STUDIES OF THE AETIOLOGY OF OESOPHAGEAL ADENOCARCINOMA

by

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Summary

Oesophageal adenocarcinoma (OAC), a cancer with dismal prognosis, has been increasing rapidly in incidence over the last 30 years, nowhere more so than in the UK. Intriguingly, it is a disease predominantly among white males, but there is a paucity of data from England.

In performing a range of epidemiological studies, it has been confirmed that OAC has risen five-fold in the West Midlands, UK, five times more common among men, and predominantly a disease among Caucasians. A reduced incidence of OAC was identified among subjects with prostate cancer, suggesting a protective effect of anti-androgen therapy.

Examination of a general practice database revealed a negative association with aspirin, non-steroidal anti-inflammatories and statins with OAC, and a positive association with inhaled steroids, increasing number of drugs with a side effect of reducing the lower oesophageal sphincter, and drugs used for asthma/COPD.

Finally, a region wide case-control study, confirmed the positive association seen with increasing body mass index, waist circumference, smoking and reflux symptoms, with negative associations seen with a diet high in fruit and vegetables.

This work has identified potentially modifiable risk factors that may be employed to reduce the incidence of oesophageal adenocarcinoma, and better help stratify those most likely to benefit from endoscopic surveillance.

Dedication

I wish to dedicate this work to my wife and daughters, who have supported me through this work with such patience and caring.

I also wish to dedicate this work to the memory of my sister, and finally to my parents, for all the support throughout my life.

Abbreviations

OAC	Oesophageal adenocarcinoma
OSCC	Oesophageal squamous cell carcinoma
BO	Barrett's oesophagus
BSG	British Society of Gastroenterology
BMI	Body mass index (mass(kg)/height(m^2))
LOS	Lower oesophageal sphincter
NSAIDs	Non-steroidal anti-inflammatory drugs
GOJ	Gastro-oesophageal junction
TLOSR	Transient lower oesophageal sphincter relaxation
GOR	Gastro-oesophageal reflux
GORD	Gastro-oesophageal reflux disease
OR	Odds ratio
CI	Confidence Intervals
OTC	Over the counter
RO	Reflux oesophagitis
HGD	High grade dysplasia
LGD	Low grade dysplasia
SSBO	Short segment Barrett's oesophagus
LSBO	Long segment Barrett's oesophagus
H.pylori	*Helicobacter pylori*
*cag*A	cytotoxin-associated gene A
IDA	Iron deficiency anaemia
PPI	Proton pump inhibitors

AGA	American Gastroenterology Association
THIN	The Health Improvement Network
WMCIU	West Midlands Cancer Intelligence Unit
MOSES	Midlands OeSophagel adenocarcinoma Epidemiology Study
ONS	Office for National Statistics
ICD10	International Classification for Diseases 10th revision
ICD-O-2	International Classification of Diseases for Oncology second edition
IMD	Index of Multiple Deprivation
HES	Hospital Episode Statistics
DDW	Digestive Diseases Week (Gastroenterology conference, USA)

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Chapter 1

An Introduction to the aetiology of oesophageal adenocarcinoma

1 Introduction

Oesophageal adenocarcinoma (OAC) is a neoplastic growth arising from the glandular cells of the oesophageal mucosa. Siewart *et al* defined the classification of oesophagus and gastro-oesophageal junction cancers: type 1 lesions originate in the oesophagus and may infiltrate to the GOJ, type 2 lesions orginate at the cardia/GOJ, and type 3 lesions originate from the sub-cardia region and extend up to the GOJ (Siewert and Stein, 1998). The aetiology of each of these types of cancer is different (Siewert and Stein, 1998); this thesis is focusing on true oesophageal adenocarcinoma, including type 1 lesions. While OAC is not one of the more common malignancies such as lung and breast cancer, it has the fastest growing incidence for any cancer in the western world, and despite advances in management, both surgical and chemotherapeutic, prognosis remains poor with less than 40% surviving 12 months from diagnosis and a 5-year survival of 12-13% (Rachet et al., 2009).

Furthermore, the disease has a five-fold greater incidence among males, and is predominantly a disease among the Caucasian population, in contrast to oesophageal squamous cell carcinoma (OSCC). OSCC incidence rates have been static or more recently declining, affecting the black population more readily than the Caucasian.

While OSCC is associated with deprivation (Brown et al., 2001), the association of OAC with socio-economic status has been more mixed in the literature. In Sweden, OAC is associated with deprivation (Jansson et al.,

2005b), with a similar finding in the USA (Brown et al., 1994). However, in Scotland (Brewster et al., 2000) and Europe (Nagel et al., 2007), no association was identified between socioeconomic status and OAC.

Existing studies into the aetiology of oesophageal adenocarcinoma have examined potential associated risk factors including gastro-oesophageal reflux disease and its complications (Lagergren et al., 1999a, Yanke et al., 2006), namely Barrett's oesophagus (BO), the influence of increasing body mass index (BMI) and other body parameters including waist circumference (Anderson et al., 2007, Merry et al., 2007), increasing number of drugs taken that reduce lower oesophageal sphincter (LOS) resting pressures (Lagergren et al., 2000, Vaughan et al., 1998), and smoking (Anderson et al., 2007, Solaymani-Dodaran et al., 2004), and also those reported to be negatively associated including medication usage including aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), *Helicobacter pylori* infection (de Martel et al., 2005), and a diet high in fruit and vegetables (Brown et al., 1995). However all these studies have been performed outside mainland UK, where the observed rapidly rising incidence is greatest.

1.1 Gastro-oesophageal reflux disease symptoms

Symptoms of gastro-oesophageal reflux (GOR) are common, affecting over one-third of adults, complaining mainly of heartburn (75% of reflux patients(Dent, 1999)) and/or acid regurgitation (Jankowski et al., 2000, Spechler et al., 2001). Epidemiology has revealed that the prevalence of

GORD is greater in Europe and the USA than in Asia (Vakil et al., 2006). While heartburn and acid regurgitation are the most common presentations of GOR (Dent, 1999), about 50% of patients identified with reflux oesophagitis complain of other symptoms, including dyspepsia, dysphagia, chest pain, and extra-oesophageal symptoms such as cough, laryngitis and bronchospasm (Vakil et al., 2006), indicating how heterogenous a diagnosis of GORD may be. Furthermore, many individuals do not seek medical opinion for reflux symptoms despite being present for years, with 50% of over the counter (OTC) antacid users being found to have reflux oesophagitis at gastroscopy.

The Genval workshop (Dent, 1999), and Montreal definition and classification of GORD (Vaughan et al., 2005) sought to overcome the semantics and confusion surrounding reflux symptoms and their sequelae: “Heartburn is defined as a burning sensation in the retrosternal area (behind the breastbone)” and “regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx” (Dent, 1999), definitions derived due to misinterpretation by patients and requiring detailed history taking (Carlsson et al., 1998). The term gastro-oesophageal reflux disease (GORD) similarly has been determined by the Genval workshop “to include all individuals who are exposed to the risk of physical complications from gastro-oesophageal reflux, or who experience clinically significant impairment of health related well being (quality of life) due to reflux related symptoms, after adequate reassurance of the benign nature of their symptoms” (Dent, 1999). This is in keeping with the Montreal definition and classification of GORD,

indicating that if reflux symptoms were not troublesome, then the term GORD should not be used (Vakil et al., 2006).

1.2 Reflux symptoms and oesophageal adenocarcinoma

With chronic GORD potentially developing into Barrett's oesophagus (BO), a known pre-cursor to OAC, reflux symptoms, whilst common, are an identified risk factor for development of OAC. It has been estimated that gastro-oesophageal reflux accounts for 29.7% of OAC through analysis of population attributable risks (Engel et al., 2003). Furthermore, laryngopharyngeal reflux symptoms such as cough, hoarse voice and sore throat are associated with OAC to a greater degree than heartburn alone, suggesting that more proximal reflux/regurgitation may well present a greater aetiological factor (Reavis et al., 2004). Early work from Sweden revealed that those with severe and long duration of symptoms were at a vastly increased risk of developing OAC (Odds ratio (OR) 43.5, 95% confidence intervals (CI) 18.3-103.5), but not OSCC (Lagergren et al., 1999a). Further research in USA revealed not only the association of OAC with reflux symptoms (OR 3.61, 95% CI 2.49-5.25), but that the presence of a hiatus hernia without reflux symptoms was also strongly associated with OAC (OR 5.85, 95% CI 3.18-10.75). A combination of hiatus hernia with reflux symptoms was the strongest association with OAC of all (OR 8.11, 95% CI 4.75-13.87) (Wu et al., 2003). Subsequent population studies have been unable to reproduce the impressive OR of association seen in Sweden, but meta-analysis has provided further supportive evidence that

increasing frequency of reflux symptoms are clearly associated with OAC (weekly symptoms with 5-fold and daily symptoms 7-fold increased risk). However duration of symptoms in meta-analysis produced varying results (Rubenstein and Taylor, 2010).

1.3 Mechanisms of gastro-oesophageal reflux

The mechanism of reflux symptoms is the contact of oesophageal mucosa with gastric contents, namely acid and pepsin (Dent, 1999), with studies indicating the increased time that the oesophageal mucosa is exposed to acid is associated with frequency of reflux symptoms. The natural barriers to reflux of gastric contents into the oesophagus are the anatomy of the hiatus and the LOS.

1.3.1 Hiatus hernia

The hiatus is the opening within the diaphragm allowing the oesophagus and vagal nerve to pass from the thorax to the abdomen, being formed by the right crura. The oesophagus is tethered to the diaphragm by the phreno-oesophageal ligament inserting around the distal oesophagus at the level of, and approximately 1cm above the gastro-oesophageal junction (proximal margin of the gastric folds (GOJ)), preventing herniation of the stomach into the thoracic cavity (Kahrilas et al., 2008). The oesophagus will shorten by approximately 2cm during a swallow and returns to its original position

through the elasticity of the phreno-oesophageal ligament (Mittal, 1997), the mechanism derived from interaction of both longitudinal and circular muscle fibres of the oesophagus (Dodds et al., 1973). The phreno-oesophageal ligament looses elasticity with increasing age, an explanation for the increase prevalence of the sliding hiatus hernia (type 1) observed among older individuals (Kahrilas et al., 2008, Menon and Trudgill, 2011). There are no gender differences in the prevalence of hiatal hernias, but there is an increasing incidence with increasing BMI (Stene-Larsen et al., 1988), however the mechanism is unclear, whether through greater intra-abdominal pressure or increased laxity of the ligament and structures of the hiatus (Gordon et al., 2004).

The presence of a hiatus hernia is associated with GORD, present in 62% of subjects with reflux symptoms compared with only 14% of controls (Stal et al., 1999). Sliding hiatus hernias are far more common than the paraoesophageal types and are associated with GORD as there is disruption of the combined effect of the LOS and normal hiatus anatomy (Kahrilas et al., 2008, Kahrilas et al., 1999). The presence of a hiatus hernia, the ‘acid pocket’ normally found in the upper stomach even in the postprandial phase may be displaced above the diaphragm, promoting GORD (Kahrilas et al., 1999, Boeckxstaens, 2010, Fletcher et al., 2001). This increases the risk of GORD during transient LOS relaxations (see below) (Boeckxstaens, 2010). Additionally, with larger hiatus hernias, reduced oesophageal peristalsis occurs, leading to reduced

clearance of refluxate from the oesophagus (Fein et al., 1999, Patti et al., 1996, Kahrilas et al., 1999).

1.3.2 Lower oesophageal sphincter

The LOS is formed by the distal 4cm of circular muscle of the oesophagus, with the proximal 2cm above the hiatus in the thorax, and the distal 2cm below, in the abdomen. The LOS forms approximately 90% of the pressure at the gastro-oesophageal junction (GOJ) (Farre and Sifrim, 2008, Boeckxstaens, 2005, Boeckxstaens, 2010), amounting to 15-30mmHg in healthy subjects (Richter et al., 1987). Reflux may occur typically when the LOS falls below 5-6mmHg (with due consideration to a functioning hiatus) (Pandolfino et al., 2006). The LOS has intrinsic pressure, as illustrated by administration of tetradotoxin, blocking neurological influence, had little impact upon LOS pressure (Goyal and Rattan, 1976). The LOS relaxes for four to six seconds during each normal swallow, via the action (inhibitory) of nitric oxide on the myenteric plexus. Other neurotransmitters are involved in the parasympathetic (vagus) autonomic control of the sphincter tone including muscarinic, nicotinic and 5-HT receptors (Farre and Sifrim, 2008). The role of the sympathetic nervous system is less clear (DiMarino and Cohen, 1973, Farre and Sifrim, 2008). Longer relaxations of the LOS occur between 5-30 seconds that are related to distension of the upper stomach/gastric cardia rather than primary peristalsis and known as transient LOS relaxation (TLOSR) (Dent et al., 1980, Kessing et al., 2011). During these episodes

belching can occur, but pathologically, reflux of gastric contents may occur (Bredenoord et al., 2006, Grossi et al., 2001). Studies of oesophageal manometry over long periods have illustrated that 98% of reflux episodes in asymptomatic individuals are associated with TLOSRs whilst just 66% of reflux events in those with RO (Kahrilas and Gupta, 1990). This suggests that it must be the association of acid with TSLOR that is implemental in the pathophysiology of GORD and might be explained by factors that reduce the overall LOS by other mechanisms including diet, smoking, medication and the function of the hiatus (Kessing et al., 2011).

1.3.2.1 Factors affecting the lower oesophageal sphincter

GORD is more prevalent with increasing age, a finding noted with greater laxity of the phreno-oesophageal ligament leading to hiatus herniation (Menon and Trudgill, 2011, Kahrilas et al., 2008), but also increasing age was found to be significantly associated with shortening of the LOS, reduction of LOS pressure and increased oesophageal dysmotility (Lee et al., 2007a).

1.3.2.2 Diet and gastro-oesophageal reflux

Whilst increasing BMI may be independent of diet and exercise as risk factor for reflux symptoms, diet is implicated in the aetiology of symptomatic reflux (Nandurkar et al., 2004). Smaller meals are less likely to induce reflux symptoms (Yamada), but this is independent of calorie density, with no

association seen between increasing calorie ingestion and reduction in LOS pressures (Pehl et al., 2001). Certain foods such as chocolate, coffee, tea, tomatoes, citrus fruit and onions precipitate reflux, mediated through relaxation of the LOS (Yamada). Alcohol precipitates dysmotility within the oesophagus (Grande et al., 1996), with reduced LOS pressures and greater incidence of reflux symptoms seen among those with chronically higher consumption (Ferdinandis et al., 2006).

GORD and RO are seen more commonly among those with diets high in fat, specifically saturated fat (El-Serag et al., 2005), and reduction of fat intake is often recommended to patients (Yamada). Moreover, saturated fat, and cholesterol, increases the sensation of reflux symptoms occurring (Shapiro et al., 2007). Three hours post-high fat ingestion the LOS pressures remains unchanged (Penagini et al., 1998), and while direct introduction of fat directly to the duodenum decreases LOS pressure this is not to a resting pressure associated with reflux (Holloway et al.). Neither does fat increase the frequency of TLOSRs, but it is noted to increase the likelihood of reflux occurring during TLOSR (Holloway et al., 1997)

1.3.2.3 Smoking and gastro-oesophageal reflux

Smoking is associated with GORD through multiple mechanisms. The acute effect of smoking has been difficult to establish due to the respiratory efforts

required to smoke altering the analytical methods. However, the longer-term LOS pressures are significantly lower among smokers with reflux symptoms than smokers without reflux symptoms and also lower than non-smokers (7mmHg vs 9mmHg vs 14mmHg) (Kahrilas and Gupta, 1990). Smokers have more TLOSRs, however these TLOSRs were not associated with reflux, where as all the TLOSRs among non-smokers produced reflux. Despite this, there were more reflux episodes noted among smokers, which were associated with deep inspiration or coughing (Kahrilas and Gupta, 1990). Furthermore, reduced salivation occurs among smokers, reducing the ability to neutralize and clear the acid refluxate from the oesophagus (Pandolfino and Kahrilas, 2000). The pharmacological mechanism is via the action of nicotine, as transdermal patches produce similar results to smoking (Pandolfino and Kahrilas, 2000).

1.3.2.4 Drugs affecting the lower oesophageal sphincter

The main inhibitory control of the intrinsic LOS pressure is mediated via the actions of nitric oxide (Farre and Sifrim, 2008). Nitroglycerine reduces LOS pressure among patients with achalasia, improving oesophageal emptying (Wong et al., 1987). Isosorbide dinitrate, a longer-term nitric oxide providing drug, taken over 3 days by healthy volunteers, does not alter oesophageal motility, but does significantly reduce LOS as compared with placebo (Stacher et al., 1997).

Other neurotransmitters acting upon the LOS include those acting upon the

muscarinic and nicotinic receptors (Farre and Sifrim, 2008). Anti-cholinergic drugs (eg propantheline bromide, pirenzepine and atropine) reduce LOS pressure significantly (Hongo et al., 1984b, Fang et al., 1999, Aggestrup and Jensen, 1991). In comparing anticholinergics that act both peripherally and centrally (atropine) and only peripherally (methscopolamine bromide), it is clear that both induce LOS relaxation, but atropine, through its centrally acting properties, reduces the frequency of reflux symptoms through reduced frequency of TLOSRs. However, anticholinergics reduce salivation and oesophageal peristalsis amplitude, inhibiting oesophageal clearance of refluxate, as well as reducing LOS pressure, and are thus implicated in GORD (Fang et al.).

While early studies did suggest that diazepam, a benzodiazepine, may actually increase LOS pressure (Weihrauch et al., 1979), it is now widely accepted that benzodiazepines reduce pressure at the LOS (Yamada), with a dose-response effect (Rushnak and Leevy, 1980). Caution must therefore be used when commenting on the laxity of the LOS during gastroscopy under benzodiazepine induced sedation (Rushnak and Leevy).

Beta-agonists reduce LOS pressures through their action upon smooth muscle, but the dose required to induce reflux symptoms is likely to be higher than standard therapeutic inhaled doses (Ayres and Miles, 1996, Berquist et al., 1984). While terbutaline reduces LOS pressure, it also improves

oesophageal clearance, a further explanation that, when taken in isolation, β - agonists may affect LOS pressures without precipitating reflux (Wong et al., 1987). Theophyllines reduce LOS pressure (Ayres and Miles, 1996), by up to 25% of resting levels (Stein et al., 1980), and to a greater degree than some beta-blockers (Wong et al., 1987, Ruzkowski et al., 1992). Moreover, theophyllines have been identified to cause reflux symptoms (Ayres and Miles), with the LOS pressure reduction occurring at time of detectable blood levels of theophylline (Stein et al., 1980).

With intracellular influx of calcium in myocytes leading to contraction, inhibition through use of calcium channel blockers induces muscle relaxation (Lake and Wong, 2006). Calcium channel blockers not only reduces LOS pressure (Hongo et al., 1984b), but does so in a dose response manner (Hongo et al., 1984a). Calcium channel blockers also reduce the magnitude of contractility within the oesophagus (Hongo et al., 1984a, Konrad-Dalhoff et al., 1991).

1.4 Complications of gastro-oesophageal reflux

Predicting who will develop complications from reflux symptoms is challenging with symptoms not always being reliable (Dent, 1999). It has been identified that reduced LOS pressure, poor oesophageal acid clearance and gastric acid production are independent risk factors (Cadiot et al., 1997). Half of those taking OTC antacids developed reflux oesophagitis (RO) and conversely frequent heartburn only produces mucosal breaks in less than 50% (Dent,

1999). While frequent reflux symptoms often lead to RO, and duration of reflux symptoms has been shown to result in RO in 50%, this is not consistent, with some larger studies showing duration of symptoms failing to correlate with RO, but doing so with BO (Lieberman et al., 1997, Conio et al., 2002).

RO underwent formal definition as the presence of mucosal breaks at or above the gastro-oesophageal junction due to reflux of gastric acid, forming the Los Angeles (LA) criteria (Armstrong et al., 1996), which correlate well with symptoms, pH levels, response to treatment and sustainability of remission (Lundell et al., 1999).

Nocturnal reflux symptoms, while among the less common features of GORD (Mann et al., 1995), are a marker of severity of RO, occurring more frequently in LA grade C and D (Robertson et al., 1987). Comparison of day and night time symptoms revealed that nocturnal, especially experiencing both day and nocturnal reflux, was significantly associated with a greater degree of RO (Demeester et al., 1976). This is due to the supine position and the increased exposure to acid within the distal oesophagus due to poor or slow clearance (Demeester et al., 1976, Orr et al., 1994).

In addition to frequency of reflux symptoms including nocturnal episodes, Kulig *et al* described demographic and lifestyle risk factors for developing RO among a cohort of subjects with reflux symptoms (Kulig et al., 2004). Increasing age and BMI, male gender, family history of GORD and smoking

were associated with GORD, in addition to severity of symptoms (as already discussed). It is of note that while reflux symptoms are equally present among men and women (Mohammed et al., 2005), the complications of GORD are more common among men.

Complications of GORD may include reflux or peptic strictures (Yamada, 1999) and BO, the latter a precursor of OAC (Orr et al., 1994). Strictures may form following deep ulceration, leading to fibrin formation, and scarring, and may be accompanied by symptoms of dysphagia.

1.4.1 Barrett's Oesophagus

First described by Norman Barrett in the 1950's, Barrett's oesophagus (BO) is the sequela of chronic gastro-oesophageal reflux with metaplasia of the stratified squamous epithelium of the oesophagus to columnar mucosa. Approximately 10-11% of individuals with chronic reflux symptoms develop BO (Kulig et al., 2004, Attwood et al., 2008), rising to 13% among higher risk individuals (Caucasian men over the age of fifty) (Westhoff et al., 2005). The length of the Barrett's segment is defined by the Prague criteria, with the 'C' length representing the maximum distance of circumferential columnar lined mucosa from the GOJ and the 'M' length the maximum overall length of BO, including tongues (Sharma et al., 2006). Short segment Barrett's oesophagus (SSBO) (circumferential length <3cm) (Sharma et al., 1998) is twice as more frequent as long segment Barrett' oesophagus (LSBO) (C >3cm) (Westhoff et al., 2005). Increasing reflux symptom duration and frequency are significantly

associated with the development of BO (Conio et al., 2002), with evidence of greater oesophageal acid exposure (determined by 24 hour pH monitoring) seen among patients with BO than those with just reflux symptoms or RO (Buttar and Falk, 2001). As with the risk of developing RO, nocturnal symptoms are a risk factor for the development of BO (Orr et al., 1988). Furthermore, reflux of both gastric and bile acids act in combination, possibly synergistically, to drive the metaplasia-dysplasia sequence (Jankowski and Anderson, 2004, Wiseman and Ang, 2011).

It is possibly unsurprising that the presence of a hiatus hernia is a risk factor for BO (Kulig et al., 2004, Gillessen et al., 2010, Conio et al., 2002) given its implication in the development of GORD. Smoking too is associated with BO, but more notably a combination of smoking and reflux symptom has a synergistic effect upon the aetiology of BO (Smith et al., 2005, Cook et al., 2012). Moreover, reflux symptoms and increased BMI are shown to act similarly in increasing the risk of developing BO (Smith et al., 2005). As with OAC, BO is more common among Caucasian men, increasing age, and appears to also be associated with affluence (Ford et al., 2005, Wong and Fitzgerald, 2005, Westhoff et al., 2005).

The incidence of BO is increasing rapidly, at a greater rate that the number of gastroscopies performed in Northern Ireland (Coleman et al., 2011), forming a plausible explanation of the increasing incidence of OAC. However, in the US where primary care physician practice includes screening patients with GORD

for BO (Chey et al., 2005), this may in part be due to increased use of gastroscopy as a diagnostic tool (Conio et al., 2001). Furthermore some of the increasing incidence of BO is seen among asymptomatic individuals (Conio et al., 2001, Shaheen, 2005), with 90% of those developing OAC never having had a prior diagnosis of BO (Ouatu-Lascar et al., 1999). Asymptomatic BO may be a result of the columnar lined mucosa being less sensitive to lower pH than normal squamous lined oesophagus (Byrne et al., 2003).

BO is recognised as a pre-malignant condition that, through development from metaplasia, low-grade and high-grade dysplasia (HGD), may progress to adenocarcinoma. It is postulated that all OAC arises from BO (Theisen et al., 2002), with those cases of adenocarcinoma without obvious columnar lined oesophagus present likely to have tumour overgrowth of any precursor Barrett's mucosa (Hamilton et al., 1988). Overall rates of progression have been estimated to vary between 0.2-2% per annum (Murray et al., 2003). Patients with BO are 30-125 fold more likely to develop OAC than the general population (Solaymani-Dodaran et al., 2004). The identification of LGD at index gastroscopy is associated with neoplastic progression (Dulai et al., 2005, de Jonge et al., 2010, Oberg et al., 2005, Hvid-Jensen et al., 2011). HGD more so, progressing to OAC in up to 50% of cases within 5 years (Altorki et al., 1991, DeMeester, 2002), with OAC often being present at first diagnosis of BO with HGD (Ell et al., 2000). The greater the length of Barrett's mucosa, the greater the risk of developing HGD and adenocarcinoma (Slehria and Sharma, 2003).

While certain parameters are understood to increase the risk of progression from BO to OAC, such as increasing length of Barrett's segment and presence of dysplasia, current BSG guidance (Watson, 2005) does not incorporate any other criteria or risk factors other than LGD. Studies of the risk factors associated with the progression of BO to OAC are often limited by the inherent selection bias in studying those undergoing endoscopic surveillance rather than an unselected cohort (El-Serag et al., 2004, Nguyen et al., 2009).

A diagnosis of BO is not only associated with development of OAC, but also has significant deleterious impact upon quality of life, and increased anxiety and depression. Much of this surrounds the understanding of the disease and of the risks of developing cancer, which may be alleviated with patient education and surveillance directed at those patients with BO at greater risk of progression to OAC (Cooper et al., 2009).

1.5 Genetic influences upon reflux and its sequelae

Reflux symptoms are observed to be common among families (Trudgill et al., 1999) but teasing the environmental from genetic factors can be challenging. Several concordance studies among monozygotic and dizygotic twins have revealed that approximately 31-43% of reflux symptoms have some form of heritability (Mohammed et al., 2003, Cameron et al., 2002). While a few published reports of strong family histories of BO and OAC are present in the literature (Drovdlic et al., 2003, Prior and Whorwell, 1986, Gelfand, 1983),

they are without consistent inherited genetic cause identified (Fitzgerald, 2005). More evidence surrounds the acquired genetic and epigenetic phenomena that may influence the metaplasia-dysplasia-adenocarcinoma sequence, with a wealth of studies examining the influence of various factors such as chromosomal imbalances (Walch et al., 2000, Wu et al., 1998), disordered proliferation (e.g. cyclin D1, TGFα, telomerase), loss of apoptosis (e.g. p53, COX-2, Bcl), loss of response to anti-growth signals (e.g. p16, APC) and invasive potential (e.g. VEGF/VEGF-R, effects upon E-cadherins and β-catenins) (Feith et al., 2004, Schneider et al., 2000, Younes et al., 1997, Fitzgerald, 2005, Wiseman and Ang, 2011). None of these individually identify those at greater risk of developing OAC, and currently have limited clinical value; the use as a reliable biomarker to identify those at greatest risk of neoplastic progression remains elusive (Wiseman and Ang, 2011, Fitzgerald, 2005).

1.6 *Helicobacter pylori*

This common pathogenic micro-organism is found worldwide, leading to a number of gastro-duodenal diseases, including gastro-duodenal ulceration and gastric cancer (Go, 2002). Importantly, it is negatively associated with the development of OAC.

1.6.1 Helicobacter pylori and atrophic gastritis

H.pylori is a common aetiological factor for chronic gastritis (Sipponen et al., 1996b). *H.pylori* was the identified cause in 26-48% of identified atrophic gastritis cases (Annibale et al., 1997, Kuwahara et al., 2000), inferring a ten-fold increased risk (Kuwahara et al., 2000). Even if *H.pylori* is eradicated, and gastric antral mucosa heals (Sipponen et al., 1996b), atrophic gastritis can persist in the corpus of the stomach (Sipponen et al., 1996b, Kokkola et al., 2003a).

Helicobacter pylori species show genetic differences, with a 40kb genomic region known as the *cag* pathogenicity island coding for 41 genes related to inflammation and virulence. The *cag*A (cytotoxin-associated gene A) gene forms a cylindrical protein that is 'injected' into host cells where it undergoes tyrosine phosphorylation, and is implicated in increasing inflammation compared to *cag*A negative *H.pylori* (Go, 2002). *cag*A positive *H.pylori* produces greater inflammation with gastritis, leading to a greater degree of chronic atrophic gastritis (Maaroos et al., 1999, Oksanen et al., 2000, Sande et al., 2001).

Atrophic gastritis (notably of the corpus) results in hypochlorhydria (Sipponen et al., 1996b, Derakhshan et al., 2006). Increased atrophy is associated with a reduced maximal acid output (Derakhshan et al., 2006, Sipponen et al., 1996a), specifically ascorbic rather than uric acid (Capurso et al., 2003).

Furthermore, *cag*A positive *H.pylori* strains of infection were associated with gastric atrophy (Beales et al., 1996).

1.6.2 Implications of gastric atrophy: gastro-oesophageal reflux

It has been proposed that *H.pylori cag*A positive infection reduces the incidence of gastro-oesophageal reflux symptoms and subsequent potential complications, including BO and OAC, by the development of atrophic gastritis and subsequent hypochlorhydria (Richter et al., 1998). There are suggestions that this hypothesis is not supported in the literature (Pace and Bianchi Porro, 1998, Peters et al., 1999), but few studies have examined the impact of *cag*A status with sufficient power (Vicari et al., 1998). The incidence of *H.pylori* was much lower in subjects with GORD and BO than control subjects in one study with a large enough sample size to derive a significant result (Werdmuller and Loffeld, 1997). Furthermore, these findings were reproduced, albeit not to significance, but accompanied by evidence that *cag*A positive *H.pylori* induced greater gastric mucosal damage, supporting the hypothesis of atrophic gastritis induced hypochlorhydria, reducing reflux (Vicari et al., 1998).

A case report elegantly demonstrates that healing of known *H.pylori* induced atrophic corpus gastritis subsequently developed into RO and 5 years later BO developed (Kokkola et al., 2003b). This observation is not in isolation; an observational study revealed those with SSBO and LSBO were less likely to have *cag*A positive *H.pylori* infection than control or RO subjects (Vaezi et al., 2000).

1.6.3 Implications of gastric atrophy: iron absorption and iron deficiency

Population studies have revealed an increase prevalence of iron deficiency anaemia (IDA) associated with *H.pylori* infection (Berg et al., 2001, Milman et al., 1998, Parkinson et al., 2000). The risk of IDA attributable to *H.pylori infection* has been found to be almost 3-fold that of non-infected (Choe et al., 2001), a 40% increase in the USA (Cardenas et al., 2006), with upper gastro-intestinal blood loss excluded from the aetiology (Hacihanefioglu et al., 2004, Annibale et al., 1999). Eradication of *H.pylori* results in reversal of IDA without the need for iron supplementation (Hacihanefioglu et al., 2004, Annibale et al., 1999, Kurekci et al., 2005). Furthermore, formal iron absorption testing revealed significantly poorer iron absorption among those infected than those who were not colonised with *H.pylori*, and that the iron absorption tests reverted to normal once successful eradication had occurred (Ciacci et al., 2004).

While some strains of *H.pylori* can compete for available gastric iron (Waidner et al., 2002, Annibale et al., 2000), the presence of atrophic gastritis is the more likely aetiology (Annibale et al., 2000). Examination of the presence of *H.pylori* induced chronic gastritis and IDA has revealed close association, suggesting this mechanism of action (Annibale et al., 1999, Nahon et al., 2003). Furthermore, intra-gastric pH is significantly higher among subjects with *H.pylori* induced gastritis (Annibale et al., 2003, Capurso et al., 2001, Baysoy et al., 2004), notably with reduced ascorbic acid (Baysoy et al., 2004, Annibale et al., 2003). This finding was most marked among subjects with

*cag*A positive *H.pylori* infection (Baysoy et al., 2004). Gastric acid is important in the reduction of dietary iron predominantly in the ferrous (Fe^{2+}) form to the absorbable ferric (Fe^{3+}) form.

1.6.4 Epidemiology of Helicobacter pylori

Helicobacter pylori (*H.pylori*) is transmitted person-to-person either by oral-oral or faecal-oral transmission, with approximately 50% of children infected worldwide (Go, 2002). Transmission occurs particularly among siblings of a similar age (Goodman and Correa, 2000), and is seen more commonly with increased number of siblings per household (Ford et al., 2007). Indeed household crowding, including the sharing of a bed with a parent appears to have strong association (Rothenbacher et al., 2002, McCallion et al., 1996), leading to observations that *H.pylori* infection appears to cluster in families and is associated with lower socio-economic status (Dominici et al., 1999, Murray et al., 1997, Moayyedi et al., 2002, Webb et al., 1994). It is observed that the prevalence of *H.pylori* increases with age (Murray et al., 1997, Macenlle Garcia et al., 2006, Everhart et al., 2000). Whilst prevalence increases with age, it is close person-to-person contact in childhood that influences infection into adulthood and beyond (Webb et al., 1994, Fall et al., 1997). In Northern Ireland overall prevalence was approximately 50%, 23.4% among young teenagers, rising to 72.7% in those in their early sixties (Murray et al., 1997).

H.pylori infection is associated with black ethnicity (compared to Caucasians) (Malaty et al., 1992, Everhart et al., 2000), and smoking (Murray et al., 1997), particularly heavy smokers (Moayyedi et al., 2002). Failure to thrive among infant boys may be related to *H.pylori* infection (Fall et al., 1997); moreover an association is observed with infection and reduced height among women (Murray et al., 1997, Moayyedi et al., 2005). It is possible that reduced height may be due to confounding (Moayyedi et al., 2005) such as lower socio-economic status and subsequent poorer diet, but it has been observed that taller individuals produce greater quantities of gastric acid that may protect against *H.pylori* colonisation (Axon, 2004).

During the last thirty to forty years the incidence of OAC has been rising rapidly. It is also noted that during this time frame that the prevalence of *H.pylori* infection has been falling steadily in developed countries (Lee et al., 2007b, Rehnberg-Laiho et al., 2001, Kosunen et al., 1997), with a fall from approximately 55% to 30% from the 1970s to the 1990s (Kosunen et al., 1997, Haruma et al., 1997). Most notably, the falling prevalence among the different strains is significantly greater reduction in *cag*A positive rather than negative *H.pylori* (Perez-Perez et al., 2002).

1.7 Body Habitus

1.7.1 Obesity

Obesity has been increasing western world, including USA and UK, and the same time as the observed increase in incidence of OAC. Increasing body mass index is associated with OAC (Anderson et al., 2007, Wu et al., 2001, Chow et al., 1998), and with BO (Stein et al., 2005). “Population attributable risks” estimate that a BMI above the lowest quartile accounts for 41.1% of OAC (Engel et al., 2003). There are two main mechanisms: firstly the impact upon GORD and secondly the biologically active nature of visceral adiposity associated with male pattern obesity.

Nilsson and Lagergren reviewed the literature finding that the majority of papers found an association between increasing BMI and reflux symptoms and/or oesophagitis (Nilsson and Lagergren, 2004). As compared with BMI <25, there was a doubling of OR for reflux symptoms being overweight, and three- to four-fold in those with a BMI 30-35 regardless of gender. This finding was reproduced in larger meta-analysis with OR 1.43 for overweight (BMI 25-30) and OR 1.94 for the obese (BMI >30) (Hampel et al., 2005). Increasing BMI >30 is associated with greater frequency and length of reflux episodes, and greater time overall with a pH<4 (El-Serag et al., 2007). It is less clear as to the mechanism by which obesity affects reflux, but it is clear the weight loss reduces symptoms (Nilsson et al., 2003). The role of obesity increasing intra-abdominal pressure, thus compressing the stomach and producing pressures that may overcome those at the LOS is postulated but not readily reproduced

in the literature (Nilsson and Lagergren, 2004, Hampel et al., 2005). However there is evidence of increased oesophageal dysmotility among the obese, with reduction in resting LOS pressures and an increase in post-prandial TLOSRs associated with reflux (Sise and Friedenberg, 2008). Obesity is associated with an increased frequency of hiatal herniation (Stene-Larsen et al., 1988), another risk for GORD.

Visceral adipose tissue is biologically active, and shown to increase insulin-like growth factor 1 (IGF-1) levels (Donohoe et al., 2012, Doyle et al., 2012). IGF-1 has been shown to reduce apoptosis and enhance the process of DNA-damage to cells, thus increasing potential in neoplastic progression (Sheppard, 2004). Intriguingly that whilst IGF-1 levels are risen in obese individuals with oesophageal squamous cell carcinoma as well as OAC, it was only the OAC cell lines that responded to IGF-1 with increasing cell proliferation (Doyle et al., 2012). Moreover, those OAC patients with higher expression of IGF-1 had a poorer prognosis (Orr et al., 1994). Leg length is a marker of pre-pubertal growth and is related to IGF-1 levels, a known mitogen(Sheppard, 2004).

1.7.2 Height

Taller individuals (Axon, 2004), and those with greater body mass have a higher gastric acid production than shorter and lower BMI individuals. It is observed that during the last 30-50 years not only has the incidence of OAC and obesity risen, but that population height is increasing in the European

countries at a rate of 1cm per decade(Axon, 2004). Moreover, *H.pylori* infection is associated with shorter stature (Moayyedi et al., 2005, Murray et al., 1997).

1.8 Influence of medications upon oesophageal adenocarcinoma

1.8.1 Medication with potential negative association with OAC

1.8.1.1Acid suppression

Proton pump inhibitors (PPI) are highly effective at managing reflux symptoms due to gastric acid reflux, and treating RO, both potential precursors of BO. The role of PPI in BO is theoretically sound, and if patients with BO are symptomatic, the dose of PPI should be increased to completely supress symptoms 24 hours a day. However, Barrett's mucosa, by the very nature of the columnar epithelium, may fail to produce symptoms (Byrne et al., 2003); in this situation symptomatic relief may not necessarily reflect complete acid suppression. There is some evidence that sufficient rising of oesophageal pH can improve oesophageal mucosal cell differentiation and reduce proliferation (Ouatu-Lascar et al., 1999), however it only requires short periods of acid exposure for damage to subsequently occur.

Both the BSG (Watson, 2005) and American Gastroenterology Association (AGA) (Sharma et al., 2004) recommend the use of PPIs in patients with BO, but also acknowledge that the evidence for reducing the progression to OAC is yet to be proven.

1.8.1.2 Aspirin and non-steroidal anti-inflammatory drugs

Early case-control studies showed a negative association with aspirin and the development of OC (Funkhouser and Sharp, 1995), and in a subsequent study examining morphology the effect was most marked for OAC (OR 0.37) rather than OSCC (OR 0.49) (Farrow et al., 1998). Regular use of aspirin and NSAIDs reduced the risk of OAC and gastric cardia adenocarcinomas (combined group) significantly (Duan et al., 2008). More detailed examinations of associations between aspirin and OAC revealed a 60% reduction in risk (Fortuny et al., 2007), and a dose-response relationship to this negative association (Jayaprakash et al., 2006). This finding was not only reproduced with both aspirin and NSAIDs, but also concluded that there was no significant increased risk of upper gastro-intestinal haemorrhage (Tsibouris et al., 2004). Meta-analysis confirms the negative association with NSAIDs with OAC (Corley et al., 2003, Liao et al., 2012), and OSCC (Corley et al., 2003), and with aspirin and both morphologies of OC (Corley et al., 2003).

Findings comparing BO and OAC with community control subjects and use of aspirin and NSAIDs revealed a negative association with both disease groups and usage. This has been suggested to reveal that aspirin and NSAIDs may exert their proposed protective effect earlier in the metaplasia-dyplasia-neoplasia sequence (Anderson et al., 2006). However, two cohort studies (Vaughan et al., 2005, Kastelein et al., 2011) and one nested case-control study (Nguyen et al., 2009) have illustrated that fewer patients with BO progress to OAC when taking aspirin and NSAIDs.

