1	1	1	2	1	6
Zhang, 2008	2	1	1	1	1	0	1	0	1	2	1	7
Zhou, 2006	2	1	1	1	1	0	1	2	2	2	2	11

Table B.11: Patient characteristics for studies included in current v never and former v never comparison

Author	Unadjusted HR (95%)	Gender	Squamous (%)	Adeno (%)	SCLC (%)	Stage 1-3a (%)	Quality score	Study de-sign[3]	Smoking exposure measurement
Current v never – surgical patients									
Gail, 1984	4.95 (1.29, 19.08)	73	48		0	100 stage 1	8	2	Medical records
Nakamura, 2008	1.51 (1.07, 2.13)	64	29		0	95	7	2	Medical records
Nia, 2005	1.67 (0.51, 5.42)	86	47		0	92	9	2	Medical records
Rice, 2003	2.44 (1.32, 4.50)	57	N/R		0	100 stage 1	8	2	N/r
Saito-Nakaya, 2006	3.10 (1.50, 6.40)	61	21		0	81	9	2	N/r
Sawabata, 2006	3.10 (0.97, 9.93)	89	100 nsclc		0	100 stage 1	8	1	Medical records
Zhou, 2006	1.99 (1.16, 3.44)	51	29		0	100	11	2	Questionnaire
Current v never – non-surgical patients									
Blanchon, 2006	0.98 (0.80, 1.20)	84	47		0	54	10	2	Medical records
Kim, 2005	1.70 (1.21, 2.39)	59	0	100	0	61*	8	2	Medical records

[3] 1 = prospective, 2 = retrospective

Nordquist, 2004	1.09 (0.85, 1.40)	41	0	100	0	44	9	1	Questionnaire
Subramanian, 2007	1.06 (0.83, 1.36)	28	8.8		0	61*	7	2	Medical records
Former v never – surgical patients									
Gail, 1984	4.52 (1.19, 17.85)	73	48		0	100 stage 1	8	2	Medical records
Nakamura, 2008	1.35 (0.92, 1.98)	64	29		0	95	7	2	Medical records
Nia, 2005	1.22 (0.51, 2.92)	86	47		0	92	9	2	Medical records
Rice, 2003	1.93 (0.53, 7.08)	57	N.r		0	100 stage 1	8	2	N.r
Saito-Nakaya, 2006	3.39 (1.49, 7.68)	61	21		0	81	9	2	N.r
Sawabata, 2006	1.34 (0.28, 6.35)	89	100 nsclc		0	100 stage 1	8	1	Medical records
Former v never – non-surgical patients									
Blanchon, 2006	1.00 (0.82, 1.23)	84	47		0	54	10	2	Medical records
Kim, 2005	1.79 (1.16, 2.74)	59	0	100	0	61*	8	2	Medical records

Table B.12: Patient characteristics for studies included in current v former and current v former never comparison

Author	Unadjusted HR (95%)	Male (%)	Squamous (%)	SCLC (%)	Stage 1-3a (%)	Quality score	Study design[4]	Smoking measurement
Current v former – surgical patients								
Gail, 1984	1.07 (0.16, 7.17)	73	48	0	100 stage 1	3	2	Medical records
Nakamura, 2008	1.21 (0.67, 2.18)	64	29	0	95	2	2	Medical records
Nia, 2005	1.22 (0.51, 2.92)	86	47	0	92	9	2	Medical records
Rice, 2003	1.26 (0.53, 2.99)	57	N.r	0	100 stage 1	8	2	N.r
Saito-Nakaya, 2006	0.91 (0.30, 2.77)	61	21	0	81	5	2	N.r
Sawabata, 2006	2.34 (0.33, 16.59)	89	100 nsclc	0	100 stage 1	6	1	Medical records
Current v former – non-surgical patients								
Blanchon, 2006	0.98 (0.74, 1.30)	84	47	0	54	6	2	Medical records
Kim, 2005	0.96 (0.55, 1.68)	59	0	0	61*	8	2	Medical records
Current v former/never – surgical patients								
Jiang, 2005	0.64 (0.23, 1.77)	52	45.4	0	100	2	2	N/r
Myrdal, 2002	1.40 (1.11, 1.79)	65	46	0	100	6	2	Medical records
Current v former/never – non-surgical patients								
Fox, 2004	1.35 (0.98, 1.86)	56	37	0	54	5	1	Medical records
Tammemagi, 2004	1.28 (1.14, 1.47)	59	26	12	63	8	2	Medical records

APPENDIX

C

SUPPLEMENTARY FIGURES FOR THE SMOKING HISTORY SYSTEMATIC REVIEW (CHAPTER 5)

Figure C.1: Risk of all cause mortality in ever compared to never smokers treated with surgery: sensitivity analysis by HR estimation (presented v calculated from other data)

Figure C.2: Risk of all cause mortality in ever compared to never smokers treated with surgery: sensitivity analysis by study quality (high v low)

Figure C.3: Risk of all cause mortality in ever compared to never smokers treated with surgery: sub group analysis by histology (NSCLC v NSCLC and SCLC)

Figure C.4: Risk of all cause mortality in ever compared to never smokers who have received surgical treatment for NSCLC only: sub group analysis by histology (Mixed NSCLC histology v adenocarcinoma only)

Figure C.5: Risk of all cause mortality between current or former smokers and never smokers treated with surgery: Sensitivity analysis, presented v calculated

Figure C.6: Risk of all cause mortality in current or former smokers compared to never smokers treated with surgery: sensitivity analysis by study quality (high v low)

Figure C.7: Risk of all cause mortality in current compared with former smokers and current with former/never smokers treated with surgery: sensitivity analysis by study quality (high v low)

Figure C.8: Risk of all cause mortality and recency of smoking in surgical patients only: sub group analysis by stage (stage 1 v mixed stage)

Figure C.9: Risk of all cause mortality in patients with heavier compared to lighter pack year history

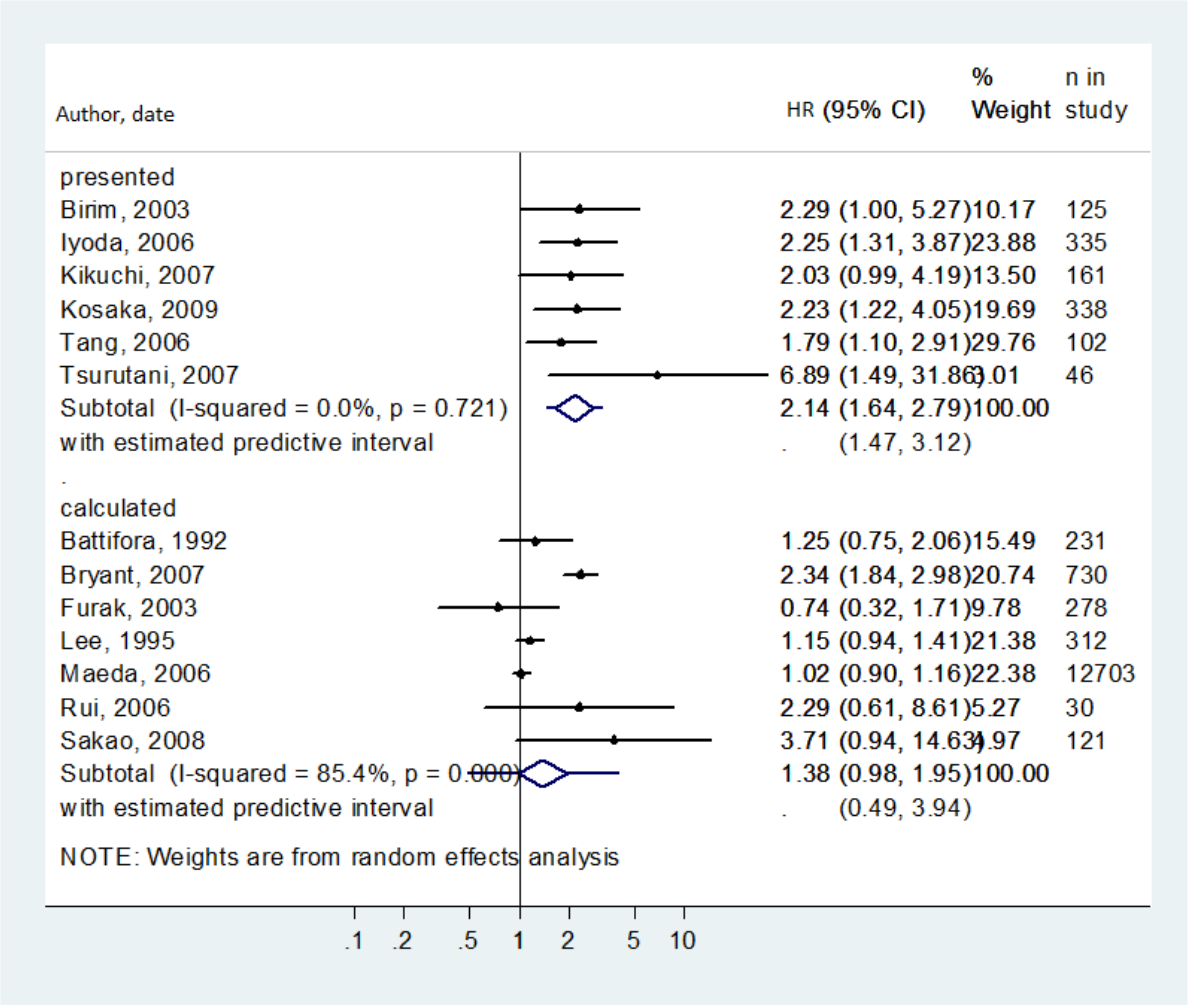


Figure C.1: Risk of all cause mortality in ever compared to never smokers treated with surgery: sensitivity analysis by HR estimation (presented v calculated from other data)

