DIETARY CONSUMPTION, FLUID CONSUMPTION AND RISK OF DEVELOPING BLADDER CANCER

By
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A thesis submitted to
The University of Birmingham
For the degree of
DOCTOR OF PHILOSOPHY

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November 2014

Abstract

This thesis focuses on three different parts: (1) An analyses of dietary consumption, diet diversity and risk of developing bladder cancer within a case-control study in China. This study showed that higher diet diversity, particularly a diet varied in fruit may reduce the risk of developing bladder cancer. In addition, there was a positive association between the consumption of red meat, organ meat, leafy vegetables, bulb vegetables or preserved vegetables may increase the risk of bladder cancer. The consumption of citrus fruits, stone fruits, vine fruits, flower vegetables, fresh fish, potatoes and dairy products may decrease the risk of developing bladder cancer. (2) A dose-response meta-analysis on the association between total fluid consumption and bladder cancer was conducted. The results of this study suggest a non-linear relationship between total fluid intake and bladder cancer risk in men. Also, the findings indicates that low to moderate fluid consumption was not associated with an increased risk of developing bladder cancer; although fluid consumption exceeding 8 cups per day might increase the risk of developing bladder cancer. (3) A pooled analysis on fluid consumption and risk of developing bladder cancer using individual patient data from the Bladder Cancer Epidemiology and Nutritional Determinant consortium. The results suggest that excess consumption of coffee per day may increase the risk of developing bladder cancer in men.

Acknowledgements

I am grateful to my supervisors, Maurice Zeegers and Raoul Reulen for their support, advice and encouragement through my entire PhD study. My sincere thanks goes to Karla Hemming for her support, advice and generous time towards my research.

I would like to thank my friends for their unconditional support: Joyeeta, Cass, Duncan, Marwa, Sharmi, Mehnaz, Sopna, Emma, Saima, Rushana Weng, Susan and my dearest Karen.

I am grateful to all my siblings for their love, support and constant motivation. I will forever be thankful to my Dad for his financial support, unconditional love, care and faith in me. I especially thank my mum for her prayers, unconditional love and emotional support. To my dearest husband Murtala thanks for understanding and for being there for me, I really appreciate your support especially during last year of my PhD. I wouldn't have made it this far without my supervisors, family and friends because the four years of my PhD was full of challenges but it made me a better person.

Dedication

I dedicate this thesis to my baby Jabir Abdullah and my husband Murtala

Publications

Chapter 2 and 3 are the description of the publications below:

- Isa F, Xie LP, Hu Z, Zhong Z, Hemelt M, Reulen RC, et al. *Dietary consumption and diet diversity and risk of developing bladder cancer: results from the South and East China case-control study*. Cancer Causes Control. 2013 May; 24(5):885-95.

- Fatima Isa, Raoul C. Reulen, Maria Goosens, Karla Hemming, Maurice P. Zeegers. *Total fluid intake and the risk of developing bladder cancer: A dose-response meta-analysis.* (Under review at the European Journal of Epidemiology)

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Abbreviations

Non-muscle invasive bladder cancer (NMIBC)

Muscle invasive bladder cancer (MIBC)

Tumour Nodes Metastases (TNM)

World Health Organization (WHO)

Papillary urothelial neoplasm of low malignant potential (PUNLMP)

Bladder Tumour Associated Antigen (BTA) test

Ultrasounds and intravenous urogram (IVU)

Magnetic resonance (MR)

Transurethral resection of the bladder tumour (TURB)

Bacille-Calmate Guerin (BCG)

4-aminobiphenyl (4-ABP)

Polycyclic aromatic hydrocarbons (PAHs)

International Agency for Research on Cancer (IARC)

Trihalomethanes (THM)

Odds ratios (OR)

95% confidence intervals (95% CI)

World Cancer Research Fund (WCRF)

Relative Risk (RR)

Hazard Ratio (HR)