Further modelling showed those benefiting most from aspirin/NSAIDs were those with frequent reflux symptoms (Sadeghi et al., 2008, Pandeya et al., 2010). Aspirin/NSAIDs act by inducing apoptosis via lipooxygenase and cyclo-oxygenase inhibitors (Shureiqi et al., 2001) and COX-2 expression in BO increases from metaplasia, dysplasia to neoplasia (Morris et al., 2001). Further evidence exists showing that aspirin and NSAIDs are most likely to exert their protective influence upon those with adenocarcinomas that overexpress cyclin D1, a cell-cycle control gene (Gammon et al., 2004).

1.8.1.3 Statins

Statins, or 3-Hydroxy-3-methylgutaryl-coenzyme A (HMG-CoA) reductase inhibitors, reduce mevalonate. Reducing mevalonate not only decreases cholesterol, but also reduce proteins involved in growth control (eg farnesylated proteins), and as such have been postulated as chemopreventative agents (Goldstein and Brown, 1990, Chan et al., 2003). Populations taking statins have a reduced incidence of cancer after just four years of use (Graaf et al., 2004), specifically colorectal cancer (Poynter et al., 2005). This proposed mechanism of action has been identified in Barrett's and OAC cells, inhibiting cell growth and proliferation, and inducing apoptosis (Sadaria et al., 2011, Ogunwobi and Beales, 2008, Konturek et al., 2007); moreover statins appear to inhibit COX-2, a mechanism already described for aspirin, NSAIDs and COX-2 inhibitors (Ogunwobi and Beales, 2008). Whilst a retrospective study of medication use among Barrett's oesophagus patients failed to show a potentially protective effect of statins (Nguyen et al., 2009),

larger prospective cohort studies have identified a reduced risk of progression from BO to OAC (Kantor et al., 2012, Kastelein et al., 2011).

1.8.2 Medication with potential positive association with OAC

1.8.2.1Drugs that reduce lower oesophageal sphincter pressure

Many drugs can exert a reduction in the pressure at the LOS, promoting gastro-oesophageal reflux e.g. nitrates, theophyllines, benzodiazepines, β-agonists anti-cholinergic drugs and calcium-channel blockers. Their influence has been examined identifying that ever versus never taking any LOS relaxing drug and taking of cumulative numbers of drugs with a LOS side effect is associated with OAC. Most notably, 84% of those taking drugs that had a side effect of relaxing the LOS experienced reflux symptoms at least once per week, more often than control subjects (Lagergren et al., 2000). This has been subsequently reproduced (Ranka et al., 2006).

Of those drugs that have a side effect of reducing LOS pressure, use of β-agonists and theophyllines, both used in asthma, have been identified to be associated with OAC (Vaughan et al., 1998, Ranka et al., 2006). Theophyllines have also been shown in meta-analysis to be associated with OAC (Alexandre et al., 2012). Identifying whether this is due to asthma or the LOS side effect profile is difficult to ascertain (Vaughan et al., 1998, Ladanchuk et al., 2010).

1.9 Diet

The diet is a strong modifiable factor in the development of cancer, with approximately 35% (estimate 20-60%) reduction of fatal cancers proposed as achievable with reduction of fat, and increasing non-digestible carbohydrates and fruit consumed (Doll, 1992).

1.9.1 Fruit and vegetables

Diets higher in foods of a plant origin, including fruit and vegetables, are negatively associated with OAC (Mayne and Navarro, 2002, Brown et al., 1995, Tzonou et al., 1996, Navarro Silvera et al., 2011, Chen et al., 2002) and BO (Thompson et al., 2009, Kubo et al., 2010, Kubo et al., 2008b). However data are mixed. The NIH-AARP Diet and Health study failed to show association with fruit and vegetables and OAC overall, but when sub-analysed, it did reveal a negative association with “dark green vegetables” (Freedman et al., 2007). Analysis of EPIC data, including dietary information from 23 centres in ten European countries, revealed an inverse association with vegetable and citrus fruit consumption, but significance was not reached, with the relatively low incidence of OAC in the countries analysed as the cause for reduced power (Gonzalez et al., 2006b). Higher consumption of fruit and vegetables has been shown to reduce the risk of OAC by 50%, with the authors estimating that 20% of cases of OAC in Sweden were attributable to a diet of less than 3 portions of fruit and vegetables per day. This however translated into an estimate of over 25 000 subjects having to alter their diet to prevent one case of OAC per year (Terry et al., 2001). A similar study based

in USA revealed population attributable risk of 15.3% due to low consumption of fruit and vegetables (Engel et al., 2003).

Biochemical explanations exist for the proposed protective role of dark green (Freedman et al., 2007) and cruciferous vegetables (Brown et al., 1995) in the development of OAC. Isothiocyanates, found in broccoli, Brussel sprouts, cauliflower and cabbage, inducing cell cycle arrest and apoptosis (Myzak and Dashwood, 2006). Indole-3-carbinols are also present in cruciferous vegetables, inhibiting cell growth at multiple levels, including transcription factors and apoptosis (Kim and Milner, 2005). A more detailed consistent finding revealed high fibre diets are inversely associated with OAC (Tzonou et al., 1996, Brown et al., 1995, Kabat et al., 1993, Zhang et al., 1997, Mayne et al., 2001). Antioxidant use is negatively associated with OAC (Terry et al., 2000), and most notably with OAC subjects with reflux, suggesting the effect of antioxidant reduce the oesophageal mucosal reactive stress during gastro-oesophageal reflux (Terry et al., 2000). Furthermore, similar dietary negative associations exist with BO (Kubo et al., 2010, Kubo et al., 2008a).

Specific nutrient analysis does reveal further negative association between diet and OAC: vitamins A, B6, and C, and folate (Mayne et al., 2001, Tzonou et al., 1996, Zhang et al., 1997, Murphy et al., 2010, Dong et al., 2008).

While the negative association of dietary folate is confirmed with additional research, a positive association was seen with selected B vitamins, and

intriguingly folate supplementation (not dietary in origin) was positively associated with BO with dysplasia (Ibiebele et al., 2011).

Other antioxidants such as vitamin E fail to show any association (Carman et al., 2009, Murphy et al., 2010), and dietary supplementation of foods high in antioxidants failed to show any change in cellular antioxidant levels, nor reduction of oxidative stress (Aiyer et al., 2011). The results with vitamin E are however inconsistent, with supplement of vitamin E negatively associated with OAC in a study in the USA (Dong et al., 2008). Moreover, vitamin E supplementation has been identified as a cause of increased all-cause mortality (Miller et al., 2005). Lycopene, a carotenoid found predominantly in tomatoes, is protective of gastro-intestinal cancers at all sites, except those of the oesophagus (Franceschi et al., 1994). Investigation of selenium, a mineral associated with the aetiology of many cancers including those of the prostate, has only shown a negative association with oesophageal cancers (not sub-divided by morphology) in a population with virtually global selenium deficient state in an area of China, Linxian, that also has a very high incidence of OSCC (Mark et al., 2000).

Carbonated soft drinks were hypothesised to be positively associated with OAC due to their potential for causing gastro-oesophageal reflux. However no overall association was identified, but use of ‘diet fizzy drinks’ were negatively associated with OAC, but this finding could be due to confounding factors

such as social class and lower overall calorie consumption (Mayne et al., 2006).

1.9.2 Meat and fat

Associations with dietary red meat and OAC are variable. When analysed by the principle component of the diet, meat and dietary nitrite intake were associated with OAC (Navarro Silvera et al., 2011), as were meat and fat predominant diets (Ibiebele et al., 2012), and animal protein (Mayne et al., 2001). However, other studies failed to show any association with dietary fat (O'Doherty et al., 2012) and red meat (Chen et al., 2002), including analysis of EPIC data (Gonzalez et al., 2006a), which did however illustrate an association of processed meats with OAC.

It is believed the inconsistencies seen with the data examining associations of meat and OAC are due to type of meat (e.g. lean cuts), the nitrite and nitrate content following any processing and the method of cooking. Meat cooked at high temperatures forms heterocylic amines and polycyclic aromatic hydrocarbons, known carcinogenic agents (Kubo et al., 2010).

Diets high in fat overall (Mayne et al., 2001) and of a dairy source are positively associated with OAC (Ibiebele et al., 2012). Polyunsaturated fat intake, at least among subjects with a normal BMI, have a negative association with OAC (O'Doherty et al., 2012), thus suggesting that fat intake may have a significant impact upon BMI as its mode of action in the

development of OAC (Kubo et al., 2010). Furthermore, supplementation with n-3 polyunsaturated fatty acids in subjects with BO increases the epithelial concentration of these fatty acids, reducing COX-2 expression (Mehta et al., 2008). The role of n-3 fatty acids has not been evaluated in enough detail to draw any conclusions (Kubo et al., 2010)

1.9.3 Alcohol

Despite high consumption of alcohol leading to oesophageal dysmotility and gastro-oesophageal reflux (Ferdinandis et al., 2006, Grande et al., 1996), the association with OAC is variable among studies, with positive association seen (Vaughan et al., 1995), as well as no association (Steevens et al., 2010), and a negative association among those of modest consumption (Freedman et al., 2011). Meta-analysis showed no association between alcohol and OAC (Tramacere et al., 2012).

1.10 Exercise and physical activity

There is a paucity of information surrounding any associations between exercise, physical activity and OAC. While the EPIC study failed to reveal any association between physical activity and OAC, there were only 80 cases (Huerta et al., 2010). In larger studies a negative association was revealed between increasing exercise/physical activity and OAC (Vigen et al., 2006), albeit with the first failing to achieve significance (Leitzmann et al., 2009). A prospective intervention trial of exercise among subjects with BO should shed further light upon this area (Winzer et al., 2010)

1.11 Nitrosative stress

The gastro-intestinal tract is exposed to N-nitrosamine compounds from various sources, with 85% arising from nitrates in the diet and water, and other routes such as smoking. Foodstuffs high in nitrates include meat, especially processed and smoked/cured meat, smoked fish and preserved vegetables. Nitrates are more concentrated in vegetables grown in low light but warm temperatures found often in greenhouses. However with the increased use of fertilisers, drinking water concentrations of nitrates have been at risk of higher levels, as have any crop grown with fertiliser use.(McKnight et al., 1999, Craddock, 1992, Jakszyn and Gonzalez, 2006)

While these N-nitrosamines may have anti-bacterial properties (McKnight et al., 1999), they have been shown to be carcinogenic (Jakszyn and Gonzalez, 2006). Ingested nitrates are first reduced to nitrites by oral bacteria and then converted to N-nitrosamines in the stomach in the presence of ascorbic acid and amines. Several studies have revealed that the creation of N-nitrosamines occurs maximally at the gastric fundus and cardia (Moriya et al., 2002, Iijima et al., 2002, Iijima et al., 2003a, Suzuki et al., 2003). It is at the gastric fundus and cardia where the ‘acid pocket’ is normally found, and when displaced above the diaphragm, promotes GORD. Nocturnal GORD especially predisposes to RO and BO as discussed. It is with interest to note that salivary nitrosamine concentration peaks at night, being more pronounced in older men (Mirvish et al., 2000). During acid reflux, the majority of nitrosative stress occurs within the distal oesophagus (Winter et al., 2007). N-

nitrosamines undergo entero-salivary circulation, with a ten-fold concentration from plasma to salivary gland, resulting in further upper gastro-intestinal tract exposure (Lowenfels et al., 1978, McKnight et al., 1999). The meeting of acid refluxate and saliva rich in nitrosamines in the distal oesophagus provides the environment for nitrosative stress to occur, promoting the carcinogenic potential to developing OAC (Suzuki et al., 2005). Nitrosative stress is believed to drive dysplasia seen within Barrett's mucosa through DNA damage, gene dysregulation and influencing metalloproteinases, implemental in "extracellular matrix remodelling and invasion" (Clemons et al., 2010).

1.11.1 Factors affecting N-nitrosamine

While PPI treatment increases pH, a subsequent increase in nitrosamine forming bacteria are seen, there is no significant change in nitrosamine formation (Verdu et al., 1994, Viani et al., 2000). Furthermore, *H.pylori* is not responsible for the formation of N-nitrosamines (Vermeer et al., 2002, Ziebarth et al., 1997). However, combination of a PPI and *H.pylori* increases pH sufficiently for nitrosamine forming bacteria to proliferate (Mowat et al., 2000, Mowat and McColl, 2001). In a neutral pH environment, the nitrites are no longer converted to nitric oxide, which is ordinarily readily absorbed by the stomach, and thus leaves a high intra-gastric nitrite level, promoting the formation of nitrosamines (Mowat and McColl, 2001)

1.12 Smoking and oesophageal adenocarcinoma

The effect of smoking upon reflux has been discussed with reduced LOS pressures, and increased reflux associated with coughing (Kahrilas and Gupta, 1990, Pandalfino and Kahrilas, 2000). Furthermore, tobacco forms nitrosamines (McKnight et al., 1999) and other carcinogens including polycyclic aromatic hydrocarbons (Kamangar et al., 2009). While the association of tobacco and oesophageal cancer is strongest with OSCC, the evidence of a weaker association with OAC is clear among the studies in the literature, averaging at least a doubling of risk (Kamangar et al., 2009). In population attributable risk analysis, smoking accounts for 39.7% of the aetiology of OAC (Engel et al., 2003, Kamangar et al., 2009).

1.13 Male predominance of OAC

With OAC more common in men, occupational hazards must be considered in aetiological factors. However many studies fail to differentiate oesophageal cancer by morphology (Kamangar et al., 2009). With the importance of nitrosamine in the aetiology of OAC, it is noted that there was no increase in overall cancer rates among nitrate fertiliser workers (Hagmar et al., 1991), but with the relatively low incidence of OAC the study may not be powered for this detection. However a Swedish study revealed significant association with OAC and exposure to cement dust and asbestos (Jansson et al., 2005a). A study in the USA revealed a negative association with “engineers, architects and surveyors”, but a positive association with “ administrative support, financial, insurance and real estate workers, and among health service

providers". However the association was weak and likely due to confounding (Engel et al., 2002).

Identification of androgen receptors on oesophageal adenocarcinoma cells raises the possibility of a role for male sex hormones in the oncogenesis of OAC (Tihan et al., 2001). Stimulation of these receptors by androgens has been shown to alter protein expression that may be implicated in the development of OAC (Awan et al., 2007). Epidemiological investigation of a cohort of prostate cancer patients in Sweden, an androgen driven tumour, failed to reveal any association with male sex hormones and OAC (Lagergren and Nyren, 1998).

A protective influence of oestrogens has been postulated, with oestrogen receptors discovered on OAC cells (oestrogen capable of inducing apoptosis) (Chandanos and Lagergren, 2009). Among a cohort of women with OAC, breast-feeding was proposed as a potential protective factor in the development of OAC, suggesting a hormonal role (Cheng et al., 2000). However, analysis of hormone-replacement therapy should no association with OAC (Lindblad et al., 2006).

Chapter 2

Aims and Objectives

1. To examine the incidence of oesophageal cancer by morphology in the West Midlands over the last 30 years, and identify trends and associations with age, gender, socio-economic status and ethnicity

2. To identify the role of androgens in the aetiology of oesophageal adenocarcinoma in the West Midlands

3. To further examine the effect of androgens, including duration of androgen effect and ethnicity in the United States of America

4. To determine potential risk factors for the progression of Barrett's oesophagus to oesophageal adenocarcinoma, focusing on the effect of medication

5. To identify the protective effect of medication in a case-control GP data-base study

6. Prospectively examine aetiological factors in the development of oesophageal adenocarcinoma within the West Midlands

Chapter 3

Materials and Methods

3.1 **West Midlands Cancer Intelligence Unit** (www.wmciu.nhs.uk)

The West Midlands Cancer Intelligence Unit (WMCIU) has collected radiotherapy data since 1936 for the central Birmingham area and been population based since 1957. The WMCIU records data from the 'West Midlands Strategic Health Authority region', a population of 5.3 million (2008), approximately 10% of the population of England and Wales.

The 28 acute National Health Service (NHS) hospitals within the West Midlands are required to send details of cancer patients admitted as either in-patients or day cases to the WMCIU. The WMCIU also receives information from hospices, pathology laboratories, community hospitals, screening centres, general practitioners and private hospitals. Death certificates with any record of cancer are also provided to the unit. Data completeness are estimated to be greater than 95%.

The data includes patient demographics (name, date of birth, gender, and address), tumour details (cancer origin, morphology and stage), diagnostic and treatment methods, and date, place and cause of death. Internal and external data quality controls are in place, including cross-referencing with the Office for National Statistics (ONS). "The International Statistical Classification of Diseases and Related Health Problems" 10th revision (ICD10) was used to identify oesophageal cancers (code c15). Cancer morphology

was identified using the “International Classification of Diseases for Oncology second edition” (ICD-O-2): adenocarcinoma (814*-838*, 848*-849*, 8550, 8570), squamous cell carcinoma (805*-808*) or other/unknown morphology.

3.1.1 Time period and case validations

The time period used for the studies utilising WMCIU data in this body of work was 1977-2004, covering 28 years of data collection. This time period was selected due to the availability of oesophageal cancer data: all case notes during this time had been abstracted into the computer registry, or copies on microfilms were readily available for examination. In the first ten years of the time period examined there was a high proportion of incomplete abstraction of notes and registration of morphology being recorded as carcinoma or unknown, and those recorded as gastric cardia (an area where doubt arose as to definition employed in the registry at that time). Along with the low numbers of subsequently incompletely abstracted notes from the later years, case note reviews were undertaken and a member of the WMCIU verified randomly selected files. A total of 4252 patient records (1731 originally coded as cardia, and 2641 as oesophageal) were re-examined. 296 (17%) of the cardia cancers were re-classified as oesophageal. Of the 138 oesophageal cancer morphologies originally coded as carcinoma, 27 (20%) were re-classified OAC, and 26 (19%) as OSCC. Of the 2641 oesophageal cancers that were either not abstracted or of non-specific/unknown morphology, 972 were re-classified as OAC, and 946 as OSCC. No other OAC or OSCC morphologies were newly identified in the remaining records examined.

3.1.2 Socio-economic status

Two different measures were employed to analyze socio-economic status: "The Townsend Index (Townsend, 1979) and the Index of Multiple Deprivation (IMD) 2004 (Noble, 2004). The Townsend Index, derived from the postcode, is based on four variables based on census data from 1991: unemployment, overcrowding, non-car ownership and non-home ownership and is focused on material deprivation. The Townsend Index was produced at the Enumeration District level: small geographical areas used for the output of census data, of which there were 10,864 in the West Midlands in 1991. Five socio-economic quintiles from 1 (most affluent) to 5 (most deprived) were derived by assigning postcodes to equal percentages of the whole West Midlands population in each group. Each patient was then allocated to one of the five groups based on their postcode. EASRs were calculated for each Townsend quintile based on the 1991 census population data. These 1991 populations were then weighted to take account of the change in the size of the West Midlands population from 1977 to 2004. For the period 1999-2004, the income domain of the IMD 2004 was used as a second measure of deprivation. The IMD provides a measure of deprivation for each Lower Super Output Area (LSOA) in England (LSOAs are small geographical areas that are fairly homogenous and consist of approximately 1,500 people; there are 3,482 LSOAs in the West Midlands). The income domain consists of several variables, such as the percentage of population in that LSOA claiming various income-based benefits and tax credits, which are then weighted and a score assigned to each LSOA. Patients were again allocated to a quintile (calculated based on

the percentage of the English population in each group) and EASRs were calculated for each quintile using the 2001 census population data. This was to check whether use of West Midlands regional derived deprivation quintiles based on the 1991 Census (Townsend) gave similar results to national quintiles based on a range of measures generally recorded in 2001 and compiled in 2004." (This explanation of methodologies and the analytical process was completed by Rosie Day at the WMCIU)

3.1.3 Ethicity

Ethnicity data were compiled via linkage of individual patients and their tumours from the cancer registration database with data from the Hospital Episode Statistics (HES). At the time of linkage, the WMCIU had access to HES data for financial years 1997/98 through to 2004/05. Ethnicity was classified as White, Asian (Indian sub-continent), or Black, and those individuals with multiple ethnicity recordings were classified as other/mixed (including Chinese/Oriental). The ethnic breakdown of the population was derived from 2001 census data (Large, 2006). (Linkage with HES and ethnicity was provided by Colin Brookes at the WMCIU)

3.1.4 Study design for examining the incidence of a second malignancy of the oesophagus following a first primary of the prostate (Chapters 5 and 6)

A population based retrospective cohort of men with a first malignant primary (excluding non-melanoma skin cancers) of PC (International Classification of Diseases tenth edition (ICD10) code C61) diagnosed between 1977 and 2004, was identified from the cancer registration database at the West Midlands Cancer Intelligence Unit (WMCIU). These patients were followed up until diagnosis of a second malignant primary (excluding non-melanoma skin), death, or the end of the follow-up period in the registry (31st December 2004). Patients with follow up of less than 3 months were excluded to prevent inclusion of concurrent or undiagnosed cancers. Ethnicity data were obtained using linkage between the cancer registration database and Hospital Episode Statistics (HES).

3.1.4.1 Data analysis

Age- and period-adjusted standardised incidence ratios (SIR) were calculated as an estimate of relative risk for a second malignant primary of the oesophagus (ICD10 code C15). These cases were further examined by morphology: coding classified as adenocarcinoma (ICD-O-2 codes: 814* - 838*, 848* - 849*, 8550, 8570), squamous cell carcinoma (ICD-O-2 codes: 805* - 808*) or other and unknown morphologies. The expected numbers of oesophageal cancers, overall and by morphology, were estimated by

multiplying the observed number of exact person-years by calendar year and quinary age specific incidence rates for the West Midlands (Breslow, 1987). The 95% confidence intervals were calculated assuming a Poisson distribution of second primary malignancies, and a two-tailed p-value calculated (Breslow, 1987). Latency intervals between a diagnosis of PC and oesophageal cancer (OC) were derived as a surrogate for length of potential exposure to anti-androgen therapy prior to the development of the OC. Statistical programming for STATA shown in appendix 1

3.2 Survival, Epidemiology, and End Results (http://seer.cancer.gov/)

The USA National Cancer Act in 1971 led to the collection of cancer data in the USA commencing in 1973 (Hankey et al., 1999). The SEER (Survival Epidemiology and End Results) 9 Registries Database has been reliably collecting data since 1977, covering approximately 10% of the population of the United States of America, providing not only an exact duplicate of the time period analysed in the WMCIU studies, but also a similar proportion of the overall population. “The SEER 9 registries are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah”. While SEER has expanded from the initial 9 areas, to include SEER 11, SEER 13, SEER 17 and SEER 18 registries, only SEER 9 registries database has recorded the selected population for the whole 28 years, thus providing comparable period of follow-up. The characteristics of the SEER populations is comparable to that of the whole of the USA, with 12.9% below the poverty line (vs 12.4% of US population), 20.4% not attaining High School diploma (vs 19.6%), urban based 88.2% (vs 79%), and 17.3% first generation immigrants (vs 11.1%) [http://seer.cancer.gov/registries/characteristics.html]

SEER is a well-utilised database, with many publications (Hankey et al., 1999), including evidence of its robustness. With 3,405,000 tumours recorded in the SEER 9 Registries database 1977-2004, we hypothesised that greater power could be generated for the anti-androgen theory by providing longer follow-up periods. Moreover, ethnicity data are available for the whole time frame.

Case ascertainment is reported as greater than 98%, with quality control procedures including “potentially case-finding, re-abstracting/recoding and reliability studies”.

The same ICD10 and ICD-O-2 codes were utilised as for the WMCIU studies.

3.3 The Health Improvement Network (http://csdmruk.cedegim.com/)

The Health Improvement Network (THIN) database utilised contains computerised and anonymised longitudinal records from 326 UK General Practice (GP) surgeries, covering 5 million patients that are regionally and demographically representative of the UK population. THIN commenced in 2002, with full data collection occurring at each practice upon joining the network, enabling follow-up data availability prior to this date. Data are then collected during routine practice, and via the specialised “Vision software” it is uploaded to the central THIN database every month (incremental update). The database was originally under the management of EPIC, now CSD Research Medical Group (part of Cedegim).

Data are provided in four files (medical, therapy, additional health data (AHD) and postcode variable indicators (PVI)) with a fifth linking file (patient file). Anonymised data are identified by practice identification and a patient identification, when combined forms a unique identifier. The patient file contains information including age, date of birth, gender, and dates of entering and leaving the practice (e.g. including transfer to another practice or death). The medical file holds data surrounding medical diagnoses coded using Read codes. The therapy file contains prescribing data gathered by each electronic prescription completed by the general practitioner and recorded by Multilex codes (and British National Formulary coding). The AHD file contains a number of items including height, weight, BMI, smoking and alcohol habits. Finally the PVI file contains postcode-linked data for socio-economic status,

ethnicity and environmental factors (e.g. air pollutants). Socio-economic status is derived at the post-code level (Townsend score, 2001 census data) and recorded in quintiles.

The strength of the database lies in the computerised prescribing practices of GPs, ensuring that all drugs prescribed for subjects in this population will be recorded. Demographic and lifestyle information (e.g. sex, age, smoking status, height and weight) are subject to “QOF” (Quality and Outcomes Framework) criteria, and thus a very high level of data entries are ensured. QOF is active among all GP surgeries in England, rewarding and incentivising high levels of accurate data collection (http://www.qof.ic.nhs.uk).

The quality of the data, while maintained by CSD, has been verified in several publications. The incidence of cancers within THIN is comparable to that of the cancer registry data: standardised incidence ratio (SIR) within 10% (Haynes et al., 2009). Prescribing data has also been verified against national dispensing data and comparing practices that do and do not report data for the General Practice Research Database (GPRD) (Langley et al., 2010, Lewis et al., 2007).

3.4 Midlands OeSophageal adenocarcinoma Epidemiology Study

3.4.1 Study design

A case-control study with subjects with OAC and three control groups, subjects with endoscopic proven LSBE (or SBE with intestinal metaplasia on histology), subjects with endoscopic proven RO and community subjects was designed: Midlands OeSophageal adenocarcinoma Epidemiology Study (MOSES). Ethical approval for the research study was obtained (MREC 05/Q2803/93), and approval obtained from each hospital and primary care trust research and development department. The study was adopted by the National Cancer Research Network. Cases of type 1 oesophageal adenocarcinoma, defined as the centre of the tumour arising above the gastro-oesophageal junction (Siewert and Stein, 1998), were identified from 12 West Midland hospital upper gastrointestinal cancer multidisciplinary meetings, where prior histology reports of the morphology of adenocarcinoma were then confirmed. OAC, RO and BO subjects were recruited from Sandwell General Hospital, City Hospital (Dudley Road, Birmingham), Dudley Group of Hospitals, New Cross Hospital (Wolverhampton), Walsall Manor Hospital, Queens Hospital (Burton-upon-Trent), Good Hope Hospital (Sutton Coldfield), Heartlands Hospital (Birmingham), University Hospital Coventry and Warwickshire, Warwick Hospital, Alexandra Hospital (Redditch) and University Hospital Birmingham. Type 2 and 3 adenocarcinomas of the gastro-oesophageal junction/cardia/upper stomach were not included in the study as their aetiological factors have differences that would confound the study. Community subjects were recruited from general practice surgeries in the

catchment area of each hospital; three practices were recruited for each hospital to enable closer geographical matching (appendices 2 and 3).

3.4.2 Sample size and statistical considerations

Recruitment of 208 cases of OA and 224 controls subjects would provide 80% power to detect a relative risk of 2 for dichotomous risk factors at the 5% significance level, except where the prevalence among controls is very low (<10%) or very high (>80%). The prevalence of each risk factor for OA being studied is within the 10-80% range in both patients and controls. Examples of prevalence in OAC include (figure in brackets community prevalence) 19% *H.pylori* prevalence (40%), 17% aspirin or NSAID use (25%), smoking 24% (18%), excess alcohol 20%, GORD symptoms 54% (17%), low education 28% and highest quartile for BMI 52% (26%).

The incidence of oesophageal cancer in the Midlands is 14 per 100000 at the planning stage of the research (personal communication, West Midlands Cancer Registry). Analysis of cases discussed at upper gastrointestinal cancer multi-disciplinary meetings over the past year in the Pan-Birmingham network, suggests 70% of all oesophageal cancers are adenocarcinomas (personal communication Mr M. Hallissey and Mr M. Richardson). The Pan-Birmingham network covers 1.8 million people and there will therefore be at least 180 cases of oesophageal adenocarcinoma available per annum for the study. A study period of 30 months was planned.

All control subjects were matched by gender, age (within 5 years), ethnicity (where possible), and geographical location. Control subjects with both incident cases of BO and endoscopically proven RO (any grade) were identified from those attending the endoscopy unit closest to the index case home address. Endoscopic evidence for Barrett's mucosa was accepted if the segment was greater than 3cm (LSBE), but necessitated histological evidence if the segment was only 1-3cm; subjects with ultra short-segment Barrett's oesophagus (<1cm) were not included. Community subjects were recruited from local general practices: for each hospital, three general practices were invited to participate in MOSES. When recruiting community subjects, the GP staff initially selected all patients within the practice by matching as detailed above. A random number generator selected six to eight cases from the list to invite.

Once inclusion criteria for OAC were met and confirmed with the Clinical Nurse Specialist (CNS), following the upper gastrointestinal cancer multi-disciplinary meeting at the subjects hospital, the CNS would approach the patient with OAC to gain consent for the research team to approach them. Information sheets and consent forms were given to the patient by the CNS, and the research team would await the confirmation of consent to contact the patient either from a return of reply slip (pre-paid envelope), or via the CNS. Informed consent was taken at time of visit.

All control subjects were provided with information sheets and consent forms by post at invitation, sent by a pre-prepared approved letter from the patient's general practitioner, confirming willingness to participate by postal return (pre-paid envelope). In the event of insufficient responses to meet the matching process, a second invitation would be sent as a final request.

One of three research staff (SCC, SP or LP) would visit the patient in order to interview the subjects (SP and LP trained by SCC in accordance with suggested technique (Jain, 1989), measure leg length (iliac crest to lateral malleolus), and take blood samples.

3.4.3 Response rates

During the study period of 30-months, 330 case of type-1 OAC were identified from the 12 recruiting hospitals across the West Midlands. 86 were not eligible for the study being incompetent to consent (n=8), having commenced treatment pathway already (eg surgery or chemotherapy) and thus likely to alter their recall and introduce confounding (n=50), ten had died before contact could be made, 17 were too poorly with WHO performance status of 4, and one had already been enrolled in another epidemiological study (SOCS). Two hundred and forty-four subjects were therefore eligible, with 32 either declining or not replying to the invitation, and four more agreeing to take part, but due to logistical difficulties could not be enrolled. Thus 208 cases were recruited, meeting the number required by the power calculation. The response rate was 86.9% of those eligible to be invited.

Among the control groups, response rates were higher among those with disease: subjects with BO 80.4%, subjects with RO 55.7% and community subjects 35.8%.

3.4.4 Interview

A twelve page questionnaire was created (appendix 4), collecting information in six sections: section A background information and demographics, section B dietary history, section C smoking and alcohol history, section D medical history including heartburn symptoms, body parameters (eg height, weight, waist measurement, finger and leg length as described above), and medication history, Section E educational history and section F family history. With respect to cancer patients all questions were asked in respect to one year prior to the interview date and 11 years prior, in order to avoid confounding from cancer symptoms or treatments.

3.4.5 Nutrition section

As dietary recall suffers from memory bias, the questions were kept to food groups rather than individual items. Food groups included: fresh vegetables (not potatoes), fresh fruit, fruit juice, potatoes, red meat (beef, pork and lamb), white meat/poultry, fish/seafood, tea, coffee and use of vitamin/mineral supplements. For portion size, a portion was determined as the amount of food each subject would place in the palm of their hand (or glass/mug as appropriate), thus keeping portion size proportional to each person. For each

food group, frequency of consumption (days of the week) and number of portions consumed on those days at the time of interview (or 1 year ago for cancer patients) and 10 years prior was requested. Alcohol consumption was recorded as current, ex or never, with duration and quantity drunk. Quantity of alcohol consumed was transcribed into units by the interviewer based on percentage and volume consumed (1litre of x% = x units) at time of interview (or 1-year prior for cancer patients), 10 years previously and at the heaviest regular period. Continuous variables were categorised into appropriate tertiles/quartiles/quintiles for logistic regression analysis to generate odds ratios with 95% confidence intervals.

3.4.6 Blood sampling

Venous blood sampling was performed by each interviewer, with 25ml of blood taken from each subject. Two EDTA tubes and three clotted/serum samples were obtained, and centrifuged for ten minutes upon return to the laboratory within 24 hours. Plasma, buffy coat and serum was pipetted manually and stored in “cryo vials” at -80 degrees Celsius in a laboratory maintained and monitored freezer.

3.4.7 Blood analysis

Serum samples were defrosted and analysed for IgG antibodies to *H.pylori* and *cag*A using ELISA kits from Genesis Diagnostics Ltd, London UK (Registered in England No. 02924988). ELISA kits were CE marked and the microbiology laboratory at City Hospital, Sandwell and West Birmingham NHS

Trust is CPA (Clinical Pathology Accreditation) approved. The ELISAs were performed by Rushana Hussain, a trained microbiology biomedical scientist.

The H.pylori IgG ELISA has a sensitivity of 91%, specificity of 100%, positive predictive value of 100% and negative predictive value 95% when compared with urease breath testing and histology. The *cag*A IgG ELISA sensitivity is 97% and specificity of 96% when compared with Western Blot techniques. Following recommendations from Genesis Diagnostics, the *cag*A ELISAs were run in duplicate for each subject, and reproducibility checked. *H.pylori* ELISA was run once for each subject.

A number of *H.pylori* samples were processed at the Dudley Group NHS Foundation Trust microbiology laboratory (n=111)(CPA approved) due to processing later than the main batch and the Sandwell and West Birmingham NHS Trust converting from ELISA to stool antigen testing, and no longer being set up to provide this assay. These last samples were processed using *H.pylori* IgG ELISA kits (CE Marked) produced by Zeus Scientific, Zierikzee Netherlands. Concordance with other commercially available *H.pylori* assays is 97.8% (tested within Zeus laboratory).

3.4.8 Reproducibility of interview

Prior to use, the reproducibility of the questionnaire was confirmed using kappa statistics by interviewing 100 non-study subjects (relatives of patients attending for out-patient clinics or day case procedures) twice, three to four

weeks apart. The reflux symptom section of the questionnaire had already been validated (Mohammed et al., 2005).

Interpretation of kappa statistics is shown in table 3.1. Of the one hundred subjects interviewed, 63 underwent a second interview within 3-4 weeks, with the remainder declining or further contact not achieved, achieving a response rate of 63%. The agreement between continuous variables was performed after categorising data into tertiles, quartiles or quintiles where appropriate.

Table 3.1 Interpretation of kappa statistics

Kappa statistic	Interpretation
<0	No agreement
0-0.2	Slight agreement
0.21-0.4	Fair agreement
0.41-0.6	Moderate agreement
0.61-0.8	Substantial agreement
0.81-1	Almost perfect agreement

As the *cag*A ELISAs were run twice, agreement between results was measured as substantial agreement (kappa 0.76). Any definite result and a second equivocal result was reported as the definitive result. There were no disagreements between a negative and positive result.

Smoking status (current, previous or never) was in perfect agreement (kappa 1), with quantity smoked 10 years ago in almost perfect agreement (kappa 0.87). Alcohol status was in substantial agreement (kappa 0.79). While the gastro-oesophageal reflux section had previously been validated, reproducibility was examined with substantial agreement with both having ever or never experience heartburn or acid regurgitation (kappa 0.77 and 0.8 respectively). Being woken by GORD symptoms also showed substantial agreement both at time of interview and 10-years prior (kappa 0.74 and 0.76 respectively).

The dietary section of the interview illustrated moderate to substantial agreement overall. Selected kappa statistics are provided: current frequency of fruit consumption kappa 0.75 (substantial agreement), frequency of fruit consumption 10 years ago: kappa 0.55 (moderate agreement); portions of fruit per day now: kappa 0.57 (moderate agreement); portions of fruit consumption 10 years ago: kappa 0.6 (moderate agreement); red meat portions per day: kappa 0.61 (substantial agreement); red meat portions per day 10 years ago: kappa 0.52 (moderate agreement); frequency of fish consumption currently 0.52 (moderate agreement); frequency of fish consumption 10 years ago: kappa 0.39 (fair agreement); portions of fish consumed per day currently and 10 years ago: kappa 0.33 and 0.32 respectively (fair agreement); cups of tea per day drunk currently and 10 years ago: kappa 0.58 and 0.56 respectively (moderate agreement).

Chapter 4

Examination of the trends in incidence of oesophageal adenocarcinoma, and the influence of ethnicity and socioeconomic status in the West Midlands

(Data from this chapter have been published: see appendix 5 for reference)

4.1 Introduction

Over the last 30 years, the incidence of oesophageal cancer (OC) has been reported to be increasing in Europe and the USA (Botterweck et al., 2000, Hesketh et al., 1989, Powell and McConkey, 1992, Wayman et al., 2001, Kocher et al., 2001, Powell et al., 2002, Devesa et al., 1998, Pera et al., 1993, Bytzer et al., 1999, Hansson et al., 1993). Oesophageal squamous cell carcinoma (OSCC) rates have been stable, or declining, while the incidence of OAC has been rising rapidly. This rapid change in incidence has been noted to be greater than for any other cancer among males in the USA (Blot et al., 1991). Examination of cancer registry data across Europe reveals that the highest incidence of OAC is in the United Kingdom (Botterweck et al., 2000).

An association between ethnic origin and the different morphologies of OC has been described in the USA, with OSCC being more common among the black population while OAC is seen most frequently among white males (Hesketh et al., 1989, Yang and Davis, 1988). The influence of ethnicity has not been examined in the UK.

OSCC has been reported to be associated with deprivation (Brown et al., 2001), however reports of the influence of socio-economic status on OAC are inconsistent, some describing an association with deprivation (Jansson et al., 2005b, Brown et al., 1994) and no association was found in Scotland (Brewster et al., 2000). A direct comparison of OSCC and OAC in Australia suggests OSCC is more clearly associated with deprivation(Nguyen et al., 2003). The influence of socio-economic status upon the incidence of OAC has

yet to be examined in England.

We have examined the incidence of OC in the West Midlands, England between 1977 and 2004 to identify changes in the incidence of its morphological subtypes and to examine the role of sex, ethnicity and affluence and deprivation.

4.2 Materials and Methods

Oesophageal cancers diagnosed in residents of the West Midlands were included in the study, and grouped by morphology code (ICD-O-2) classified as adenocarcinoma codes, squamous cell carcinoma or other and unknown morphologies.

Incidence rates were calculated and cancers were grouped into five-year diagnosis periods and directly age standardised incidence rates per 100,000 population, using the European Standard Population (EASRs), were calculated for each morphological group by sex for the years 1977-2004. A Mann Whitney U test (SPSS 12.0.1, Apache Software Foundation, USA) was employed to detect if any difference in age at diagnosis was significant between men and women in the two time-periods 1977-81 and 2000-4.

4.3 Results

4.3.1 Incidence

During the 28-year period 1977-2004, 15,138 OC cases were registered with the WMCIU, including 5517 cases of OAC, and 6314 OSCC. In 1977, 20% were OAC (n=78), and 48% OSCC (n=185), with 32% (n=124) either another morphology or unclassified. By 2004 the majority of OC was OAC (53%, n=366), with OSCC 31% (n=213) and other morphology/unclassified 17% (n=116). Changes in five year EASRs, with 95% confidence intervals (CI) for the different morphologies are shown in table 4.1 and figure 4.1. The significant rise observed for all OC in males was due to the marked increase in OAC (greater than four-fold), while there was no significant change for OSCC and a fall in those with other morphology/unclassified. In females, the picture was different, with significant increases being seen for both OAC (greater than three-fold) and a smaller but significant rise in OSCC. A small fall in unclassified/other morphology was also observed in women.