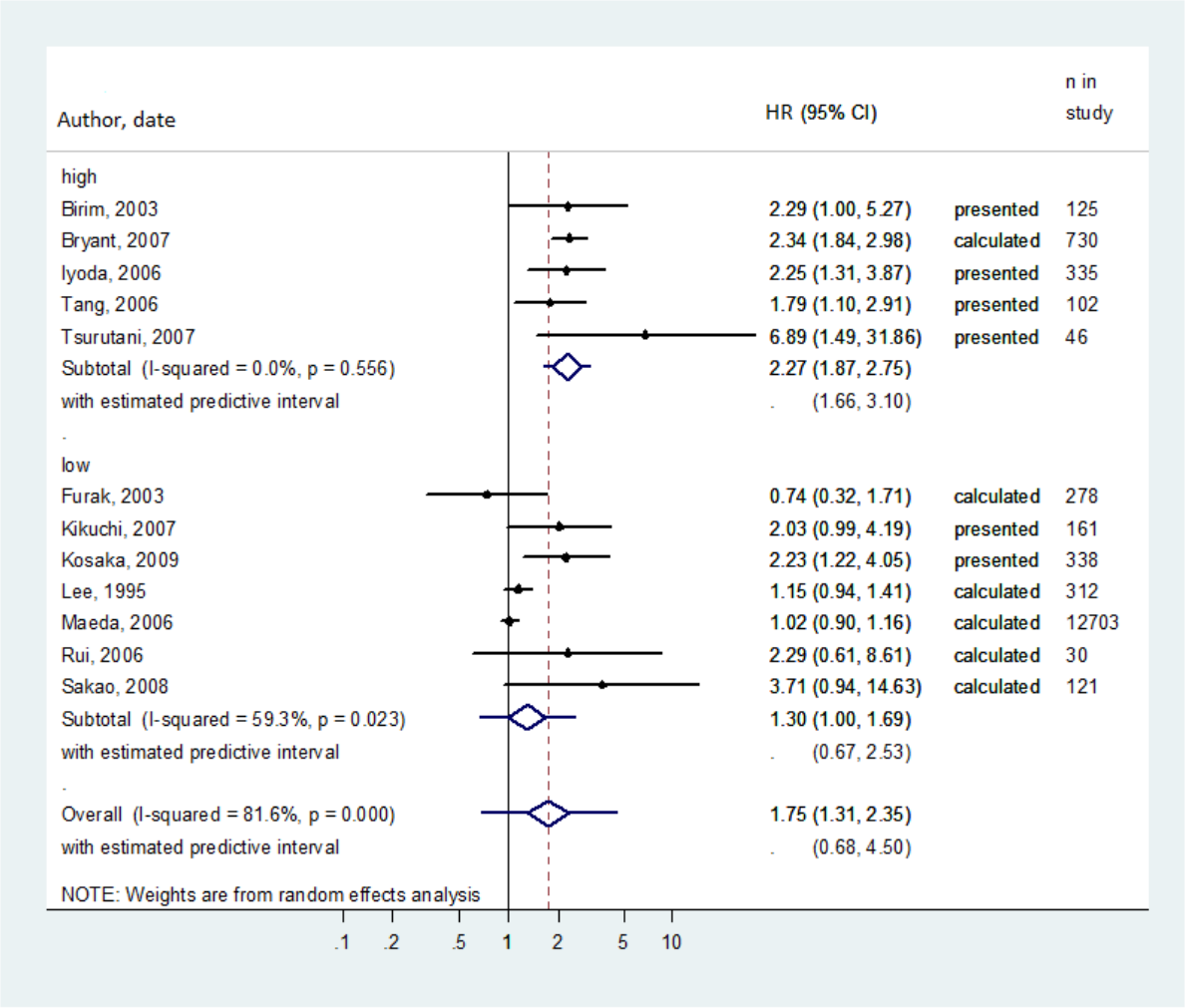


Figure C.2: Risk of all cause mortality in ever compared to never smokers treated with surgery: sensitivity analysis by study quality (high v low)

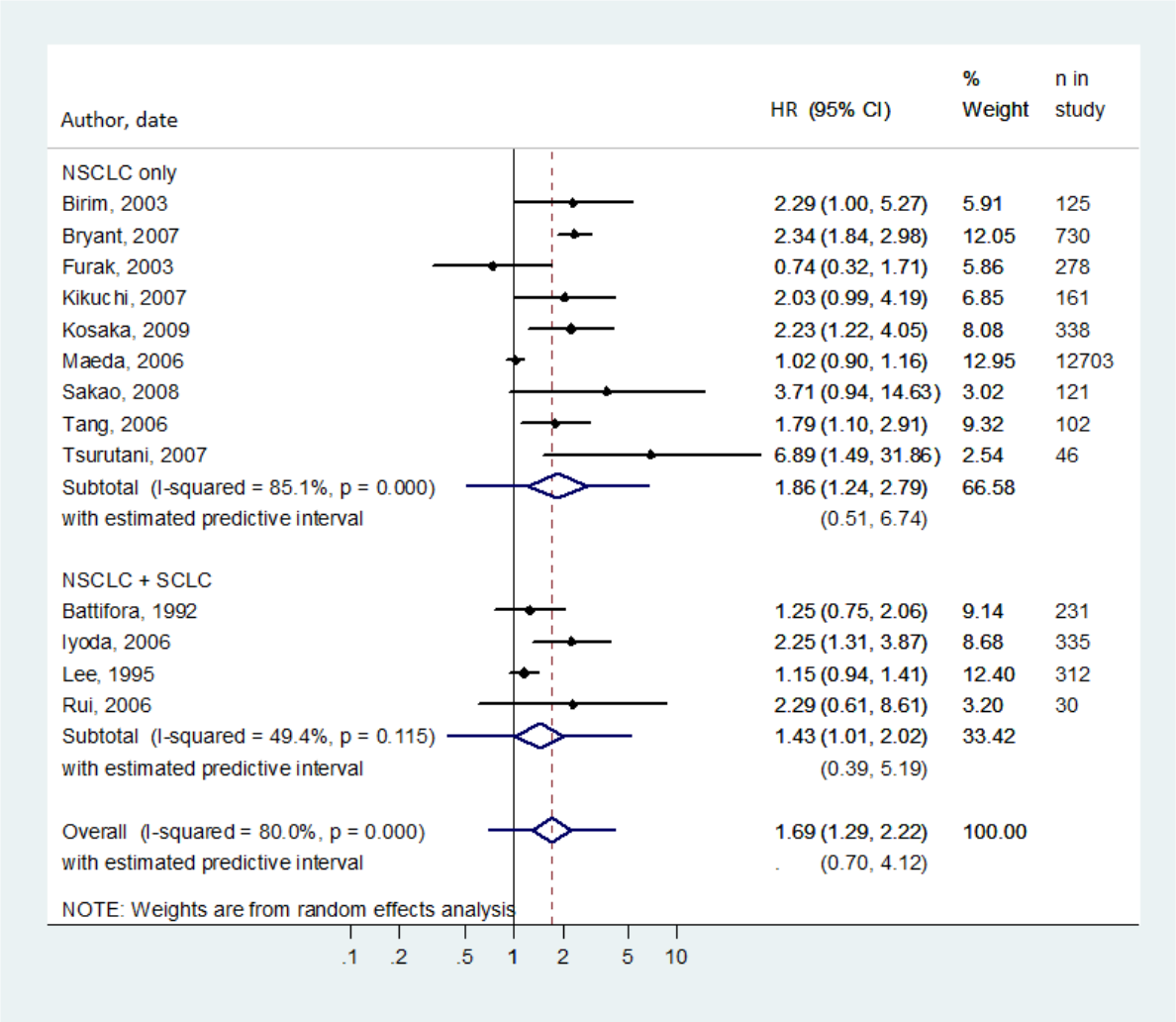


Figure C.3: Risk of all cause mortality in ever compared to never smokers treated with surgery: sub group analysis by histology (NSCLC v NSCLC and SCLC)