Surveillance Epidemiology and End Results program (SEER)

1.0 CHAPTER ONE

Introduction

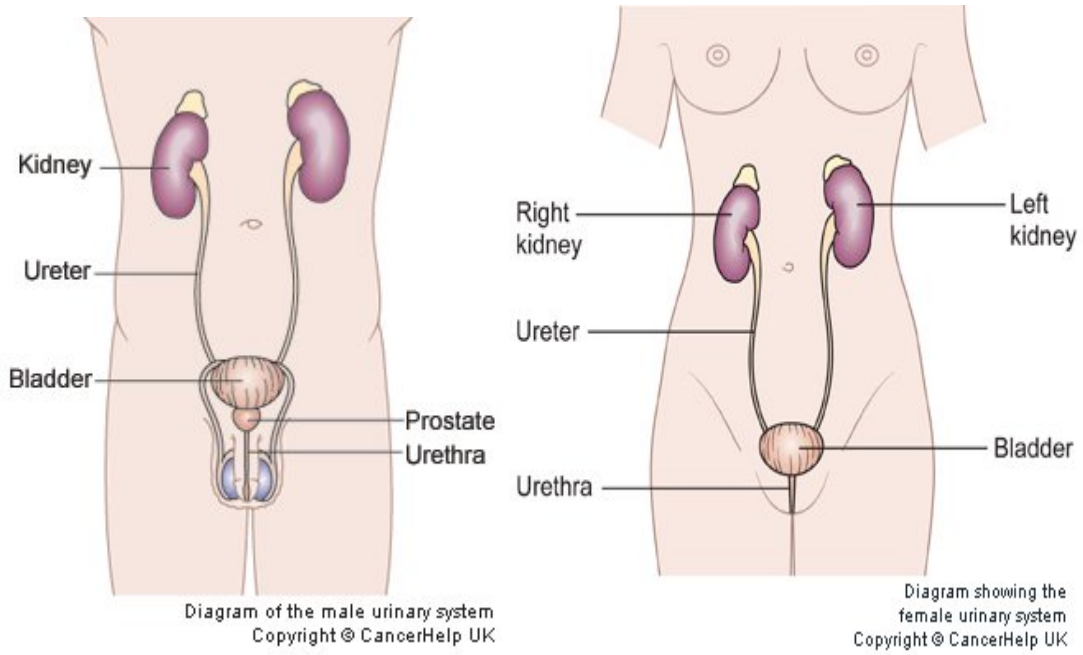
This thesis focuses on the association between dietary consumption, fluid consumption and bladder cancer risk. The overall structure of this thesis takes the form of six chapters including the introduction and discussion. Chapter one presents an overview and general background information including epidemiology of bladder cancer, current gaps in research into dietary consumption, fluid consumption and risk of developing bladder cancer, the rationale for carrying out this research, and the aims and objectives of the thesis.

1.1 Background

1.2 Anatomy and physiology of the urinary bladder

The urinary bladder is a concave, muscular organ that is located within the lower part of the pelvis.[1] The kidneys produce urine and the ureters transport the urine from the kidneys into the bladder. The main function of the urinary bladder is to collect and store urine for excretion.[2] The bladder can store approximately 500 millilitres for approximately two to five hours.[3] The bladder is made up of a muscle called the 'detrusor muscle' which expands depending on the amount of urine accumulated. When the urinary bladder is full, the brain sends signals to the detrusor muscle to contract and excrete urine out through a tube called the urethra.[4] In males, the urethra runs from the base of the bladder through the prostate gland and ends at the tip of the penis. In females, the urethra is shorter, straight and runs from the base of the bladder and ends just above the vagina (Figure 1.1).[5]

Figure 1.1: The urinary tract organs (male left – female right)



"Taken from the patient information website of Cancer Research UK: http://www.cancerresearchuk.org/about-cancer/".