Table 4.1 Five year EASRs (95% CI) for oesophageal cancer by morphology and sex

Cancer Morphology	Males				Females			
	1977-1981		2000-2004		1977-1981		2000-2004	
	EASR	95% CI	EASR	95% CI	EASR	95% CI	EASR	95% CI
All	8.57	8.03 - 9.10	13.73	13.13 - 14.32	5.04	4.69 - 5.39	6.28	5.92 - 6.64
OAC	2.14	1.87 - 2.40	8.53	8.06 - 9.00	0.52	0.41 - 0.64	1.72	1.53 - 1.90
OSCC	3.65	3.30 - 3.99	3.37	3.08 - 3.67	2.91	2.64 - 3.19	3.50	3.22 - 3.77
Other/unclassified	2.78	2.46 - 3.11	1.83	1.61 - 2.04	1.60	1.42 - 1.79	1.07	0.93 - 1.21

Figures 4.1a and 4.1b: Incidence of oesophageal adenocarcinoma and oesophageal squamous cell carcinoma in England (West Midlands) 1977-2004 - Five year EASRs (95% CI) for oesophageal cancer for males (figure 4.1a) and females (figure 4.1b)

Figure 4.1a

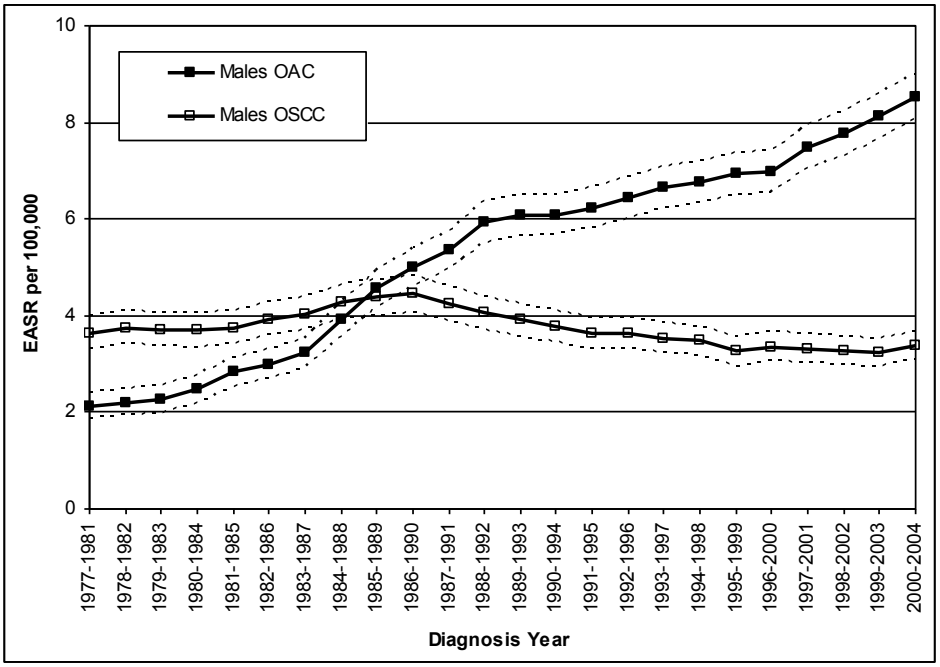
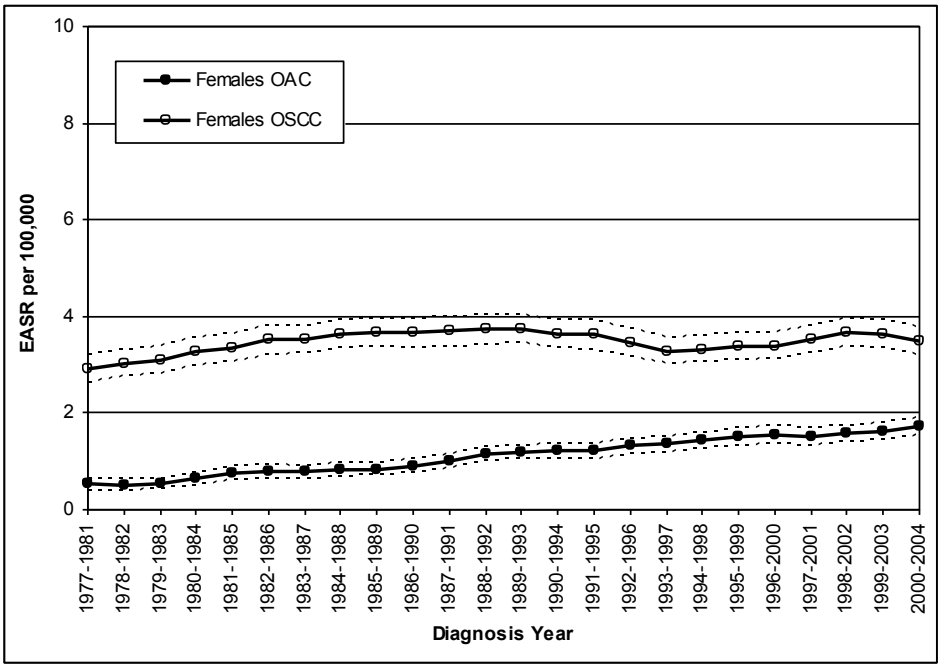


Figure 4.1b



The age at diagnosis of OAC was older in females during 1977-81 median 72.5 (IQR 63.3-78) than in males 65 (51-71.8), and also in 2000-4 (78 (69-83) vs 70 (61-77)) ($p<0.0001$ both time periods), and has increased in both men and women during the time period examined.

4.3.2 Socio-economic status

Figures 4.2 and 4.3 illustrate the effect of socioeconomic status on the incidence of OAC and OSCC respectively, over the time-period 1977-2004 for both sexes, giving the least and most deprived quintiles. It can be seen that there was no consistent relationship between socioeconomic status and the incidence of OAC in men (figure 4.2a) or women (figure 4.2b) during the 28-year period. In contrast, figure 3a illustrates clearly that while OSCC was significantly more common in the most deprived (EASR (95%CI) 6.19 (5.05-7.33)) than the affluent (1.85 (1.31-2.4)) for men in the earlier years, this association with deprivation was no longer evident in the latter years of the study period, with both affluent and deprived males having rates of about 4 per 100,000 population. A similar pattern was found for women with OSCC (most deprived 3.67 (2.88-4.45), most affluent 2.03 (1.52-2.54) in the early years of the study period (figure 4.3b). However, the difference by socio-economic status was less marked, and was not apparent after the 1992-6 period.

Figures 4.2a and 4.2b: Incidence of oesophageal adenocarcinoma in most affluent and most deprived Townsend quintiles in males (figure 4.2a) and females (figure 4.2b) in England (West Midlands)

Figure 4.2a

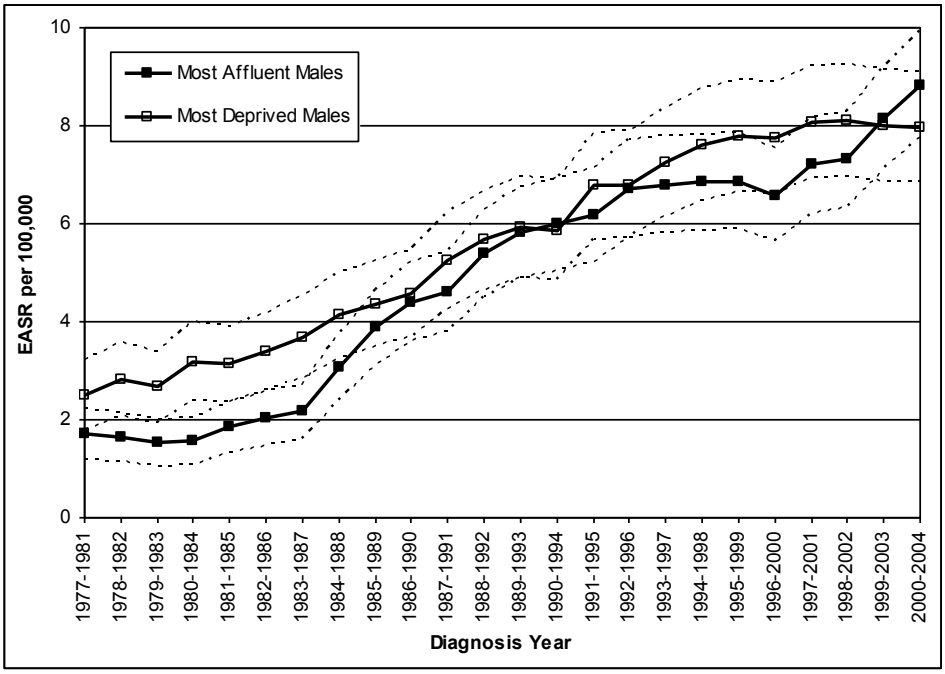
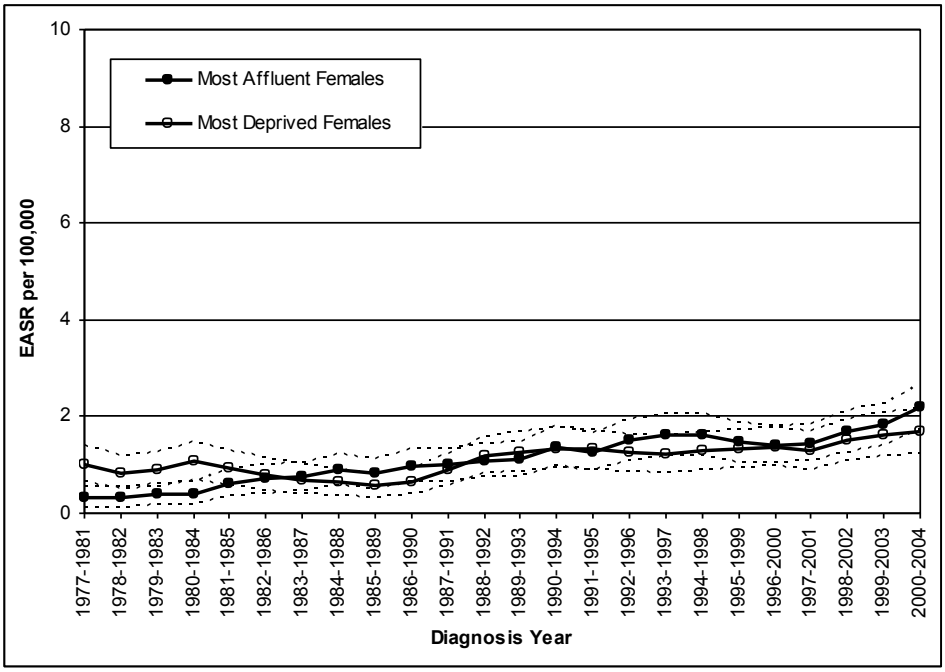


Figure 4.2b



Figures 4.3a and 4.3b: Incidence of oesophageal squamous cell carcinoma in most affluent and most deprived Townsend quintiles in males (figure 4.3a) and females (figure 4.3b) in England (West Midlands)

Figure 4.3a

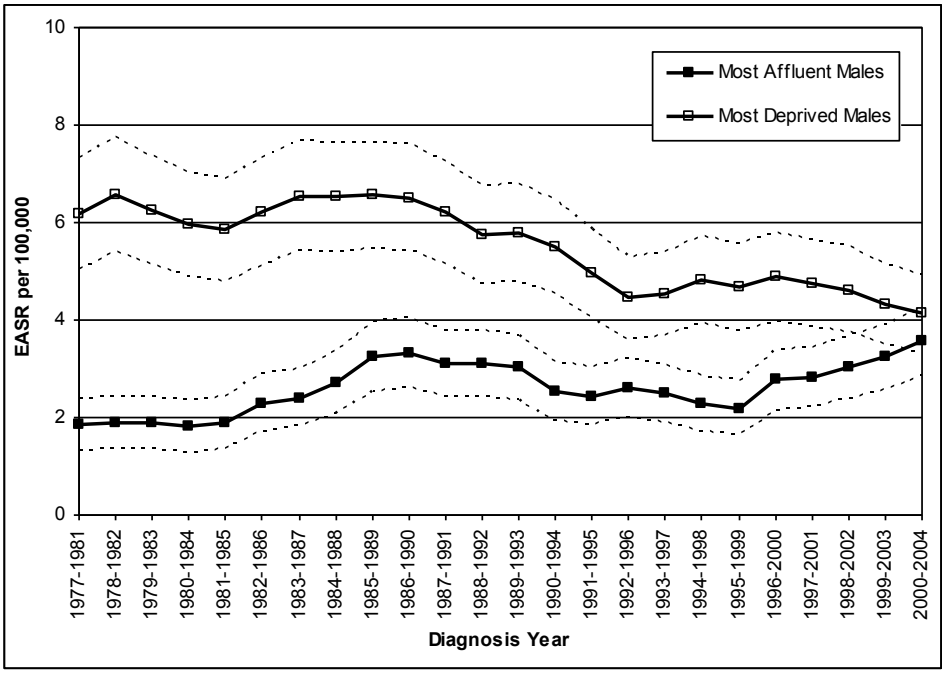
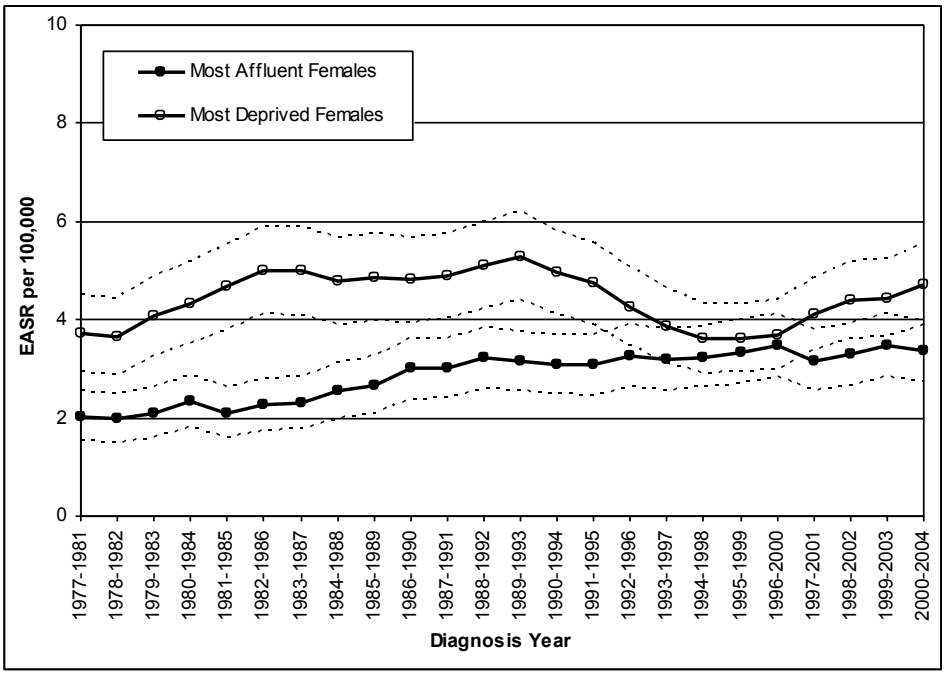


Figure 4.3b



When the analyses were repeated using the IMD 2004 for cancers diagnosed in 2000 to 2004, the results agreed with the Townsend Index for OAC, with no association between socio-economic status and incidence of OAC. However, the incidence of OSCC was positively associated with deprivation, with the most deprived quintile having EASRs of 4.73 (3.96-5.5) in males and 4.96 (4.22-5.69) in females. In contrast the rates of OSCC in the most affluent quintile were 2.55 (1.93-3.17) in males and 2.53 (1.97-3.1) in females, respectively.

4.3.3 Ethnicity

Figures 4.4a and 4.4b shows the EASRs of OAC and OSCC by ethnic group for the period 1998- 2004. OAC was significantly more common among the white population than other ethnic groups for both sexes. Indeed, no cases of OAC were observed among women in any ethnic groups other than white during the seven years examined. In contrast, OSCC was significantly more common than OAC among black men. OSCC was more common among black men than in white men, although this difference was not statistically significant.

Figures 4.4a and 4.4b: EASRs for oesophageal adenocarcinoma and oesophageal squamous cell carcinoma diagnosed in males (figure 4.4a) and females (figure 4.4b) in England (West Midlands) between 1998 and 2004 by ethnicity

Figure 4.4a

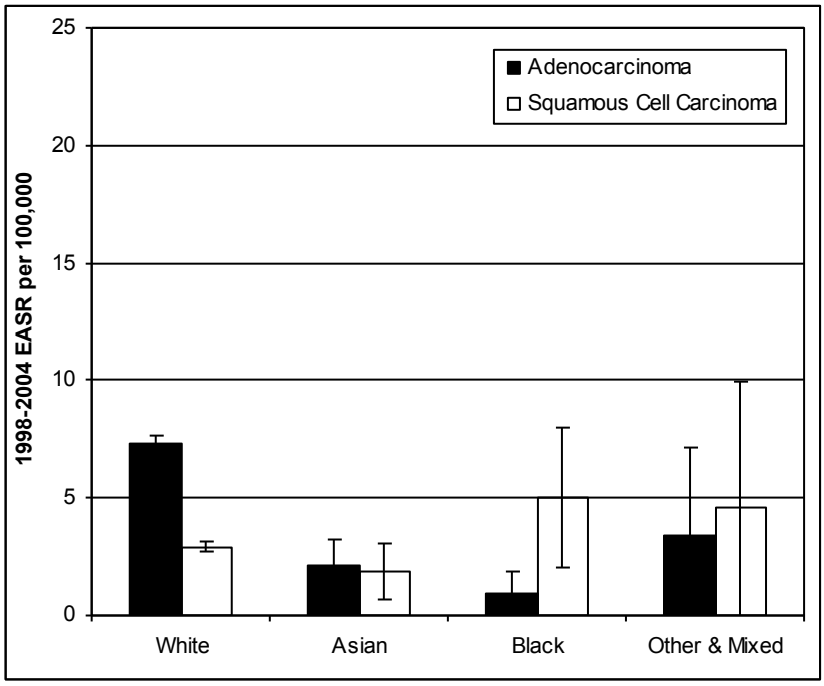
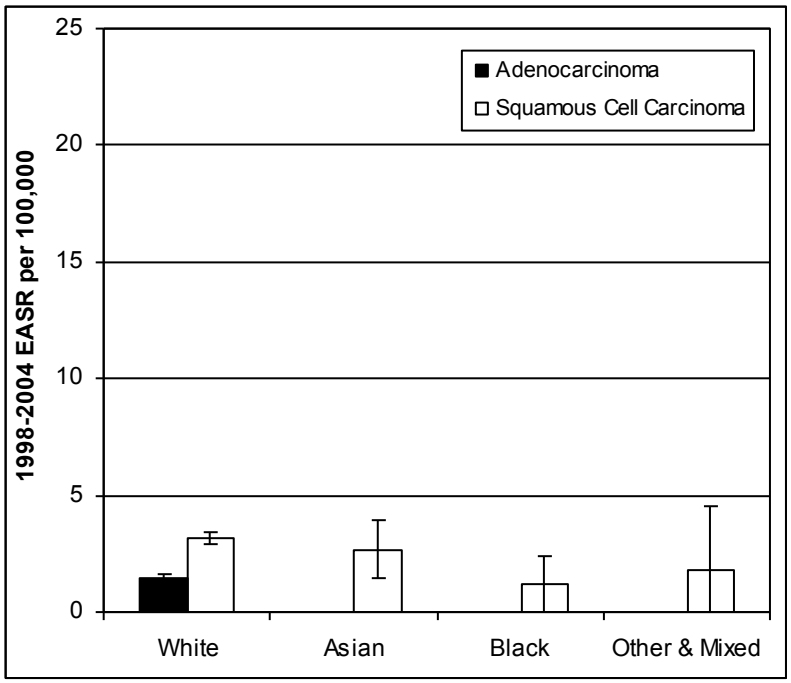


Figure 4.4b



4.4 Discussion

The rising incidence of OC, specifically OAC, observed in the UK ten years ago (Botterweck et al., 2000, Powell and McConkey, 1992, Wayman et al., 2001, Kocher et al., 2001, Powell et al., 2002) continues unabated during the past decade. In comparison, the incidence of OSCC has altered little in England, confirming that the rise in OAC is very unlikely to be a result of improved diagnostic or reporting methods, despite there being a fall in the rates of the unclassified cases. Re-examination of 4252 of the records for this study further strengthens this conclusion with similar percentages reclassified as OAC and OSCC from cases previously unclassified.

The development of OAC is positively associated with gastro-oesophageal reflux (Lagergren et al., 1999a, Wu et al., 2003), obesity (Wu et al., 2003, Lagergren et al., 1999b, Vaughan et al., 1995) and being male (Blot et al., 1991). Limited data suggest an increase in recent years in the endoscopic incidence of the pre-malignant complication of chronic gastro-oesophageal reflux BO (Prach et al., 1997). This change may in part be due to increasing use of endoscopy but also due to greater awareness of BO among endoscopists (Conio et al., 2001). Obesity in the US has been increasing for 50 years(Parikh et al., 2007), with the incidence of obesity within the UK doubling from 1985-1992 (Prentice and Jebb, 1995). This rapid change, with obesity also associated with an increased incidence of gastro-oesophageal reflux symptoms (Mohammed et al., 2005), may well have contributed to the

rise in OAC seen. The rise in incidence of OAC was greatest in men, although a significant but smaller rise was also seen among women. Male pattern obesity with increased abdominal or visceral fat is particularly associated OAC (Vaughan et al., 2002). Occupational exposure to cement dust and asbestos (Jansson et al., 2005a) has been associated with development of OAC. Males develop OAC on average 8 years younger than females and cases of OAC before the menopause are very unusual. This raises the possibility that female sex hormones may protect against the development of OAC, or OAC oncogenesis may be, in part, driven by androgens.

It has also been shown that the development of OAC is negatively associated with *Helicobacter pylori* (de Martel et al., 2005) and increasing consumption of fruit, vegetables and fibre (Brown et al., 1995). The incidence of *Helicobacter pylori* has fallen by 25% between the 1970s and 1990s (Haruma et al., 1997, Kosunen et al., 1997). A significant minority of patients with *Helicobacter pylori* develop atrophic gastritis and are rendered achlorhydric (Kuipers et al., 1995, Harford et al., 2000) and therefore not at risk of acid gastro-oesophageal reflux and its complications BO (Vicari et al., 1998, Vaezi et al., 2000) and OAC (Vicari et al., 1998). The fall in incidence of *Helicobacter pylori* may have therefore increased the numbers of individuals in the population at risk of OAC. The consumption of fruit has changed little, whilst that of green vegetables has fallen in the UK during the study time-period (Statistics). However, it has been hypothesised that the use of nitrogenous fertilizers on

vegetables may have contributed to the rise in incidence of OAC (Iijima et al., 2003b, Suzuki et al., 2005).

The present study used two measures of socio-economic status, the Townsend score based on the 1991 Census using regional quintiles and the IMD 2004 using national quintiles based on 2001 data, with almost identical results, showing there was no association between socio-economic status and OAC. Thus it is unlikely that deprivation or affluence contribute to the development of OAC in England, in keeping with findings in Scotland from 1987-1996 (Brewster et al., 2000).

In contrast, deprivation was strongly associated with OSCC as has been previously noted (Brown et al., 2001). Unexpectedly, this association appeared to become weaker in the 1990's using the Townsend index, due to a declining incidence in the deprived in addition to an increasing incidence in the affluent. However, the IMD 2004 measure showed that the association between deprivation and OSCC remained strong at the end of the study period, with a higher incidence in the deprived group than in the affluent group. It is not clear why the two measures of socio-economic status are discordant. The Townsend index focuses more on material deprivation rather than income and benefit allowances identified by the IMD, potentially leading to discrepancies between the scoring systems. The deprivation level of an area can change considerably, for example with the introduction of new

housing and redevelopment schemes, which may have altered over the study period. It is possible that since the Townsend index utilised was based on the 1991 census, that for cases diagnosed in the late 1990s and 2000s this is a less reliable measure than the IMD. In our study, the Townsend Index was preferred, as the data used to construct this index were taken from around the mid-point of the study period 1991. It is known that OSCC is associated with a diet poor in fruit and vegetables (Bosetti et al., 2000), smoking and excess alcohol (Vaughan et al., 1995), all of which are more common among those from deprived backgrounds (Lallukka et al., 2007, Roos et al., 2008, Casswell et al., 2003, Jefferis et al., 2004).

The higher rates of OAC in both men and women with white ethnicity than in other ethnic groups, confirms the findings of studies in other countries (Hesketh et al., 1989, Roos et al., 2008). Although GORD symptoms appear equally common among non-white subjects, endoscopic oesophagitis and Barrett's oesophagus are much less common in these groups (Ford et al., 2005). The higher incidence of *Helicobacter pylori* among non-white subjects (Everhart et al., 2000) may partly explain these differences but further research into this striking difference in incidence is clearly needed. It must be noted that this analysis is limited by the fact that 13.3% of the population (523 out of 3909) were either unknown or not HES matched. However, as HES data are derived directly from the patient, interpretation of ethnicity by data collectors will not have been an issue. The creation of the National

Cancer Intelligence Network should serve to improve the quality of ethnicity data, enabling application to the whole of the population of England.

Through examination of those cases incompletely abstracted with unknown morphology and those coded as gastric cardia between 1977 and 1986, the validity of the data has been strengthened. The proportionally high number of other or unknown cancer morphologies, particularly early in the time period examined, may mean an under representation of the incidence of OAC or OSCC, but there is no reason to suspect that this would be preferential for either morphology. During the time period examined, while the number of unknown/other morphologies did not change as an absolute figure (124 cancers in 1977 to 116 in 2004), there was a significant fall in the rates of cancers without a specific known morphology. Thus, there has been an improvement in either reporting trends, or classification by histopathologists, but this is similar for both OAC and OSCC. The data presented here are only for patients who live within the unchanging boundaries of the WMCIU, and do not include individuals referred from outside the region. Thus referral patterns for treatment do not explain any of the incidence patterns.

This analysis of the incidence of oesophageal cancer covers one of the longest periods examined in the literature (28 years), includes a novel examination of the influence of socioeconomic status in a representative population of England, and is the first to report on the influence of ethnicity in

the UK. The incidence of oesophageal cancer continues to rise in England due to a marked rise in OAC, which is strongly associated with male gender and white ethnicity. Socio-economic status does not appear to influence the incidence of OAC. The incidence of OSCC has not changed, and is the most common tumour morphology in black men and white women. OSCC is strongly associated with measures of deprivation.

Chapter 5

Patients with prostate cancer are less likely to develop oesophageal adenocarcinoma - could androgens have a role in the aetiology of oesophageal adenocarcinoma?

(Data from this chapter have been published: see appendix 5 for reference)

5.1 Introduction

Men have a five-fold increased incidence of oesophageal adenocarcinoma (OAC), as compared with women (Blot et al., 1991). Epidemiological studies of the aetiology of OAC have identified a number of consistent associations, but only male pattern obesity is of relevance to gender. Occupational exposures have been examined, with positive associations with the development of OAC reported for exposure to cement dust and asbestos (Jansson et al., 2005a). However none of these associations can fully provide an explanation for the five-fold increased incidence of OAC in men (Blot et al., 1991).

Differences in sex hormones such as higher concentrations of androgens in men may provide a potential explanation for the difference in OAC incidence by sex. Prostate cancer (PC), an androgen sensitive tumour with a long natural history (five-year relative survival of over 70% for non-metastatic tumours at presentation (Cancer Research, 2008)), should allow insight into this putative explanation. We have therefore examined the incidence of a second primary of OAC in those with a first primary of PC in the West Midlands, UK, to examine whether androgens may potentially contribute to the higher incidence of OAC among men.

5.2 Materials and Methods

5.2.1 Study design

A population based retrospective cohort of men with a first malignant primary of PC diagnosed between 1977 and 2004, was identified from the cancer registration database at the West Midlands Cancer Intelligence Unit (WMCIU) as described in Chapter 3. Inclusion in the WMCIU database requires histology, clinician evaluation or on the basis of a death certificate, and is never purely from a raised serum marker such as “Prostate Specific Antigen” (PSA). These patients were followed up until diagnosis of a second malignant primary, death, or the end of the follow-up period in the registry (31st December 2004). Ethnicity data were obtained using linkage between the cancer registration database and Hospital Episode Statistics (HES).

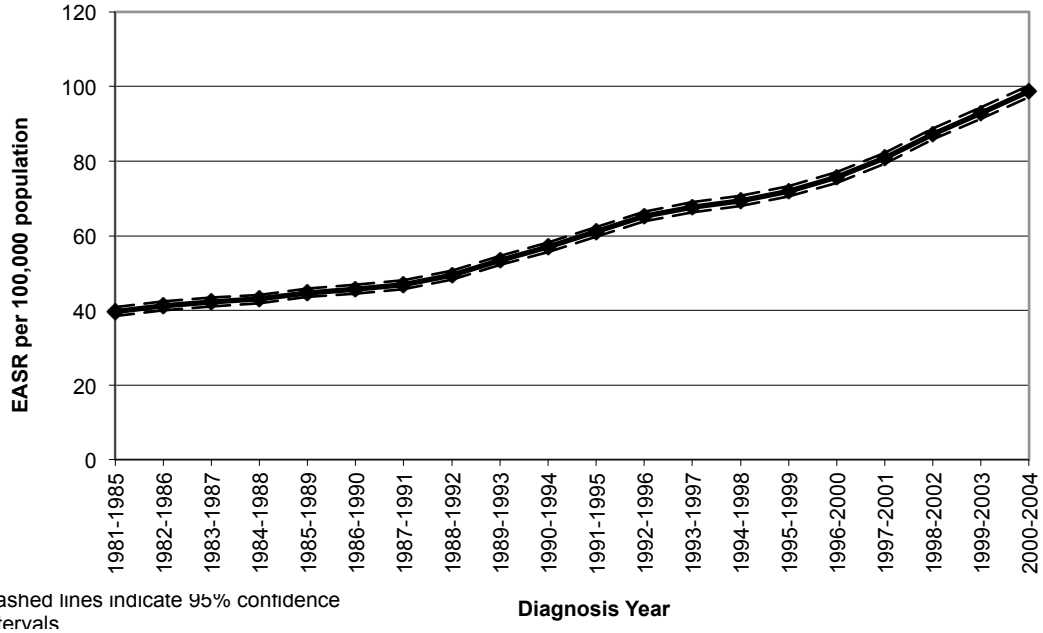
Statistical analysis was performed (by Stacey Croft, WMCIU) using STATA version 9 (StataCorp, 2005).

5.3 Results

5.3.1 Study subjects

From 1977-2004, 44 189 patients developed PC as a first primary malignant tumour within the West Midlands. Following exclusion for follow-up of less than three months, 38 627 were eligible for study, providing 143 526 patient years of follow-up (mean 4.0 years, range 3 months to 27.8 years). Figure 5.1 shows an increasing incidence of PC in the West Midlands over this time period, initially quite gradual until the early 1990s, when the rise becomes more rapid following the introduction of PSA testing in the UK.

Figure 5.1 The incidence of prostate cancer in the West Midlands 1977-2004 directly standardised to the European Standard Population



Dashed lines indicate 95% confidence intervals

5.3.2 Ethnicity

Examination of ethnicity for the 19 071 patients diagnosed with OC during 1998-2004 revealed that the vast majority (83%) of PC patients included in the study from this period were white (n=15 751), with only 7 black individuals, and one South Asian subject (table 5.1). However, there were 3 312 cases for whom ethnicity could not be determined.

Table 5.1 Ethnicity of patients with a first primary of prostate cancer 1998-2004 (HES data availability) with end of follow-up reason stated

End of follow-up reason	**Ethnicity**				
	Mixed, other, Unknown	**Black**	**White**	**South Asian**	**Total**
Developed oesophageal cancer	4	1	34	0	39
Developed other malignant tumour	64	6	639	0	709
Died	707	0	4635	0	5342
Alive and free from second cancer at end of follow-up	2537	0	10443	1	12981
Total	**3312**	**7**	**15751**	**1**	**19071**

5.3.3 Risk of second oesophageal malignancy

Table 5.2 and figure 5.2 show the observed incidence of a second malignancy of OC following a primary of PC, with the expected incidence of OC among an age- and period-adjusted general population, and the SIR as an estimate of relative risk. The SIR (95% CI) of developing OC following PC is significantly lower than expected at 0.78 (0.62-0.96). Examination of morphologies reveals that this overall decreased SIR is due to the reduced SIR of OAC at 0.70 (0.50-0.95), with the SIR of developing OSCC being no different from that that would be expected in the general population, 1.03 (0.69-1.47).

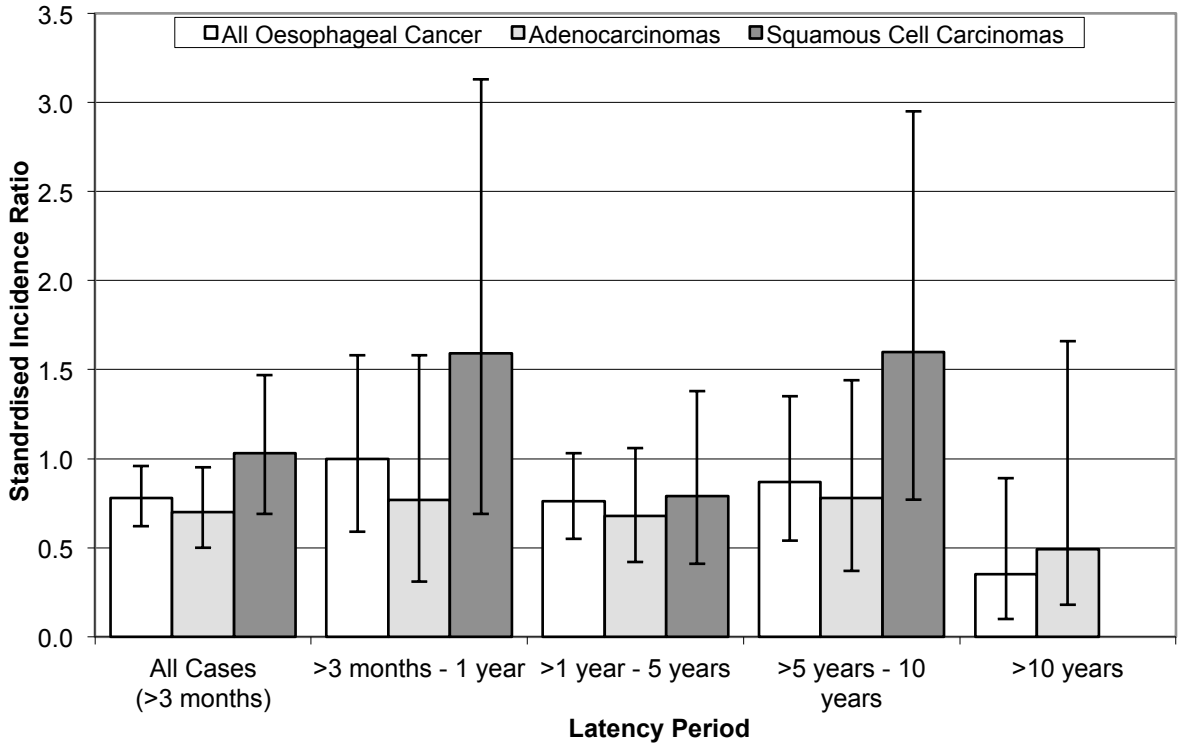
5.3.4 Time between diagnosis of prostate cancer and the diagnosis of oesophageal cancer (latency intervals)

Examination of latency (table 5.2 and figure 5.2) shows that no time period was individually associated with a reduced risk of OC, overall or when examined by individual morphology. Furthermore, there was no evidence of a declining risk over the entire time period.

Table 5.2 Observed and expected incidence of oesophageal cancer by morphology with SIR and 95% confidence intervals

	All cases	3mths - 1yr	1yr - 5yrs	5yrs - 10yrs	>10yrs
Person years	143525.9	26446.24	76848.13	28864.81	11366.69
Patients	38627	38627	31760	10391	2699
All Oesophageal cancer					
Observed	86	18	43	21	4
Expected	110.1	18	56.4	24.2	11.5
SIR (95% CI)	0.78 (0.62-0.96)	1.00 (0.59-1.58)	0.76 (0.55-1.03)	0.87 (0.54-1.35)	0.35 (0.1-0.89)
Oesophageal Adenocarcinoma					
Observed	40	7	20	10	3
Expected	57.3	9.1	29.3	12.8	6.2
SIR (95% CI)	0.70 (0.5-0.95)	0.77 (0.31-1.58)	0.68 (0.42-1.06)	0.78 (0.37-1.44)	0.49 (0.18-1.66)
Oesophageal Squamous Cell Carcinoma					
Observed	30	8	12	10	0
Expected	29.2	5	15.2	6.2	2.7
SIR (95% CI)	1.03 (0.69-1.47)	1.59 (0.69-3.13)	0.79 (0.41-1.38)	1.60 (0.77-2.95)	0

Figure 5.2 SIR (95% confidence intervals) for oesophageal cancer by morphology following a first primary of prostate cancer compared to the general population



5.4 Discussion

The strikingly increased incidence of OAC in men relative to women remains largely unexplained. Although male pattern obesity has been reported to be associated with the pre-malignant condition Barrett's oesophagus (Vaughan et al., 2002) and industrial exposure to potential carcinogens (Jansson et al., 2005a) have been hypothesised to play a role, it seems unlikely that either are a plausible explanation for all of the difference in incidence observed between the sexes. OAC cells express greater concentrations of androgen receptors than non-malignant oesophageal cells in animal models and in human oesophageal resection specimens (Awan et al., 2007, Tihan et al., 2001, Waraich, 2008), providing a molecular basis for the hypothesis that OAC oncogenesis may be, at least in part, androgen driven.

PC, as an androgen sensitive tumour (Balk and Knudsen, 2008), is typically treated with anti-androgen therapy, either surgically by orchidectomy, or medically with cyproterone or gonaderalin analogues (Jones, 1983). We have demonstrated that there is a significantly reduced risk of developing OAC following a first primary malignancy of the prostate, but not OSCC. To establish whether this could be as a result of anti-androgen therapy we have examined for a latency effect during follow-up following the initial diagnosis of PC, as a surrogate marker for exposure to anti-androgen therapy. It would be expected that there would be a progressive fall in the incidence of OAC, following commencing anti-androgen therapy if androgens had an important

role in the pathogenesis of OAC. No effect of latency was observed, suggesting that either increased exposure to anti-androgen therapy may not be associated with the reduced risk observed in developing OAC after PC or that there may be a latency effect but that the study lacks sufficient power to detect it, as it is important to recognise that the numbers of observed and expected cases of OAC in the longer time periods are small.

An examination of the SEER-9 registries database 1973-2003 revealed that OC was significantly less common among PC patients than the general population, SIR 0.83, but did not examine the different morphologies of OC separately (Hayat et al., 2007). An earlier study examining the combined incidence of OAC and gastric cardia adenocarcinoma following PC failed to reveal any association(Ahsan et al., 1997). However, although OAC and gastric cardia tumours share some aetiological factors, others differ (e.g. *Helicobacter pylori*) (El-Serag et al., 2002). A study among Swedish men between 1958 and 1992 reported no significant difference between observed and expected numbers of new cases of OAC following PC (Lagergren and Nyren, 1998). However, despite 400 000 patient years of follow-up, it is possible that this study lacked statistical power due to the low incidence of OAC in Sweden during this time period (Lagergren and Nyren, 1998). OAC is 5-fold more common in the United Kingdom than in Sweden (el-Serag, 2002).

PC and OAC share a number of aetiological risk factors. Obesity is associated with OAC and PC, although the association with the latter is with a more aggressive form of the disease (Hsing et al., 2007). This may potentially mean that some longer-term survivors of PC would be less obese, and thus at less risk of developing OAC. Greater levels of IGF-I (insulin-like growth factor-I), a "noted mitogen", are seen in both PC (Stattin et al., 2000) and OAC (Siahpush et al., 2007).

While PC is more common among the affluent (Rowan, 2007) and OSCC is more common among the deprived (Brown et al., 2001, Nguyen et al., 2003), there is no association between socio-economic status and the incidence of OAC (Brewster et al., 2000). This would suggest that affluence should not influence the risk of OAC among PC patients, but would perhaps lower the risk of OSCC among PC patients. It is therefore likely that the socio-economic status of the PC patients is not influencing the development of either OAC or OSCC. Black ethnicity is associated with PC (Yanke et al., 2006), and white ethnicity with OAC (Chapter 4). Thus, if a significant number of the PC patients were of black ethnic origin, and therefore at lower risk of OAC, this could provide a plausible explanation for the effect observed. However, examination of HES data from 1997/8-2004/5 revealed that the number of black subjects developing PC in this cohort was extremely small, and thus unlikely to influence the results, although there were a large number of patients with unknown ethnicity and so we cannot entirely rule out this

explanation.