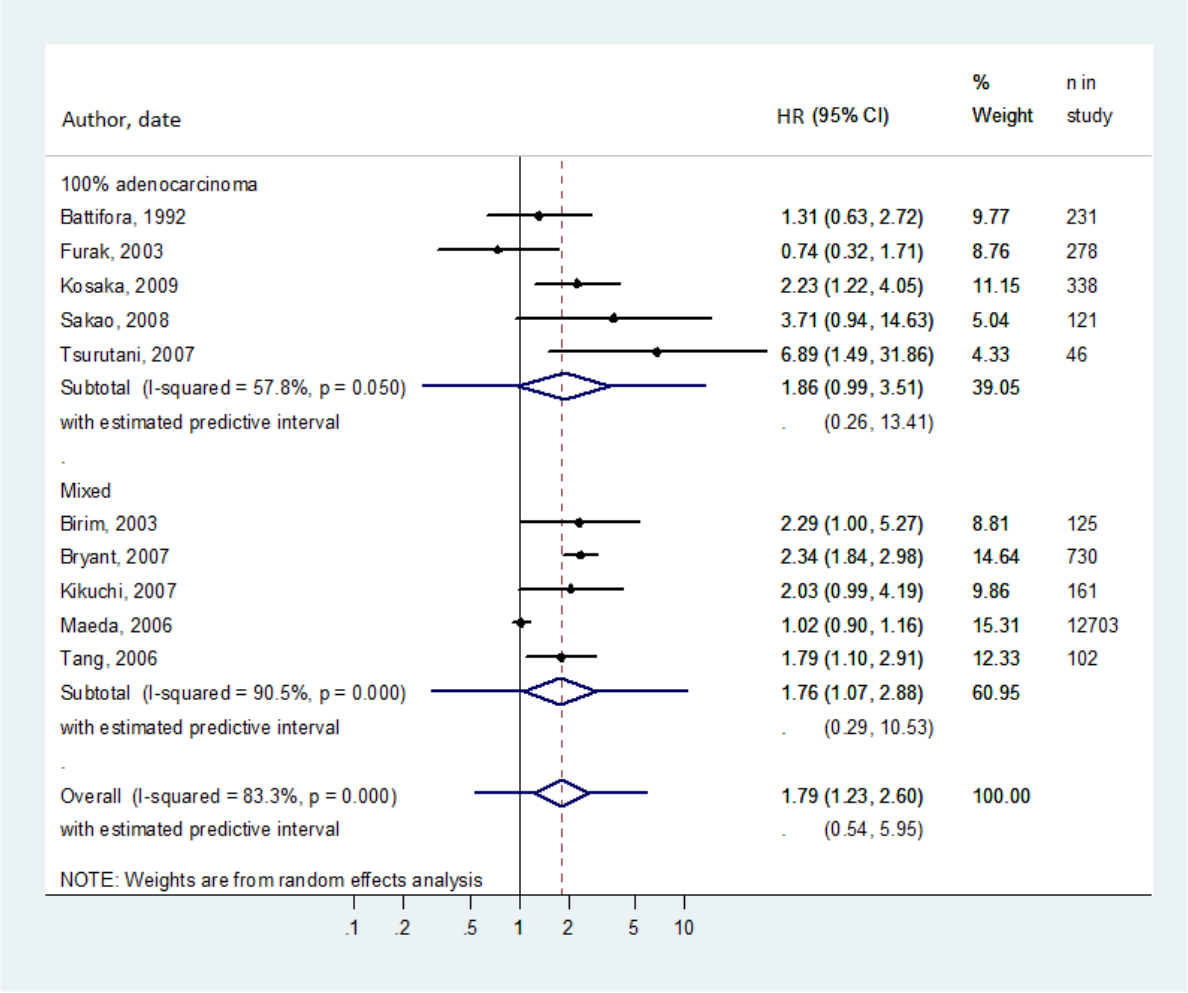


Figure C.4: Risk of all cause mortality in ever compared to never smokers who have received surgical treatment for NSCLC only: sub group analysis by histology (Mixed NSCLC histology v adenocarcinoma only)

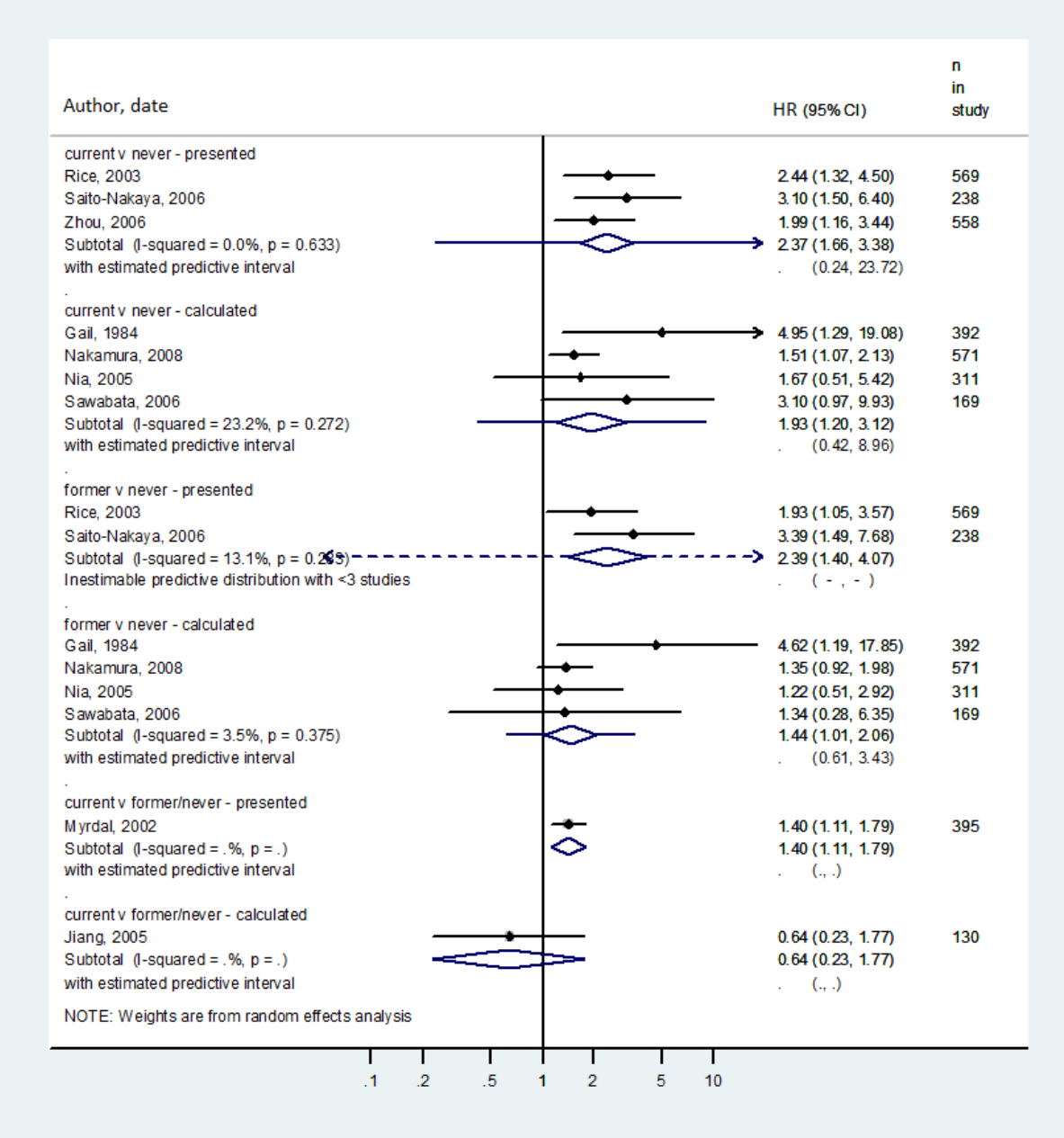


Figure C.5: Risk of all cause mortality between current or former smokers and never smokers treated with surgery: Sensitivity analysis, presented v calculated