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1.3 Cancer

Cancer is a heterogeneous group of diseases characterised by uncontrolled proliferation of abnormal cells.[6] A tumour develops typically when cells proliferate in an uncontrolled manner, and if left untreated or diagnosed at a benign stage, the tumour might later progress into cancer. Each cell in the body contains genes that regulate cell division and differentiation. Alterations which occur in the DNA sequence within a gene is a natural process called mutation.[7] The four types of genes most frequently implicated in the development of cancer are: (1) oncogenes, (2) tumour suppressor genes, (3) suicide genes and (4) DNA repair genes.[8] The oncogenes stimulate cell growth, while the tumour suppressor genes are inhibitors of cell growth.[8] The suicide genes carry out apoptosis or

"programmed cell death" and during cell division, the DNA repair genes repair damages in the DNA sequence.[7] Therefore, damage to one or more of these genes can lead to cancer. There are different types of cancers and the name of the cancer usually relates to the type of cells or the organ they originate from.

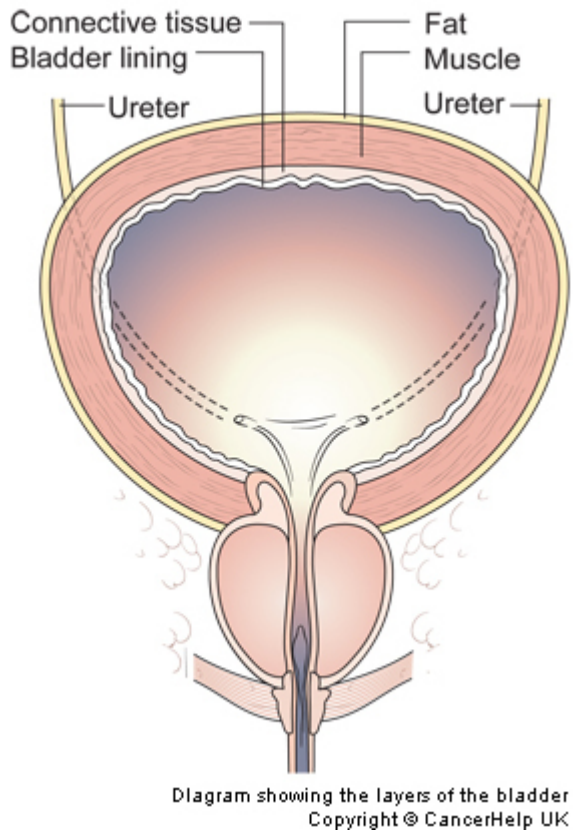
1.4 Bladder cancer

Bladder cancer is an abnormal growth of cells that emerges from the tissue of the bladder.[9] Bladder cancer may develop when urinary bladder cells undergo mutations in suppressor genes, for example the TP53 or RB1 gene,[10] and FGFR or RAS oncogenes.[11] Bladder cancer can be classified according to the extent which the cancer has spread into the wall of the bladder (stage) and the pattern of growth (grade) and also the type of cells that make up the tumour (morphology).

1.5 Histology of the urinary bladder and staging

The wall of the bladder is consists of four different layers: epithelium (bladder lining), lamina propria (connective tissue), muscularis propria or detursor muscle and perivesical soft tissue (layer of fat) (Figure 1.2).[12]

Figure 1.2: Four different layers of the wall of the bladder



"Taken from the patient information website of Cancer Research UK: http://www.cancerresearchuk.org/about-cancer/"

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The epithelium is the innermost lining of the bladder that comes into contact with the urine. The function of the epithelium is to prevent urine from being reabsorbed into the body. The epithelium is also referred to as transitional epithelium or urothelium and consists of multiple layers of transitional cells. The transitional cells are the cells lining the innermost part of the bladder.