The incidence of PC has been rising over the past 30 years (figure 5.1), the more rapid growth since the early 1990s being largely due to an increased public awareness and “screening” with serum markers such as PSA (Cancer Research, 2008). Such patients identified through screening may have “healthier lifestyles” than patients who do not undergo screening (Sutton et al., 2000). Such patients may therefore be at a lower risk of OAC. A diagnosis of PC may also induce patients to alter their lifestyle, becoming a “healthy cohort” (akin to the “healthy worker effect”) (Li and Sung, 1999), thus reducing their risk of developing a subsequent malignancy. However, as the risk of OSCC, in contrast to OAC, remains broadly similar to that of the age- and time-period adjusted male population, these potential explanations for the study findings would appear unlikely.

In summary, we have demonstrated that a first primary cancer of the prostate is associated with a reduced risk of developing a second primary of oesophageal cancer, specifically adenocarcinoma rather than squamous cell carcinoma. Prostate cancer may be associated with unrecognised risk factors that are negatively associated with oesophageal adenocarcinoma. While it was not possible to demonstrate a latency effect to support the hypothesis that cumulative use of anti-androgen therapy is the mechanism reducing OAC incidence in this cohort, this remains a plausible explanation.

Chapter 6

Subjects with prostate cancer are less likely to develop oesophageal cancer – analysis of SEER 9 Registries Database

(Data from this chapter have been published: see appendix 5 for reference)

6.1 Introduction

Oesophageal adenocarcinoma is five times more common among men than women in both the UK (Chapter 4) and the US (Blot et al., 1991). Examination of animal-model and human OAC pathology specimens has revealed increased androgen receptor expression on OAC as compared with normal oesophageal cells(Waraich, 2008, Awan et al., 2007, Tihan et al., 2001).

We have previously investigated the hypothesis that androgens may contribute to the aetiology OAC by identifying subjects with a first primary of prostate cancer, an androgen sensitive tumour (Balk and Knudsen, 2008) with a long natural history (five year survival of over 70% for those presenting without metastases (Cancer Research, 2008)) in the West Midlands Cancer Intelligence Unit registry (UK) and examining the risk of developing a second cancer of the oesophagus, compared with the general population (Chapter 5). The study identified a reduced risk of developing OAC following PC, but not OSCC. We hypothesised that anti-androgen therapy (surgical or medical), often employed in the management of PC (Jones, 1983), may reduce the risk of developing OAC after PC. However, we were unable to identify the increasing reduction in OAC incidence with time that would be expected if this hypothesis was correct.

We have therefore re-examined the association between PC and subsequent oesophageal cancer in the SEER 9 Registries Database (Hankey et al., 1999). The SEER database includes ethnicity data, enabling us to control for

the potential confounding effect of PC being more common in black subjects (Yanke et al., 2006), while OAC is more common in whites.

6.2 Materials and Methods

The study design and data analysis (chapter 3) are identical to the study in chapter 5, but uses the SEER 9 registries database, providing an almost ten-fold greater patient year of follow-up, aiming to improve the power to identify a latency effect. Moreover, the SEER dataset contains ethnicity dataset for the whole time-period. Enabling thorough examination of the impact of ethnicity.

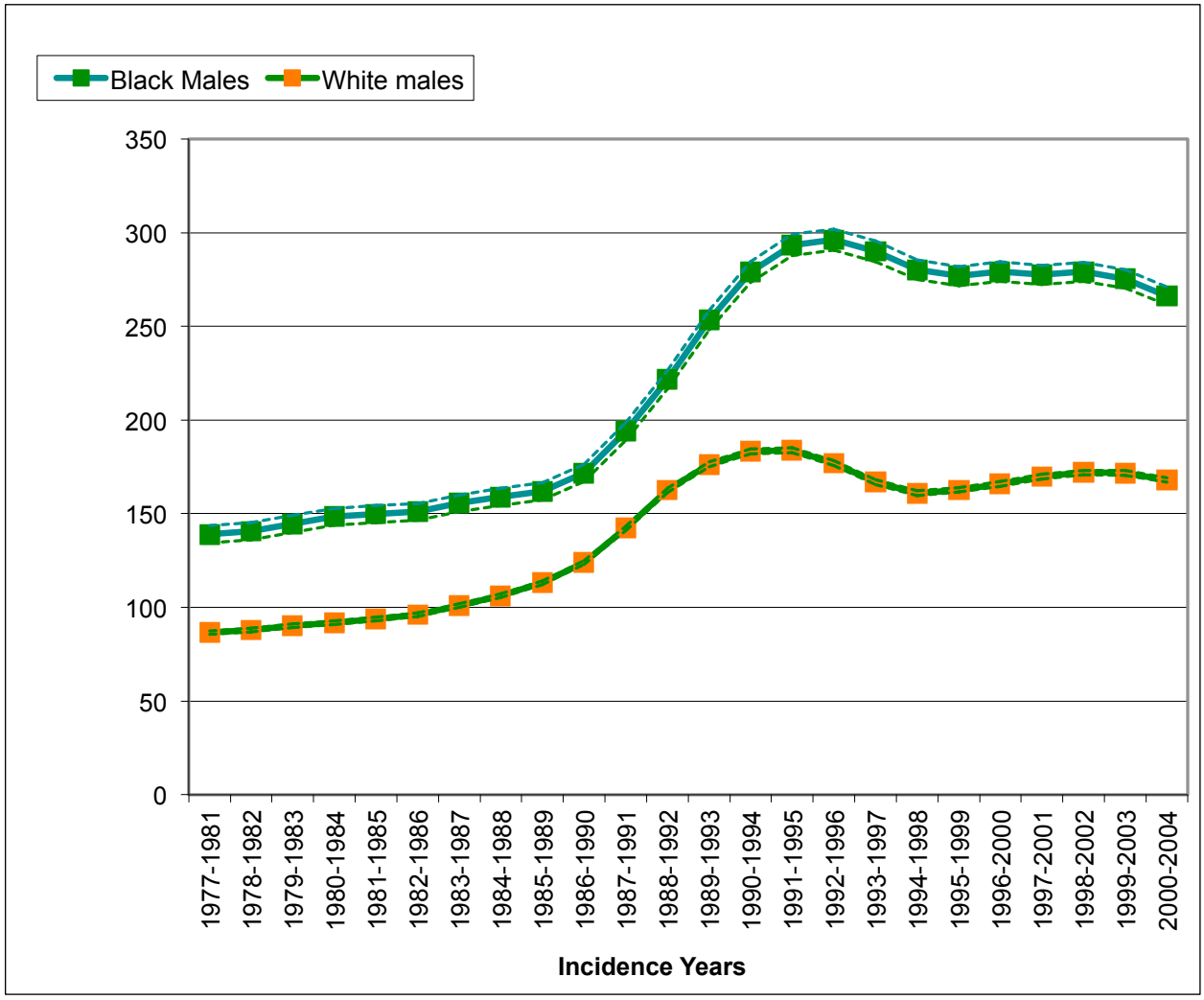
Statistical analysis was performed personally using STATA version 10 (StataCorp, 2005).

6.3 Results

6.3.1 Study subjects

Between 1977 and 2004, 362 553 subjects (301 576 white and 41 141 black) developed PC as a first primary malignant tumour within the SEER 9 registries. Following exclusion criteria, 343 538 were eligible for study, providing 2 014 337 years of follow-up. The incidence of PC was highest among black individuals, but has been rising steadily among both black and white ethnicities, with a sharp rise seen from the late 1980s (figure 6.1).

Figure 6.1 The incidence of prostate cancer by ethnicity using five year rolling directly age-standardised rates per 100 000.



There has been a steady rise in the incidence of OAC during the study period, predominantly among white men (figure 6.2). OSCC is more common among black men, however, there has been a sharp decline in OSCC incidence among this ethnic group in the last two decades (figure 6.3).

Figure 6.2 The incidence of oesophageal adenocarcinoma by gender and ethnicity using five year rolling directly age standardised rates per 100,000.

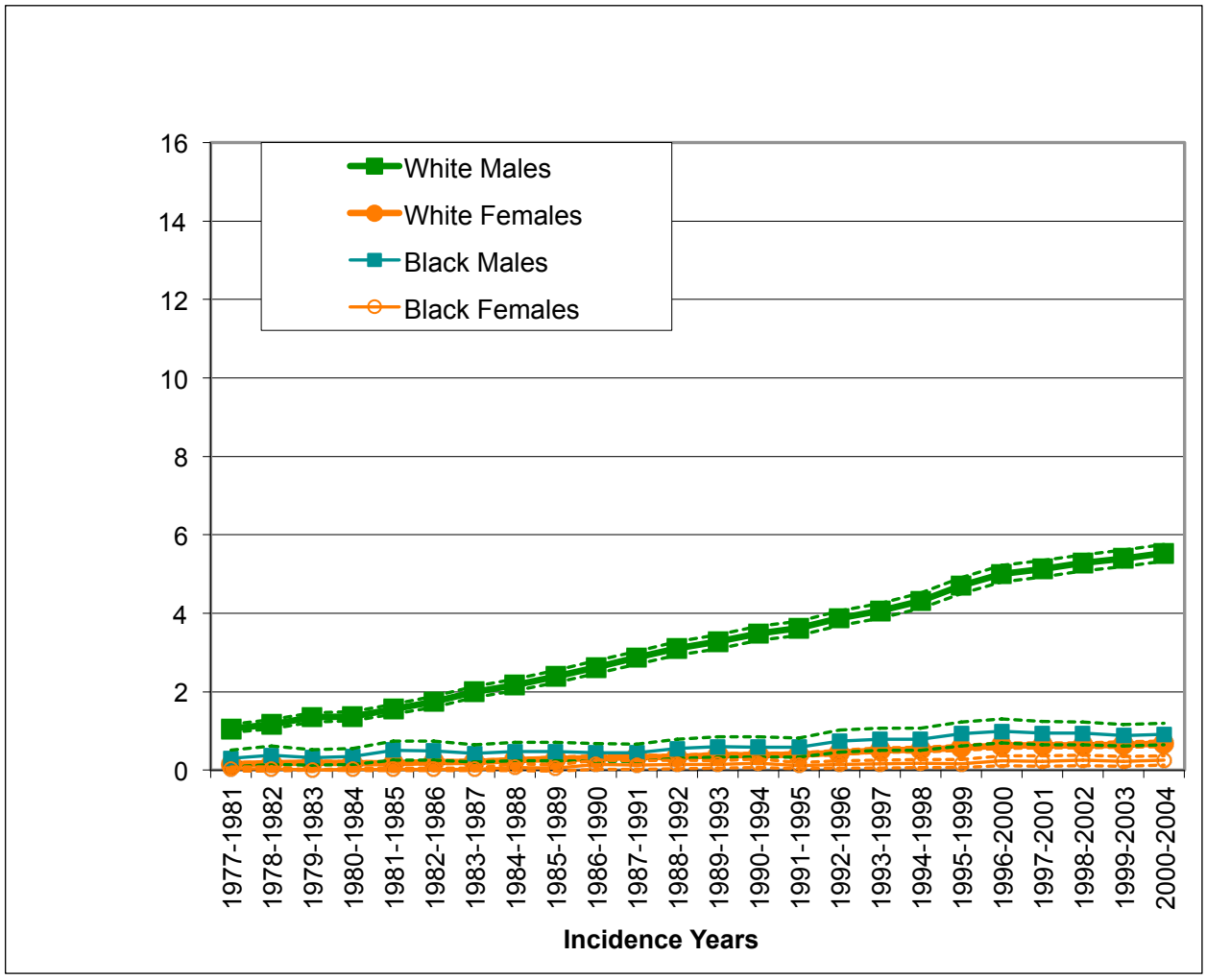
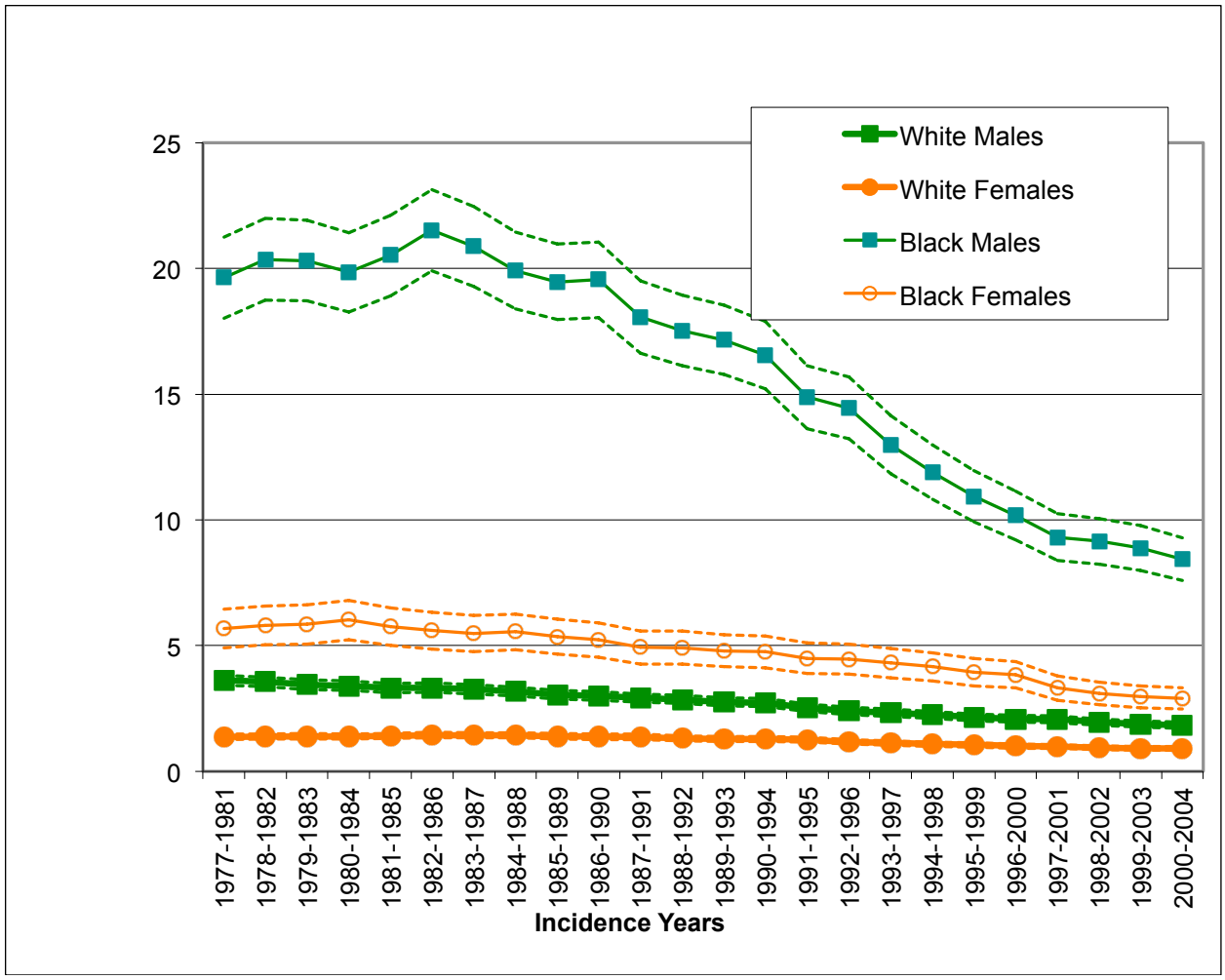


Figure 6.3 The incidence of oesophageal squamous cell carcinoma by gender and ethnicity using five year rolling directly age standardised rates per 100 000.



6.3.2 Risk of a second malignant primary of oesophageal cancer

The observed standardised incidence ratios (SIR) of both OAC (0.83(95% CI 0.74-0.93) and OSCC (0.79(0.69-0.89) following a first primary of PC were significantly less common than would be expected for an age and time-period adjusted population (table 6.1).

Moreover, the SIR fall with increasing time interval from the date of diagnosis of PC for both OC morphologies, suggesting a latency effect.

Table 6.1. Observed and expected incidence and standardised incidence ratios of oesophageal adenocarcinoma and squamous cell carcinoma among men of all races following a first primary cancer of the prostate.

	>3 months	3 months-1 year	1-5 years	>5 years
PC years of follow-up	2 104 337	246 515	952 243	815 578
Subjects	343 538	343 538	312 436	172 990
Oesophageal adenocarcinoma				
Observed	305	40	135	130
Expected	369	36	159	174
SIR (95% CI)	0.83 (0.74-0.93)	1.1 (0.79-1.5)	0.85 (0.71-1.01)	0.75 (0.62-0.89)
Oesophageal squamous cell carcinoma				
Observed	240	38	115	87
Expected	305	38	145	122
SIR (95% CI)	0.79 (0.69-0.89)	1.01 (0.72-1.39)	0.79 (0.66-0.95)	0.71 (0.57-0.88)

6.3.3 Ethnicity

The SIR of OC, OAC and OSCC following a first primary of PC by ethnicity are shown in table 6.2. The SIR for all OC and OSCC following a diagnosis of PC is reduced in both whites and blacks. The SIR for OAC is also reduced in white men following a diagnosis of PC (0.83(0.73-0.92), but not among black men (0.95(0.35-2.07)), although very few black subjects developed OAC during the study period.

Table 6.2 Observed and expected incidence and standardised incidence ratios for oesophageal cancer by morphology and ethnicity following a first primary cancer of the prostate.

	All races	White	Black
PC subjects	343 538	286 162	38 837
Years follow-up	2 014 337	1 711 512	202 910
All oesophageal cancers			
Observed	604	501	81
Expected	758	639	108
SIR (95% CI)	0.8 (0.73-0.86)	0.78 (0.72-0.86)	0.75 (0.6-0.93)
Oesophageal adenocarcinoma			
Observed	305	297	6
Expected	369	360	6
SIR (95% CI)	0.83 (0.74-0.93)	0.83 (0.73-0.92)	0.95 (0.35-2.07)
Oesophageal squamous cell carcinoma			
Observed	240	155	68
Expected	305	208	90
SIR (95% CI)	0.79 (0.69-0.89)	0.75 (0.63-0.87)	0.76 (0.59-0.96)

6.4 Discussion

The higher incidence of OAC among males has not been satisfactorily explained by differential exposure to potential risk factors for OAC. However, a putative molecular basis for androgens contributing to the oncogenesis of OAC has been reported (Waraich, 2008, Awan et al., 2007, Tihan et al., 2001) and epidemiological evidence of a reduced incidence of OAC following PC (Chapter 5). In chapter 5, we could not identify a latency effect that would support the hypothesis that androgens play a role in the aetiology of OAC but postulated that the lack of an effect was likely to be due to a relative lack of power to demonstrate it.

By examining the SEER dataset, we have been able to include nearly ten times as many patients and over 14 times more patient years of follow up, over the same time-period and in the same percentage of the country's population, using the same methodology, thus providing greater power to identify a possible latency effect. The use of more accurate and extensive ethnicity data within SEER has enabled the examination of potential confounding due the greater incidence of OAC among white males, but greater incidence of PC among blacks (Yanke et al., 2006)

Previous studies of this subject have revealed conflicting results. A Swedish study reported no change in the incidence of OAC following PC with a SIR of

0.9 (95% CI 0.5-1.5) but was hampered by the rarity of OAC during the study period in Sweden (Lagergren and Nyren, 1998). A previous examination of the SEER dataset from 1973-2003 revealed a reduced incidence of OC following PC with a SIR of 0.83 ($p<0.05$), in keeping with the findings of the present study, despite a slightly earlier time period (Hayat et al., 2007). OC morphology (OAC and OSCC) was not examined in that study. However, a study that did examine the combined the incidence of OAC and adenocarcinoma of the gastric cardia reported finding an increased incidence following a diagnosis of PC (Ahsan et al., 1997). Although OAC and gastric cardia adenocarcinoma share some aetiological factors, others are completely divergent in their influence (e.g. Helicobacter pylori)(El-Serag et al., 2002).

In the present study, a reduced incidence of OAC following PC was again observed of a similar order of magnitude to that seen in the UK (0.83 versus 0.7 in the UK). Furthermore, a latency effect has been demonstrated, with a lower SIR the longer the time period since developing PC. This is compatible with our original hypothesis that since a greater time period following development of PC is plausibly a surrogate for cumulative anti-androgen treatment, androgens may contribute to the increased incidence of OAC in men.

In contrast to the previous study from the UK, there was also a reduced risk of developing OSCC following a diagnosis of PC, an observation identified in

both ethnic groups studied. Moreover, an apparent latency effect was also observed for OSCC with a lower SIR with longer follow up. Whilst OSCC is more common among males, the incidence is falling in all genders and ethnicities, although this appears greatest among black men (figure 6.3). Androgen receptor expression was reported in 3 out of 14 OSCC resections compared with 5 out of 11 OAC (Tihan et al., 2001). It is therefore possible that anti-androgen therapy is responsible for the latency effect observed. However, a plausible alternative explanation is the fact that PC is associated with affluence (Rowan, 2007), while OSCC is more common among deprived populations (Brown et al., 2001, Nguyen et al., 2003). OSCC may therefore be less common in subjects with PC than among the general population as the PC subjects come from more affluent backgrounds. However, this is unlikely to be the explanation either for the latency effect demonstrated of decreased incidence of OSCC following PC or for the lower incidence of OAC after PC.

Figure 6.1 clearly shows the rising incidence of prostate cancer, with a sharper increase seen in the middle of the time period examined. This was also seen in the UK and is a reflection of increased public awareness of PC and the presence of acceptable screening tests, such as the serum marker prostate-specific antigen. This has resulted in more than one million additional diagnoses of PC in the US since the advent of screening (Welch and Albertsen, 2009). Particular reference must be made to the changing demographics of those diagnosed with PC with the average age of diagnosis

dropping from 72 to 67 years and the black population in particular were more likely to be diagnosed at a younger age in 2004/5 compared with 1988/9. Furthermore, screening has led to much improved or earlier staging at diagnosis, with the incidence of T3/4 disease dropping from 52.7 to 7.9 per 100 000 among whites and 90.9 to 13.3 per 100 000 among blacks (Shao et al., 2009). Not only will younger age at diagnosis affect the subsequent risk of developing a second malignancy in subsequent years, but earlier disease may reflect survival advantage and less reliance on longer term anti-androgen treatment, with much debate surrounding long- or short-term hormone therapy for locally advanced prostate cancer (Brower, 2009), thus impacting upon the latency effects observed. The use of anti-androgens in the therapy for PC has increased in the US, most notably among those in whom it is prescribed as neo- adjuvant therapy prior to radiotherapy (from 9.8% to 74.6%), thus suggesting that the overall duration of anti-androgen therapy has been reduced in recent years (Cooperberg et al., 2003). This casts some doubt on the potential role of anti-androgen therapy in the latency effect noted in the present study.

Patients who attend screening are more likely to be affluent, to have better access healthcare and a healthier lifestyle (Sutton et al., 2000, Thomas et al., 2002) and thus may be at a lower risk of developing subsequent cancers including OC. Moreover, developing PC may encourage patients to attend to unhealthy aspects to their lifestyle, thus reducing their risk of subsequent

cancer. For example, it has been identified that cancer survivors are more likely to take vitamin and mineral supplements than the cancer-free general population (Velicer and Ulrich, 2008). A reduction in the incidence of a variety of second malignancies following PC have been identified in the SEER dataset, including colon, stomach and interestingly also cancers often associated with tobacco usage such as lung, oral cavity/pharynx (Hayat et al., 2007). The effect of adopting a healthier lifestyle is a plausible explanation for this widespread reduction in second malignancy incidence. It must be acknowledged that since PC has one of the better prognoses (Cancer Research, 2008), there is often an opportunity to alter lifestyle that may not be available with malignancies with a worse prognosis. However, since OSCC is strongly associated with smoking and subjects were excluded following developing a second malignancy, the development of other smoking related malignancies may also partly explain the latency effect observed for a reduced incidence of OSCC following PC in the present study.

The rapidly decreasing incidence of OSCC during the time-period examined, especially among black males in whom the incidence of PC is greatest, may contribute to the reduced risk of developing OSCC following a diagnosis of PC. The age and staging of PC at diagnosis has fallen markedly among black males (1988/9 compared with 2004/5) (Shao et al., 2009), allowing for potential greater longevity in this ethnic group in whom OSCC is more prevalent. Indeed, examining the incidence of OSCC following PC in the

SEER 1973-1990 dataset, a time period before the sharp decline in the incidence of OSCC, revealed no difference in the incidence of OSCC compared with the PC free matched general population (Ahsan et al., 1997). This is in keeping with the UK study, where the incidence of OSCC has remained relatively stable between 1977-2004 (Chapter 4). Although we have attempted to correct for time- period in the analysis, this may explain at least part of the difference between the reduced SIR for OSCC after PC in the SEER dataset and the lack of an effect in the UK study. However, differences in ethnicity between patients with PC and OAC are clearly not the explanation for the lower incidence of OC following PC.

Interestingly, although colorectal cancer is less common following PC (SIR 0.95($p<0.05$)) (Hayat et al., 2007), its incidence is increased among men who have undergone orchidectomy (hazard ratio 1.37) or medical anti-androgen therapy (HR 1.31) (Gillessen et al., 2010). A study utilising a similar combined healthcare and cancer registry database would allow clarification of the effect of anti- androgen therapy on the development of OAC and OSCC.

In summary, using the SEER 9 registries dataset we found that the incidence of both OAC and OSCC was reduced following PC. Furthermore, there was evidence of a latency effect suggesting that changes following a PC diagnosis progressively reduced the incidence of OAC and OSCC. The influence of anti-androgen therapy, the healthier lifestyle that subjects may adopt following a

diagnosis of PC and the rapidly falling incidence of OSCC in the USA are all potential explanations for the study findings.

Chapter 7

Risk factors for the development of oesophageal adenocarcinoma in Barrett's oesophagus: a UK primary care nested case-control study

7.1 Introduction

The incidence of OAC is rapidly rising across the Western world, particularly in the UK (Chapter 4). The five-year survival of patients developing OAC remains dismal (Rachet et al., 2009). BO, a sequela of chronic GORD, is a pre-malignant pre-cursor of OAC. The annual risk of progression from BO to OAC has been reported to be between 0.2-2% (Spechler, 1992, Eckardt et al., 2001, Drewitz et al., 1997, de Jonge et al., 2010). However a recent large-scale population cohort study based on pathology records suggested this was an over estimate, with the annual progression rate among 11 028 Danish BO patients reported to be 0.12% (Hvid-Jensen et al., 2011). Since the annual OAC progression rate is a big predictor of the cost effectiveness of BO endoscopic surveillance in mathematical model, the value of surveillance has been questioned (Barbiere and Lyratzopoulos, 2009).

Studies of the risk factors associated with the progression of BO to OAC are often limited by the inherent selection bias in studying those undergoing endoscopic surveillance rather than an unselected cohort (El-Serag et al., 2004, Nguyen et al., 2009). An unselected study of risk factors for progression to OAC among BO patients has not been previously performed in the UK despite the availability of primary care databases with substantial longitudinal data.

We have therefore examined a retrospective cohort of BO subjects, from a UK primary care database, and examined risk factors for the development of

oesophageal cancer (OC) to guide surveillance efforts and suggest other interventions to lower the risk of OAC in BO.

7.2 Methods

7.2.1 Subjects

BO subjects were identified from The Health Improvement Network (THIN) database. Only BO subjects with a minimum of one year of follow-up, and, when applicable, a minimum of one year between a diagnosis of BO and oesophageal cancer (OC) were included in the study. Study subjects were followed from the first coded entry of BO or Barrett's ulcer until either end of registration with the database, death, end of data capture period or diagnosis of OC.

7.2.2 Data extracted

Patient demographics (sex, age, period of follow-up with BO, proportion developing OC, socioeconomic status by Townsend quintile, BMI and smoking status (never versus ever)) were extracted. Both smoking status and BMI data were extracted from closest to the first recorded entry code for BO. To avoid confounding from subjects' smoking status changing as a result of a diagnosis of a potential pre-malignant condition (BO), smoking status was established as never or ever having smoked. If there was no entry for BMI, it was calculated (mass(kg)/height(m)^2) using an entry for height from age 18 onwards, and a weight closest to the first recorded code for BO.

7.2.3 Oesophageal cancer morphology

As the database does not record the morphology of OC, verification of OC diagnosis and subtype was sought. The "free text entry" of the THIN database

was examined for each OC patient, and enquiries were made of the subjects' GPs or by death certification (via an anonymised process through EPIC-UK (now Cedegim), the company administering THIN) to verify the morphology as OAC or other morphology. Cases proven to be squamous cell carcinoma of the oesophagus were excluded.

Study subjects were followed from the first coded entry of BO or Barrett's ulcer until either end of registration with the database, death, end of data capture within the database, or diagnosis of OC, whichever the former is. Use of drugs, by class, was initially examined as having ever, or never, been prescribed. In subjects developing OC, drug prescription was censored from examination 1 year before first coding of OC to prevent confounding from drugs that may have been prescribed for cancer symptoms. Drug classes examined include those believed to be negatively associated with OAC: aspirin, NSAIDs, proton-pump inhibitors (PPI), statins, and angiotensin converting enzyme inhibitors (ACE-I), and those potentially implicated in the aetiology of OAC by their side-effect of relaxation of the lower oesophageal sphincter (LOS): tri-cyclic antidepressants (TCAs)/anti-cholinergics, benzodiazepines, calcium channel antagonists, b-agonists, nitrates, and theophyllines, and those used for asthma including inhaled steroids.

Ethical approval (MREC) was obtained for use of THIN data (London MREC: 06/MRE02/93).

7.3.4 Statistical methods

SPSS version 19.0.0 (IBM, USA) was used to perform Cox regression analysis to produce hazard-ratios (HR) with 95% confidence intervals, adjusting for age and gender, to evaluate the association of risk factors with the development of OAC. For drugs associated with smoking related COPD management, correction for smoking status was also employed, to control for potential confounding from smoking.

To establish if dose-response relationships existed for the drugs examined, the number of scripts prescribed during the time period on the database was extracted, providing prescription density. Prescription density data were separated into quintiles and further Cox regression analysis performed as detailed above. Cumulative use of drugs associated with LOS relaxation and also cumulative use of drugs used to treat asthma/COPD including inhaled b-agonists, inhaled steroids (and combined steroid and beta-agonist inhalers), and oral theophyllines were also examined using Cox regression analysis.

7.3 Results

7.3.1 Subjects and validation

3 752 subjects with BO were eligible for inclusion in the study, following exclusion for those with less than one year of follow-up within the database, and those subjects developing OC within one year of the first recorded diagnosis of BO (n=34).

Fifty-three of the 58 identified OC subjects were successfully verified as having cancer of the oesophagus by the methods described. Three subjects had no free-text or death certification and did not belong to a registering practice that was signed up to respond to queries; two subjects had no useful information in their free text or death certificate and their GP was not available to respond or failed to respond to a query. 38 free text entries revealed the morphology for 31 subjects was OAC, two cancers required chemotherapy consistent with treatment of OAC, one was recorded as poorly differentiated (no morphology entered), one small cell cancer (an acknowledged complication of BO, thus remaining in the study), and three were oesophageal squamous cell carcinoma (one in a Barrett's segment), subsequently excluded from the study. Examination of 16 death certificates confirmed the presence of oesophageal cancer in 15 (only one revealing morphology as OAC) and one having no mention of OC, but the death was certified over 3 years from the initial OC code entry, and there was an acute unrelated diagnosis on the certificate (subject not excluded). Six subjects with 'free text comments' were also assessed by viewing of death certification with no contradicting

comments discovered. Fifteen enquiries were made to general practitioners via EPIC-UK (thus remained anonymised): nine were confirmed as adenocarcinoma, five as cancer/carcinoma and one none response.

7.3.2 Oesophageal cancer risk

With exclusion of three cases of squamous call carcinoma after the verification process, 3 749 subjects with BO were included in the study, providing 17 743 subject years of follow-up (median 4 (interquartile range (IQR) 3-6) years). Median age was 63 (IQR 52-72) years, and 2731 were male (63%). Fifty-five subjects developed OC, a progression rate of 0.3% per annum.

7.3.3 Risk factors for oesophageal cancer

Table 7.1 shows the influence of age, gender, smoking status, BMI, and having ever been prescribed specified drugs within the study period among BO subjects who did and did not progress to OC. Male gender was associated with progression to OC HR 3.1 (1.5-6.2), p=0.002, as was increasing age HR (for each year) 1.03 (95% CI 1.01-1.05), p=0.005. BMI data were not entered/calculable from the database in 744 subjects (19.8%): 733 of the BO only group (19.8%) and 11 of the OC group (20%). Once corrected for age and gender there was no association between increasing BMI and progression to OC (0.99 (0.92-1.06)). Furthermore, no association was seen when analysed by categorising BMI up to 25, overweight (BMI 25.1-30) and obese (BMI >30) (data not shown). Smoking status was not recorded in 333

subjects (8.8%): 320 of the BO only group (8.7%) and 13 of the OC group (23.6%). 2037 (55%) of the BO only group and 33 (60%) of the OC group had ever smoked. Having smoked doubled the risk for progression to OC (2.36 (1.13-4.93), p=0.023).

Use of the following prescribed drugs (by class) was not associated with progression to OC after correction for age and gender (and smoking for inhaled b-agonists and theophyllines): PPI (130,021 (0.0-5.6E232), aspirin (0.81 (0.46-1.43)), NSAIDs (1.12 (0.65-1.91)), COX-2 inhibitors (0.49 (0.15-1.56)), statins (0.94 (0.53-1.65)), oral iron preparations (1.38 (0.77-2.48)), oral anticholinergic drugs (1.67 (0.6-4.65))(including TCAs [1.18 (0.64-2.17)] and antispasmodics [1.35 (0.65-2.76)]), ACE-inhibitors (0.94 (0.53-1.66)), calcium channel blockers (1.04 (0.59-1.82)), hypnotics (including benzodiazepines [1.37 (0.79-2.36)]), inhaled β-agonists (1.27 (0.68-2.38)), nitrates (1.47 (0.84-2.57)) and nicorandil (0.72 (0.17-2.95)). There was also no association with socio-economic status as determined by Townsend quintile (p=0.49 for trend).

The use of inhaled steroids was associated with progression to OC (2.11 (1.12-3.97) p=0.021), as was the use of inhaled steroid and b-agonists combination inhalers 2.54 (1.17-5.51) p=0.018 (both corrected for age, gender and smoking). Theophylline use failed to reach a significant association with progression to OC 2.31 (0.9-5.93) p=0.082 (corrected for age, gender and smoking).

When examined by prescription density, the fourth quintile of increasing inhaled steroid use was associated with developing OC corrected for age, gender and smoking status (2.78 (1.15-6.77) p=0.024) and also for trend through the quintiles (p=0.028) (figure 7.1). Examining prescription density for combined inhaled steroid and b-agonists (corrected for age, gender and smoking) revealed an association with developing OC (figure 7.2), reaching significance in the fourth and fifth quintiles (3.79 (1.16-12.39) p=0.027 and 3.58 (1.09-11.8) p=0.036 respectively) with an increasing association across the quintiles (p=0.005). While theophyllines on an ever/never basis were not associated with progression to OC, the fourth quintile, after correction for age, gender and smoking status, exhibits a HR of 4.89 (1.17-20.37), p=0.029.

Cumulative use of drugs used for asthma/COPD showed an increasing association with progression to (OC p=0.027 for trend), with HR 2.75 (1.14-6.64) (p= 0.024) for the use of all three examined drugs (figure 7.3). This did not alter greatly when corrected for smoking (in addition to age and gender) with a HR 2.91 (1.1-7.68) p=0.031 for the use of all three drugs.

The cumulative use of drugs that are known to have a side-effect of reducing LOS pressure was also associated with progression to OC. Figure 7.4 illustrates an increasing risk with the use of one, two and three or more drugs within this category, with HR increasing from 0.86 (p=ns) for 1 drug, 1.71 (p=ns) for any 2 drugs, reaching significance with 3 or more drugs HR 2.31 (1.09-4.88) p=0.029 and p=0.009 for the trend seen. Given the associations

seen with cumulative asthma/COPD drugs, beta-agonists and theophylllines were subsequently removed from the cumulative LOS analysis, with loss of association, although there was still an increasing trend (non-significant p=0.283): 1 drug 1.15 (0.56-2.35), 2 drugs 1.38 (0.64-3), and 3 or more drugs 1.46 (0.68-3.12).