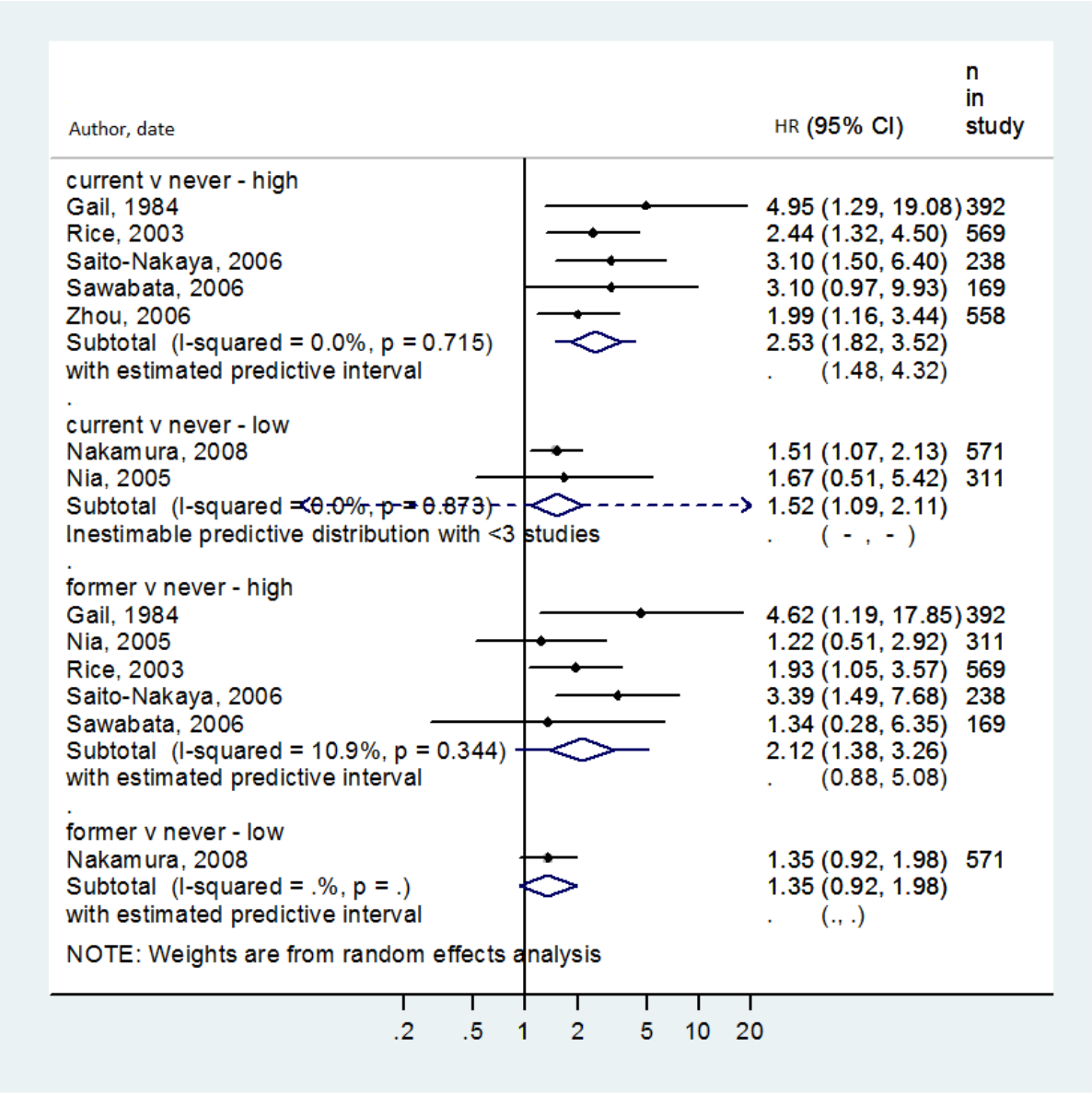


Figure C.6: Risk of all cause mortality in current or former smokers compared to never smokers treated with surgery: sensitivity analysis by study quality (high v low)

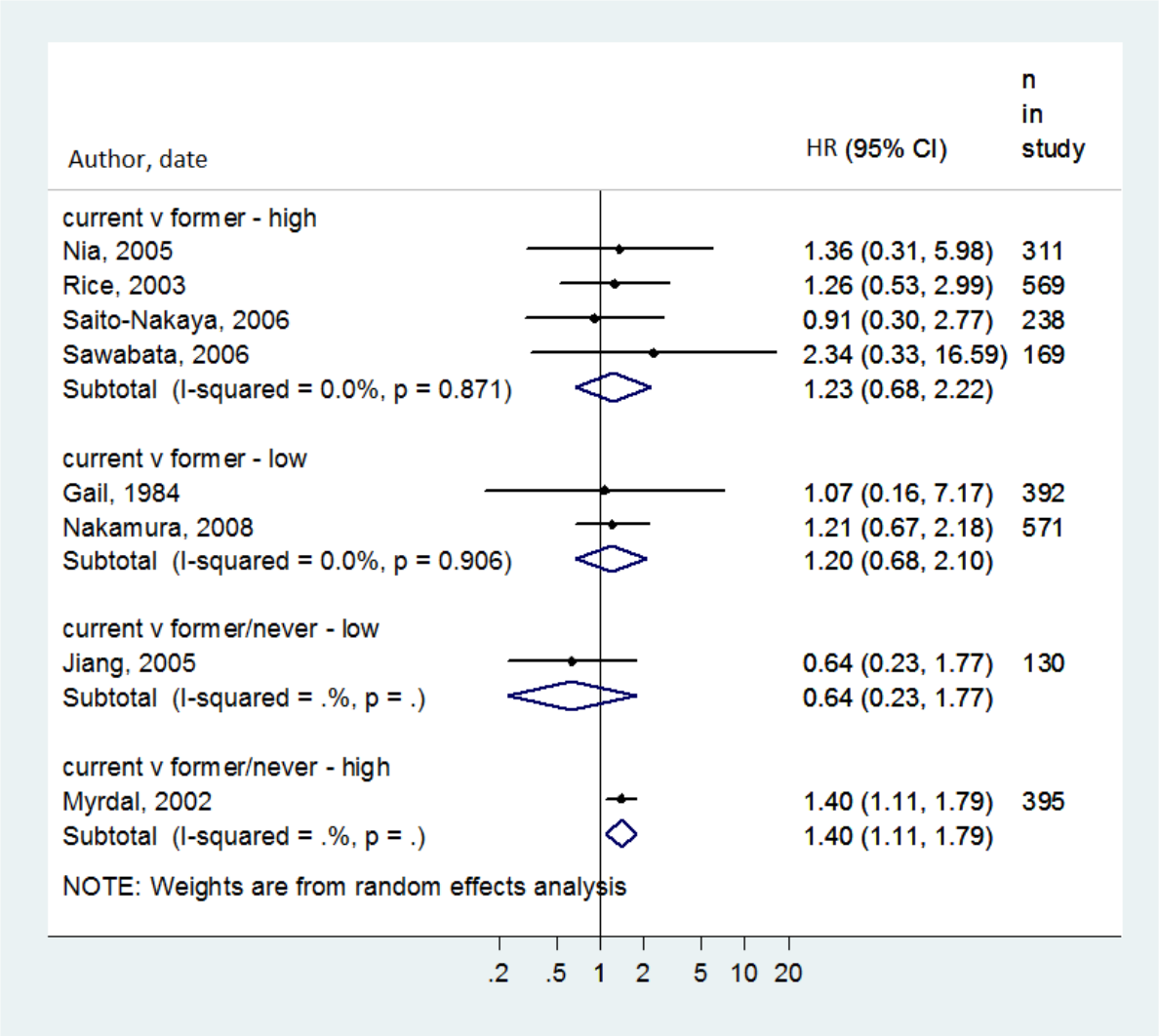


Figure C.7: Risk of all cause mortality in current compared with former smokers and current with former/never smokers treated with surgery: sensitivity analysis by study quality (high v low)