The layer below the epithelium is the lamina propria (connective tissue) which consists of connective tissue and blood vessels. Found within the lamina propria (connective tissue) is

the superficial layer of the muscle called the muscularis muscosae. Below the lamina propria is a layer of deep muscle known as the detursor muscle. The outermost layer is the perivesical soft tissue consisting of fats, fibrous tissue and blood vessels.[13]

Urologists usually differentiate bladder cancer cases based on the histological characteristics of the bladder wall. The cells usually appear in three different shapes: cuboidal, flattened and umbrella. There are three main histological types of bladder cancer: transitional cell carcinomas, squamous cell carcinomas and adenocarcinomas. Approximately 90% of all diagnosed bladder cancers are transitional cell carcinomas and the remaining 10% are other types of bladder cancer which include squamous cell carcinomas and adenocarcinomas.[14]

1.5.1 Tumour staging

Bladder cancer can be divided into two types: non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). The Tumour Nodes Metastases (TNM) classification system is widely used by clinicians to report the degree of cancer spread. The TNM classification system is used to evaluate cancer in three aspects: (1) extent and size of the tumour that developed in the bladder wall (T), (2) cancer spread to the regional lymph nodes near the bladder (N) and (3) distant metastases to adjacent organs, abdominal wall and pelvis (M).[15]

Table 1.1 presents the staging of bladder cancer based on the TNM classification 7th edition from 2009.[15] Confined to the epithelium and lamina propria are the Tis, Ta and T1 tumours which are non-invasive or superficial tumours. The T2-T4 tumours are muscle invasive tumours invading the muscularis propria (T2), perivesical tissue (T3) and other adjacent organs (T4).[16]

TABLE 1.1: TNM classification of bladder cancer 2009

T-Primary	Tumour
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle:
	T2a Tumour invades superficial muscle (inner half)
	T2b Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue:
	T3a Microscopically
	T3b Macroscopically (extravesical mass)
T4	Tumour invades any of the following organs: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a Tumour invades prostate, uterus or vagina
	T4b Tumour invades pelvic wall or abdominal wall
N-Lymph	Nodes
NX	Regional lymph nodes cannot be assessed due to lack of information
N0	No cancer in any lymph nodes
N1	There is cancer in one lymph node in the pelvis (the lower part of the tummy, between your hip bones)
N2	There is cancer more than one lymph node in the pelvis
N3	There is cancer in one or more lymph nodes just outside the pelvis
Metastasis	
M0	There are no signs of distant spread
M1	The cancer has spread to distant parts of the body. (The most common sites are distant lymph nodes, the bones, the lungs, and the liver

1.5.2 Tumour grading

Tumour grading is described as the degree of differentiation of tumour cells.[17] In bladder cancer, grading is based on the microscopic comparison of bladder cancer cells to normal bladder cells. The World Health Organization (WHO) has two grading systems (Table 1.2); one developed in 1973, and the second subsequently updated in 2004, both grading systems are commonly used by oncologists and pathologists for reporting of the various grades of bladder cancer.[18] Based on the 1973 grading system bladder cancer cells are graded as low, medium and high. For low grade cancers the cells are well differentiated and are confined in the bladder lining. In medium grade, the cells are moderately differentiated and may have started spreading to the muscle layer. For high grade cancers, the cells are poorly differentiated and grow very quickly and may have spread to the muscle layer of the bladder. The 2004 grading system is used to grade early bladder cancer and is divided into four groups: urothelial papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade papillary urothelial carcinoma and high-grade papillary urothelial carcinoma.[19]

Table 1.2: WHO grading in 1973 and 2004

1973 WHO grading
Urothelial papilloma
Grade 1: well (low) differentiated
Grade 2: moderately (medium) differentiated
Grade 3: poorly (high) differentiated
2004 WHO grading
Urothelial papilloma
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma

1.6 Symptoms of bladder cancer

Bladder cancer can go undetectable for a long time due to the lack of clear symptoms in many patients. Painless haematuria is the presence of blood in the urine and is one of the most common indicators of bladder cancer.[20] However, haematuria is often not detectable with the naked eye and only urine analysis may be able to identify the presence of blood in the urine. Patients may experience other symptoms such as vesicle irritation (i.e. burning sensation when passing urine), increased frequency or urgency of urination.[20]