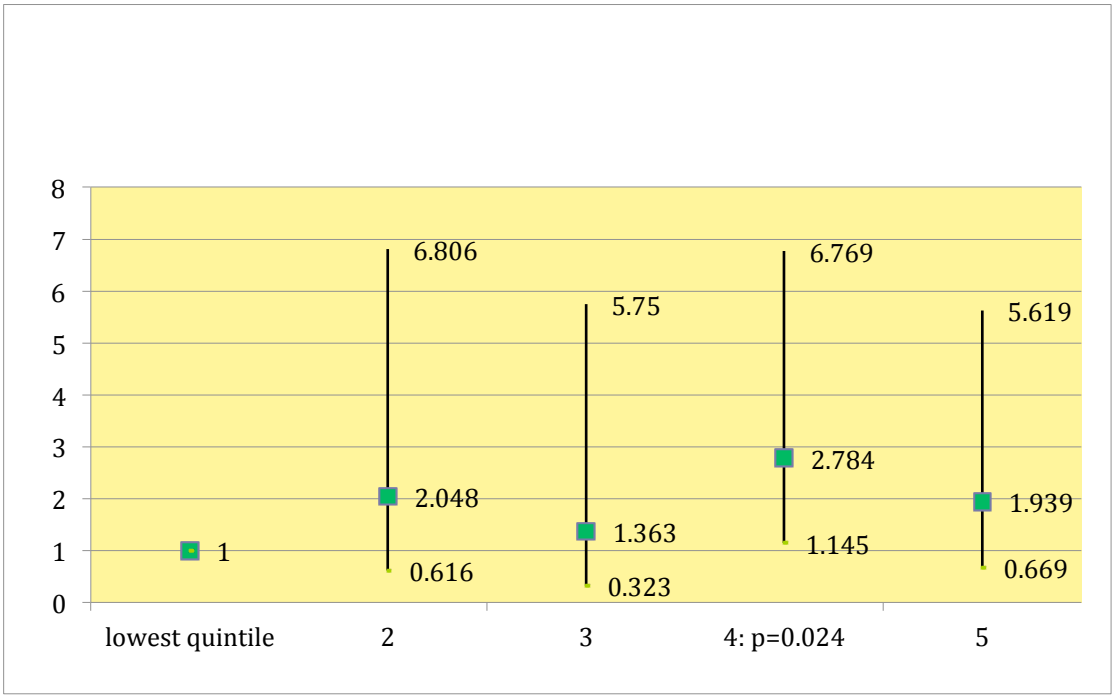
Table 7.1 Risk factors implicated in the progression from Barrett's oesophagus to oesophageal cancer

	Median age (IQR)	Gender	Median BMI (IQR) *	Smoking status	Aspirin *	Inhaled steroids #	Inhaled steroids/b-agonist #	Theophylline #
BO only (n=3694)	63 (52-72)	63% male (n=2 325)	25.9 (23.7-28.3)	55% ever smoked (n=2 037)	32% (n=1194)	19% (n=702)	7% (n=259)	4% (n=161)
OC (n=55)	67 (59-73)	84% male (n=46)	25.8 (23.7-28.5)	60% ever smoked (n=33)	35% (n=19)	33% (n=18)	15% (n=8)	11% (n=6)
Hazard ratio (95% CI)	1.03 (1.01-1.05) p=0.005	3.06 (1.5-6.24) p=0.002	0.99 (0.92-1.06) p=NS	2.36 (1.13-4.93) p=0.023	0.81 (0.46-1.43) p=NS	2.11 (1.12-3.97) p=0.021	2.54 (1.17-5.51) p=0.018	2.31 (0.9-5.93) p=NS

* corrected for age and gender

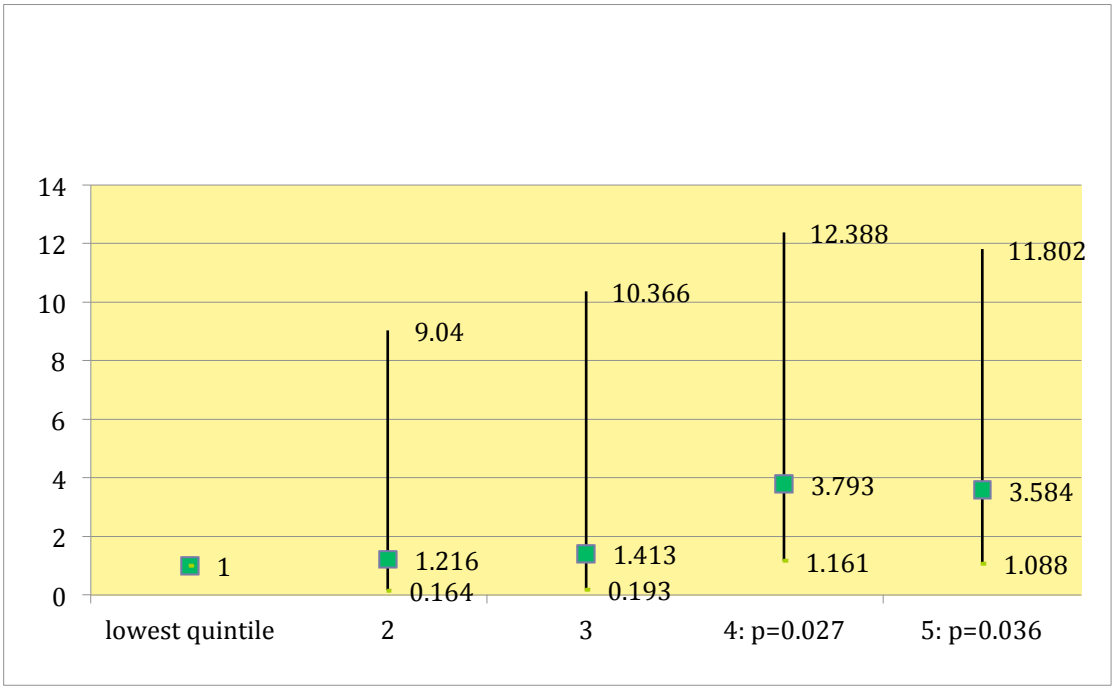
corrected for age, gender and smoking

Figure 7.1 Hazard ratios (95% confidence intervals) for the risk of developing oesophageal cancer from Barrett's oesophagus by prescription density of inhaled steroids in quintiles



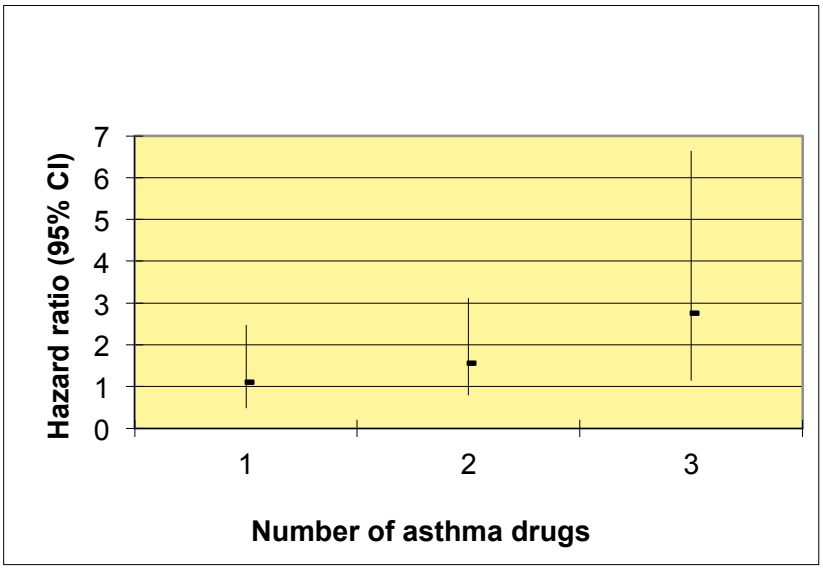
p=0.028 for trend

Figure 7.2 Hazard ratios (95% confidence intervals) for the estimation of risk of developing oesophageal cancer from Barrett's oesophagus by prescription density of inhaled combined steroids/beta-agonist in quintiles



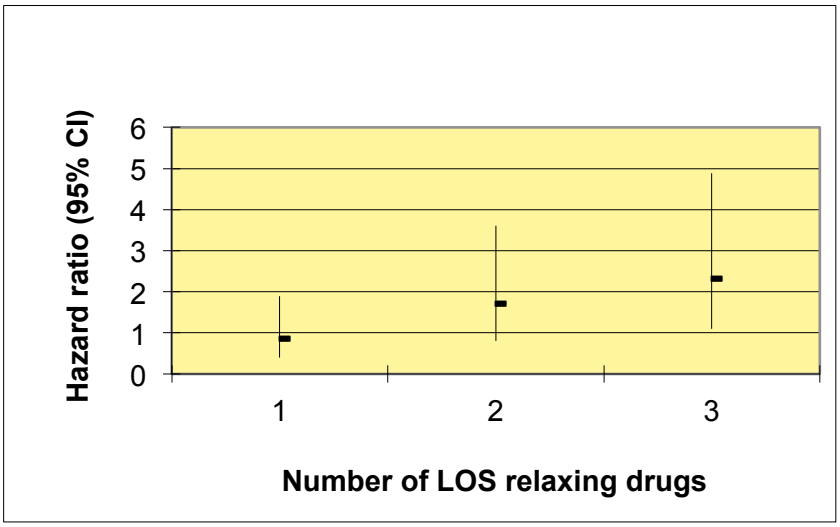
p=0.005 for trend

Figure 7.3 Risk of developing oesophageal cancer from Barrett's oesophagus shown as hazard ratio (95% CI) by cumulative number of drugs prescribed for the treatment of asthma or chronic obstructive pulmonary disease



p=0.027 for trend

Figure 7.4 Risk of developing oesophageal cancer from Barrett's oesophagus shown as hazard ratios (95% CI) by cumulative number of drugs with a side-effect profile of relaxation of the lower oesophageal sphincter



p=0.009 for trend

7.4 **Discussion**

Previous studies of BO and its progression to OAC often have inherent limitations with small numbers of subjects, often restricted to endoscopic surveillance patients with their inherent biases, and relatively short follow-up periods. This study aimed to overcome some of these issues by following subjects from a long-standing population based general practice database rather than a BO surveillance programme. The 0.3% per annum conversion rate from BO to OAC is at the lower end of previously published rates and is in keeping with more recent large Dutch and Danish studies (Hvid-Jensen et al., 2011, de Jonge et al., 2010). The THIN database will rarely record the histological confirmation of BO with intestinal metaplasia, nor the degree of dysplasia present. Moreover, the length of Barrett's segment will not usually be recorded either. The cohort would be expected to include many subjects with short segments of BO, since these are much more common than longer segments (Westhoff et al., 2005). Despite these inherent weaknesses of a general practice database study of BO, it is extremely unlikely that a diagnosis of BO would be coded for by a GP unless prompted by an endoscopic report of BO. The length of follow-up generated, with almost 18 000 subject years and a median follow-up per subject of 4 years, are strengths compared with many other studies of BO progression.

OAC is more common in men and a number of potential explanations have been suggested including work-place exposure to potential carcinogens (Jansson et al., 2005a), the influence of sex hormones (Chandanos and

Lagergren, 2009, Yang et al., 2012) and the influence of increasing BMI (Anderson et al., 2007, Merry et al., 2007). In the present study there was a greater than three-fold increased risk of men developing OC. However no association was found between increasing BMI and progression to OC suggesting that the effect of gender at this stage of oncogenesis is unlikely to be related to visceral obesity. BMI may therefore be associated with OAC in other studies through influencing the frequency and severity of gastro-oesophageal reflux disease and in turn the development of reflux oesophagitis and BO, rather than the development of OAC in BO subjects.

Of the common OC morphologies, squamous cell carcinoma has been considered to be most influenced by smoking (Vaughan et al., 1995) and lower socio-economic status (Chapter 4). Our simplified analysis of smoking status (never versus ever) was designed to overcome some of the limitations of the database in the recording of smoking status at random rather than set intervals (an inherent weakness in a retrospective database study). Having ever smoked more than doubled the risk of developing OC from BO. Similar findings were reported in work from the Northern Ireland Barrett's Oesophagus Registry (Coleman et al., 2012). On a practical note, the results of the present study and others on the influence of smoking in OAC strongly suggests that strenuous efforts should be made to encourage BO patients to stop smoking as a readily modifiable risk factor for OAC. There was no association between OAC progression and socio-economic status as

determined by Townsend quintile in the present study, a finding in keeping with an observational UK study of OAC (Chapter 4).

Aspirin use was associated with a slightly reduced hazard ratio and NSAIDs a slightly increased hazard ratio for development of OC in this study but these both failed to reach statistical significance when examined ever versus never use, and also in prescription density analysis (data not shown). Previous case-control studies have shown a reduced risk of OAC with aspirin and /or NSAIDs (Sadeghi et al., 2008, Duan et al., 2008, Fortuny et al., 2007, Jayaprakash et al., 2006, Anderson et al., 2006), including a meta-analysis (Corley et al., 2003, Liao et al., 2012), and further modelling suggested that those who benefited most from aspirin/NSAIDs were those with frequent reflux symptoms (Pandeya et al., 2010). While several studies of aspirin/NSAIDs have shown a reduced risk of neoplastic progression from BO both retrospectively (Tsibouris et al., 2004) and prospectively (Vaughan et al., 2005), including a reduction in aneuploidy and tetrapoidy (Vaughan et al., 2005), analysis of the UK National Barrett's Oesophagus Registry also failed to show an impact of aspirin use on not only on the development of OAC, but also on dysplasia (Gatenby et al., 2009). NSAID and aspirin use is not solely by prescription, with widespread over the counter (OTC) use. OTC aspirin and NSAID consumption will not be recorded in THIN, and the use of NSAIDs and aspirin is therefore likely to be an underestimate, potentially explaining the lack of a significant association in the present study. The results of the AspECT randomised control trial examining aspirin among BO patients, will

shed further light on the role of aspirin in progression of BO (Jankowski and Moayyedi, 2004).

None of the medications that have a side-effect of reducing LOS pressure were individually associated with neoplastic progression. When analysed by increasing number of drugs (one, two and three or more) there was a significant trend for increasing relative risk of neoplastic progression seen. This finding is in keeping with previous case-control studies (Lagergren et al., 2000, Corley et al., 2006), with the underlying mechanism of promoting gastro-oesophageal reflux. However, when beta-agonists and theophyllines were removed from the analysis of LOS relaxing drugs in order to further remove any confounding from asthma/COPD, the significant finding was lost. An increasing hazard ratio was still seen with increasing number of LOS relaxing drugs taken, although this failed to reach significance. It is likely that the failure to reach significance is due to reduction in power rather than confounding, especially as both theophyllines and beta-agonists failed to show significant association with progression to OC on an individual basis. An alternative and plausible explanation is that both beta-agonists and theophyllines may be implicated as they treat asthma/COPD, and these respiratory diseases are implicated in the progression form BO to OAC, rather than their LOS relaxation side effect.

Some medications that may lead to reduced LOS pressure are also used for asthma, for example beta-agonists and theophyllines (Corley et al., 2006,

Vaughan et al., 1998). There is potential for confounding to occur between the association of asthma medication use, gastro-oesophageal reflux symptoms and Barrett's oesophagus (Ladanchuk et al., 2010). Asthma/COPD drugs may be associated with developing OAC through GORD causing asthma and this combination being associated with an increased risk of COPD. Alternatively asthma/COPD drugs, through their effect on LOS pressure, may worsen gastro-oesophageal reflux and thereby increase OAC risk. Theophyllines have been shown to be associated with OAC in a meta-analysis (Alexandre et al., 2012), but in the present study although there was an increased hazard ratio this failed to reach statistical significance, and in prescription density analysis the fourth quintile did reach significance (4.89 (1.17-20.37)), but there was no significant association was seen across the quintiles (data not shown). Inhaled steroids have not been shown to affect LOS pressure, but in the present study a doubling of the risk of progression to OC was seen not only comparing ever versus never use, but also with increasing prescription density suggesting a dose effect response, or more likely an association with increasing disease severity. The 5th quintile of prescription density was not significantly associated with OC, both with inhaled steroids and theophyllines, but this may be due to those with a greater severity of asthma or COPD developing complications of pulmonary disease, rather than OC, shortening their time on the database. Furthermore, combined inhalers containing both inhaled steroid and beta-agonist doubled the risk of neoplastic progression from BO with not only ever versus never use but also increasing across all quintiles, reaching significance in both 4th and 5th quintiles. There was

association between cumulative use of increasing numbers of different drugs used for asthma/COPD ad OC development, reaching significance with three drugs used.

We were unable to definitively distinguish whether the association between asthma/COPD drugs and progression to OC relates to the side effects of the drugs on LOS pressure promoting reflux, or asthma/COPD in BO patients being associated with a higher risk of OC. However, the latter seems the more plausible explanation given the association of inhaled steroids with progression to OC. Controlling for smoking during the analysis removes one potential source of confounding in this association.

There are inherent limitations in performing a nested case-control study from GP entered data such as the THIN database. While all prescriptions issued are accurately recorded as they are generally computer generated scripts, it cannot be guaranteed that the script is either dispensed, or that the prescribed medication is taken by the patient. In some cases, for example with beta-agonist inhalers, multiple devices may be obtained by the patient, but not taken. Developing prescription density data (number of scripts issued per year) not only enables identification of any dose-response effects, but also reduces confounding from infrequent users of medication. Furthermore, OTC medication and drugs prescribed at other institutions will not be recorded. While these limitations exist, their impact is likely to be uniform among all patients, so bias is unlikely to affect the analysis.

The present study is reliant on correct data entry of the diagnosis of both OC and BO in the database. While we have undertaken a verification process concerning the OC entries, finding that cancer entries are accurate, although a few cases of squamous cell carcinoma were identified and excluded. We were unable to undertake a similar verification process for the diagnosis of BO as we did not have access to endoscopy or histology reports, but as this is an endoscopic and histological diagnosis as noted above, it is not one that general practitioners will make without a secondary care report based on endoscopy. Finally, we were unable to derive data on symptom patterns of GORD or dietary data, the prevalence of *Helicobacter pylori*, all of which may contribute to the development of OAC.

We have shown that progression to OC from BO is more common among men, smokers and as age increases. Our study is in keeping with previous papers reporting the association between increasing numbers of LOS relaxing drugs and OC, although removal of beta-agonists and theophyllines from this analysis removes this association, illustrating their important role in this finding. We have examined the hypothesis that drugs used for asthma or COPD are implicated in the progression to OC from BO. The association of inhaled steroids with OC development strongly suggests that it is the pathophysiolology of asthma/COPD or the severity of gastro-oesophageal reflux necessary to cause asthma rather the drugs themselves that are associated with progression to OC.

Chapter 8

The influence of aspirin, non-steroidal anti-inflammatory drugs and statins on oesophageal adenocarcinoma: a UK primary care case-control study

8.1 Introduction

With the rising incidence of OAC and continued poor prognosis, the search for modifiable aetiological factors is a subject of interest. Increasing body-mass index (BMI) (Anderson et al., 2007, Merry et al., 2007), smoking (Anderson et al., 2007, Solaymani-Dodaran et al., 2004), are positively associated with OAC, and aspirin and NSAIDs use have been reported to be negatively associated with OAC, but inconsistent results have been reported with statins (Shureiqi et al., 2001, Nguyen et al., 2009, Kantor et al., 2012, Kastelein et al., 2011).

Prospective case-control studies are often limited by the relatively low incidence of this cancer, restricting the study population size. We have therefore undertaken a case-control study of subjects with OAC in a UK primary care database with computerised prescribing data in comparison with subjects with BO, GORD and unselected control subjects.

8.2 Methods

8.2.1 Subjects

Oesophageal cancer patients were identified from The Health Improvement Network (THIN) database and those with a free text entry at this time period examined in order to select those with a confirmed diagnosis of OAC (anonymised by Cegedim the organisation managing the dataset). Cases were subjects with oesophageal cancer were identified by “Read” codes and adenocarcinoma morphology confirmed from the “free text” in-put by the General Practitioner. Three control groups were then identified: Barrett’s oesophagus (ratio of OAC:BO of 1:4), reflux oesophagitis (1:4) and unselected controls (1:10). All control subjects were matched by age (within 5 years), gender, geographical location (by GP practice) and time of diagnosis of OAC (within 5 years).

Ethics approval was obtained for use of THIN data (REC reference number 06/MRE02/92).

8.2.2 Variables examined

The influence of socio-economic status (Townsend quintile based on postcode), height, weight, body mass index (BMI), smoking status (never, ex or current) and drugs potentially negatively associated with the development of OAC (proton-pump inhibitors (PPI), aspirin, NSAIDs, statins, and COX-2 inhibitors), were assessed in the ten years prior to the year before a diagnosis of OAC, or 10 years prior to the matching date for control subjects. The data

within 1 year of diagnosis of OAC were censored to avoid confounding from a diagnosis of cancer or from drugs that may have been prescribed for cancer symptoms. Both smoking status and BMI data were extracted from during the study period, closest to the first recorded entry code for the period studied. If there was no entry for BMI, it was calculated (mass(kg)/height(m)^2) using an entry of height from age 18 onwards, and a weight closest to the first recorded code within the study period.

8.2.3 Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI), correcting for age and gender, were generated by performing logistic regression analysis, using SPSS version 19.0.0 (IBM, USA).

8.3 **Results**

8.3.1 Subjects

From 1825 subjects with Read codes for oesophageal cancer in THIN, 468 cases with a free text confirmation of adenocarcinoma were identified and eligible for the study, with at least one year of follow-up. 4652 unselected control subjects, 1636 BO subjects and 1644 RO subjects were matched according to the criteria described. The desired matching frequency was not always achievable (1:10, 1:4 and 1:4 respectively) due to limitations of case-matching to geographical area, then age, gender and time-period: two OAC subjects were not matched to any control subjects; two different OAC subjects were not matched to RO subjects; and two further different OAC subjects were not matched to any BO patients. All other cases had at least one control in the three control groups successfully matched. Table 8.1 demonstrates the subject demographics. While age, gender, Townsend score (quintile) and drug data were all complete, table 8.2 shows the proportion of missing data for other variables.

8.3.2 Logistic regression analysis

Increasing height (analysed by deci-meter), weight and BMI were significantly associated with OAC when compared with all control groups (table 8.3).

Current smoking was associated with OAC when compared to BO and unselected subjects but not with RO. No association was seen with being an ex-smoker with OAC, but a significant trend of smoking status from never, ex-

to current smoker was seen in the comparison of OAC with BO p=0.006, but fell just short of significance with OAC compared with RO (p=0.056) or with unselected controls (p=0.061).

There was no consistent association between OAC and socio-economic status by Townsend quintile (table 8.4).

The use of PPI was negatively associated with OAC as compared with BO and RO subjects, but positively when compared with community subjects. Aspirin and NSAIDs were negatively associated with OAC compared with RO and NSAIDs negatively associated with OAC compared with BO. The negative association between OAC and aspirin compared with BO fell just short of significance (table 8.3). There was no significant association with COX-2 inhibitor use. Statin use among unselected and RO subjects were negatively associated with OAC. The negative association seen with statins and OAC remained after correction for use of aspirin: unselected subjects (0.66 (0.46-0.97) p=0.032), RO subjects (0.6 (0.41-0.89) p=0.011), but not BO (0.81 (0.54-1.2) p=0.283).

Table 8.1 Demographics of the oesophageal adenocarcinoma subjects and the Barrett's oesophagus, reflux oesophagitis and unselected control subjects

	Oesophageal adenocarcinoma	Barrett's oesophagus	Reflux oesophagitis	Unselected control subjects
Number of subjects	468	1636	1644	4652
Gender (male)	384 (82.1%)	1326 (81.1%)	1332 (81%)	3812 (81.9%)
Median age (IQR) (years)	69 (59-77)	69 (59-77)	69.4 (59.5-76.6)	69.5 (59.5-77.5)
Townsend quintile (IQR)	3 (2-4)	3 (1-4)	3 (1-4)	3 (1-4)
Median weight (IQR) (kg)	80.2 (72.2-90)	76.2 (68.1-85.7)	76.2 (68.5-85.7)	76.2 (68.1-85.7)
Median height (IQR) (m)	1.73 (1.68-1.78)	1.71 (1.65-1.77)	1.72 (1.65-1.77)	1.73 (1.65-1.78)
Median BMI (IQR) (kgm^{-2})	26.9 (24-29.3)	26 (23.8-28.5)	25.9 (23.7-28.3)	25.7 (23.4-28.3)
PPI	131 (28%)	673 (41.1%)	847 (51.5%)	793 (17%)
Aspirin	96 (20.5%)	417 (25.5%)	485 (29.5%)	1107 (23.8%)
NSAIDs	186 (39.7%)	782 (47.8%)	929 (56.5%)	2056 (44.2%)
COX-2	10 (2.1%)	34 (2.1%)	69 (4.2%)	122 (2.6%)
Statins	14 (3%)	215 (13.1%)	275 (16.7%)	635 (13.7%)

Table 8.2 Missing data for study variables by subject group

	Oesophageal adenocarcinoma	Barrett's oesophagus	Reflux oesophagitis	Unselected control subjects
Weight	158 (33.8%)	457 (27.9%)	394 (24%)	1633 (35.1%)
Height	128 (27.4%)	204 (12.5%)	148 (9%)	846 (18.2%)
BMI	181 (38.7%)	494 (30.2%)	423 (25.7%)	1736 (37.3%)
Smoking	204 (43.6%)	742 (45.4%)	748 (45.5%)	2332 (50.1%)

Table 8.3 Logistic regression analysis (odds ratio with 95% confidence intervals) corrected for age and gender as estimates of the relative risks for variables potentially associated with oesophageal adenocarcinoma

	OAC vs Barrett's oesophagus	OAC vs reflux oesophagitis	OAC vs community control
Height (m)	1.53 (1.28-1.84) p<0.0001	1.3 (1.1-1.54) p=0.002	1.33 (1.12-1.57) p=0.001
Weight (kg)	1.02 (1.01-1.03) p<0.0001	1.02 (1.01-1.03) p<0.0001	1.02 (1.01-1.03) p<0.0001
BMI (kgm^{-2})	1.04 (1.01-1.07) p=0.025	1.05 (1.01-1.08) p=0.005	1.05 (1.02-1.08) p=0.003
Ex-smoker	1.2 (0.8-1.79) p=0.39	1.09 (0.73-1.63) p=0.69	1.42 (0.97-2.08) p=0.075
Smoker	1.71 (1.15-2.53) p=0.008	1.43 (0.97-2.12) p= 0.071	1.45 (1-2.09) p=0.047
PPI	0.42 (0.32-0.54) p<0.0001	0.26 (0.2-0.33) p<0.0001	1.33 (1.03-1.71) p=0.028
Aspirin	0.78 (0.59-1.03) p=0.076	0.62 (0.47-0.81) p=0.001	0.88 (0.68-1.14) p=0.32
NSAIDs	0.74 (0.59-0.93) p=0.009	0.53 (0.42-0.66) p<0.0001	0.86 (0.7-1.06) p=0.17
COX-2	1.2 (0.56-2.55) p=0.64	0.52 (0.26-1.06) p=0.072	0.87 (0.44-1.72) p=0.68
Statins	0.73 (0.51-1.06) p=0.097	0.52 (0.36-0.74) p<0.0001	0.66 (0.47-0.94) p=0.02

Table 8.4 Logistic regression analysis (odds ratios with 95% confidence intervals) as estimates for risk of socio-economic status (detmined by Tonwsend quintiles) and OAC

Townsend quintile	OAC vs Barrett's oesophagus	OAC vs reflux oesophagitis	OAC vs community control
1st quintile (highest)	1	1	1
2nd quintile	1.07 (0.78-1.47) p=0.678	1.15 (0.84-1.58) p=0.381	1.07 (0.8-1.44) p=0.65
3rd quintile	1.26 (0.91-1.73) p=0.16	1.17 (0.85-1.61) p=0.326	1.2 (0.89-1.61) p=0.225
4th quintile	1.26 (0.91-1.75) p=0.17	1.21 (0.87-1.68) p=0.25	1.2 (0.88-1.62) p=0.243
5th quintile (lowest)	1.39 (0.98-1.98) p=0.065	1.24 (0.88-1.76) p=0.225	1.47 (1.06-2.03) p=0.021
p value for trend	p=0.02	p=0.189	p=0.033

8.4 Discussion

Increasing BMI was clearly associated with OAC compared all three control groups, despite increasing BMI being associated with both RO (Hampel et al., 2005) and BO (Stein et al., 2005) as well as OAC (Anderson et al., 2007, Beddy et al., 2010) in previous studies. Visceral obesity is biologically active and has been shown to increase insulin-like growth factor 1 (IGF-1) levels (Donohoe et al., 2012, Doyle et al., 2012). Intriguingly while IGF-1 levels were higher in obese individuals with oesophageal squamous cell carcinoma as well as OAC, it was only OAC cell lines that responded to IGF-1 with increasing cell proliferation (Doyle et al., 2012). Moreover, OAC patients with increased levels of IGF-1 have been reported to have a poorer prognosis (Donohoe et al., 2012). Obesity also increases gastro-oesophageal reflux and oesophageal acid exposure, on 24-hour oesophageal pH monitoring (El-Serag et al., 2007).

Increasing height was associated with OAC in comparison with all three control groups in the present study. This is the first time to our knowledge this association has been reported, although it has been hypothesised that the increased acid production seen among taller individuals (Baron, 1964, Marks, 1961), together with the increase in population height over the last fifty years (1cm per decade) (Hauspie et al., 1996, Cole, 2000, Kuh et al., 1991), may contribute to the recent increase in incidence of OAC (Axon, 2004).

While oesophageal squamous cell carcinoma is considered to be strongly related to smoking (Vaughan et al., 1995), it is clear that OAC is also related to smoking (Anderson et al., 2007, Solaymani-Dodaran et al., 2004). The present study found an increasing risk of smoking when compared with BO and unselected controls subjects. Being a ex-smoker was not significantly associated with OAC, suggesting an important role for smoking cessation in reducing the risk of OAC.

Classically, OSCC is strongly associated with deprivation (Brown et al., 2001), however, no association has been revealed in Scotland (Brewster et al., 2000) and the West Midlands (Chapter 4). This present study, while revealing an association with the most deprived quintile when comparing OAC with unselected control subjects, there is no overall pattern of significance. It is proposed that the positive association seen with smoking in this study, known to be associated with deprivation (Vaughan et al., 1995), may be counteracted by the potentially protective effect of *H.pylori* (de Martel et al., 2005), also associated with lower socio-economic status (Moayyedi et al., 2002, Murray et al., 1997).

The negative association of PPI use with BO versus OAC is likely to represent the appropriate prescribing in those with an established endoscopic diagnosis. Use of PPI among reflux oesophagitis patients, producing a similar negative association, is again likely to be due to the use of the drug for symptoms following an endoscopic diagnosis. Likewise the positive association of PPI

use with OAC versus community controls will be a reflection of reflux symptoms being more common among those developing OAC, even with the censoring of data in the year prior to a code for OAC.

Previous case-control studies have shown a reduced risk of OAC with aspirin and/or NSAID, including meta-analyses (Corley et al., 2003, Liao et al., 2012). Further modelling showed those benefiting most from aspirin/NSAIDs were those with frequent reflux symptoms (Pandeya et al., 2010). While we are unable to retrospectively identify reflux symptoms in the dataset employed, we have identified that aspirin use was negatively associated with OAC when compared with RO subjects, and NSAID use with BO and RO subjects, who all have established GORD. Aspirin and NSAIDs are thought to act by inducing apoptosis via lipo-oxygenase and cyclo-oxygenase inhibition (Shureiqi et al., 2001) and COX-2 expression in BO increases from metaplasia to dysplasia and neoplasia (Morris et al., 2001). Despite this we were unable to show any significant negative association between OAC and COX-2 inhibitor prescribing. However, this may be a result of relatively few patients receiving COX-2 inhibitors in this dataset (between 2.1 - 4.2%) compared with aspirin and NSAIDs, reducing the power to detect an association. The results of AspECT, a randomised trial of PPI and aspirin among BO patients, should shed further light on the potential beneficial effect of aspirin in the oncogenesis of OAC (Jankowski and Moayyedi, 2004).

Statins, or 3-Hydroxy-3-methylgutaryl-coenzyme A (HMG-CoA) reductase inhibitors, reduce mevalonate (Goldstein and Brown, 1990). Reducing mevalonate not only decreases cholesterol, but also reduce proteins involved in growth control (e.g. farnesylated proteins), and as such have been postulated as chemopreventative agents (Graaf et al., 2004, Chan et al., 2003). Populations taking statins have been identified to have a reduced incidence of all cancers after just four years of use (Graaf et al., 2004), in particular reducing colorectal cancer (Poynter et al., 2005). This proposed mechanism of action has been identified in Barrett's and OAC cells, inhibiting cell growth and proliferation, and inducing apoptosis (Sadaria et al., 2011, Ogunwobi and Beales, 2008, Konturek et al., 2007). Moreover statins appear to inhibit COX-2, a potential mechanism already described for the negative association of aspirin and NSAIDs with OAC (Ogunwobi and Beales, 2008, Konturek et al., 2007). While a retrospective study of medication use among Barrett's oesophagus patients failed to show a potentially protective effect of statins (Nguyen et al., 2009), larger prospective cohort studies have identified a reduced risk of progression from BO to OAC (Kantor et al., 2012, Kastelein et al., 2011). In this large case-control database study, we have identified a reduced relative risk of OAC at least equivalent to that seen with aspirin and NSAIDs when compared to not only BO, but also RO and unselected control subjects, although statistical significance was only reached in the latter two groups. This case-control data adds to the tissue and cell model data, strengthening the hypothesis of a potential for chemoprevention among those

at increase risk of OAC, for example BO patients. This hypothesis needs to be tested in a prospective intervention trial using statins in BO.

There are a number of important limitations with the database examined. Even if the medication examined is prescribed via the same computer that records the database entries, it cannot be guaranteed that it is dispensed or taken by the patient, either as directed or indeed at all. Furthermore, OTC medication and drugs prescribed at other institutions will not be recorded in the dataset. As described in the results section, although data were complete for many of the variables examined, there were important missing data, particularly smoking and weight (and consequently BMI). However, the prevalence of missing data was very similar for these variables across the four groups examined.

BO and RO are endoscopic and/or histological diagnoses that general practitioners are very unlikely to make without a gastroscopy being performed, thus unlikely to be entered in error on the database. Neither the degree of reflux oesophagitis, nor the presence or degree of dysplasia in BO is entered. Moreover the length of BO segment is known influence the risk of developing OAC (Watson, 2005) and this also not coded for in the database. We were thus unable to correct for the severity of RO or BO. Finally, we were unable to derive the frequency or severity of symptoms of GORD, derive dietary data or accurately identify the incidence of *Helicobacter pylori*. We were thus unable

to correct for these factors that are known to be associated with OAC in the statistical analysis.

In conclusion, increasing weight and importantly BMI were clearly associated with OAC compared with all three control groups, but additionally we found a novel association between OAC and increasing height. Smoking also appeared to be an important risk factor for OAC and our data suggests smoking cessation diminishes the risk, although the time period required for cessation to be effective was not ascertained in this study. Both aspirin and NSAID use were negatively associated with OAC. Finally, HMG-CoA reductase inhibitors (statins) were negatively associated with OAC compared with unselected subjects and reflux oesophagitis controls.

Chapter 9

Midlands OeSophageal adenocarcinoma Epidemiology Study (MOSES)

9.1 Introduction

The aetiology OAC has been investigated by a number of research studies in the last few decades as a result of some intriguing and hitherto fully unexplained observations. The incidence of OAC has been rising rapidly, more so in the UK than elsewhere in the world, and is now five times more common than 30-years ago. Moreover it is a disease predominantly of white men. While a number of positive associations including reflux symptoms, smoking and obesity have been identified, and negative associations including the presence of *H.pylori* and a diet high in fruit and vegetables, few studies have investigated the interaction of these risk factors. Many of these risk factors may well be synergistic in potential oncogenic risks, e.g. obesity, smoking and reflux, while others may act to negate or prevent the effect of other potential risks, e.g. *H.pylori* and reflux symptoms.

We aim to investigate the aetiology of OAC in the West Midlands, England, UK, a kingdom with the highest incidence of this disease.

9.2 Methods

Data from prospective interviews and blood sampling were used as part of this study: Midlands OeSophageal adenocarcinoma Epidemiology Study (MOSES). OAC subjects were matched (age within five-years, gender, geographical area and ethnicity) to three control groups: community subjects, subjects with RO, and subjects with BO. Continuous variables (e.g. duration of smoking, heartburn symptoms etc, and dietary intakes) were separated into appropriate tertiles/quartiles/quintiles. Logistic regression analysis generated OR with 95%CI as estimates of risk for potential aetiological factors. Following univariate analysis, multivariate analysis was performed to adjust for confounding from other variables. Statistical analysis was performed using SPSS version 19.0.0 (IBM, USA).

9.3 Results

9.3.1 Subjects

Two hundred and eight OAC subjects were recruited, 177 male, median age 68 (IQR 60-75). 283 community subjects, 236 male, median age 67 (IQR 60-74), 224 RO subjects, 178 male, median age 66 (IQR 59-75), and 78 subjects with BO, 65 male, median age 65 (IQR 56-71.3) were matched. With respect to ethnicity, three subjects were of Asian (Indian sub-continent) origins, matched with only one community control subject and four RO subjects, but no cases of BO; two subjects were black, one matched with two community subjects, one subject with RO and one subject with BO, however one black subject was female and matching was not achieved with regard to ethnicity with any control group but still included in the analysis. Demographics of the subjects are seen in table 9.1.

Table 9.1 Demographics of subjects recruited within MOSES (median (IQR))

	OAC	Community	RO	BO
Male gender	177 (85.1%)	236 (83.4%)	178 (79.5%)	65 (83.3%)
Age	68 (60-75)	67 (60-74)	66 (59-75)	65 (56-71.3)
H.pylori +ve	69 (33.2%)	88 (31.1%)	71 (31.7%)	28 (35.9%)
Townsend quintile	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-5)
Height (m)	1.74 (1.68-1.8)	1.74 (1.69-1.8)	1.73 (1.65-1.79)	1.73 (1.68-1.78)
Leg length (cm)	98 (95-102)	97 (93-102)	95 (90-98.1)	93 (91-97.2)
BMI now (kg/m^2)	27.6 (24.7-30.7)	26.6 (24-29.8)	26.4 (24.4-29.1)	27.8 (24.8-29.8)
BMI 10 years ago	26.9 (24.5-29.8)	25.2 (23.2-28.5)	25.1 (23.1-27.3)	26.2 (23-29.3)
BMI aged 18	22.7 (21-24.8)	22.1 (20.3-23.8)	21.8 (20.1-23.6)	21.9 (19.7-23.4)
Waist now (cm)	96.5 (86.4-96.5)	91.4 (86.4-101.6)	91.4 (86.4-96.5)	91.4 (86.4-96.5)
Waist 10 years ago	91.4 (86.4-96.5)	91.4 (81.3-96.5)	86.4 (81.3-92.6)	86.4 (81.3-96.5)
Waist aged 18	81.3 (76.2-89.5)	81.3 (76.2-86.4)	81.3 (71.1-86.4)	76.2 (71.1-81.3)

9.3.2 Helicobacter pylori and cag*A*

The prevalence of *H.pylori* infection among OAC subjects was 33.2%, 31.1% among community subjects, 31.7% among subjects with RO and 35.9% of subjects with BO. Logistic regression analysis revealed no association with *H.pylori* and OAC in comparison with any of the three control groups: OR (95%CI) vs community subjects 1.13 (0.76-1.66) p=0.548; vs RO 1.08 (0.72-1.63) p=0.713; vs BO 0.96 (0.55-1.66) p=0.879. There was also no association with *cagA* status OR (95%CI) vs community subjects 0.68 (0.37-1.23) p=0.203; vs RO 0.89 (0.46-1.72) p=0.73; vs BO 3.57 (0.81-15.8) p=0.094.

9.3.3 Socio-economic status

There was no overall association with socio-economic status and OAC compared with all three control groups (table 9.2). While there was a negative association with the most deprived Townsend quintile in comparison with subjects with BO, there was no trend seen.

Table 9.2 Logistic regression analysis with 95% confidence intervals showing associations with socio-economic status defined by Townsend quintile and OAC in comparison with community, RO and BO subjects

	Townsend Quintile (1 most affluent to 5 most deprived)				
	1	2	3	4	5
Community	1	0.81 (0.47-1.4)	0.65 (0.38-1.13)	1.17 (0.67-2.03)	1.13 (0.6-2.11)
RO	1	1.22 (0.68-2.19)	0.98 (0.55-1.77)	0.93 (0.53-1.62)	1.07 (0.57-2.08)
BO	1	0.6 (0.25-1.46)	0.57 (0.23-1.4)	0.68 (0.28-1.67)	0.31* (0.13-0.75)

*p=0.009

9.3.4 Smoking

Significant associations were observed with smoking status and all three-control groups (figures 9.1-9.3). A reduced but still positive association was seen with ex smoking and OAC. A dose-response response is observed with all three-control groups, with increasing positive association with duration (figures 9.4-9.6) and quantity smoked (figures 9.7 and 9.8).