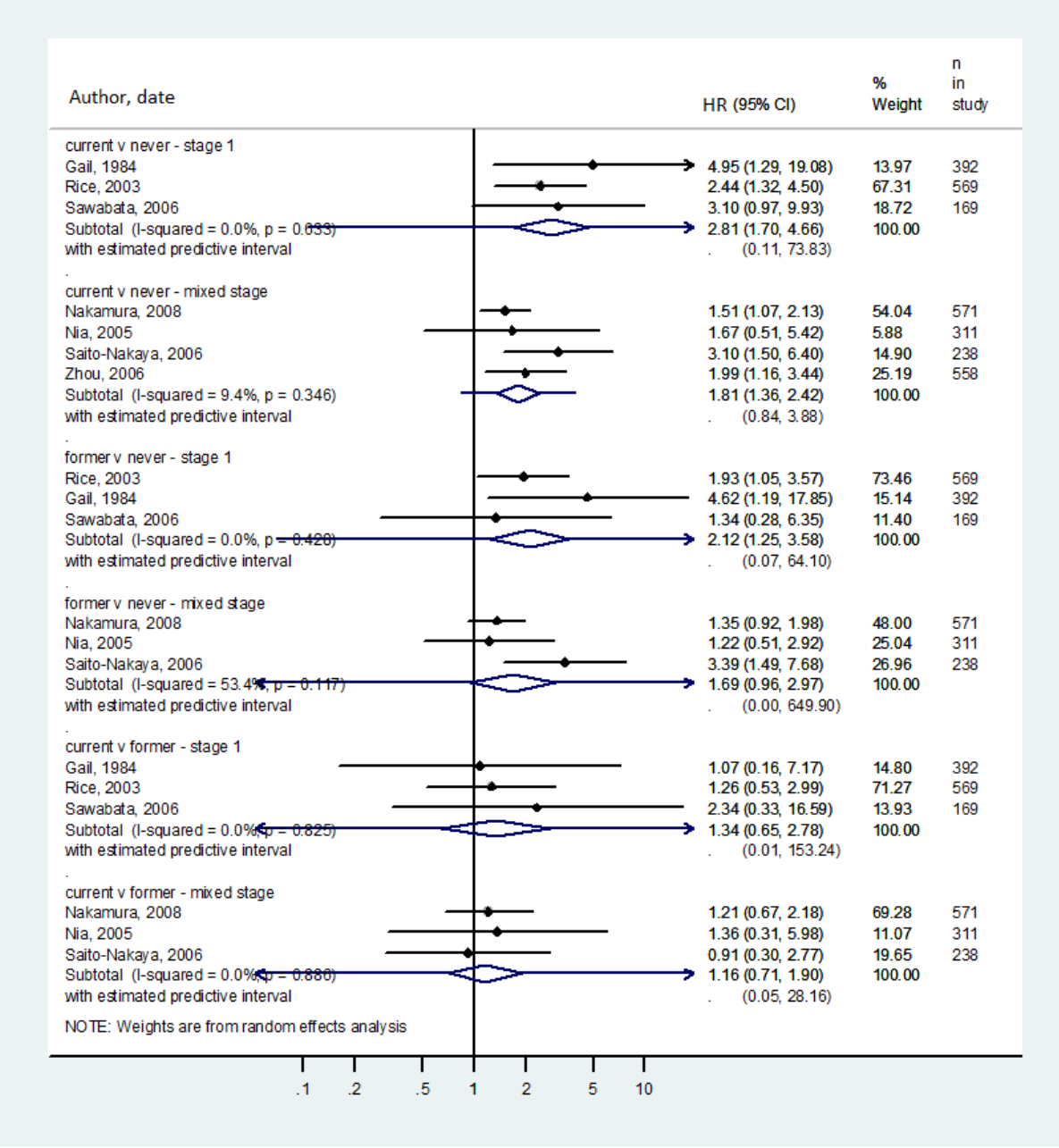


Figure C.8: Risk of all cause mortality and recency of smoking in surgical patients only: sub group analysis by stage (stage 1 v mixed stage)