1.7 Diagnosis of bladder cancer

At the early stage of a diagnosis of bladder cancer, approximately 70-80% of patients are typically diagnosed with non-invasive tumours and approximately 20-30% are typically diagnosed with muscle invasive tumours.[21]

1.7.1 Cystoscopy

Cystoscopy is recognised as the gold standard for diagnosis of bladder cancer. For this procedure, a thin light tube, with a camera called the cystoscope, is inserted into the bladder of the patient to examine the inside of the bladder wall for abnormalities.[22] First, a local anaesthetic gel is applied to the urethra of the patient to facilitate insertion of the cytoscope. The cytoscope is then inserted via the urethra into the bladder. Despite the local anaesthesia used for this procedure, patients may still experience discomfort and distress. Other procedures for detecting bladder cancer that may be used by the urologist include biopsy, urine cytology, imaging techniques such as ultrasound and intravenous urogram.

1.7.2 Biopsy

A biopsy is conducted by the urologist after the cystoscopy procedure. During the biopsy procedure the patient is usually given a general anaesthetic and a small sample of the bladder tissue is removed. The pathologist then investigates the tissue for abnormal cells.[23]

1.7.3 Urine cytology

Urine cytology is helpful in detecting bladder cancer and potential bladder cancer recurrence(s) during follow-up of bladder cancer patients. Urine tests such as the Bladder Tumour Associated Antigen (BTA) test and Nuclear Matrix Protein 22 (NMP22) test are carried out to detect bladder tumours. The patients provide a sample of urine which is then examined for any abnormal cells. Urine cytology is not always 100% accurate because it detects abnormal cells that are not cancerous and in addition, has poor accuracy in detecting low-grade tumours.[24]

1.7.4 Ultrasound and intravenous urogram

Ultrasounds and intravenous urogram (IVU) are frequently used for identifying the presence of tumours in the bladder or urinary tract. The intravenous urogram is an X-ray that is used to examine the urinary system.[25] There are also other procedures that may aid in the diagnosis of bladder cancer such as the computerised tomography scan and magnetic resonance (MR).[26]

1.8 Treatment of bladder cancer

1.8.1 Transurethral resection of the bladder tumour (TURB)

Initial treatment for non-invasive bladder tumours usually consists of transurethral resection of the bladder tumour (TURB).[27] Transurethral resection is a surgical procedure in which the urologist inserts a cystoscope and a resection instrument into the bladder through the urethra and removes any tumour tissue present from the bladder wall. Adjuvant treatments, such as Bacille-Calmate Guerin (BCG) and chemotherapy usually involving cytotoxic drug mitomycin, are typically used to eradicate any tumour cells that might

remain after the TURB. The adjuvant treatments given to patients with non-muscle invasive bladder cancer depend on the grade of the tumour.[28]