Figure 9.1 Associated risk (odds ratio) of smoking status: community control subjects vs OAC

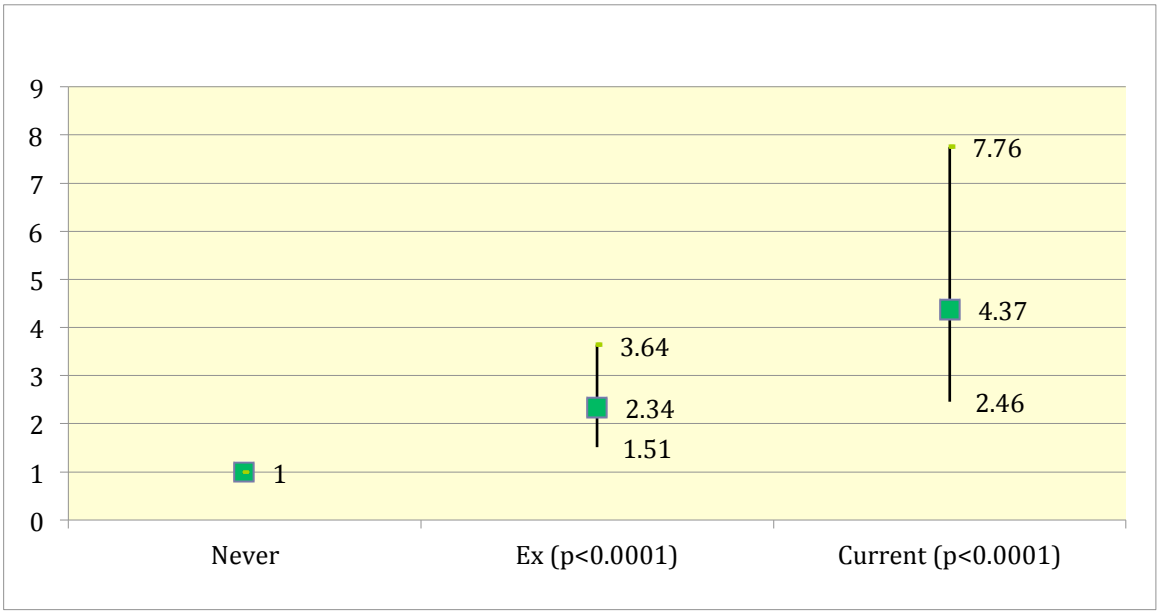


Figure 9.2 Associated risk (odds ratio) of smoking status: reflux oesophagitis patients vs OAC

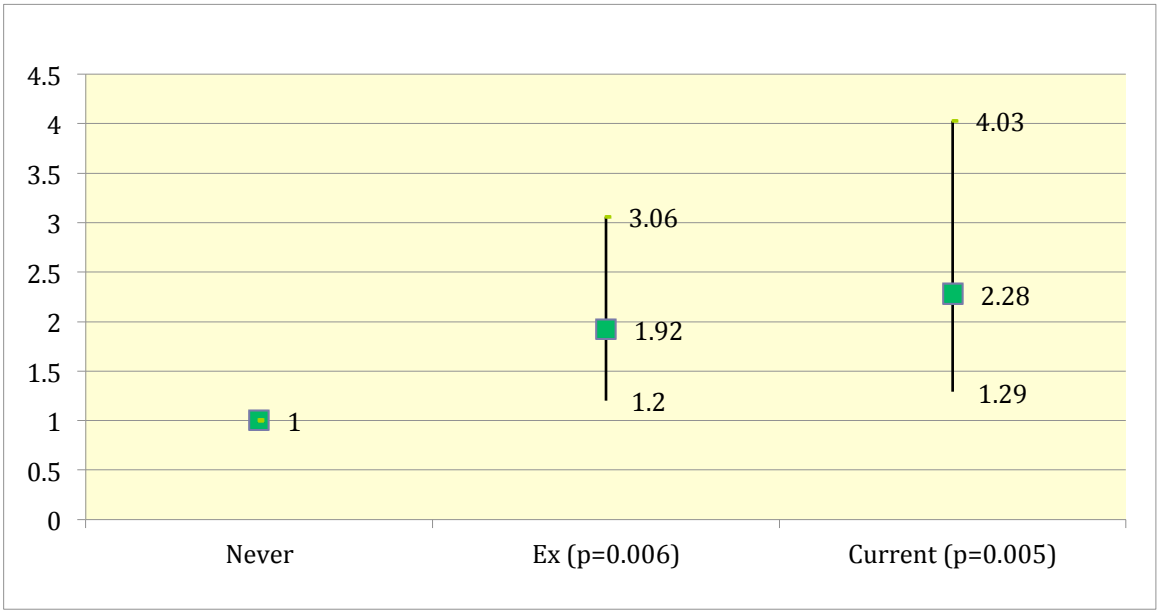


Figure 9.3 Associated risk (odds ratio) of smoking status: subjects with BO vs OAC

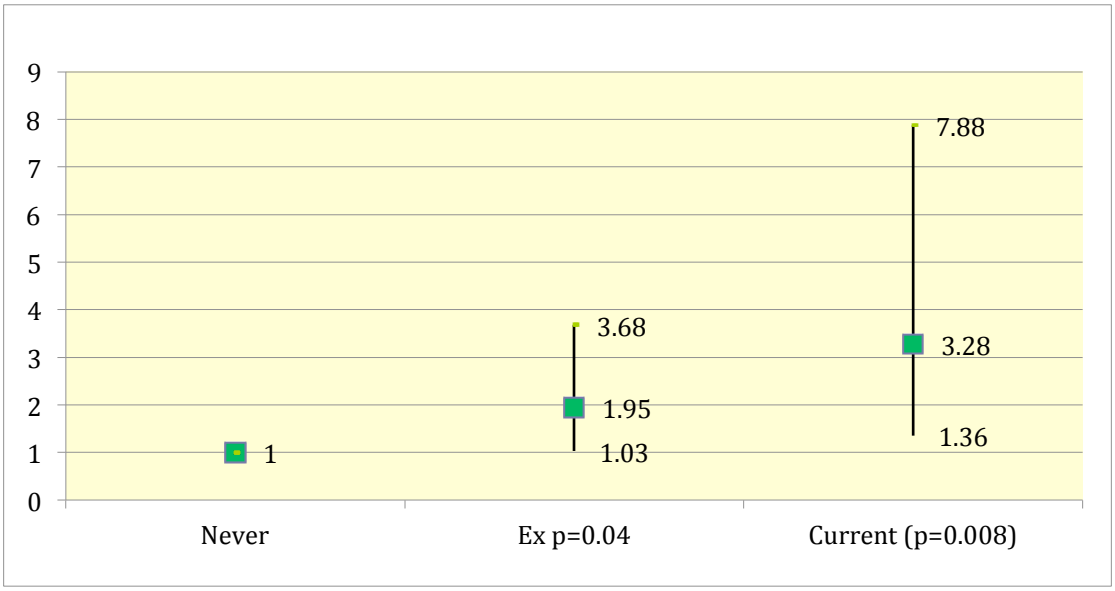


Figure 9.4 Associated risk (odds ratio) of increasing duration of smoking (by quintile): community subjects vs OAC

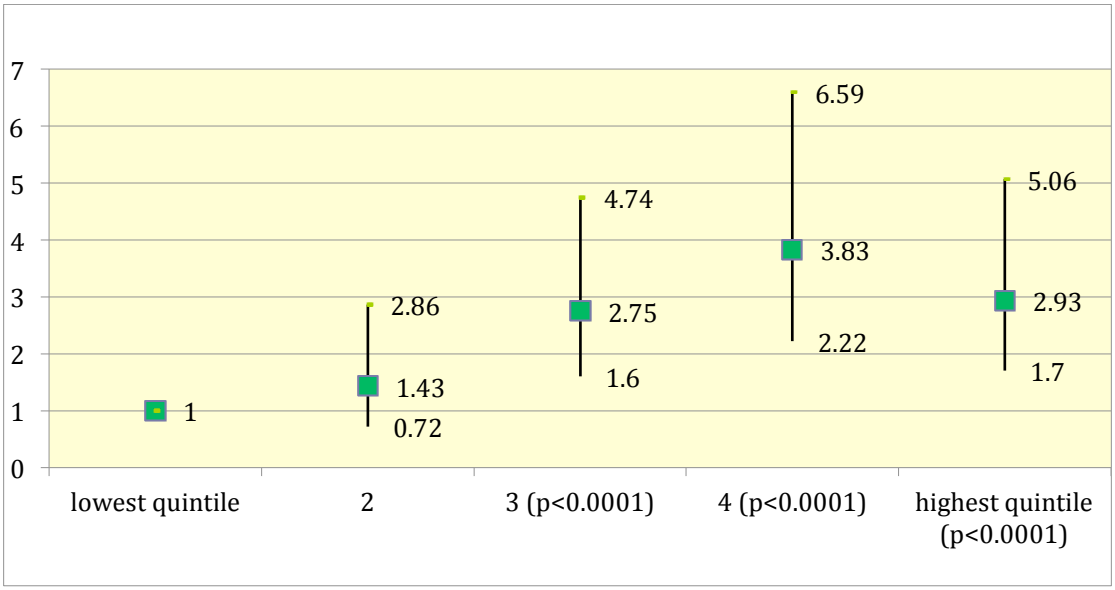


Figure 9.5 Associated risk (odds ratio) of increasing duration of smoking (by quintile): reflux oesophagitis patients vs OAC

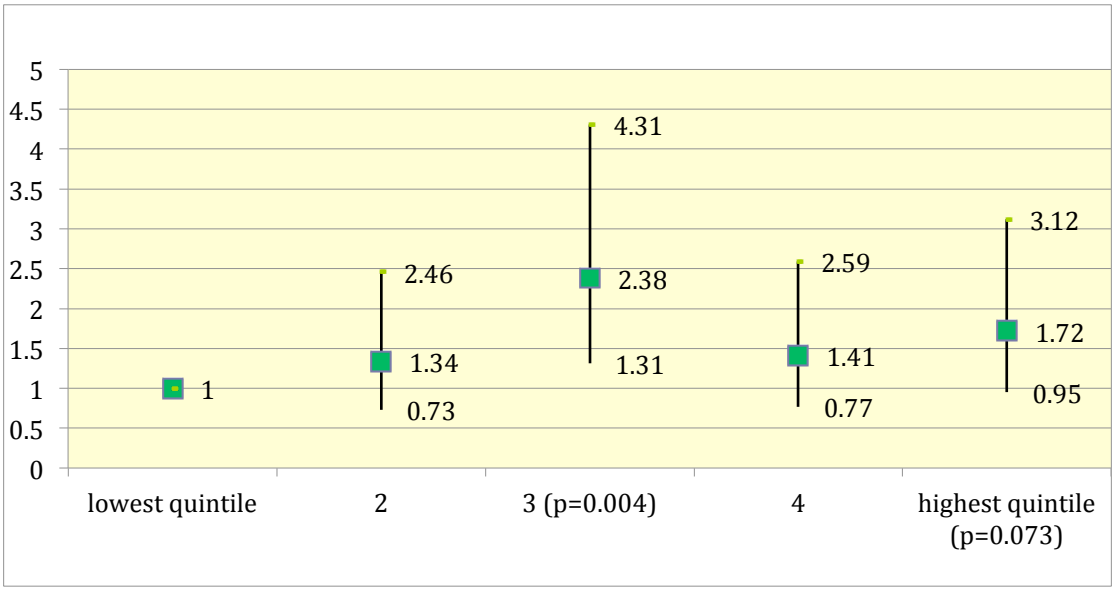
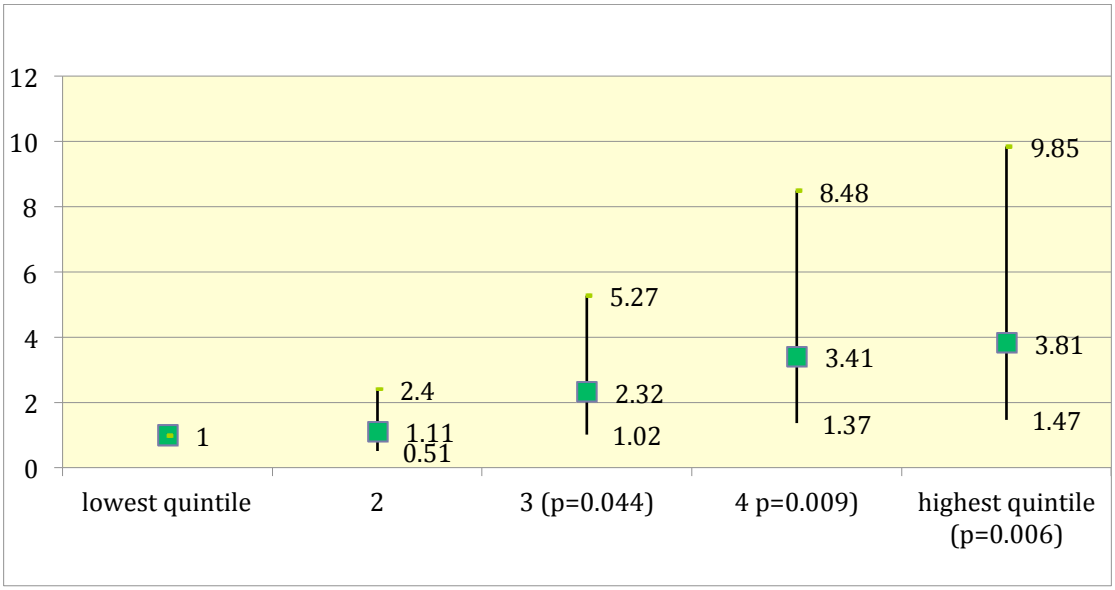


Figure 9.6 Associated risk (odds ratio) of increasing duration of smoking (by quintile): subjects with BO vs OAC



Due to narrow distribution of the data of quantity smoked, the current quantity could only be split into high and low for current and tertiles for 10 years previously. Heavier current consumption was associated with OAC in comparison with community subjects: 2.48 (1.47-4.18) p=0.001); RO 1.67 (1.02-2.75) p=0.043; BO 2.55 (1.11-5.88) p=0.028. Ten years previously comparing OAC with subjects with RO, there was an association with the middle tertile (2.15 (1.1-4.19) p=0.025) but not the heaviest quantity tertile (1.35 (0.82-2.23) p=0.044). An increasing positive association was seen with increasing quantity smoked and OAC in comparison with community (figure 9.7) and BO subjects (figure 9.8).

Figure 9.7 Associated risk (odds ratio) of quantity smoked 10-years prior to interview: community subjects vs OAC

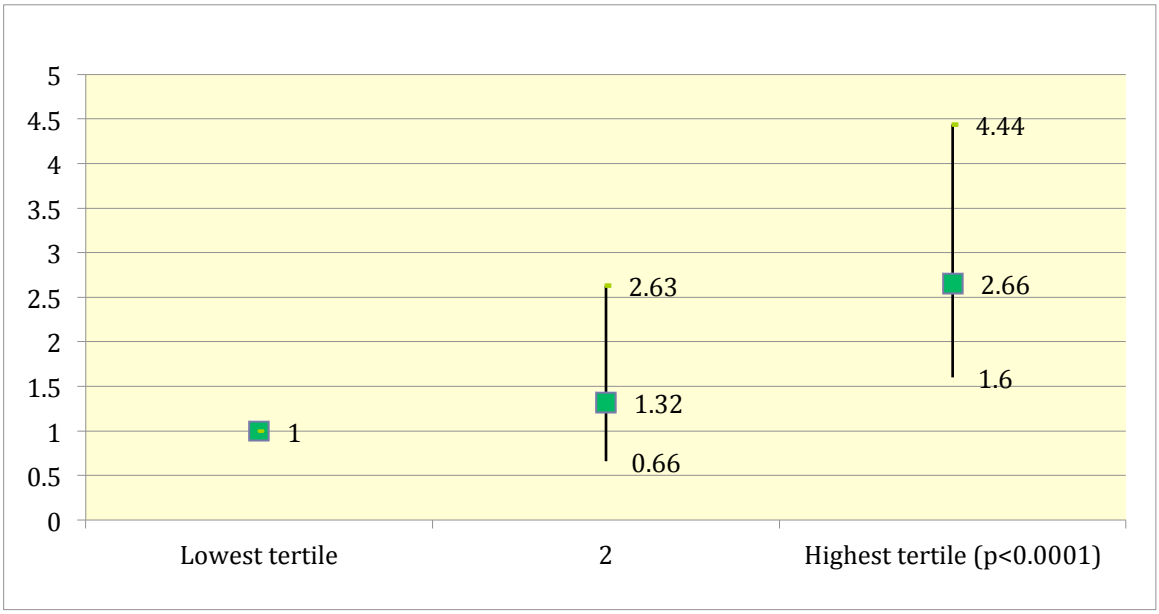
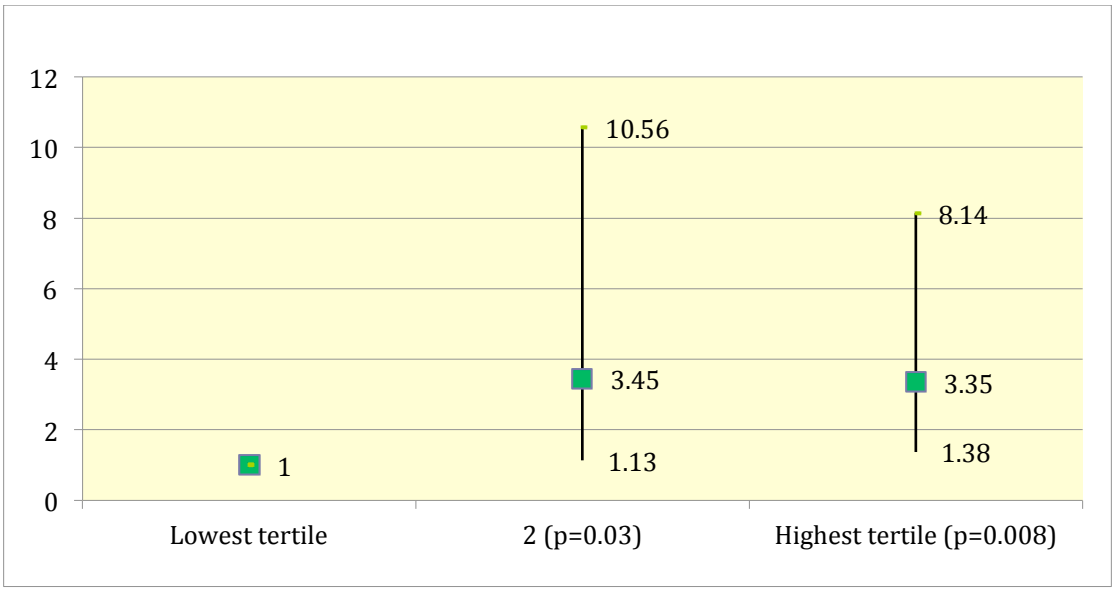


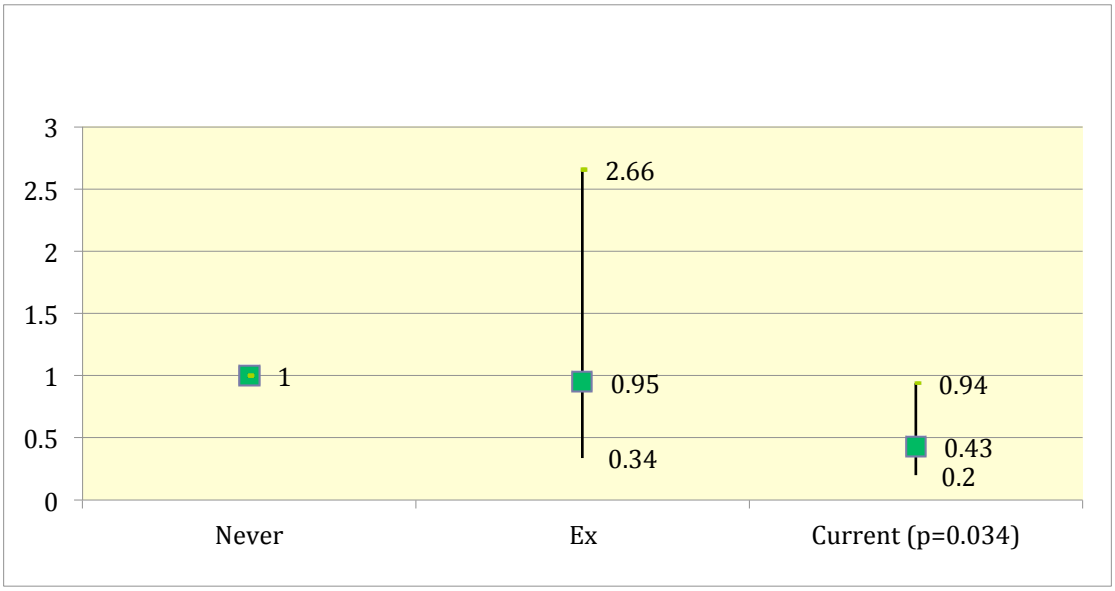
Figure 9.8 Associated risk (odds ratio) of quantity smoked 10-years prior to interview: subjects with BO vs OAC



9.3.5 Alcohol consumption

A negative association with current alcohol consumption was observed in comparison of OAC with community subjects (figure 9.9), which was also observed with duration but not quantity drunk. In comparison with subjects with RO a reduced risk was observed with an OR of 0.68 (figure 9.10) and similarly with BO an OR of 0.16 (figure 9.11), but neither reached significance, and no effect of duration (figures 9.12-9.14) or quantity consumed (table 9.3) was observed.

Figure 9.9 Associated risk (OR 95%CI) of alcohol status OAC vs community subjects



p=0.006 for trend

Figure 9.10 Associated risk (OR 95%CI) of alcohol status OAC vs subjects with RO

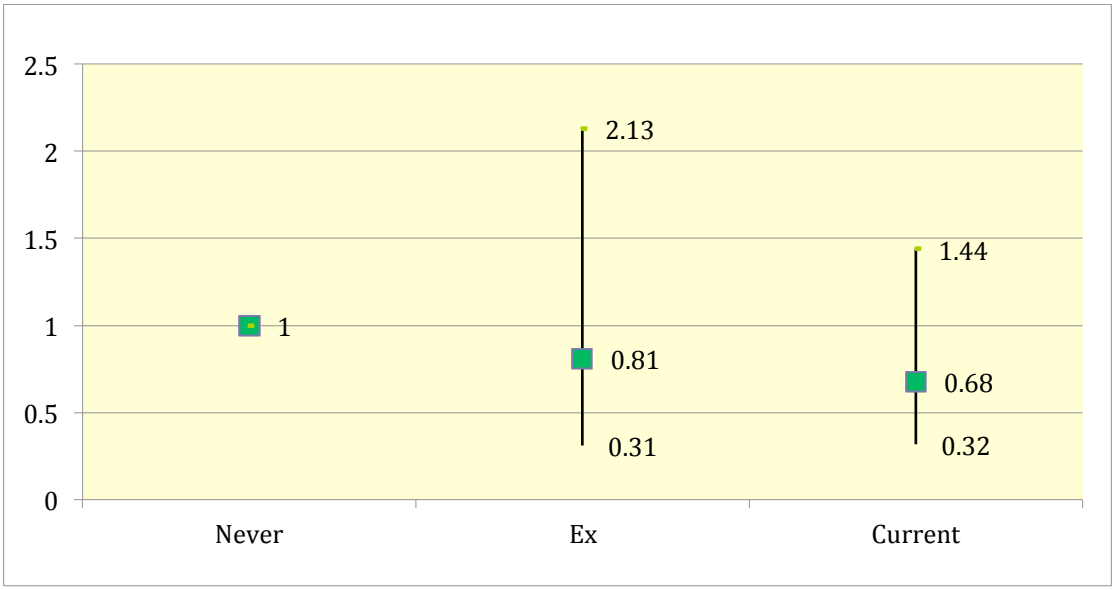


Figure 9.11 Associated risk (OR 95%CI) of alcohol status OAC vs subjects with BO

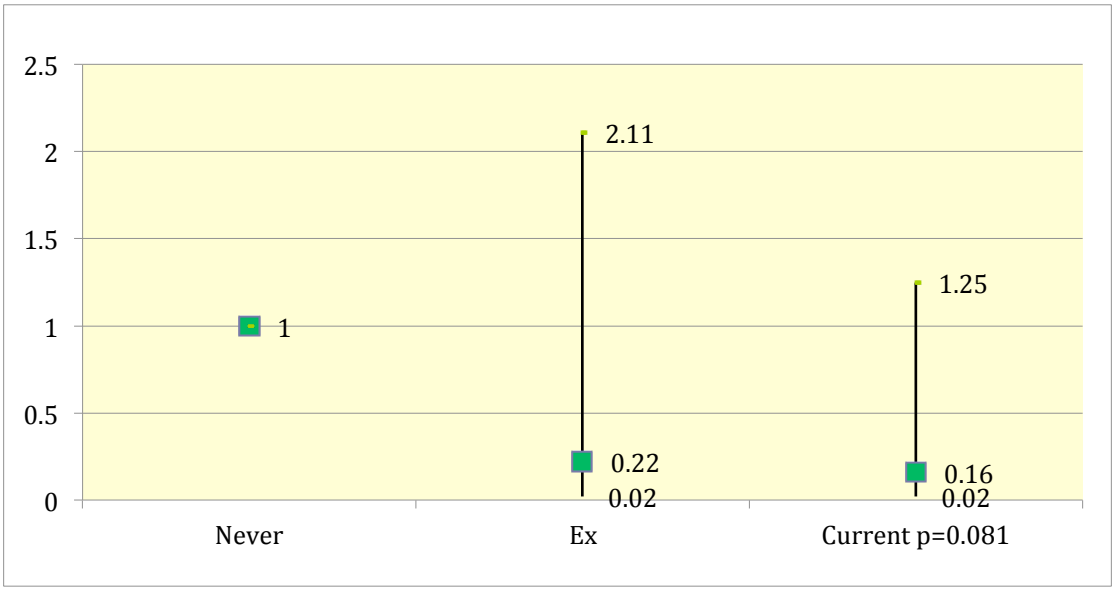
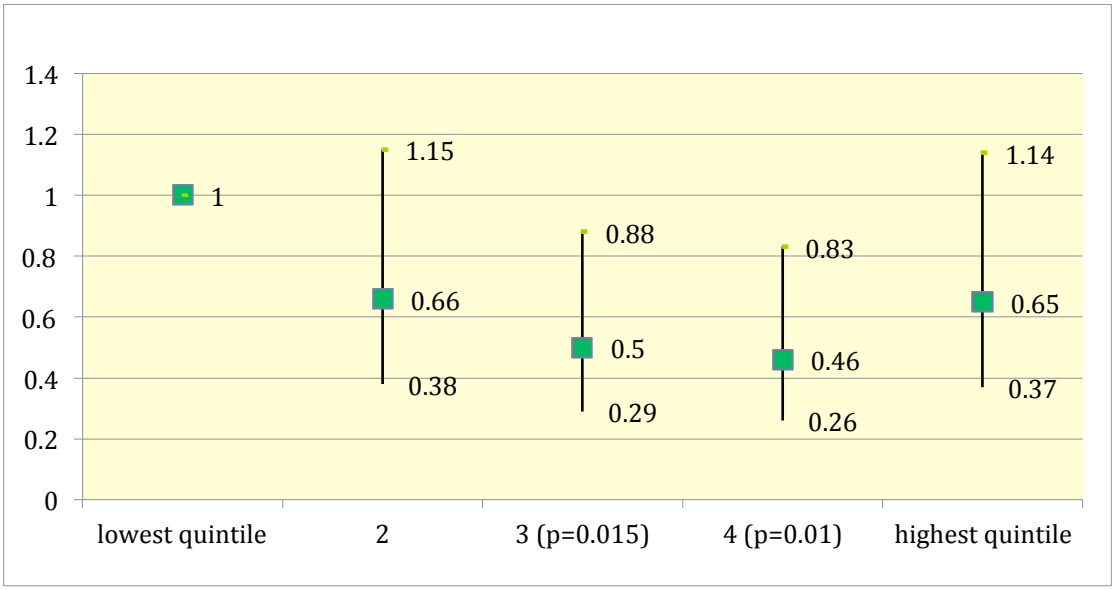


Figure 9.12 Associated risk (OR 95%CI) of duration of alcohol consumption OAC vs community subjects



p=0.053 for trend

Figure 9.13 Associated risk (OR 95%CI) of duration of alcohol consumption

OAC vs subjects with RO

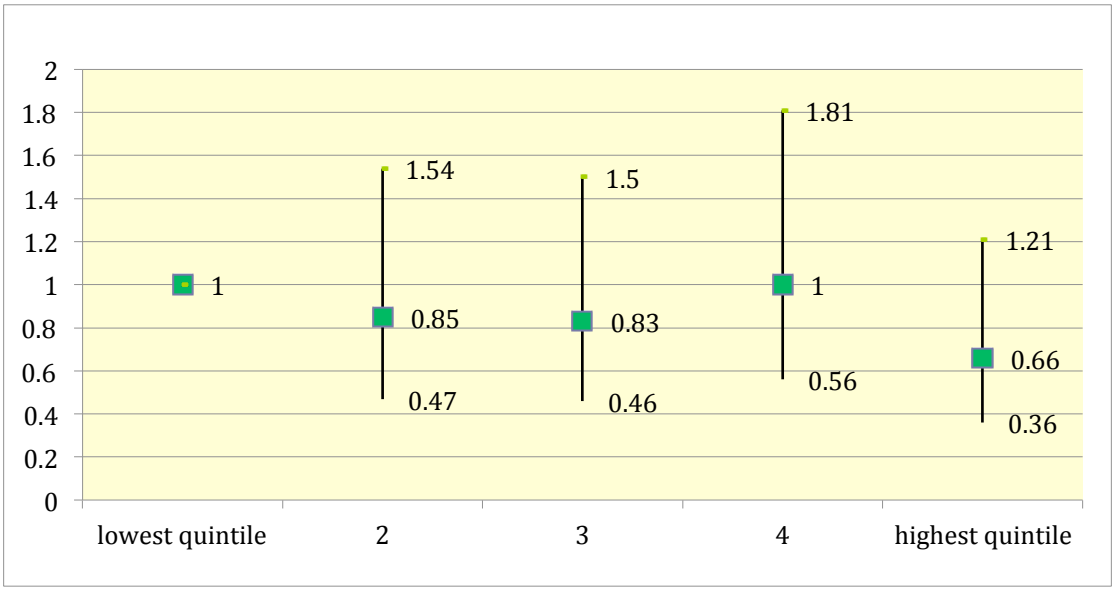


Figure 9.14 Associated risk (OR 95%CI) of duration of alcohol consumption

OAC vs subjects with BO

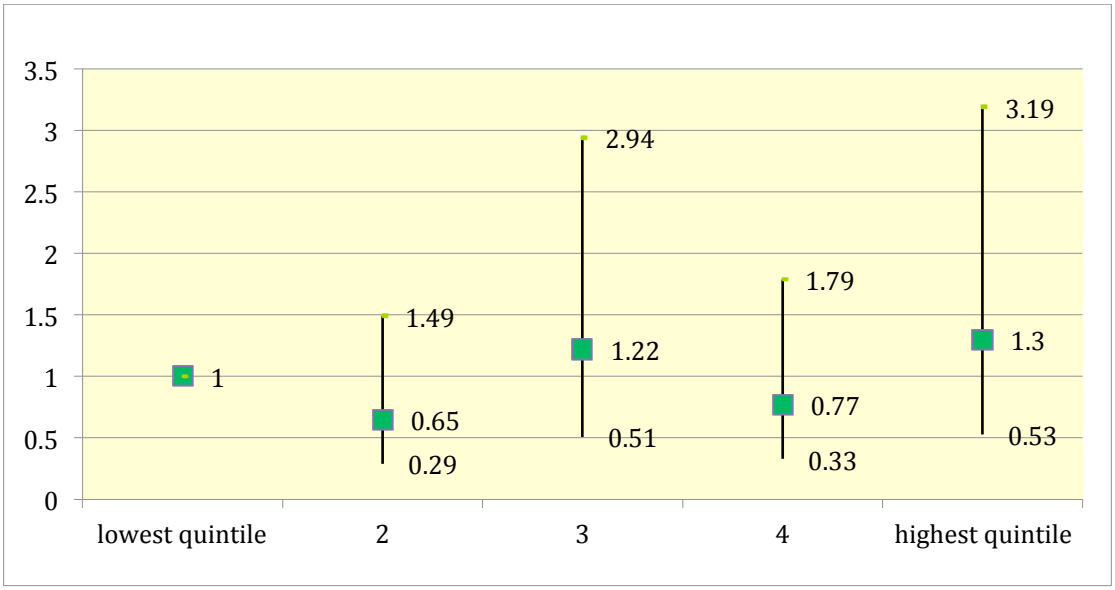


Table 9.3 Associated risk (OR 95%CI) of quantity of alcohol consumed at time of interview and 10 years previously with OAC compared with all control groups

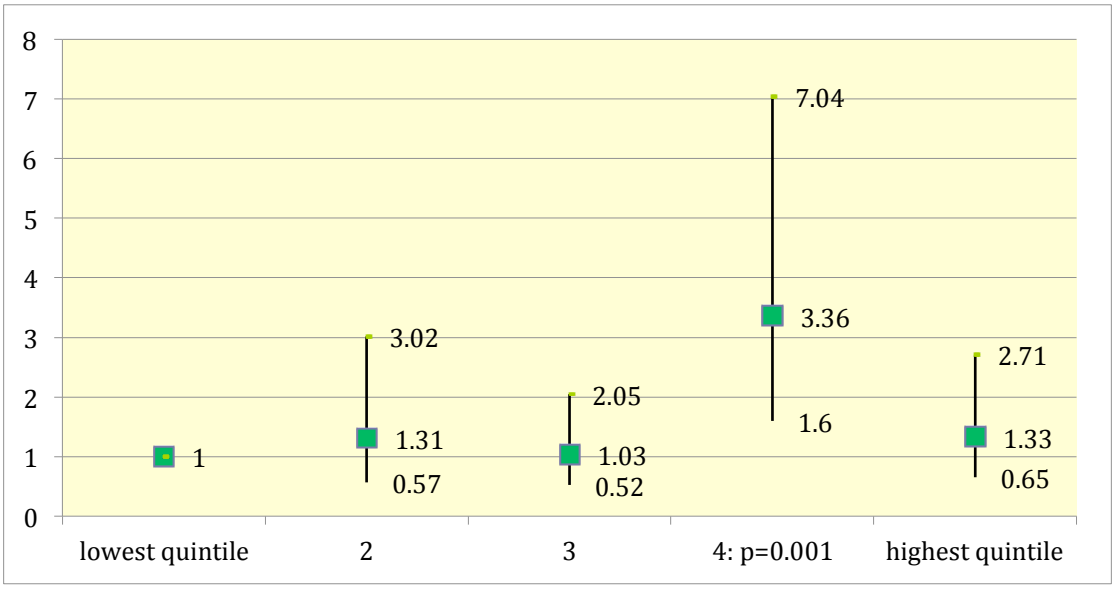
Control group	Alcohol consumption by tertile		
	1	2	3
Community now	1	0.71 (0.45-1.1)	0.82 (0.52-1.32)
Community 10 yrs ago	1	0.87 (0.55-1.37)	1.06 (0.67-1.68)
RO now	1	1.03 (0.64-1.66)	1.43 (0.88-2.31)
RO 10 yrs ago	1	1.16 (0.72-1.85)	0.96 (0.58-1.56)
BO now	1	0.64 (0.33-1.27)	0.94 (0.46-1.91)
BO 10 yrs ago	1	0.72 (0.36-1.43)	0.59 (0.3-1.17)

9.3.6 Symptoms of gastro-oesophageal reflux

The occurrence of heartburn symptoms (ever versus never) were associated with OAC compared with community controls OR (95%CI) and 2.85 (1.95-4.16) p<0.0001, but not with subjects with RO 0.75 (0.49-1.15), and negatively associated with subjects with BO 0.34 (0.17-0.77) p=0.008.

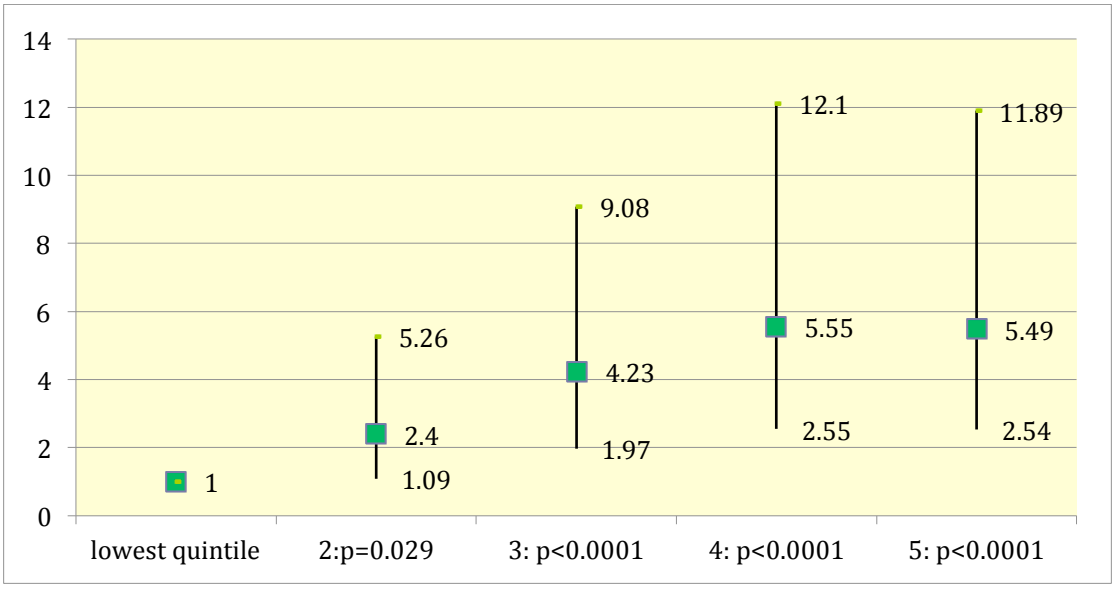
The occurrence of symptoms of acid regurgitation (ever versus never) were associated with OAC compared with community subjects 2.06 (1.43-2.96) p<0.0001, negatively associated with subjects with RO 0.42 (0.28-0.64) p<0.0001 and those with BO 0.26 (0.13-0.51) p<0.0001.