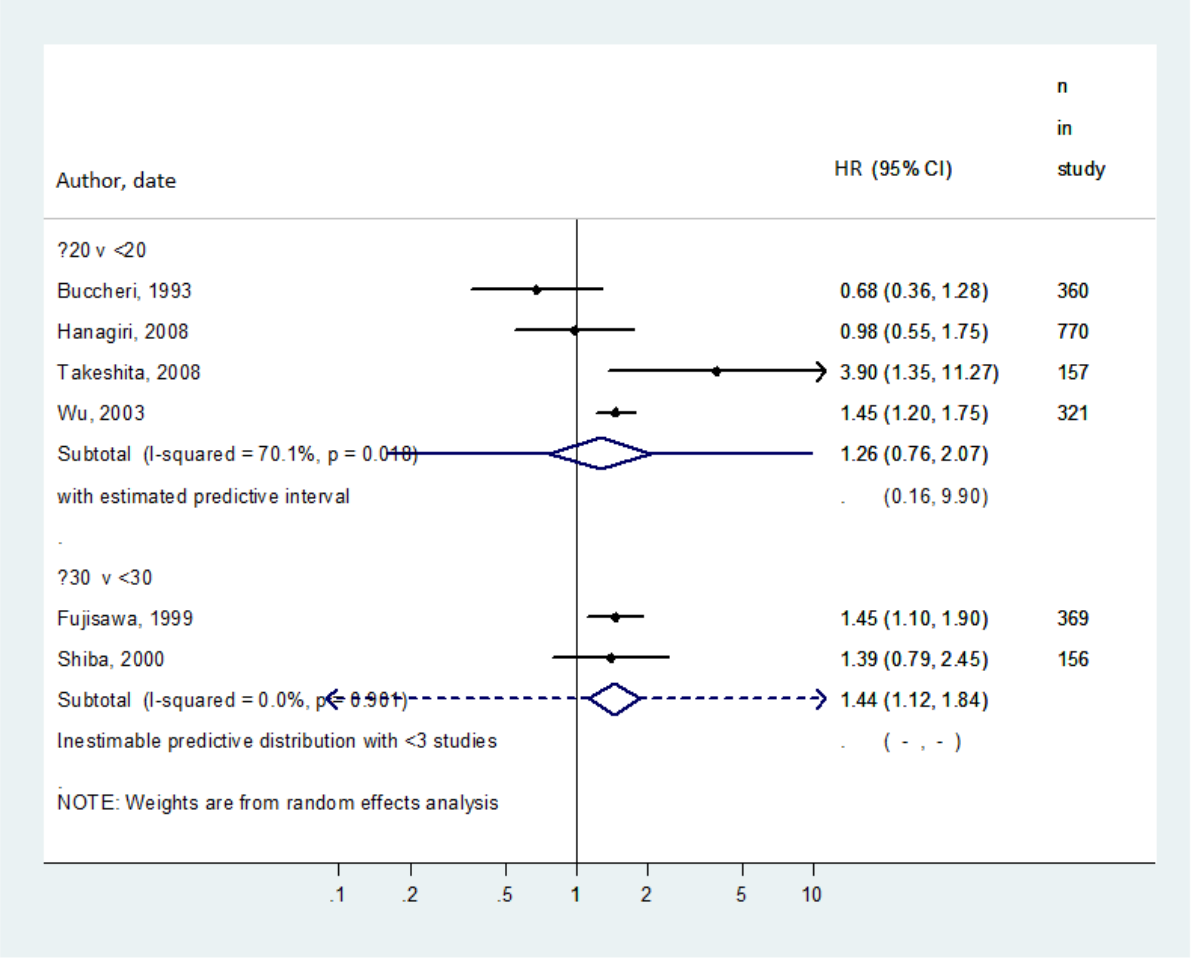


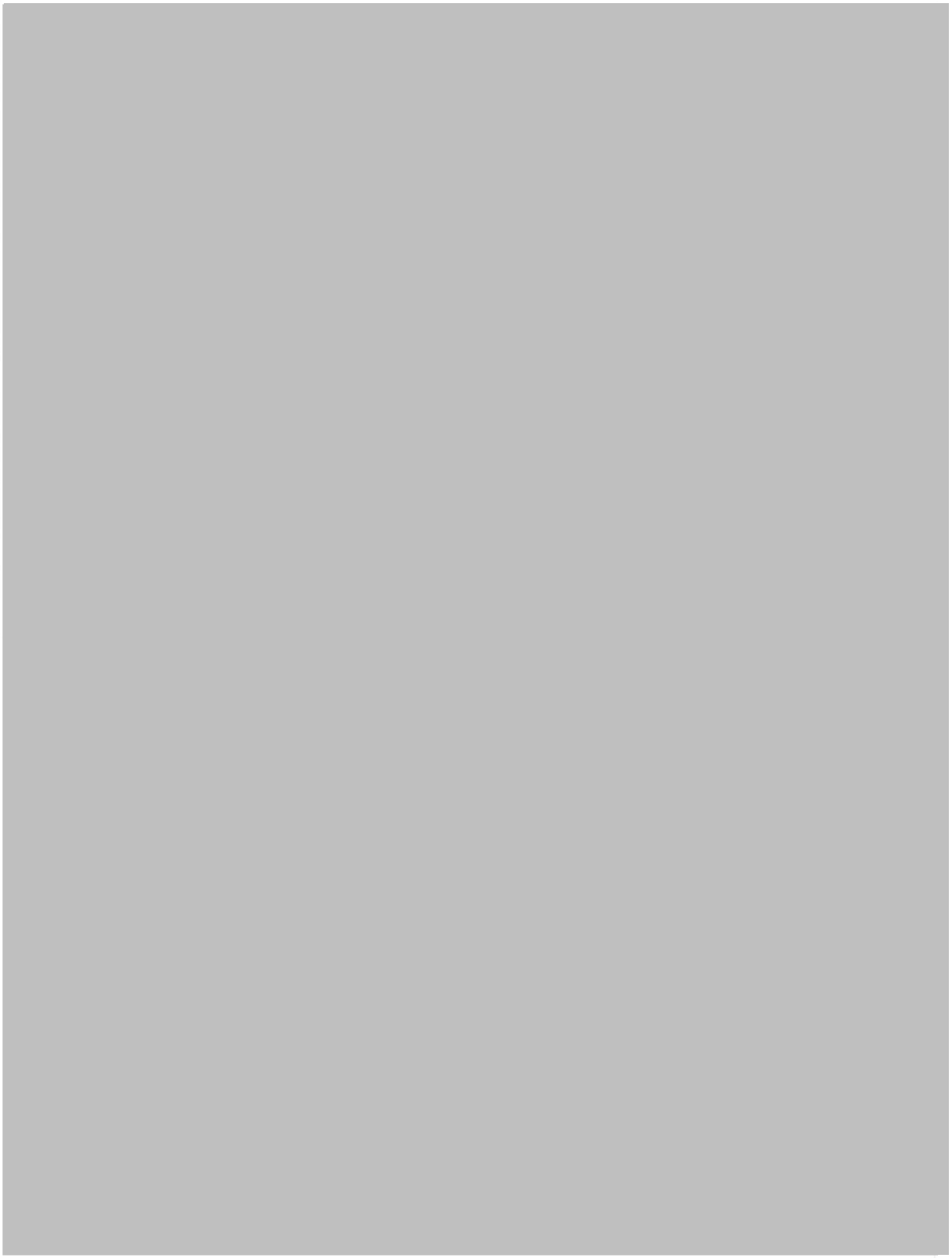
Figure C.9: Risk of all cause mortality in patients with heavier compared to lighter pack year history