Figure 9.15 Associated risk (odds ratio) of increasing duration of heartburn symptoms (by quintile): community subjects vs OAC



p=0.055 for trend

Figure 9.16 Associated risk (odds ratio) of increasing duration of heartburn symptoms (by quintile): reflux oesophagitis subjects vs OAC



p<0.0001 for trend

Figure 9.17 Associated risk (odds ratio) of increasing duration of heartburn symptoms (by quintile): BO subjects vs OAC

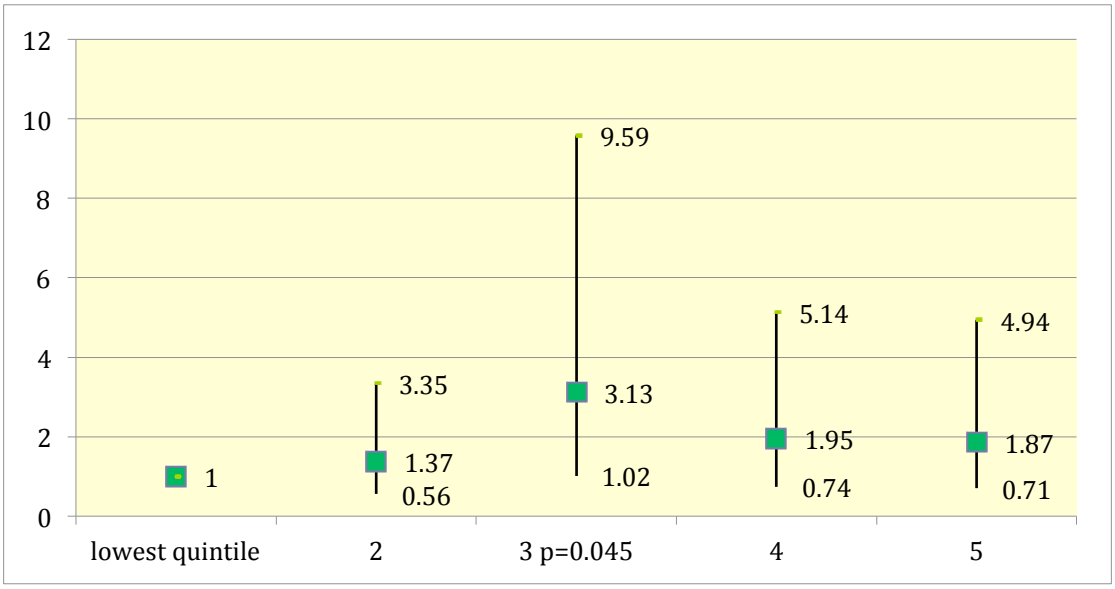
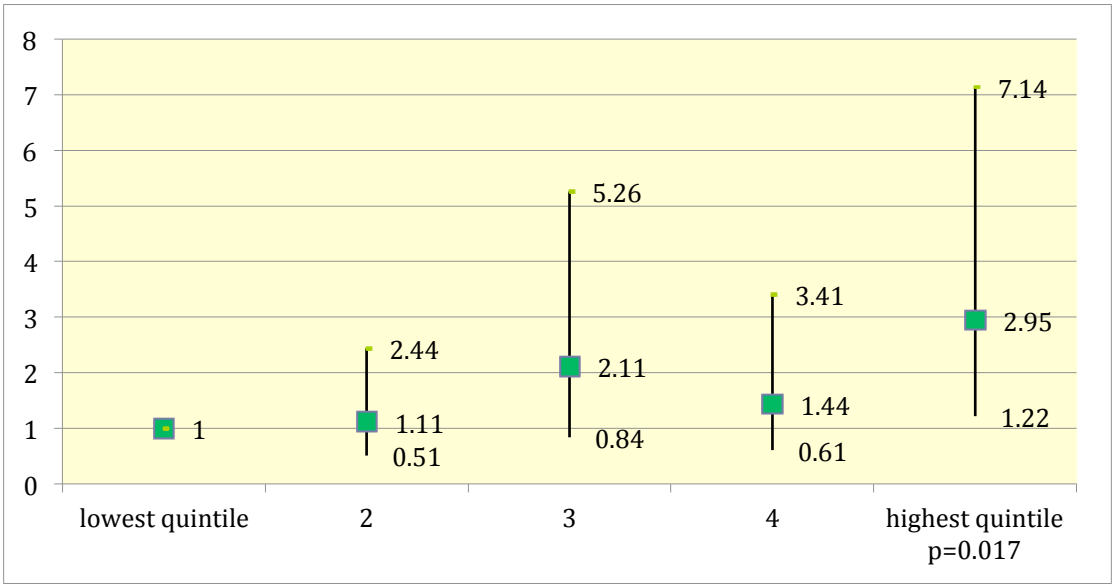


Figure 9.18 Associated risk (odds ratio) of increasing duration of acid regurgitation symptoms (by quintile): community subjects vs OAC



p=0.013 for trend

Figure 9.19 Associated risk (odds ratio) of increasing duration of acid regurgitation symptoms (by quintile): reflux oeophagitis subjects vs OAC

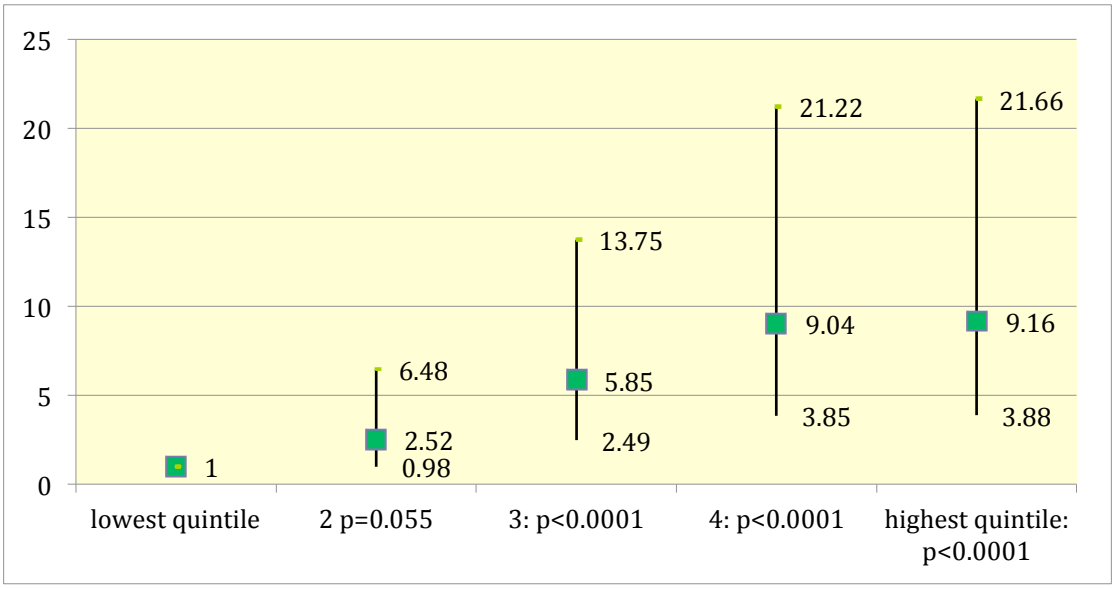


Figure 9.20 Associated risk (odds ratio) of increasing duration of acid regurgitation symptoms (by quintile): subjects with BO vs OAC

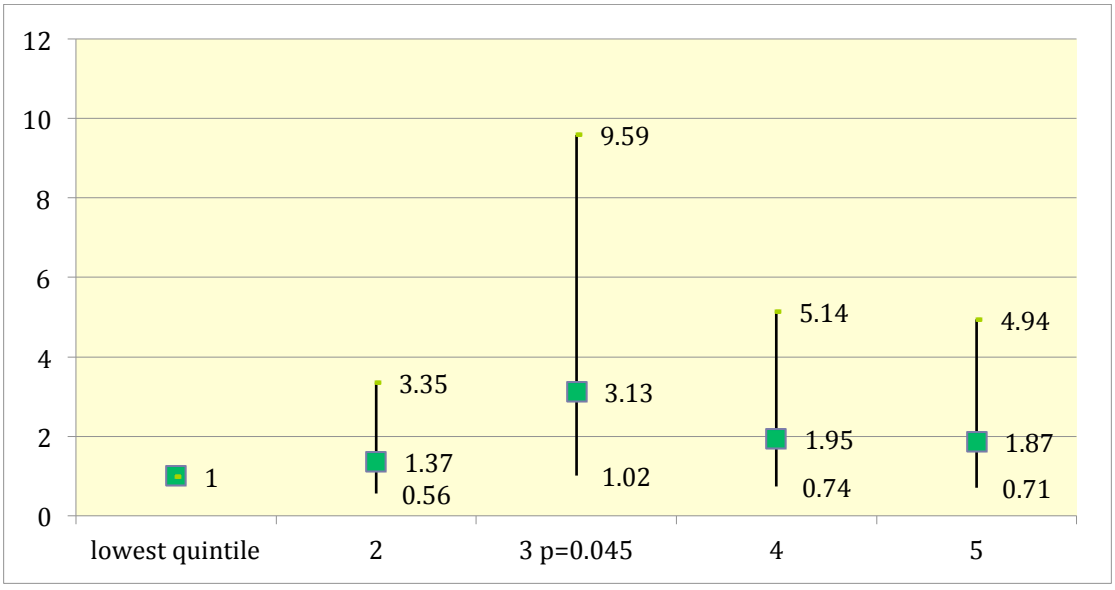


Table 9.4 Associated risks of frequency of heartburn symptoms with OAC by control group and time

		Monthly or less	Weekly/occ day	Daily or greater
Heartburn in year prior to interview	Community p=0.014 for trend	1	1.18 (0.69-2.01)	2.82 (1.31-6.06) p=0.008
	RO	1	1.07 (0.64-1.79)	0.89 (0.5-1.59)
	BO p=0.001 for trend	1	4.79 (1.89-12.12) p=0.001	3.16 (1.22-8.18) p=0.018
Heartburn 10 years prior to interview	Community p=0.036 for trend	1	0.96 (0.56-1.63)	2.54 (1.23-5.23) p=0.012
	RO p=0.035 for trend	1	1.26 (0.76-2.1)	1.93 (1.05-3.56) p=0.034
	BO	1	1.23 (0.58-2.6)	0.72 (0.35-1.48)

Table 9.5 Associated risks of frequency of acid regurgitation symptoms with OAC by control group and time

		Monthly or less	Weekly/occ day	Daily or greater
Regurgitation in year prior to interview	Community p=0.003 for trend	1	1.18 (0.66-2.12)	10.33 (2.3-46.32) p=0.002
	RO	1	0.72 (0.42-1.24)	0.81 (0.41-1.6)
	BO P=0.001 for trend	1	3.3 (1.4-7.78) p=0.006	6.79 (1.5-30.73) p=0.013
Regurgitation 10 years prior to interview	Community	1	1.4 (0.76-2.57)	1.97 (0.69-5.6)
	RO P=0.011 for trend	1	1.8 (1.03-3.14) p=0.04	2.47 (0.95-6.44) p=0.064
	BO	1	0.99 (0.48-2.01)	1.08 (0.35-3.37)

At the time of interview (one year prior for OAC cases) OAC subjects were no more likely to be woken with nocturnal heartburn symptoms than community subjects OR 1.21 (0.74-1.99), or subjects with BO 0.93 (0.5-1.74), but less likely than RO subjects 0.53 (0.34-0.83) p=0.006. Ten years prior being woken by heartburn symptoms was more common among those with OAC, compared with community subjects 2.07 (1.23-3.48) p=0.006 and RO subjects 3.45 (2.02-5.88), but no association with subjects with BO 1.05 (0.56-1.95).

Being awoken by symptoms of acid regurgitation was more frequently observed among OAC subjects one year prior to interview than community subjects OR (95%CI) 2.25 (1.29-3.92) p=0.004, but no association with subjects with RO 0.77 (0.48-1.25) and BO 1.53 (0.8-2.94). Ten years prior to interview, OAC subjects were similarly more likely to be awoken by acid regurgitation symptoms than community subjects 2.19 (1.22-3.92) p=0.009 and RO subjects 3.94 (2.23-6.98) p<0.0001, but no association seen with subjects with BO 1.2 (0.62-2.33).

Table 9.6 Associated risks of frequency of antacid use with OAC by control group and time

		Monthly or less	Weekly/occ day	Daily or greater
Antacid use in year prior to interview	Community p<0.0001 for trend	1	2.07 (1.27-3.38) p=0.004	6.41 (3.08-13.35) p<0.0001
	RO	1	0.93 (0.58-1.49)	1.14 (0.67-1.93)
	BO p=0.015 for trend	1	3.08 (1.24-7.66) p=0.015	2.21 (0.93-5.27) p=0.074
Antacid use 10 years prior to interview	Community p=0.036 for trend	1	1.79 (1.1-2.92) p=0.019	6.47 (3.11-13.45) p<0.0001
	RO p=0.008 for trend	1	1.3 (0.79-2.14)	2.18 (1.21-3.91) p=0.009
	BO	1	0.82 (0.41-1.66)	0.74 (0.37-1.49)

Increasing use of OTC antacids was associated with OAC in comparison with community controls both currently and 10-years prior to the interview; similarly in comparison with subjects with RO 10 years ago, but not currently. There was also observed an increased association with use of antacids when compared with subjects with BO at time of interview Table 9.6).

9.3.6.1 Multivariate analysis of gastro-oesophageal reflux symptoms

Symptoms of gastro-oesophageal reflux were adjusted for the presence of *H.pylori* and smoking status, in comparison with all three-control groups. There was no alteration to the findings: ever experienced heartburn or acid regurgitation symptoms, being woken by heartburn or acid regurgitation, either currently or 10-years prior to interview. The OR did not alter to any significant degree, and there was no change in any of the statistical significances reported.

9.3.8 Body parameters

No association was observed between red and left hand dominance, nor with height and OAC with comparison with all three-control groups (table 9.7). Leg-length, a marker of IGF-1 levels, showed no association with OAC in comparison with community subjects, but an increasing leg-length was associated with OAC in comparison with subjects with RO and those with BO (table 9.8).

Table 9.7 Odds ratio (95%CI) as estimate of association between height by quintile and oesophageal adenocarcinoma compared with all three-control group

	Lowest quintile	2nd	3rd	4th	Highest quintile
Community	1	0.82 (0.48-1.38)	0.97 (05-1.89)	1.04 (0.59-1.84)	0.69 (0.38-1.23)
RO	1	1.42 (0.78-2.61)	1.35 (0.76-2.38)	1.78 (1-3.18) p=0.051	1.38 (0.75-2.56)
BO	1	0.9 (0.43-1.89)	1.47 (0.5-4.29)	2.22 (0.89-5.56)	1.4 (0.56-3.48)

Table 9.8 Odds ratio (95% CI) as estimate for the association of leg length by quintile (as a marker of IGF-1) with OAC, compared with all three control groups

	Lowest quintile	2nd	3rd	4th	Highest quintile	Trend
Community	1	1.33 (0.75-2.34)	2.6 (1.47-4.58)	1.39 (0.81-2.4)	1.66 (0.92-2.97)	p=0.083
RO	1	1.86 (0.98-3.53) p=0.056	3.23 (1.73-6.03) p<0.0001	4.54 (2.32-8.88) p<0.0001	6.24 (3.23-12.05) p<0.0001	p<0.0001
BO	1	2.96 (1.39-6.32) p=0.005	3.43 (1.43-8.24) p=0.006	11.57 (4.05-33.1) p<0.0001	7.86 (2.9-21.28) p<0.0001	p<0.0001

Increasing BMI was associated with OAC almost uniformly in comparison with all three-control subjects at all three time intervals, except in comparison with subjects with BO at the time of interview only, when no association was observed (table 9.9). Moreover, increasing waist circumference was associated with OAC in comparison with subjects with RO and BO, but not with community subjects (table 9.11).

Table 9.9 Odds ratio (95%CI) as estimate for association between BMI by quintile and OAC, in comparison with three control groups

		Lowest quintile	2nd	3rd	4th	Highest quintile	Trend
Current	Community	1	1.05 (0.58-1.88)	1.43 (0.8-2.56)	1.77 (1-3.14) p=0.049	1.81 (1.02-3.21) p=0.043	p=0.009
	RO	1	0.8 (0.44-1.47)	1.09 (0.6-2)	1.52 (0.83-2.75)	1.79 (0.98-3.27) p=0.058	p=0.009
	BO	1	0.68 (0.29-1.62)	0.74 (0.31-1.78)	0.9 (0.37-2.2)	1 (0.41-2.47)	
10 years ago	Community	1	1.26 (0.69-2.29)	1.87 (1.05-3.35) p=0.034	1.77 (0.98-3.2)	2.63 (1.46-4.73) p=0.001	p=0.001
	RO	1	1.33 (0.72-2.47)	1.34 (0.73-2.48)	3.05 (1.64-5.67) p<0.0001	3.05 (1.64-5.67) p<0.0001	p<0.0001
	BO	1	1.55 (0.68-3.52)	2.7 (1.09-6.67) p=0.032	1.41 (0.62-3.17)	2.11 (0.89-5.01) p=0.09	
Aged 18	Community	1	1.27 (0.71-2.28)	1.11 (0.62-1.99)	1.86 (1.05-3.3) p=0.033	2.07 (1.16-3.68) p=0.014	p=0.005
	RO	1	1.5 (0.81-2.8)	1.67 (0.92-3.01)	1.96 (1.08-3.55) p=0.027	2.71 (1.49-4.93) p<0.0001	p=0.001
	BO	1	2.21 (0.96-5.13) p=0.064	1.43 (0.64-3.18)	2.66 (1.11-6.39) p=0.029	3.29 (1.35-8.07) p=0.009	P=0.01

Table 9.10 Odds ratio (95%CI) as estimate for association between waist circumference by quintile and OAC in comparison with control groups

		Lowest quintile	2nd	3rd	4th	Highest quintile	Trend
Current	Community	1	0.82 (0.47-1.43)	1.4 (0.78-2.49)	0.84 (0.42-1.68)	1.54 (0.89-2.69)	
	RO	1	0.86 (0.48-1.55)	1.26 (0.7-2.28)	1.55 (0.69-2.28)	2.13 (1.15-3.95) p=0.017	p=0.007
	BO	1	1.21 (0.54-2.68)	1.77 (0.76-4.1)	1.85 (0.78-4.43)	4.25 (1.18-15.35) p=0.027	P=0.011
10 years ago	Community	1	0.77 (0.42-1.41)	0.91 (0.51-1.65)	1.82 (0.98-3.4) p=0.059	1.34 (0.75-2.41)	p=0.055
	RO	1	0.64 (0.35-1.19)	1.36 (0.71-2.6)	2.27 (1.15-4.49) p=0.018	1.99 (1.04-3.83) p=0.039	p=0.001
	BO	1	1.04 (0.46-2.33)	2.53 (0.96-6.65)	3.04 (1.26-7.31) p=0.013	1.81 (0.71-4.65)	p=0.014
Aged 18	Community	1	0.7 (0.43-1.16)	1.35 (0.84-2.18)	1.35 (0.62-2.94)	No 5th quintile	
	RO	1	1.23 (0.65-2.33)	1.08 (0.58-2.01)	1.64 (0.8-3.37)	2.56 (1.31-4.99) p=0.006	p=0.005
	BO	1	0.99 (0.43-2.31)	1.12 (0.48-2.62)	2.33 (0.96-5.64)	1.65 (0.47-5.83)	p=0.06

9.3.9 Dietary intake

Tables 9.11 And 9.12 show the median (IQR) frequency (number of days of the week) of dietary consumption by food type, and median (IQR) total weekly portion intake (tea and coffee by daily cup total).

Increasing frequency of vegetable consumption ten years prior to interview, but not at time of interview, was negatively associated with OAC in comparison with community and BO subjects (table 9.13). Increasing frequency of fruit consumption (table 9.14) also was negatively associated with OAC, but both at time of interview and 10 years prior in comparison with community subjects and also with subjects with RO but only at time of interview, when there was also a negative association seen with fruit juice consumption (table 9.15)

Frequency of potato consumption (table 9.16) showed a mix of results with some quartiles positively associated with OAC in comparison with all three-control groups but only at the time of interview. Increasing red meat consumption frequency was positively associated with OAC, but only in comparison with community and RO subjects in the current time frame (table 9.17).

No associations were seen with poultry or fish frequency (tables 9.18 and 9.19) or total weekly portion consumption (9.25 and 9.26).

Both fruit and vegetable consumption (tables 9.21 And 9.20) was negatively associated with OAC in comparison with community subjects only, and most notably fruit consumption with OR of 0.33 and 0.37 for the highest quintiles of consumption at time and 10-years prior to interview. While weekly total fruit juice consumption showed a negative association with OAC among community and RO subjects, it only reached significance in comparison with subjects with RO at time of interview (table 9.22)

Increasing total weekly potato consumption is associated with OAC as compared with community subjects (reaching significance in the fourth and highest quintiles) and also with subjects with RO, but only at the time of interview (table 9.23. Red meat consumption was also positively associated with OAC, with second through to fourth quintiles, but not the highest and also in comparison with subjects with RO with third and fourth quintiles (table 9.24).

Finally, analysis of hot beverage consumption revealed an increasing positive association with OAC with cups of tea drunk (table 9.27), reaching significance in the highest quintile in comparison with community subjects at both time periods examined. Coffee consumption was only associated with OAC in comparison with subjects with BO and the third quartile, not the highest (table 9.28).

Table 9.11 Median (IQR) frequency of consumption of dietary components by group and by time

Frequency of consumption (days)	OAC	Community	RO	BO
Vegetable now	5 (3-7)	5 (4-7)	5 (3.5-7)	4 (3-6.8)
Vegetables 10 years ago	5 (3-7)	5 (4-7)	5 (3.1-7)	4 (3-6)
Potatoes now	5 (4-6)	5 (3-6)	5 (3-6)	5 (4-6)
Potatoes 10 years ago	5 (4-7)	5 (4-6)	5 (4-7)	5 (4-7)
Fruit now	4 (1-7)	7 (3-7)	5 (2-7)	4 (1-7)
Fruit 10 years ago	3 (1-6.8)	5 (2-7)	3 (1-7)	3 (0.6-6)
Fruit juice now	0 (0-6)	1 (0-7)	1 (0-6.8)	0 (0-2.8)
Fruit juice 10 years ago	0 (0-3)	0.5 (0-3)	0 (0-3)	0 (0-3)
Red meat now	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4.8)
Red meat 10 years ago	4 (3-5)	3 (2-4)	4 (2.1-5)	4 (3-5)
Poultry now	2 (1-2)	2 (1-2)	2 (1-2)	2 (1-3)
Poultry 10 years ago	2 (1-2)	2 (1-2)	2 (1-2)	2 (1-3)
Fish now	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)
Fish 10 years ago	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)

Table 9.12 Median (IQR) weekly portion consumption of dietary components by group and time

Weekly consumption (days)	OAC	Community	RO	BO
Vegetable now	7.5 (4.5-14)	10 (6-14)	8 (5-14)	7 (3-12)
Vegetables 10 years ago	8 (4.5-14)	10 (6-14)	8 (4.5-14)	6 (3.5-12)
Potatoes now	6 (5-10)	6 (4-7)	6 (3.5-7.9)	6 (4-9.5)
Potatoes 10 years ago	7 (5-12)	6 (5-10)	6 (4-10)	7 (4.3-10)
Fruit now	6 (1-14)	9 (4-14)	7 (2.3-14)	4 (0-14)
Fruit 10 years ago	3 (1-12)	6 (2-14)	3 (2-12)	3 (0-7)
Fruit juice now	0 (0-6.8)	1 (0-7)	1 (0-7)	0 (0-3.5)
Fruit juice 10 years ago	0 (0-3)	0.5 (0-4)	0 (0-4)	0 (0-4)
Red meat now	4 (2-5)	3 (2-5)	3 (2-5)	4 (2-6)
Red meat 10 years ago	4 (3-6)	4 (2-6)	4 (3-7)	5 (3-10)
Poultry now	2 (1-2)	2 (1-2)	2 (1-3)	2 (1-3)
Poultry 10 years ago	2 (1-2.8)	2 (1-3)	2 (1-2.8)	2 (1-3)
Fish now	2 (1-2)	2 (1-2)	2 (1-2)	1 (1-2)
Fish 10 years ago	1 (1-2)	1 (1-2)	1 (1-2)	1 (0-2)
Tea now (cups/day)	4 (2-6)	4 (2-5)	4 (2-6)	4 (2-6.8)
Tea 10 years ago (cups/day)	5 (3-7)	4 (2-6)	5 (2-7)	5 (2-6.8)
Coffee now (cups/day)	1 (0-3)	1 (0-3)	1 (0-2)	1 (0-3)
Coffee 10 years ago (cups/day)	1 (0-4)	1 (0-4)	1 (0-3)	1 (0-5)

Table 9.13 Odds ratio (95%CI) as estimate for associated risk of frequency of vegetable consumption, by tertile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest ‘tile	2nd	3rd
Current	Community	1	1.09 (0.64-1.85)	0.72 (0.48-1.08)
	RO	1	0.77 (0.47-1.27)	0.82 (0.51-1.32)
	BO	1	1.05 (0.53-2.07)	1.48 (0.75-2.9)
10 years ago	Community	1	0.62 (0.37-1.04) p=0.067	0.64 (0.43-0.96) p=0.032
	RO	1	0.92 (0.55-1.53)	1.01 (0.62-1.65)
	BO	1	0.07 (0.55-2.09)	2.07 (1.02-4.2) p=0.044

Table 9.14 Odds ratio (95%CI) as estimate for associated risk of frequency of fruit consumption, by tertile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest 'tile	2nd	3rd
Current	Community	1	0.49 (0.3-0.81) p=0.005	0.35 (0.22-0.54) p<0.0001
	RO	1	0.58 (0.34-0.99) p=0.044	0.61 (0.39-0.94) p=0.026
	BO	1	2.2 (0.98-4.93) p=0.056	1.32 (0.71-2.45)
10 years ago	Community	1	0.61 (0.36-1.02) p=0.059	0.46 (0.31-0.69) p<0.0001
	RO	1	0.69 (0.41-1.15)	0.73 (0.46-1.17)
	BO	1	1.55 (0.74-3.26)	1.36 (0.6-3.06)

Table 9.15 Odds ratio (95%CI) as estimate for associated risk of frequency of fruit juice consumption, by tertile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest 'tile	2nd	3rd
Current	Community	1	0.76 (0.47-1.23)	0.78 (0.51-1.18)
	RO	1	0.87 (0.53-1.44)	0.62 (0.4-0.97) p=0.038
	BO	1	1.21 (0.54-2.69)	1.62 (0.85-3.09)
10 years ago	Community	1	0.77 (0.47-1.27)	0.77 (0.51-1.16)
	RO	1	0.88 (0.51-1.53)	0.72 (0.46-1.12)
	BO	1	1.1 (0.49-2.44)	1 (0.53-1.89)

Table 9.16 Odds ratio (95%CI) as estimate for associated risk of frequency of potato consumption, by quartile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest 'tile	2nd	3rd	4th
Current	Community	1	1.29 (0.8-2.09)	1.17 (0.7-1.96)	1.72 (1.05-2.83) p=0.032
	RO	1	1.57 (0.93-2.64) p=0.093	1.72 (0.98-3.04) p=0.06	1.331 (0.8-2.16)
	BO	1	1.43 (0.71-2.9)	2.61 (1.05-6.48) p=0.04	1.72 (0.83-3.57)
10 years ago	Community	1	0.93 (0.56-1.52)	0.86 (0.52-1.43)	1.19 (0.73-1.94)
	RO	1	1.28 (0.74-2.19)	1.27 (0.82-1.99)	Distributed by tertile
	BO	1	0.87 (0.42-1.8)	1.24 (0.65-2.39)	Distributed by tertile

Table 9.17 Odds ratio (95%CI) as estimate for associated risk of frequency of red meat consumption, by quartile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest 'tile	2nd	3rd	4th
Current	Community	1	1.95 (1.2-3.18) p=0.007	1.76 (1.07-2.88) p=0.025	2.04 (1.21-3.43) p=0.008
	RO	1	1.44 (0.86-2.4)	1.77 (1.03-3.04) p=0.039	1.15 (0.68-1.95)
	BO	1	0.89 (0.43-1.83)	1.52 (0.66-3.49)	0.85 (0.4-1.81)
10 years ago	Community	1	1.17 (0.75-1.82)	1.4 (0.78-2.5)	1.33 (0.7-2.53)
	RO	1	1.05 (0.65-1.7)	1 (0.58-1.75)	0.84 (0.45-1.55)
	BO	1	1.11 (0.53-2.31)	0.88 (0.4-1.98)	0.43 (0.2-0.92) p=0.03

Table 9.18 Odds ratio (95%CI) as estimate for associated risk of frequency of poultry consumption, by tertile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest 'tile	2nd	3rd
Current	Community	1	1.08 (0.72-1.62)	0.73 (0.44-1.21)
	RO	1	1.19 (0.78-1.83)	0.73 (0.44-1.24)
	BO	1	0.95 (0.5-1.81)	0.5 (0.25-1.02) p=0.057
10 years ago	Community	1	0.85 (0.57-1.26)	0.73 (0.44-1.19)
	RO	1	0.92 (0.6-1.42)	0.9 (0.53-1.53)
	BO	1	0.87 (0.46-1.64)	0.54 (0.27-1.1) p=0.088

Table 9.19 Odds ratio (95%CI) as estimate for associated risk of frequency of fish consumption, by quintile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest 'tile	2nd	3rd
Current	Community	1	0.93 (0.62-1.4)	0.64 (0.38-1.07)
	RO	1	1.01 (0.66-1.55)	0.71 (0.41-1.24)
	BO	1	1.03 (0.55-1.91)	0.78 (0.36-1.68)
10 years ago	Community	1	0.87 (0.58-1.31)	0.88 (0.49-1.6)
	RO	1	0.78 (0.5-1.21)	0.55 (0.3-1.03) p=0.06
	BO	1	1.27 (0.65-2.47)	0.72 (0.32-1.65)

Table 9.20 Odds ratio (95%CI) as estimate for associated risk of total weekly vegetable consumption, by quintile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest quintile	2nd	3rd	4th	Highest quintile
Current	Community	1	1.02 (0.58-1.77)	0.78 (0.45-1.35)	0.63 (0.34-1.16)	0.41 (0.22-0.74) p=0.004
	RO	1	1 (0.57-1.75)	0.91 (0.48-1.72)	1.12 (0.63-2)	0.54 (0.29-1.01) p=0.055
	BO	1	1.55 (0.64-3.71)	1.11 (0.52-2.4)	1.58 (0.7-3.54)	1.34 (0.52-3.47)
10 years ago	Community	1	0.71 (0.41-1.23)	0.72 (0.42-1.23)	0.54 (0.29-1) p=0.051	0.41 (0.23-0.73) p=0.003
	RO	1	1.16 (0.65-2.06)	1.13 (0.6-2.14)	1.15 (0.64-2.05)	0.69 (0.37-1.27)
	BO	1	1.32 (0.56-3.12)	1.23 (0.58-2.62)	1.47 (0.67-3.24)	2.57 (0.87-7.55) p=0.086

Table 9.21 Odds ratio (95%CI) as estimate for associated risk of total weekly fruit consumption, by quintile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest quintile	2nd	3rd	4th	Highest quintile
Current	Community	1	0.5 (0.28-0.87) p=0.014	0.33 (0.18-0.6) p<0.0001	0.44 (0.26-0.76) p=0.003	0.33 (0.19-0.59) p<0.0001
	RO	1	0.82 (0.45-1.48)	0.68 (0.37-1.24)	0.87 (0.5-1.51)	0.63 (0.34-1.2)
	BO	1	3.82 (1.22-12) p=0.022	1.36 (0.62-3.01)	2.14 (0.95-4.81)	Distributed by quartile
10 years ago	Community	1	0.44 (0.25-0.77) p=0.004	0.3 (0.17-0.51) p<0.0001	0.4 (0.22-0.67) p=0.001	0.37 (0.18-0.74) p=0.005
	RO	1	0.58 (0.33-1) p=0.051	0.71 (0.35-1.46)	0.76 (0.45-1.28)	0.6 (0.29-1.23)
	BO	1	1.34 (0.58-3.08)	0.91 (0.39-2.11)	2.13 (0.9-5.07) p=0.087	0.6 (0.24-1.51)

Table 9.22 Odds ratio (95%CI) as estimate for associated risk of total weekly fruit juice consumption, by tertile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest tertile	2nd	3rd
Current	Community	1	0.81 (0.5-1.31)	0.75 (0.5-1.14)
	RO	1	0.87 (0.53-1.44)	0.62 (0.4-0.97) p=0.038
	BO	1	1.72 (0.7-4.23)	1.37 (0.74-2.55)
10 years ago	Community	1	0.75 (0.45-1.24)	0.76 (0.5-1.14)
	RO	1	0.9 (0.51-1.59)	0.7 (0.5-1.08)
	BO	1	1.69 (0.65-4.36)	0.84 (0.46-1.53)

Table 9.23 Odds ratio (95%CI) as estimate for associated risk of total weekly potato consumption, by quintile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest quintile	2nd	3rd	4th	Highest quintile
Current	Community	1	1.21 (0.69-2.12)	1.42 (0.76-2.64)	2.08 (1.18-3.64) p=0.011	2.24 (1.21-4.14) p=0.01
	RO	1	1.56 (0.85-2.87)	1.5 (0.85-2.66)	1.81 (0.92-3.57) p=0.085	2.2 (1.15-4.2) p=0.017
	BO	1	1.73 (0.82-3.64)	1.7 (0.63-4.55)	1.17 (0.51-2.68)	1.92 (0.81-4.55)
10 years ago	Community	1	1.1 (0.66-1.85)	1.01 (0.53-1.94)	1.62 (0.93-2.8) p=0.086	1.87 (0.99-3.55) p=0.054
	RO	1	1.6 (0.91-2.79)	0.9 (0.46-1.78)	0.66 (0.93-2.95) p=0.087	0.91 (0.97-3.77) p=0.062
	BO	1	1.17 (0.44-3.12)	0.67 (0.26-1.72)	0.99 (0.43-2.29)	1.17 (0.44-3.12)

Table 9.24 Odds ratio (95%CI) as estimate for associated risk of total weekly red meat consumption, by quintile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest quintile	2nd	3rd	4th	Highest quintile
Current	Community	1	1.92 (1.12-3.28) p=0.017	2.3 (1.36-3.88) p=0.002	2.51 (1.36-4.62) p=0.003	1.6 (0.92-2.77) p=0.096
	RO	1	1.48 (0.84-2.59)	2.42 (1.35-4.35) p=0.003	2 (1.05-3.8) p=0.035	1.09 (0.61-1.92)
	BO	1	1.06 (0.47-2.42)	2.05 (0.81-5.15)	0.88 (0.37-2.06)	0.67 (0.3-1.49)
10 years ago	Community	1	1.27 (0.72-2.25)	1.62 (0.93-2.8) p=0.088	1.42 (0.81-2.51)	1.51 (0.87-2.63)
	RO	1	1.28 (0.75-2.16)	1.25 (0.6-2.62)	0.91 (0.48-1.73)	0.98 (0.51-1.89)
	BO	1	1 (0.43-2.35)	1.06 (0.32-3.52)	0.54 (0.21-1.38)	0.35 (0.14-0.87) p=0.024

Table 9.25 Odds ratio (95%CI) as estimate for associated risk of total weekly poultry consumption, by quartile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest quartile	2nd	3rd	4th
Current	Community	1	0.29 (0.03-2.63)	1.01 (0.66-1.53)	0.94 (0.52-1.7)
	RO	1	1.12 (0.72-1.75)	0.91 (0.56-1.49)	Distributed by tertile
	BO	1	1.13 (0.57-2.25)	0.61 (0.27-1.4)	0.47 (0.21-1.07) p=0.071
10 years ago	Community	1	0.85 (0.14-5.23)	0.94 (0.62-1.43)	0.73 (0.4-1.33)
	RO	1	0.94 (0.6-1.48)	0.98 (0.6-1.62)	Distributed by tertile
	BO	1	1.08 (0.54-2.13)	0.5 (0.22-1.14) p=0.098	0.69 (0.31-1.56)

Table 9.26 Odds ratio (95%CI) as estimate for associated risk of total weekly fish consumption, by tertile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest tertile	2nd	3rd
Current	Community	1	1.07 (0.71-1.62)	0.77 (0.47-1.24)
	RO	1	1.16 (0.75-1.79)	0.84 (0.5-1.4)
	BO	1	1.23 (0.65-2.31)	0.94 (0.46-1.95)
10 years ago	Community	1	0.99 (0.65-1.49)	1.09 (0.66-1.82)
	RO	1	0.84 (0.54-1.32)	0.8 (0.47-1.39)
	BO	1	1.4 (0.72-2.74)	1.11 (0.52-2.4)

Table 9.27 Odds ratio (95%CI) as estimate for associated risk of total weekly tea consumption, by quintile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest quintile	2nd	3rd	4th	Highest quintile
Current	Community	1	1.22 (0.69-2.13)	0.98 (0.57-1.68)	1.66 (0.86-3.21)	2.02 (1.11-3.67) p=0.022
	RO	1	0.83 (0.49-1.41)	1.09 (0.58-2.05)	1.16 (0.65-2.09)	1.13 (0.63-2.03)
	BO	1	0.95 (0.37-2.48)	0.93 (0.45-1.93)	1.77 (0.68-4.61)	0.9 (0.41-2.01)
10 years ago	Community	1	1.37 (0.74-2.54)	1.52 (0.93-2.5) p=0.095	1.63 (0.91-2.9) p=0.098	2.27 (1.32-3.92) p=0.003
	RO	1	1.09 (0.62-1.92)	1.99 (1-3.97) p=0.052	0.89 (0.51-1.53)	1.2 (0.63-2.92)
	BO	1	1.55 (0.68-3.55)	0.76 (0.34-1.71)	1.52 (0.66-3.48)	1.32 (0.53-3.3)

Table 9.28 Odds ratio (95%CI) as estimate for associated risk of total weekly coffee consumption, by quartile and corrected by BMI, and OAC, in comparison with three control groups

		Lowest quartile	2nd	3rd	Highest quartile
Current	Community	1	0.84 (0.51-1.39)	1.35 (0.74-2.47)	1.18 (0.63-2.21)
	RO	1	1.15 (0.68-1.96)	1.56 (0.94-2.6) p=0.086	1.44 (0.84-2.49)
	BO	1	1.52 (0.68-3.38)	2.24 (1.01-5) p=0.049	1.23 (0.59-2.57)
10 years ago	Community	1	1.04 (0.61-1.75)	1.14 (0.62-2.11)	0.83 (0.48-1.43)
	RO	1	1.24 (0.72-2.16)	1.42 (0.83-2.43)	1.47 (0.88-2.44)
	BO	1	1.22 (0.55-2.71)	2.48 (1.07-5.74) p=0.034	0.69 (0.34-1.4)

9.4 Discussion

Recruitment met with the power calculation for number of OAC subjects, community subjects and with subjects with RO. Analysis of potential risk factors associated with OAC in comparison with subjects with BO is unfortunately underpowered due to the difficulties in recruiting incident cases of BO at the same time as an on-going drug intervention trial among these individuals (AspECT). Moreover, as not recruiting prevalent cases of BO, the numbers presenting were limited and unlike the low numbers of OAC, they are not routinely discussed in a multi-disciplinary meeting were they can be easily identified. As anticipated the vast majority of OAC subjects were male, with a median age matching that seen in the study of incidence of OAC in the West Midlands (Chapter 4). The disease was predominantly seen among the Caucasian population with very few ethnic cases.

Intriguingly no association was observed with the presence of *H.pylori*, with the prevalence of the infection 31.1-35.9% across all groups. This is in contrast to previous studies, and a lower prevalence is observed among the population studied than expected (Murray et al., 1997). While a low response rate among community subjects may introduce a degree of selection bias, there were much better response rates seen among the subjects with RO and BO, yet no association was identified. This suggests that selection bias may not a major confounding factor, but should be acknowledged. This may be a reflection of the testing method employed, as serological testing only reflects the last two years of life; a negative test may not represent *H.pylori* infection

that has been eradicated over two years prior. No association was observed with *cag*A status of *H.pylori*.

In keeping with previous data (Chapter 4), there was no association with socio-economic status and OAC. We hypothesis that the association of *H.pylori* with deprivation as a potential protective factor may be offset by the better dietary habits seen among the more affluent, resulting in a lack of association with socio-economic status and OAC.

The impact of smoking is clearly a deleterious one with between a two- to four-fold increased risk of OAC observed with current smoking when compared with all control groups. While being an ex-smoker reduced this association, a significant positive association remained with OAC in comparison with all three-control groups. There is also a clear dose-response seen with positive association seen with duration of smoking and amount smoked per day. While this study does not examine the mechanism of action, we have adjusted symptoms of gastro-oesophageal reflux for smoking, and no appreciable change was observed, suggesting that smoking has not impacted upon oesophageal function, TLOSRs and clearance of acid refluxate from the oesophagus to a significant level. However, as noted, smokers may appreciate symptoms of reflux less than non-smokers, thus masking effects of smoking upon GORD rather than symptoms as analysed. Performing oesophageal pH monitoring was not feasible during this study. The role of direct action of nitrosamines and polycyclic aromatic hydrocarbons as

carcinogenic agents must play an important role (McKnight et al., 1999, Kamangar et al., 2009), especially as some of the inhaled smoke is likely to be swallowed and reach the oesophagus in saliva.

No association was observed with alcohol consumption status, duration of consumption and amount drunk and OAC in comparison with subjects with RO and BO. However, in comparison with community subjects, being a current drinker of alcohol revealed a negative association with OAC, together with a decreasing negative association with duration of consumption of alcohol, except for the highest quintile of duration. Previous studies have found a mixture of associations, and MOSES adds to these findings (Freedman et al., 2011)

Symptoms of heartburn and acid regurgitation are associated with OAC in comparison with community controls, suggesting a direct action of acid upon the oesophageal mucosa. Moreover the increasing positive association seen with frequency of symptoms and duration strengthens the finding, and the significant association with nocturnal waking is in keeping with studies showing that nocturnal oesophageal acid exposure is more likely to result in complications from GORD (Robertson et al., 1987). The absent or negative association of ever having had heartburn or acid regurgitation symptoms may be in part due, at least among the BO subjects, the reduced ability for columnar-lined mucosa to produce symptoms in response to low pH (Byrne et al., 2003). Furthermore, these groups of individuals are more likely to be on

formal acid suppressing medication such as PPI masking any symptoms. Despite this suggestion, increasing duration of heartburn and acid regurgitation symptoms, and frequency of symptoms, are associated with OAC in comparison with subjects with RO and BO. The use of antacids for symptoms is increasingly associated with OAC, strengthening the aetiology of GORD in OAC.

Several factors influence gastro-oesophageal reflux, with chronic *H.pylori* leading to atrophic gastritis and reduced gastric acid production, and thus less symptomatic gastro-oesophageal reflux (Richter et al., 1998). Smoking also reduces LOS pressures, increases TLOSRs, and with coughing and reduced salivation reducing clearance of oesophageal acid clearance, may increase oesophageal acid exposure (Kahrilas and Gupta, 1990, Pandolfino and Kahrilas, 2000). Statistical methods employed to correct for these potential confounding, but little change was seen with the OR derived, and no change to the overall findings and their statistical significance.

With the general population heights increasing over the last 50 years, and OAC incidence rising at the same time, hypotheses have been made that the increased acid exposure seen among taller individuals may lead to greater oesophageal acid exposure in those with GORD (Axon, 2004). We failed to reveal any association in the current study. It was however observed that increasing leg length was associated with OAC in comparison with subjects with RO and BO, but not community subjects. It has previously been identified

that leg length is a marker pre-pubertal growth and of IGF-1 levels (Sheppard, 2004). OAC cell lines have increased proliferation when exposed to IGF-1, and OAC patients with higher IGF-1 levels have a worse prognosis (Donohoe., et al, 2012, Doyle et al., 2012)

Previous research has shown an association with increasing BMI and both OAC (Engel et al., 2003) and BO (Stein et al., 2005). The current study has observed similar findings with an association of increasing BMI and OAC with comparison to community and RO subjects. While no association is observed in comparison with BO at the time and 10 years prior to the interview, an association is seen at the age 18. This suggests that the impact of increased BMI is earlier in the reflux to RO to BO to OAC sequence. Obesity is noted to be strongly associated with hiatus hernia (Stene-Larsen et al., 1988), a known precipitant of GORD, but other mechanism of increasing reflux such as increasing intra-abdominal pressure is less well substantiated (Gordon et al., 2004). The association with increasing waist circumference and OAC compared with subjects with RO and BO suggests that visceral adiposity is key in the effects seen with increasing BMI, but not in comparison with community subjects where IGF-1 may not have any effect. It is noted that visceral adiposity leads to increased IGF-1 levels, known to reduce apoptosis and increasing OAC cell proliferation (Sheppard, 2004).

Most of the associations with diet and OAC are apparent in comparison with community and RO subjects, suggesting that the effects of diet are negligible

at the stage of BO, or that insufficient power has been achieved with the low number of subjects with BO. In keeping with previous case-control studies, diet high in fruit and vegetables (frequency and total weekly portion quantity), especially fruit is negatively associated with OAC. The presence of phytoprotectants such as isothiocyanates and indol-3-carbinols and diets high in fibre have proven mechanism of action in apoptosis (Myzak and Dashwood, 2006, Kim and Milner, 2005, Tzonou et al., 1996). If the theory that increased fertiliser use in the latter half of the 20th century has led to increased nitrate concentration in crops, led to increased nitrosative stress in the oesophagus and thus increased incidence of OAC were to be true, then it would be reasonable to expect a positive association with fruit and vegetables. The nitrosative stress theory may hold more truth with the nitrates present in red meat. The current study revealed a positive association with red meat. Heterocyclic amines and polycyclic hydrocarbons, known to be carcinogenic, are produced when cooking meat at high temperatures (Kubo et al., 2010); the method of cooking was not examined in this study. A further explanation is the high saturated fat content of meat, known to be associated with OAC (Mayne et al., 2001)

No association was seen with OAC and dietary poultry and fish intake. The effect of n-3 fatty acids is of interest, and has been studied in BO (Mehta et al., 2008). However, n-3 fatty acids are seen greatest in oily fish such as salmon, mackerel, sardines and fresh tuna. The interview did not differentiate type of fish, and thus unable to examine this.

Increasing tea consumption, notably the highest quintile in comparison with community subjects is associated with OAC, presumably by the known effects of relaxing the LOS, and allowing greater reflux of gastric contents. The impact of coffee was only noted among subjects with BO and is not powered fully, especially with tea being a more common hot beverage than coffee.

Dietary analysis is subject to much confounding with re-call bias as a key issue. By examining reproducibility of the interview, showing moderate to substantial agreement, we have attempted to overcome this, but it still remains as confounding, but should affect all subjects equally. The reflux section of the interview has already been validated previously. By censoring the last year before diagnosis of cancer, we aimed to have overcome the influence of cancer upon the diet and other factors such as BMI. Finally, while correction for BMI has occurred in the dietary intake analysis, it is ideal to adjust dietary intake by total energy expenditure to provide a more exact appreciation of any potential associations (Willett and Stampfer, 1986, Willett et al., 1997). It was felt however that any attempt to estimate total energy expenditure would be subject to too many inaccuracies and confounding to be able to include in this study.

In summary, with a lower than expected prevalence of *H.pylori*, no association with OAC was observed. Increasing BMI and waist circumference, as a marker of visceral adiposity and thus IGF-1 is associated with OAC, as is

increasing leg length, a marker of IGF-1, known to promote oncogenesis, among those with sequalae of GORD. Increasing BMI may also influence the positive association by increasing the prevalence of hiatus herniation and thus predisposing to gastro-oesophageal reflux, the symptoms of which has been identified in this study to be strongly associated with OAC. Smoking is clearly implicated in the aetiology of OAC with a dose-response effect observed. Alcohol may have negative associations with OAC, but results are mixed, as is the current literature. Finally a diet high in fruit and vegetables, especially fruit has negative associations with OAC and plausible mechanisms already established. Similarly, dietary intake high in red meat also has proven biochemical mechanisms of action in the positive association with OAC.

Chapter 10

Conclusions and Implications

10.1 Conclusions and Implications

The aetiology of OAC is the subject of much interest as the rapidly increasing incidence over the last 30 years remains largely unexplained, most notably the predominance of the disease among white men. While many studies have examined the aetiology, many are underpowered due to the relatively low incidence in some of the countries in which the research is based. The UK has the highest incidence of OAC, but there are very few studies based in England.

10.2 Summary of findings

Table 10.2 illustrates the summary of findings examined in more than one study in order to allow comparison of findings. The median age, and gender predominance is clearly observed to be very similar in all studies, with the majority of subjects noted to be Caucasian. Consistent positive associations were seen with increasing BMI and smoking with OAC, less consistent with height and leg length as a surrogate of IGF-1, while negative associations (e.g. aspirin, NSAID and PPI use) are discussed in more detail as less consistent across the studies. Some factors were examined in only one or two of the studies in this thesis but provide the hypothesis for further investigation, for example the reduce incidence in OAC following a diagnosis of PC was observed in both WMCIU and SEER datasets, and the negative association seen with the use of statins. Increasing positive associations were observed with drugs used for COPD and those with a side effect of relaxing the LOS,

but only in the THIN nested case-control study. Furthermore MOSES revealed a positive association with GOR symptoms, increasing quantities of red meat and tea consumption and a negative association with fruit and vegetable consumption.

Table 10.2 Summary of factors examined in multiple studies

	WMCIU data	THIN Nested case-control	THIN case control	MOSES
Median age (IQR)	70 (61-77)	67 (59-73)	69 (59-77)	68 (60-75)
Gender	4-5 fold men	84% male	82% male	85% male
Socioeconomic status	No association	No association	No association	No association
Height	N/E	N/E	+ve association	none for height, +ve for leg length
BMI	N/E	No association	+ve association	+ve association
Smoking status	N/E	+ve association	+ve association	+ve association
Alcohol consumption	N/E	N/E	N/E	-ve association
PPI use	N/E	No association	Mixed	N/E
Aspirin/NSAIDS	N/E	No association	Some –ve association	N/E

N/E: not examined

10.3 Discussion

By examining the WMCIU database, the incidence of OAC in comparison with OSCC has been observed to be rising rapidly among both men and women, but most notably men, rising to almost 9 per 100 000 at the end of the study period. The age of diagnosis has increased, but is approximately 8 years later among women. The median ages in the WMCIU data were in keeping entirely with the nested case-control study of subjects with BO developing OAC, the THIN case-control study and also MOSES, being 67-69 years of age, and male predominant. Indeed male predominance while noted among subjects with BO, was a significant risk factor in the progression to OAC.

A handful of studies in the literature have reported association with industrial/occupational exposure and OAC, it is not sufficient to explain the difference observed. By examining men with a diagnosis of PC, an androgen sensitive tumour, the influence of male sex hormones could be examined through epidemiological methods. The data from the WMCIU raised the hypothesis that anti-androgen therapy employed in the treatment of PC (medical or surgical) may be the reason by the reduced incidence of OAC in men with a first diagnosis of PC, but was unable to reveal a latency effect of longer duration of anti-androgen having a greater negative impact upon the incidence of OAC. By examining the SEER 9 registries dataset from the USA, almost ten times the number of subjects with PC were identified, increasing the number of patient years to over 2 million. A latency effect was thus demonstrated, but not only among subjects with OAC, but also OSCC.

Androgen receptors have been identified on both OAC and OSCC cells (Awan et al., 2007, Tihan et al., 2001, Waraich, 2008), and with this explanation being still plausible, although it is noted that there is little differentiation in incidence of OSCC between the genders, but other factors such as smoking and alcohol are much more influential in the aetiology of OSCC.

A further explanation for male predominance in this cancer is the pattern of male obesity. Male pattern obesity is defined by an increase in visceral adiposity. This is associated with a greater incidence of hiatus herniation that predisposes to gastro-oesophageal reflux, known to be an important aetiological factor inn OAC. Furthermore, visceral adiposity is biochemically more active than subcutaneous fat, and linked with high levels of IGF-1. IGF-1 is noted to influence cell proliferation and apoptosis, having an increase in oncgenesis (Sheppard, 2004). Increasing BMI was associated with OAC in both the THIN case-control study and MOSES. More importantly, in the MOSES study, an increase in reported waist circumference was associated with OAC, but only among subjects with RO and BO. The lack of association seen with waist circumference and OAC in comparison with community subjects adds to the conjecture that IGF-1 levels in the stressed oesophageal mucosa may have a key role as well as the effect of increasing reflux. This statement however does require substantiation and further investigation, and currently remains as a hypothesis for future work.

Association with height and OAC was assessed in both the THIN case-control study and MOSES. While no association was observed in MOSES, increasing leg length was associated with OAC. Furthermore, increasing height was associated with OAC in comparison with all three-control groups in THIN case-control study. One explanation for this is that those subjects with increasing height have greater gastric acid production (Axon, 2004), leading to a greater degree of oesophageal acid exposure should reflux occur. It is noted that population heights have been steadily increasing at the same time that OAC incidence has been rising. It is notable though that leg-length is a marker of pre-pubertal growth, and as such is a surrogate marker for IGF-1 (Sheppard, 2004). Leg length is a significant contributor for height, and therefore the observation in the THIN case-control study may be a marker of leg length. A potential role for raised IGF-1 levels in the aetiology of OAC is postulated, but remains a hypothesis for future study.

The impact of smoking is well established in the aetiology of OSCC, but is more modest in that of OAC. Both case-control studies have revealed a strong association with smoking, with MOSES revealing a clear dose-response effect. The carcinogens in tobacco are likely to influence the oncogenic process (McKnight et al., 1999, Kamangar et al., 2009), but it is noted that smoking does reduce LOS pressures, increase TLOSRs (although not associated with reflux), reduced saliva and thus clearance of oesophageal refluxate and causes reflux through coughing (Kahrilas and Gupta, 1990, Pandolfino and Kahrilas, 2000). However, when the association of reflux

symptoms and OAC were examined in MOSES, adjusting for smoking made very little difference to the overall OR and levels of significance. Importantly having ever smoked is a risk factor for progression from BO to OAC in the THIN nested case-control study and both the THIN case-control and MOSES studies show a much-reduced association with being an ex-smoker as compared with a smoker. Smoking cessation may therefore be a key modifiable risk factor in the aetiology of OAC, and should be actively encouraged, especially among individuals with BO.

Only one of the studies examined the influence of *H.pylori* and despite being suitably powered, no association with OAC was observed. There was a lower than expected prevalence of infection among control subjects and a higher than expected prevalence among subjects with OAC. Furthermore, adjusting statistical analysis for reflux symptoms with the presence or absence of infection did not alter the outcome, suggesting that *H.pylori* not only had little association with OAC, but also that few subjects reflux symptoms were affected by the bacteria.

In keeping with the literature, reflux symptoms were associated with OAC, with respect to presence, frequency and duration, including markers of severity (nocturnal symptoms). While there was a less clear association with comparison with subjects with RO and BO, this is in part due to the likely universal symptom experienced among those diagnosed with RO, and the potential use of acid suppression medication that was observed almost

universally among the nested case-control study subjects with BO. The THIN case-control study too identified that use of acid suppressing drugs, PPIs, were associated with OAC in comparison to community subjects, suggesting that reflux symptoms were more apparent in the OAC subjects. Furthermore, analysis of antacid use was examined in MOSES and seen to be positively associated with OAC, further revealing the severity of acid reflux symptoms.

The nested case-control study of subjects with BO revealed that an increasing number of drugs with associated side effects of relaxation of the LOS, and thus promoting gastro-oesophageal reflux, was associated with progression to developing OAC. Furthermore, this study revealed that use of inhaled steroids, and the increasing number of drugs taken for asthma/COPD were associated with progression to OAC. The effects were not due to that of smoking as the association remains after statistical adjustment for this potential confounding. This suggested that either the drugs themselves (β-blockers and theophyllines) were reducing the LOS pressure (but is not supported by the association seen with inhaled steroid use) or that the disease the drugs were prescribed for was part of the aetiology for oncogenic progression. There is evidence in the literature that coughing and asthma may be associated with increasing reflux into the oesophagus (Vaughan et al., 1998), thus strengthening further the evidence for the strong aetiological influence of gastro-oesophageal reflux in the development of OAC.

Examining the aetiology of any cancer is most fruitful when a potential modifiable risk factor is identified, and thus suitable for consideration in therapeutic interventional drug trials. The use of aspirin has good biochemical mechanisms but no association was observed in the nested case-control study examining risk factors associated with the progression of BO to OAC. However, a negative association with aspirin and with NSAIDs was observed in the THIN case-control study, offering hope of a chemotherapeutic option in those most at risk. The results of AspECT, an on-going prospective aspirin and PPI intervention trial among subjects with BO should provide more conclusive evidence (Jankowski and Moayyedi, 2004).

A further class of drugs were identified to be negatively associated with OAC in the THIN case-control study: statins. Statins have been shown at the cellular level to reduce cell proliferation and induce apoptosis in BO cell lines (Sadaria et al., 2011, Ogunwobi and Beales, 2008, Konturek et al, 2007), and reduce overall cancer development (Graaf et al., 2004). Mixed results have been seen in epidemiological studies of the aetiology of OAC, but the current finding is as strong as that of aspirin and NSAIDs, suggesting the potential for further investigation with chemotherapeutic trials of statins.

One of the biggest modifiable risk factors for cancers, second only to smoking, is the diet (Doll, 1992). Dietary examination is fraught with difficulties and confounding, with recall bias, correction for total energy expenditure, and consistency with portion size. Only one of the epidemiological studies was

geared to analysing diet: MOSES. While inconsistencies were observed, it is evident that a diet high in fruit and vegetables, especially fruit, was negatively associated with OAC, and diet high in red meat was positively associated with OAC. These associations are backed up with plausible mechanisms of action, with fruit and vegetables being high in phytoprotectants and fibre, both shown to protect against cellular damage (Myzak and Dashwood, 2006, Kim and Milner, 2005, Tzonou et al., 1996), and red meat, especially if cooked over an open-flame is high in heterocylic amines and polycyclic aromatic hydrocarbons, known carcinogenic agents, that increase nitrosative stress at the lower oesophagus (Kubo et al., 2010). We did not examine cooking methods. Furthermore, in comparison with community subjects at least, high consumption of tea was identified to be positively associated with OAC, and coffee to a certain extent with comparison with subjects with BO. Both tea and coffee contain caffeine known to relax the LOS.

While we have identified a statistically significant negative association with consuming alcohol and duration of the drinking habit and OAC (in comparison with community controls) there are mixed results in other published studies. The OR produced however is quite strong however the mechanism of action is not understood and may be as a result of confounding, thus limiting the ability to employ alcohol as a modifiable risk factor in the aetiology of OAC at this stage.

The use of postcode has enabled examination of socioeconomic status with the Townsend index in several of the studies in this thesis: WMCIU database, THIN case-control study and MOSES. The findings were consistent across the studies, with no association observed between socioeconomic status and OAC. While the Townsend index is based on material wealth, the IMD is based more on benefits and allowances. The IMD also revealed no association between OAC and socioeconomic status (WMCIU data) further confirming the findings by different methodology. The lack of association is likely to be the mix of different aetiological factors, for example with negatively associated factors, diets high in fruit and vegetables are more likely to be seen among the affluent, while *H.pylori* is more common among the deprived.

Examination of the WMCIU data from 1977-2004 confirms the rapidly increasing rise in incidence of OAC, and while not examined, many of the associations revealed have changed in prevalence of the last few decades. BMI and waist sizes have been increasing leading to a greater likelihood of hiatus hernia development and GORD, as has height. With leg length being part of height a plausible impact of IGF-1 is implicated, along side that with visceral adiposity. Since the discovery of *H.pylori* and its role in gastro-duodenal ulceration and gastric cancer, the medical world has sought to eradicate the bacteria whenever symptoms or pathology present. Furthermore, while the consumption of fruit has not altered significantly, green vegetables are eaten to a lesser degree as compared with several decades ago (Office of National Statistics).

As well as offering the basis for hypotheses to be tested by drug intervention trials, for example aspirin/NSAIDs and statins, the results of this thesis offer the potential for identifying those at greater risk of developing OAC, and increasing the screening or surveillance. The surveillance of those individuals with BO is contentious currently, and while studies such as BOSS are due to report on the value of surveillance, identification of risk factors in the development of OAC may enable stratification of potential surveillance programmes. Finally, data revealing modifiable risk factors enables clinicians to counsel patients and empower them to take control of their chances of developing this rapidly rising cancer with poor prognosis.

Chapter 11

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Appendices

Appendix 1 Statistaical programming for calculating SIR following a diagnosis of oesophageal cancer following proastet cancer using STATA (chapters 5-6)

Change available memory:
set mem 200m

Import ref rates data into Stata:
insheet using “Z:StataData\listratesmale.csv”

Rename year Calendar_year
gen year=Calendar_year-1900

To sort ref_rates:
sort age year

Save ref rates:
save male_ref_rates.dta

Clear

Imprt cases:
insheet using “Z:StataData\Prostate1stPrimary.csv”

To format dates:
gen diagdate = mdy(diag_month, diag_day, diag_year)
format diagdate %dD_m_CY

reason:
gen reason = 6 if nd_primary == ”Death”
replace reason = 6 if nd_primary == “NSTS Death”
replace reason = 0 if nd_primary == “Withdrawn”
replace reason = 4 if substr(nd_primary,1,1) == “C”
replace reason = 1 if c15morph == “Adeno”
replace reason = 2 if c15morph == “Squamous”
replace reason = 3 if c15morph == “Other”

Save cohort data:
Save prostatecohort.dta

To calc Observed pop and SIR (changing enter and exit times):

```
use prostatecohort

stset eofu, failure(reason=1-3) enter(time diagdate + 90) exit(time
diagdate + 365.25)
origin(time dob) scale(365.25) id(id)
stsplit, at (0(5)85)
stsplit year, after(time=d(01jan1900)) at(77(1)104)
gen Y = _t - _t0
gen D = _d
sort age year
merge age year using male_ref_rates
keep if _merge == 3

gen Expected = Y*oseo/malepop

gen O
egen E = sum(Expected)
gen SIR = O/E

local dflo = 2*O
local dfhi = 2*O + 2
scalar SIRLx = 0.5*invchi2tail(‘dflo’, 0.975)/E
scalar SIRUx = 0.5*invchi2tail(‘dflo’, 0.025)/E
```

Appendix 2 General practices recruiting for MOSES

Hospital	GP1	GP2	GP3
City	Dr DK Nandi Tower Hill Medical Practice 25 Tower Hill Great Barr B42 1CG	Dr Lawrence F Miller Sherwood House Medical Practice 9 Sandon Road B17 8DP	Dr David Child Cape Hill Medical Practice Raglan Road Smethwick
Sandwell	Dr Keith Holtom Oldbury Health Centre Albert Street Oldbury B69 4DE	Dr Catherine Swain Neptune Health Park Sedgley Road West Tipton DY4 8PX	Dr John Gilbert Linkway Medical Practice Lyng Centre Frank Fisher Way West Bromwich B70 7AW
Russell's Hall	Dr Jonathan Darby St Margaret's Well Surgery 2 Quarry Lane Halesowen B63 3WD	Dr Nancarrow Worcester Street Surgery 24 Worcester Street Stourbridge DY8 1AW	Dr Dominic Faux Albion House Surgery Albion Street Brierley Hill DY5 3EE
Walsall Manor	Dr Angela Haire Lichfield Street Surgery 19 Lichfield Street Walsall WS1 1UG	Dr Moszuto Little London Surgery Little London Caldmore Walsall WS1 3EP	Dr Julie Harrison Portland Medical Practice Anchor Meadow Health Centr Westfield Drive Aldridge Walsall WS9 8AJ
New Cross	Dr Angus Jones Dale Medical Practice Planks Lane Wombourne Wolverhampton WV5 8DX	Dr Robert Stoves The Health Centre Alfred Squire Road Wednesfield Wolverhampton WV11 1XU	Dr Peter Maidment Bilbrook Medical centre Brookfield Road Bilbrook Codsall Wolverhampton WV8 1DX
UHB	Dr Chris Leigh Wychall Lane Surgery 11 Wychall Lane Kings Norton Birmingham B38 8TE	Dr Patrick Ireland Selly Park Surgery 2 Reaview Drive Pershore Road Selly Park Surgery Birmingham B29 7NT	Dr Roger Light/Phil Saunders Ridgeacre House Surgery 83 Ridgeacre Road Quinton Birmingham B32 2TJ

Alexandra Redditch	Dr Philip Clamp St John's Surgery 5 Kidderminster Road Bromsgrove B61 7JJ	Dr Sian Hotham New Road Surgery 46 New Road Bromsgrove B60 2JS	Dr C Mark Johnstone Elgar House Church Road Redditch B97 4AB
Warwick	Dr Nigel Wood Arden Medical Centre Albany Road Stratford-upon-Avon CV37 6PG	Dr Mark Palmer Emscote Road Surgery 88-90 Emscote Road Warwick CV34 5QJ	Dr Richard Seymour-Mead Henley-in-Arden Medical Centre Prince Harry Road Henley-in-Arden Warwickshire B95 5DD
Good Hope	Dr Vivian Boss Aldergate Medical Practice Salters Lane Tamworth B79 8BH	Dr Broomhead Hawthorns Surgery 331 Birmingham Road Wylde Green Sutton Coldfield B72 1DL	Dr Blake Poplar Surgery 17 Holly Lane Erdington B24 9JN
Heartlands	Dr Anand Chitnis The Castle Practice 2 Hawthorne Road Castle Bromwich B36 0HH	Dr Liz Nyholm Yardley Green Medical Practice 73 Yardley Green Road Bordesley Green B9 5PU	Dr Irvine Stuart The Blythe Practice 1500 Warwick Road Solihull B93 9LE
Walsgrave	Dr Ham Central Surgery Corporation Street Rugby CV21 3SP	Dr Jane Smith Mansfield Medical Centre 56 Binley Road Coventry CV3 1JB	Dr David Shore The Revel Surgery Barr Lane Brinklow CV23 0LU
Burton	Gorden Street Surgery Burton-on-Trent Staffordshire DE14 2JB		

Appendix 3

Geographical distribution of recruiting hospitals and associated general practice surgeries across the West Midlands

Sandwell and West Birmingham Hospitals NHS
NHS Trust

Diet and Lifestyle Questionnaire

Midlands Oesophageal Adenocarcinoma Epidemiology Study

(Version 2 27/01/2006)

Department of Gastroenterology
Sandwell General Hospital

SECTION A: BACKGROUND INFORMATION

1. Reference Number:…..……..

2. Date of interview:……

3. Interviewer: ……

4. Status: □ Cancer □ Oesophagitis □ Barrett's oesophagus □ Control

5. Sex: □ Male □ Female

6. Date of Birth: ……

7. Postcode: …….

8. Postcode 10 years ago: …….

9. How would you describe your ethnic or racial origin? *(Tick one)*

□	White	□	Black (Caribbean)
□	Black (African)	□	Black (Other)
□	Indian	□	Pakistani
□	Bangladeshi	□	Chinese
□	Other – please specify	……..	

10. Consultant: ……..

11. Hospital: ……..

12. Hospital number: ……

13. Patient's name: ……

14. Pathology reference number: …….

SECTION B: DIET HISTORY

For each question, please consider current consumption (or in cancer patient: consumption in the 12-month period up to about one year ago), and consumption 10 years ago. 1 portion is hand palm size.

1. How many days of the week did/do you eat fresh vegetables other than potatoes?
   Current:…….
   10 years ago:…….

2. How many portions per day of fresh vegetables other than potatoes did/do you eat?
   Current:…….
   10 years ago:…….

3. How many days of the week did/do you eat potatoes?
   Current:…….
   10 years ago:…….

4. How many portions per day of potatoes did/do you eat?
   Current:…….
   10 years ago:…….

5. How many days of the week did/do you eat fresh fruit?
   Current:…….
   10 years ago:…….

6. How many portions of fresh fruit did/do you have per day?
(1 serving = 1 fruit of apple/banana/orange/pear/satsuma/mandarin, half a grapefruit, 1 slice of melon or 1 cup of grapes/strawberries/raspberries/blackberries)
   Current:……..
   10 years ago:……..

7. How many days of the week did/do you eat nuts?
   Current:…….
   10 years ago:…….

8. How many portions of nuts (all sort) did/do you have per day?
   Current:……..
   10 years ago:……..

9. How many days of the week did/do you drink pure fruit juice (e.g. orange, apple, grapefruit) and/or pure vegetable juice (e.g. carrot, tomato)?
   Current:…….
   10 years ago:…….

10. How many glasses of pure fruit juice and/or pure vegetable juice did/do you drink per day? (glass=200ml)
   Current:…….
   10 years ago:…….

11. Did/do you add salt to cooking (always, usually, sometimes, rarely, never)?
    Current:……..
    10 years ago:……..

12. Did/do you add salt at the table (always, usually, sometimes, rarely, never)?
    Current:…….
    10 years ago:…….

13. Did/do you add pepper to cooking (always, usually, sometimes, rarely, never)?
    Current:…….
    10 years ago:…….

14. Did/do you add pepper at the table (always, usually, sometimes, rarely, never)?
    Current:…….
    10 years ago:…….

15. How many days of the week did/do you eat red meat e.g. pork, beef, lamb?
    Current:…….
    10 years ago:…….

16. How many portions per day did/do you eat red meat e.g. pork, beef, lamb?
    Current:…….
    10 years ago:…….

17. How many days of the week did/do you eat white meat e.g. chicken, turkey?
    Current:…….
    10 years ago:…….

18. How many portions per day did/do you eat white meat e.g. chicken, turkey?
    Current:…….
    10 years ago:…….

19. How many days of the week did/do you eat fish/sea food?
    Current:……
    10 years ago:……

20. How many portions per day did/do you eat fish/sea food?
    Current:…….
    10 years ago:…….

21. How often did/do you drink coffee (cup per day)?
    Current:……
    10 years ago:……

22. How often did/do you drink tea (cup per day)?
    Current:……
    10 years ago:……

23. Did you ever take any vitamin or mineral supplements at least once a week for six months or longer?

 Yes No

If yes, please indicate the average level of use for each of the following supplements:

Supplement	Unit dose/strength if known (mg/I.U.)	Current		10 years ago	
		Per day	Week	Per day	Week
Multivitamins					
Vitamin A					
Vitamin C					
Vitamin E					
Other (specify):					

24. How often did/do you use toothpaste? (times per day or week)
Current:……. per ……
10 years ago:……..per …….

SECTION C: SMOKING & ALCOHOL

1. SMOKING

Have you ever smoked cigarettes regularly (at least one cigarette per day for at least 30 days)? □ Yes □ No

If "Yes",

At what age did you start? ……

When smoking the heaviest, how many cigarettes did you smoke per day? ……

How many cigarettes do you currently smoke? (or in the 12 month period up to one year ago for cancer patient) …….

How many cigarettes did you smoke 10 years ago? …….

If you have stopped smoking, at what age did you stop? ……

2. ALCOHOL

(One drink is equal to half a can or half a pint of beer, a glass of wine or a single measure of spirits)

Have you ever drunk alcohol? □ Yes □ No

If "Yes",

At what age did you start? …….

When drinking the heaviest, how many drinks did you have per week? …….

How many drinks do you currently have per week? (or in the 12 month period up to one year ago for cancer patient) …….

How many drinks did you have per week 10 years ago? …….

If you have stopped drinking, at what age did you stop? ……

SECTION D: MEDICAL HISTORY

1. How tall are you? ..…feet …...inches OR ……..cm

2. What is your leg length? (measure lateral malleolus to iliac crest)
…….feet ……..inches OR …….cm

3.What is your weight (or what was your usual weight in the 12-month period up to one year ago for cancer patient)?
…….stones ……pounds OR ……kg

4. What was your weight 10 years ago?
……stones ……pounds OR ……kg

5. What was you weight when you were 18 years old?
……. Stones ……pounds OR ……kg

6. What is your waist measurement, OR what is your dress size for women (or in the 12-month period up to one year ago for cancer patient)?
…….inches OR …….cm OR dress size……..

7. What was your waist measurement 10 years ago, OR what was your dress size 10 years ago for women? ……..inches OR ……cm OR dress size …….

8. What was your waist measurement when you were 18 years old, OR what was your dress size when you were 18 years old for women?
……inches OR …….cm OR dress size ……

HEARTBURN is a burning pain or discomfort behind the breast bone or in the top part of the stomach.

9. Have you ever had heartburn? ☐ Yes ☐ No

If 'yes',

At what age did you start having heartburn? …….

How often do you have heartburn?

- ☐ None
- ☐ Less than once a month
- ☐ Once a month
- ☐ Once a week
- ☐ 2 to 6 times a week
- ☐ 7 to 15 times a week
- ☐ More than 15 times a week

How often did you have heartburn 10 years ago?

- ☐ None
- ☐ Less than once a month

□ Once a month
□ Once a week
□ 2 to 6 times a week
□ 7 to 15 times a week
□ More than 15 times a week

Has your heartburn woken you at night in the last year?
□ Yes □ No

Did your heartburn wake you at night 10 years ago?
□ Yes □ No

ACID REGURGITATION is fluid coming up into your throat or mouth, which may be burning or have a sour or bitter taste

10. Have you ever had acid regurgitation? □ Yes □ No

If 'yes',

At what age did you start having acid regurgitation? ……

How often do you have acid regurgitation?
□ None
□ Less than once a month
□ Once a month
□ Once a week
□ 2 to 6 times a week
□ 7 to 15 times a week
□ More than 15 times a week

How often did you have acid regurgitation 10 years ago?
□ None
□ Less than once a month
□ Once a month
□ Once a week
□ 2 to 6 times a week
□ 7 to 15 times a week
□ More than 15 times a week

Has your acid regurgitation woken you at night in the last year?
□ Yes □ No

Did your acid regurgitation wake you at night 10 years ago?
□ Yes □ No

11. How often do you take over the counter antacid (or for cancer patient: how often did you take over the counter antacid in the 12-month period up to 1 year ago)?
□ Never
□ Less than once a month
□ Once a month

- ☐ Once a week
- ☐ Several times a week
- ☐ Everyday

Which brand of antacid? …….

12. How often did you take over the counter antacid 10 years ago?

- ☐ Never
- ☐ Less than once a month
- ☐ Once a month
- ☐ Once a week
- ☐ Several times a week
- ☐ Everyday

Which brand of antacid? …….

13. How many bowel movements do you have in a day or week if not everyday (or in cancer patients: how many bowel movements did you have in a day in the 12-month period up to one year ago) …….

14. How many bowel movements in a day or week if not everyday did you have 10 years ago? ……..

15. What medications are you taking currently? (or in the 12 month period up to one year ago for cancer patient)

……
……
……
……

16. What medications did you take 10 years ago? ……..
……
……
……

17. Have you taken any of the following medicines? (See separate sheet for list)

If 'yes', which medicines and since what age did you start taking them
……
……
……

18. Before 10 years ago, did a doctor tell you that you had any of the following medical conditions?

- ☐ Oesophagitis (inflammation of the oesophagus or gullet)
- ☐ Barrett's oesophagus
- ☐ Ulcers in the oesophagus
- ☐ Gastric ulcer
- ☐ Duodenal ulcer
- ☐ Hiatus hernia

□ Anaemia or iron deficiency

19. Have you had any test at the hospital for heartburn or acid regurgitation (like a barium x-ray or endoscopy) □ Yes □ No

If 'yes',

□ What test? ……..

□ When was it done? ……

20. Have you had a previous operation/dilatation on your gullet? □ Yes □ No

If 'yes',

□ What procedure? ……

□ When was it done? …….

21. Have you had your gallbladder removed? □ Yes □ No

If 'yes', when was it done? …….

22. How many times did you visit a doctor, for any reason, in the 12-month period up to about a year ago? *(Tick one)*

0 □ None
1 □ 1 to 2 times
2 □ 3 to 5 times
3 □ 6 to 10 times
4 □ More than 10 times

If you have visited a doctor, why did you go? …….
……..……

23. Have you ever been told by your GP that you have high blood pressure?

□ Yes □ No

If 'yes', were you prescribed medication for high blood pressure?

□ Yes □ No

SECTION E: EDUCATIONAL HISTORY

1. How old were you when you left school? ……..

2. Do you have any educational qualifications?
- ☐ None
- ☐ City and Guilds
- ☐ O levels
- ☐ A levels
- ☐ University degree
- ☐ Other, (please specify)…….

3. What is (or was) the name and title of your main job?
Occupation: ……
Industry: …….

4. What is (or was) the name and title of your father's main job?
Occupation: ……
Industry: …….

SECTION F: FAMILY HISTORY

1. How many parents have you had contact with in your adult life?……
If less than 2,
please elaborate:……

2. Do/did either of your parents suffer from heartburn or acid reflux, Barrett's oesophagus or cancer of the oesophagus? ☐ Yes ☐ No
If 'yes',
Who? ……..
…….
What condition? ……..
…….
If cancer, where were they treated? ……
…….

3. Do/did either of your parents suffer from any cancer other than oesophageal cancer?
☐ Yes ☐ No
If 'yes',
Who? ……..
…….
What cancer? …….
…….
Where were they treated? ……
…….

4. How many older and younger siblings (brothers and sisters) did you have as a child?

Older:…….. Younger: ……

5. Do any of your brothers or sisters suffer from heartburn or acid reflux, Barrett's oesophagus or cancer of the oesophagus? □ Yes □ No

If 'yes',

Who (older/younger)? ……..
…….
What condition? ……..
…….
If cancer, where were they treated? ……
…….

6. Do/did any of your brothers or sisters suffer from any cancer other than oesophageal cancer? □ Yes □ No

If 'yes',

Who? ……..
…….
What cancer? …….
…….
Where were they treated? ……
…….

7. How many children do you have? ……..

8. Do any of your children suffer from heartburn or acid reflux, Barrett's oesophagus or cancer of the oesophagus? □ Yes □ No

If 'yes',

Who? ……..
…….
What condition? ……..
…….
If cancer, where were they treated? ……
…….

9. Do/did any of your children suffer from any cancer other than oesophageal cancer?

□ Yes □ No

If 'yes',

Who? ……..
…….
What cancer? …….
…….
Where were they treated? ……
…….

10. Does your spouse/partner suffer from heartburn or acid reflux, Barrett's oesophagus or cancer of the oesophagus?

☐ Yes ☐ No

If 'yes', what condition? ……..

……

If cancer, where were they treated? ……

……

11. Did either of your parents smoke in the house whilst you were a child?

☐ Yes ☐ No

Appendix 5

Prizes arising from this work

BSG Oesophageal Section Prize, March 2008: Best free paper

Evans and Gaisford Research Prize, Sandwell and West Birmingham Hospitals NHS Trust, December 2007

Midlands Gastroenterological Society Prize, November 2006: Best poster presentation

Publications arising from this work

Papers

Cooper SC, Trudgill NJ. Subjects with prostate cancer are less likely to develop esophageal cancer – analysis of SEER 9 Registries Database. Cancer, Causes and Control 2012; 23(5): 9950

Cooper SC, Croft S, Day R, Thomson CS, Trudgill NJ. The risk of oesophageal cancer is not affected by a diagnosis of breast cancer. European Journal of Cancer Prevention 2010; 19(3): 182-5

Cooper SC, Day R, Brooks C, Livings C, Thomson CS, Trudgill NJ. The influence of deprivation and ethnicity on the incidence of esophageal cancer in England. Cancer, Causes and Control 2009; 20(8): 1459-1467

Cooper SC, Croft S, Day R, Thomson CS, Trudgill NJ. Patients with prostate cancer are less likely to develop oesophageal adenocarcinoma; could anti-androgen therapy have a protective role? Cancer Causes and Control 2009; 20(8): 1363-1368

Presentations at Learned Societies with publication of abstracts

Poster presentation at DDW 2010
Cooper SC, Prew S, Podmore L, Trudgill NJ. The effect of body mass index, and waist circumference on the development of oesophageal adenocarcinoma: comparison with community and reflux oesophagitis controls from MOSES (Midlands OeSophageal adenocarcinoma Epidemiology Study). Gastroenterology 2010, W1880

Poster presentation at DDW 2010
Cooper SC, Prew S, Podmore L, Trudgill NJ. The effect of diet on the development of oesophageal adenocarcinoma: comparison with community and reflux oesophagitis controls from MOSES (Midlands OeSophageal adenocarcinoma Epidemiology Study)
Gastroenterology 2010, W1877

Poster presentation at DDW 2010
Cooper SC, Prew S, Podmore L, Trudgill NJ. The effect of smoking and alcohol consumption on the development of oesophageal adenocarcinoma: comparison with community and reflux oesophagitis controls from MOSES (Midlands OeSophageal adenocarcinoma Epidemiology Study).
Gastroenterology 2010, W1878

Poster presentation at BSG 2010
Cooper SC, Prew S, Podmore L, Trudgill NJ. Gastro-oesophageal reflux symptoms and the development of oesophageal adenocarcinoma: comparison with community and reflux oesophagitis controls from MOSES (Midlands OeSophageal adenocarcinoma Epidemiology Study). Gut 2010; 59(Suppl 1): A114

Poster presentation at DDW 2009
Cooper SC, Prew S, Podmore L, Nightingale P, Trudgill NJ. The effect of diet on the development of oesophageal adenocarcinoma: results from MOSES (Midlands OeSophageal adenocarcinoma Epidemiology Study)
Gastroenterology 2009; 136(5 Suppl 1): 403

Poster presentation at BSG and DDW 2009
Cooper SC, Prew S, Podmore L, Nightingale P, Trudgill NJ. The effect of smoking, alcohol, body mass index, and waist circumference in the development of oesophageal adenocarcinoma: results from MOSES (Midlands OeSophageal adenocarcinoma Study). Gut 2009; 58 Suppl 1: A144 and Gastroenterology 2009; 136(5 Suppl 1): 402

Poster presentation at BSG and DDW 2009
Cooper SC, Prew S, Podmore L, Nightingale P, Trudgill NJ. The influence of symptoms of Gastro-oesophageal reflux in the development of oesophageal adenocarcinoma: results from MOSES (Midlands OeSophageal adenocarcinoma Study). Gut 2009; 58 Suppl 1: A144 and Gastroenterology 2009; 136(5 Suppl 1): 403

Poster presentation at DDW 2008, San Diego
Cooper SC, Croft SH, Day R, Nightingale P, Thomson CS, Trudgill NJ. Patients with prostate cancer are less likely to develop oesophageal cancer – Analysis of the SEER 9 registries database. Gastroenterology 2008; 134(4) Suppl 1: P-234

Poster presentation at DDW 2008, San Diego
Cooper SC, Graham P, Nightingale P, Trudgill NJ. Risk factors for the development of oesophageal adenocarcinoma: A United Kingdom case-control study. Gastroenterology 2008; 134(4) Suppl 1: P-234

Verbal presentation at BSG 2008, Birmingham (Best paper prize), and
Cooper SC, Graham P, Trudgill NJ. Risk factors for the development of oesophageal cancer in Barrett's oesophagus: a primary care nested case-control study. Gut 2008; 57 Suppl 1: A15

Poster presentation at DDW 2007, Washington DC
Cooper SC, Croft S, Day R, Thomson CS, Trudgill NJ. Previous radiotherapy for breast cancer does not increase the risk of developing oesophageal cancer: analysis of over half a million-person years of risk. Gastroenterology 2007; 132(4) Suppl 2: A419.

Poster presentation at DDW 2007, Washington DC
Cooper SC, Graham P, Trudgill NJ. Risk factors for the development of oesophageal cancer in Barrett's oesophagus: a primary care cohort study. Gastroenterology 2007; 132(4) Suppl 2: A420.

Poster presentation at BSG and DDW 2007, Washington DC
Cooper SC, Day R, Brooks C, Livings C, Trudgill NJ. Oesophageal carcinoma in the West Midlands, United Kingdom: changing incidence and the influence of socio-economic status and ethnicity. Gastroenterology 2007; 132(4) Suppl 2: A418, and Gut 2007; 56(Suppl 11): A68.

Poster presentation at DDW 2007, Washington DC
Cooper SC, Croft S, Day R, Thomson CS, Trudgill NJ. Patients with prostate cancer are less likely to develop oesophageal adenocarcinoma; could anti-androgen therapy have a protective role? Gastroenterology 2007; 132(4) Suppl 2: A418.