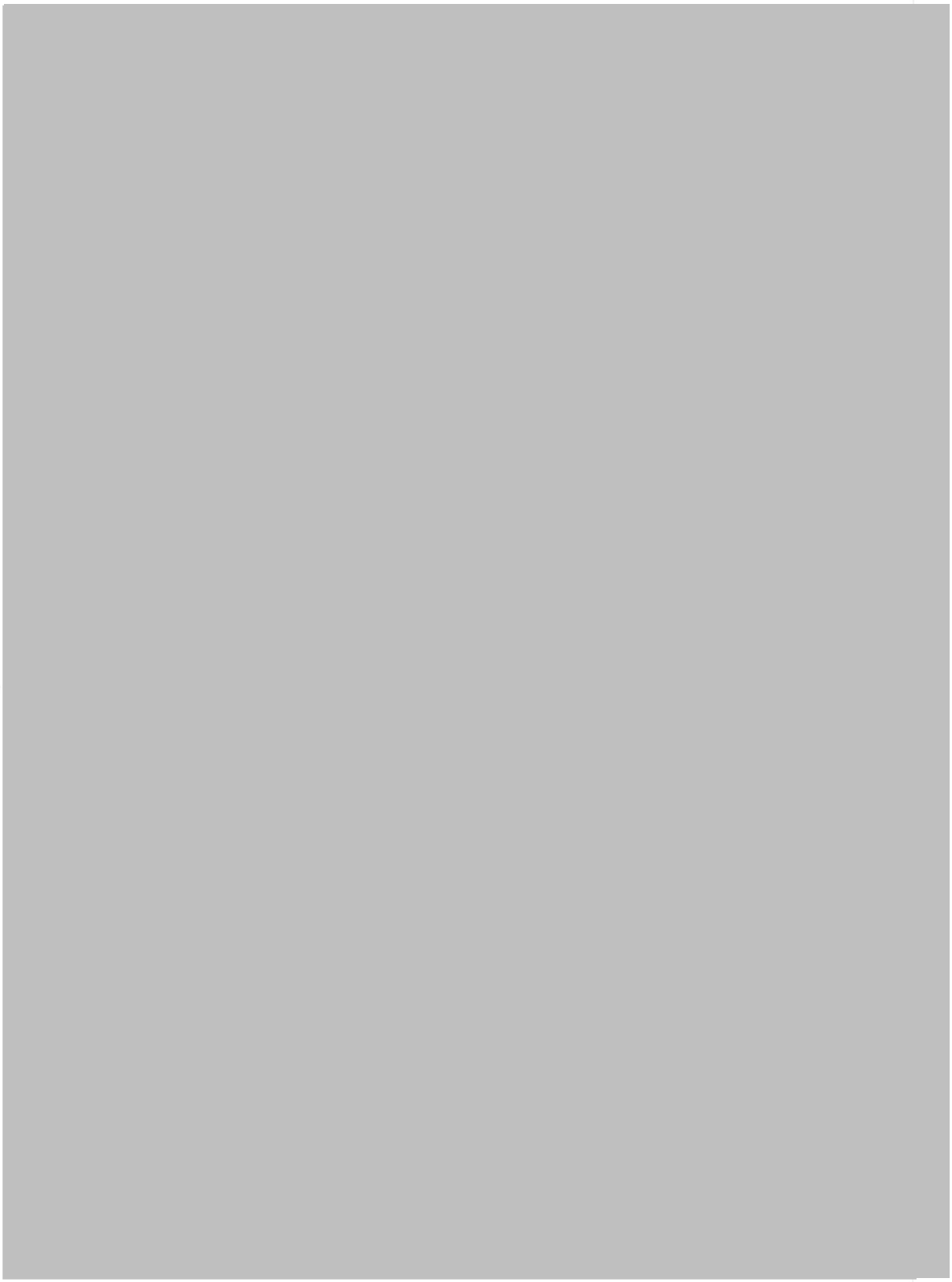
APPENDIX

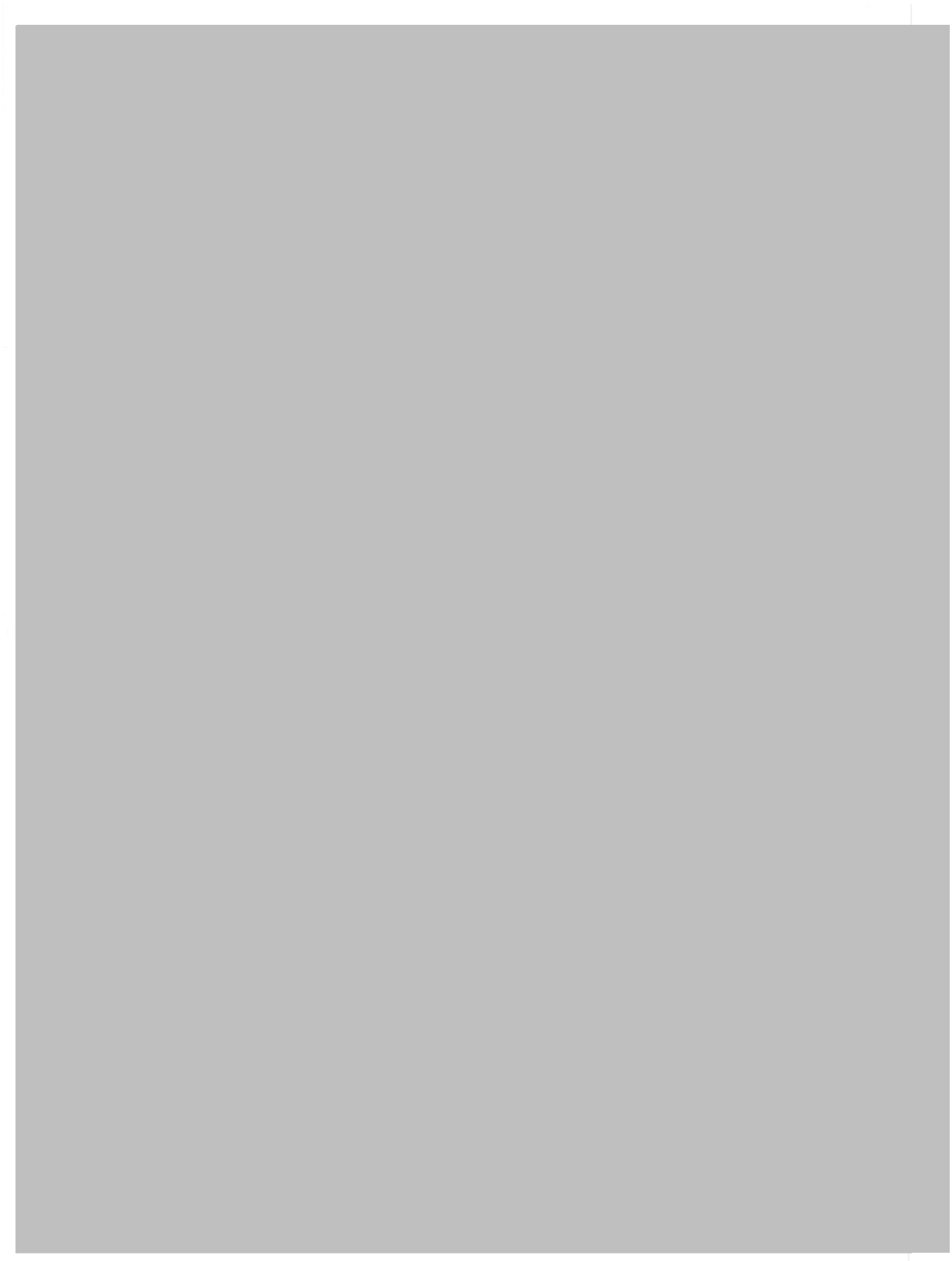
D

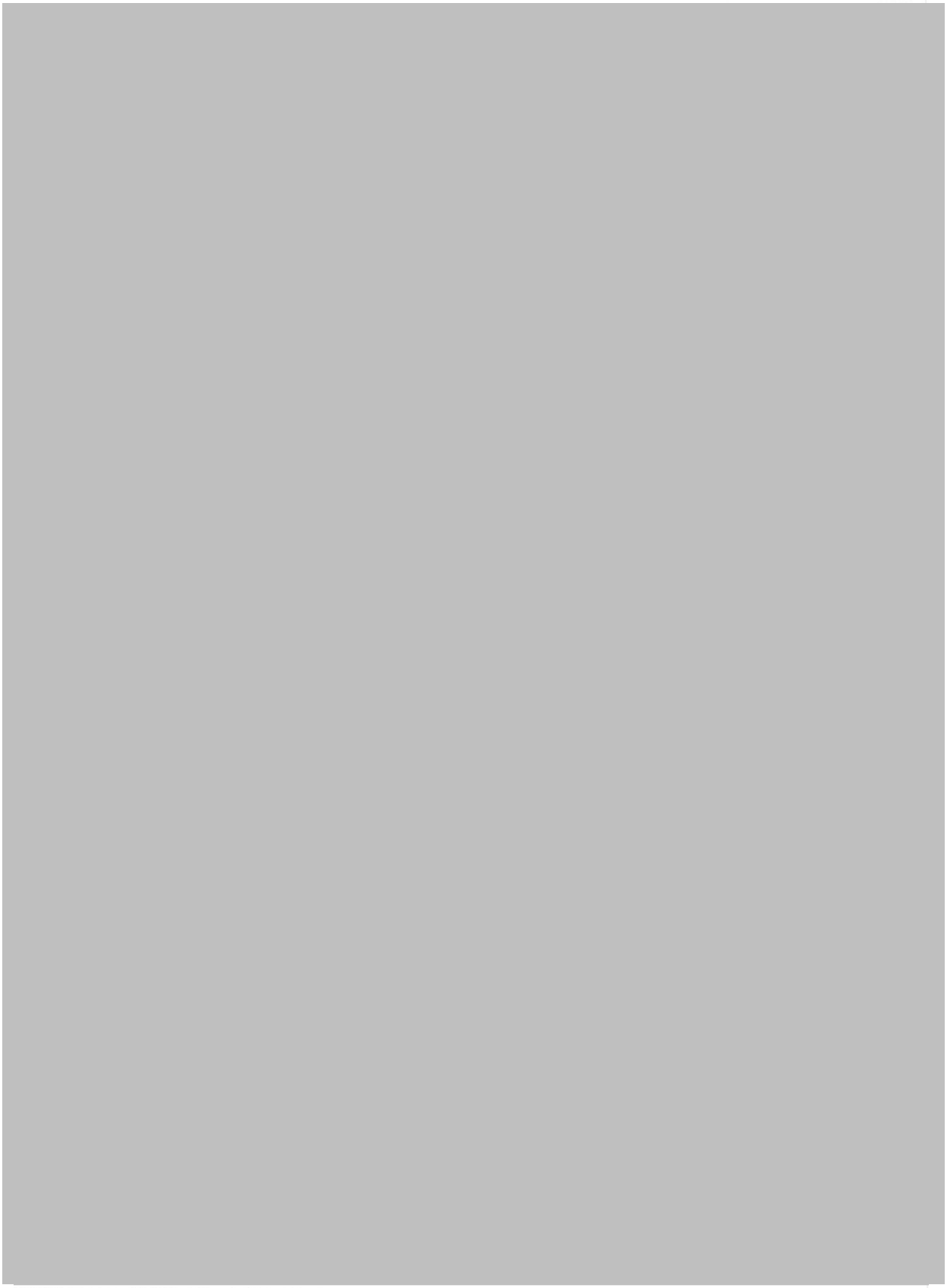
PUBLICATION OF THE POST DIAGNOSIS SYSTEMATIC REVIEW (CHAPTER 6)

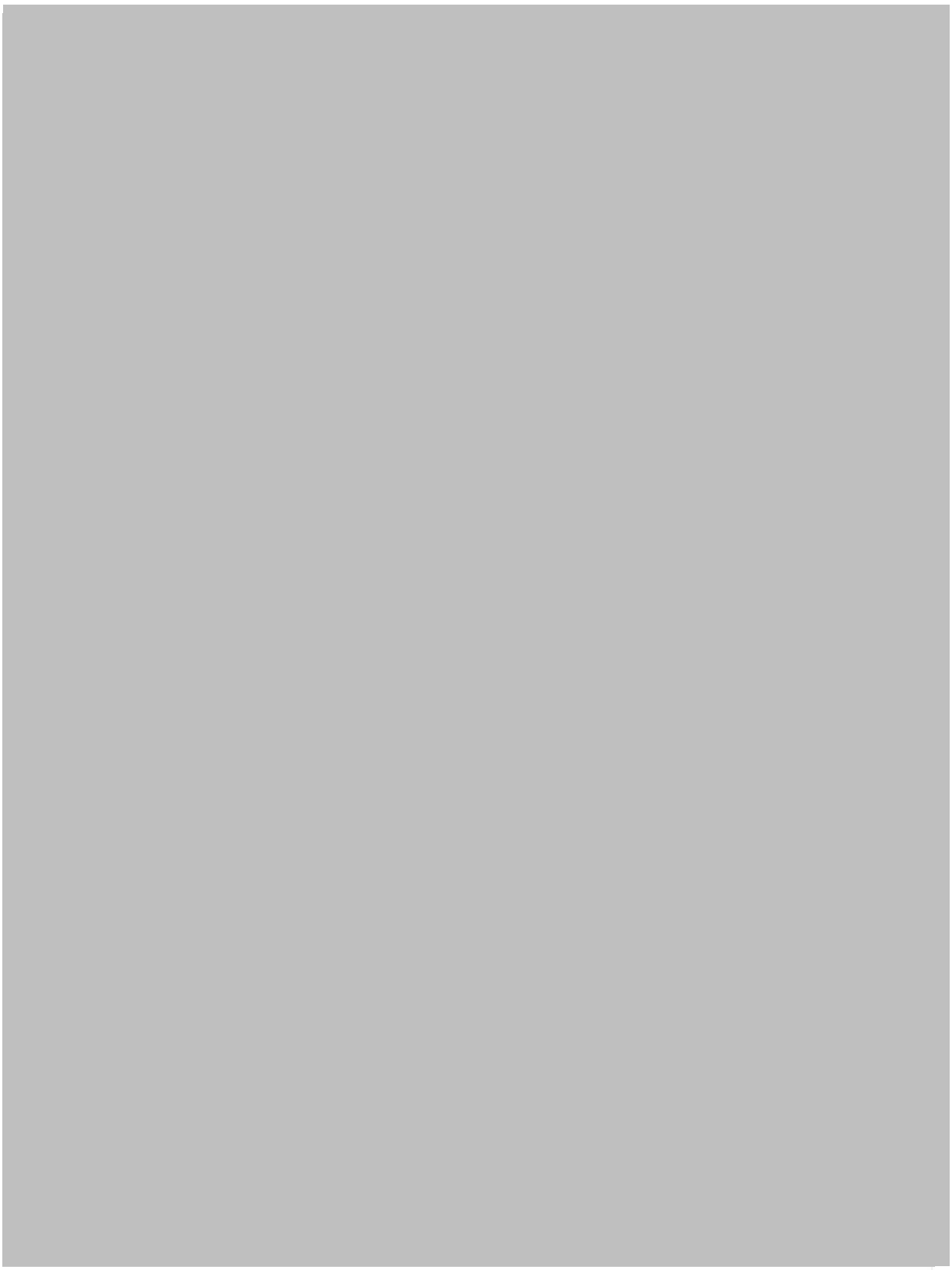
Figure D.1: BMJ Publication

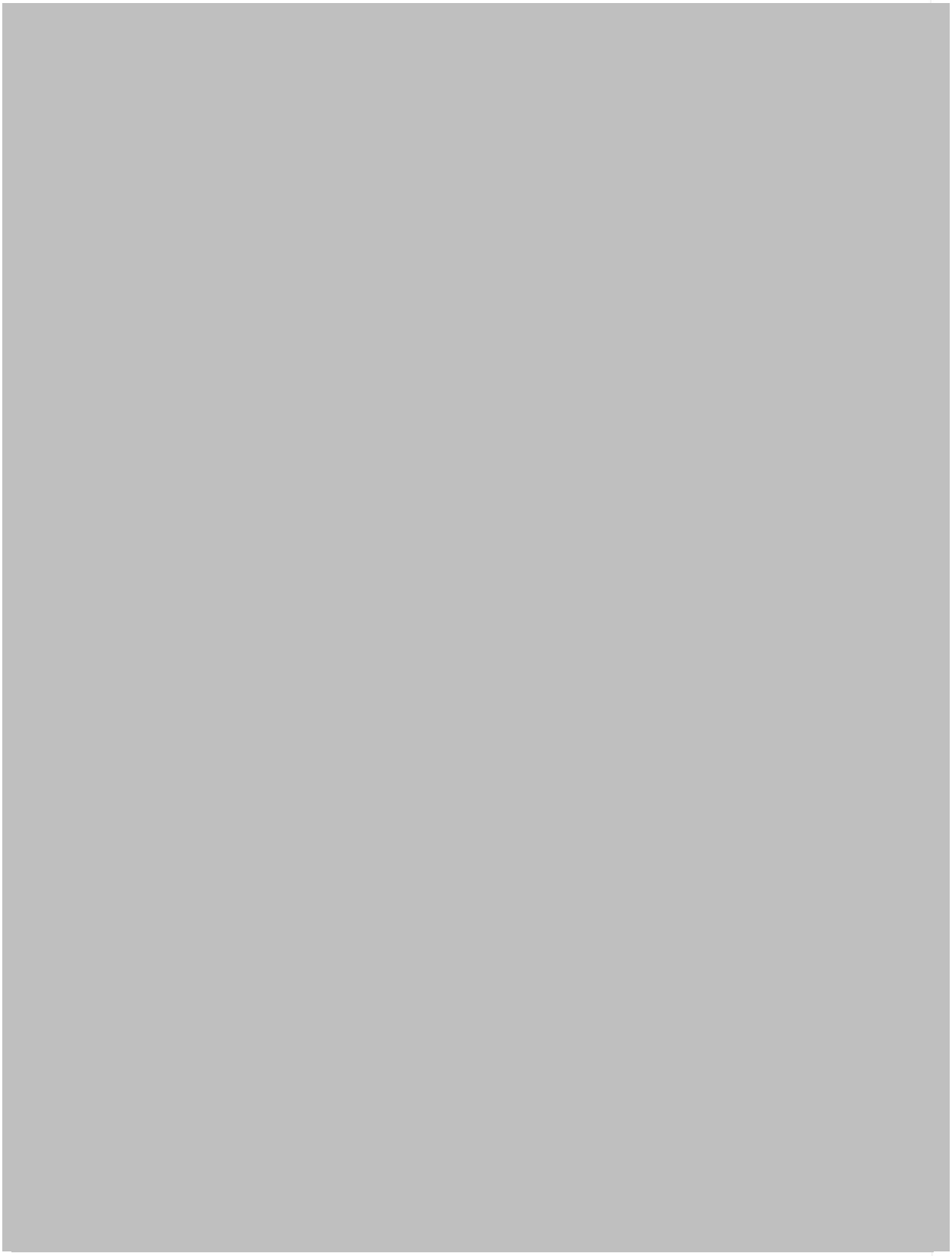


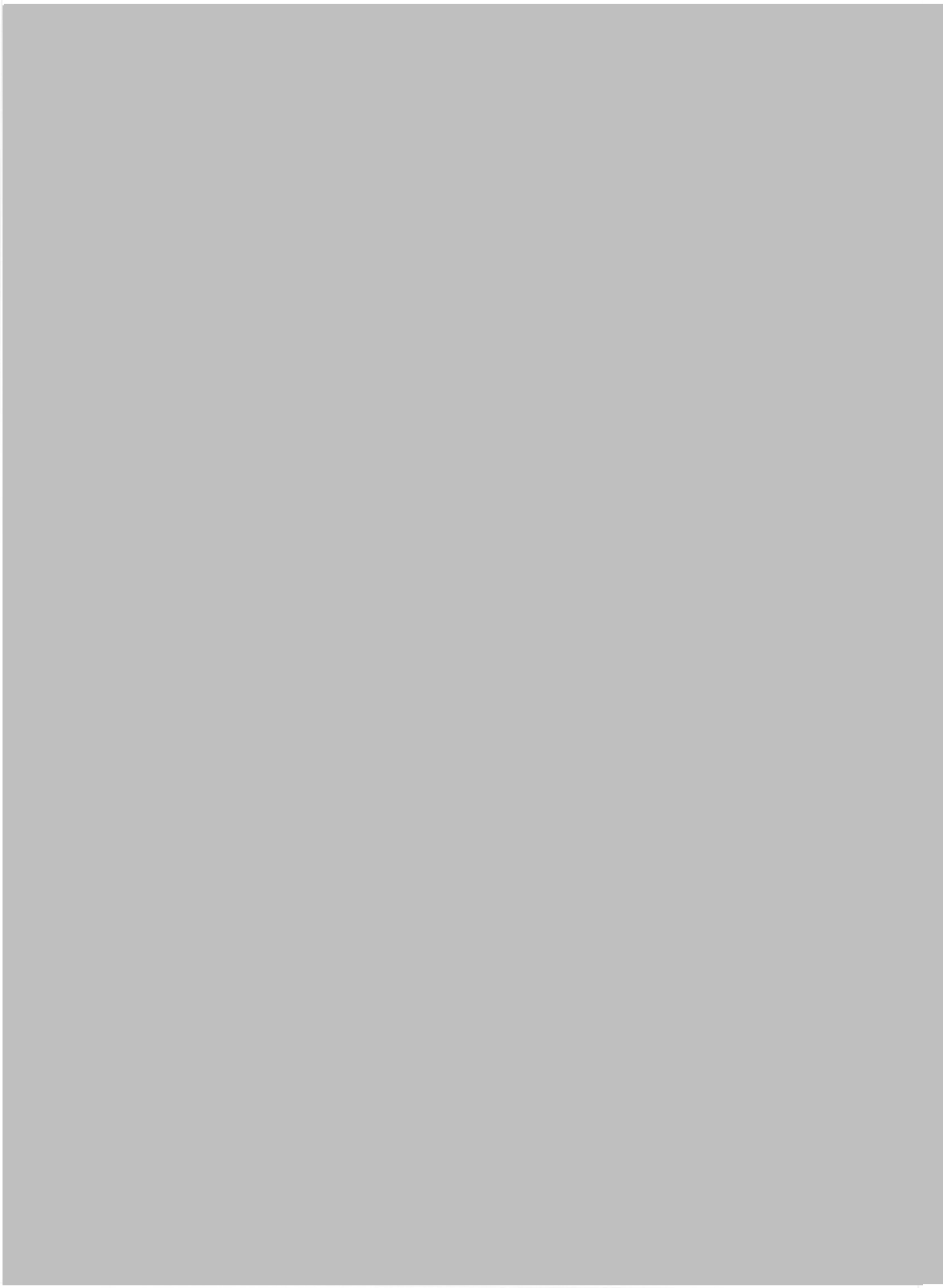












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