1.8.2 Radical cystectomy

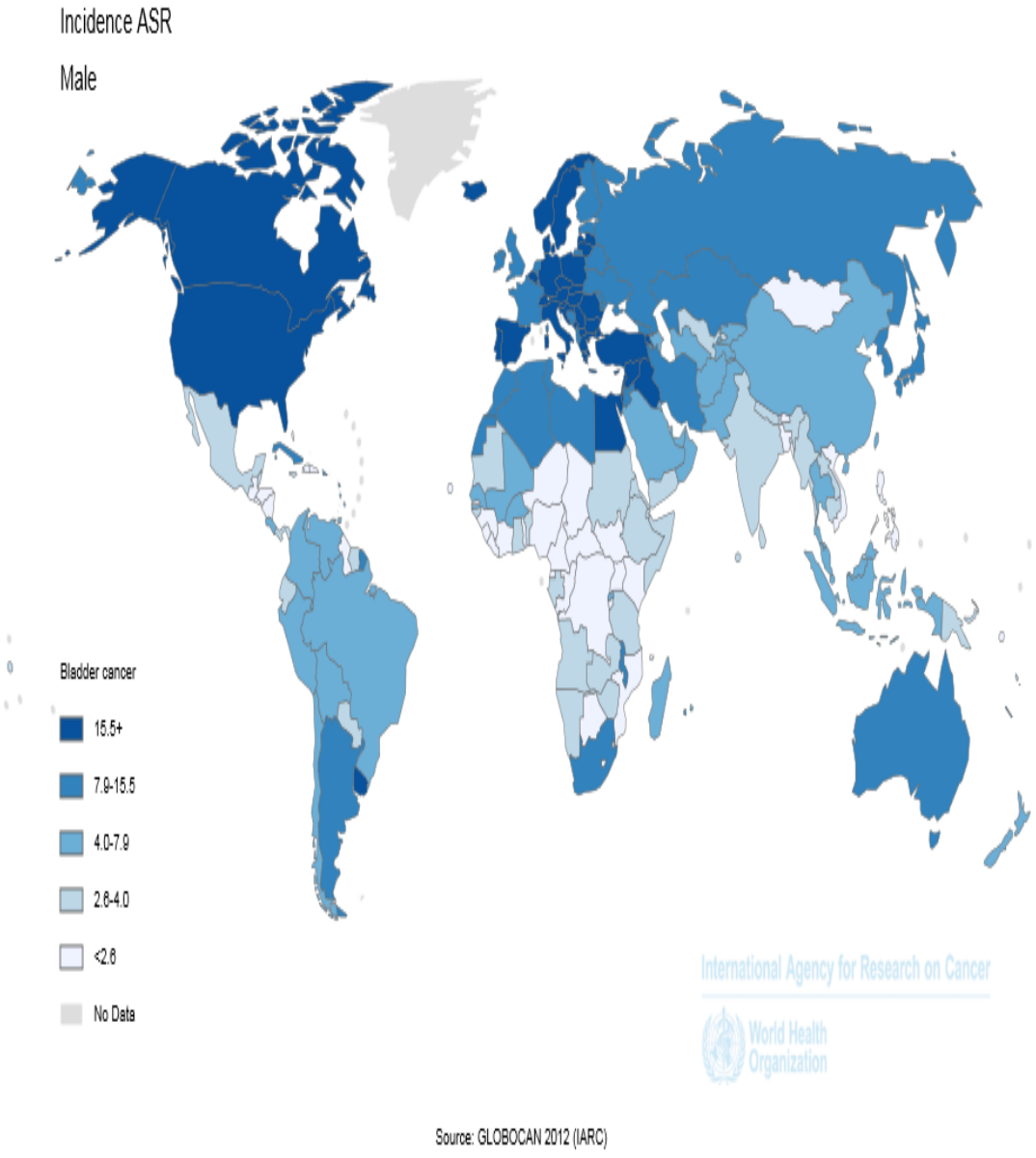
Approximately 23–46% of all patients who undergo a radical cystectomy can expect to survive at least five years from original bladder cancer diagnosis.[29] Radical cystectomy is the standard treatment for patients diagnosed with muscle invasive bladder cancer.[30] Radical cystectomy involves the surgical removal of the entire bladder. In addition to the removal of the bladder in men, the prostate and seminal vesicles are usually removed. In women, the cervix, uterus, fallopian tubes, ovaries and the vaginal wall may also be removed.[30] However, patients above the age of 75 years, who are more likely to have co-morbidities such as cardiac diseases, and cannot have radical cystectomy may undergo a different treatment approach which involves a combination of radiotherapy and chemotherapy, usually cisplatin medication.[31]

1.9 Epidemiology of bladder cancer

1.9.1 Worldwide occurrence of bladder cancer

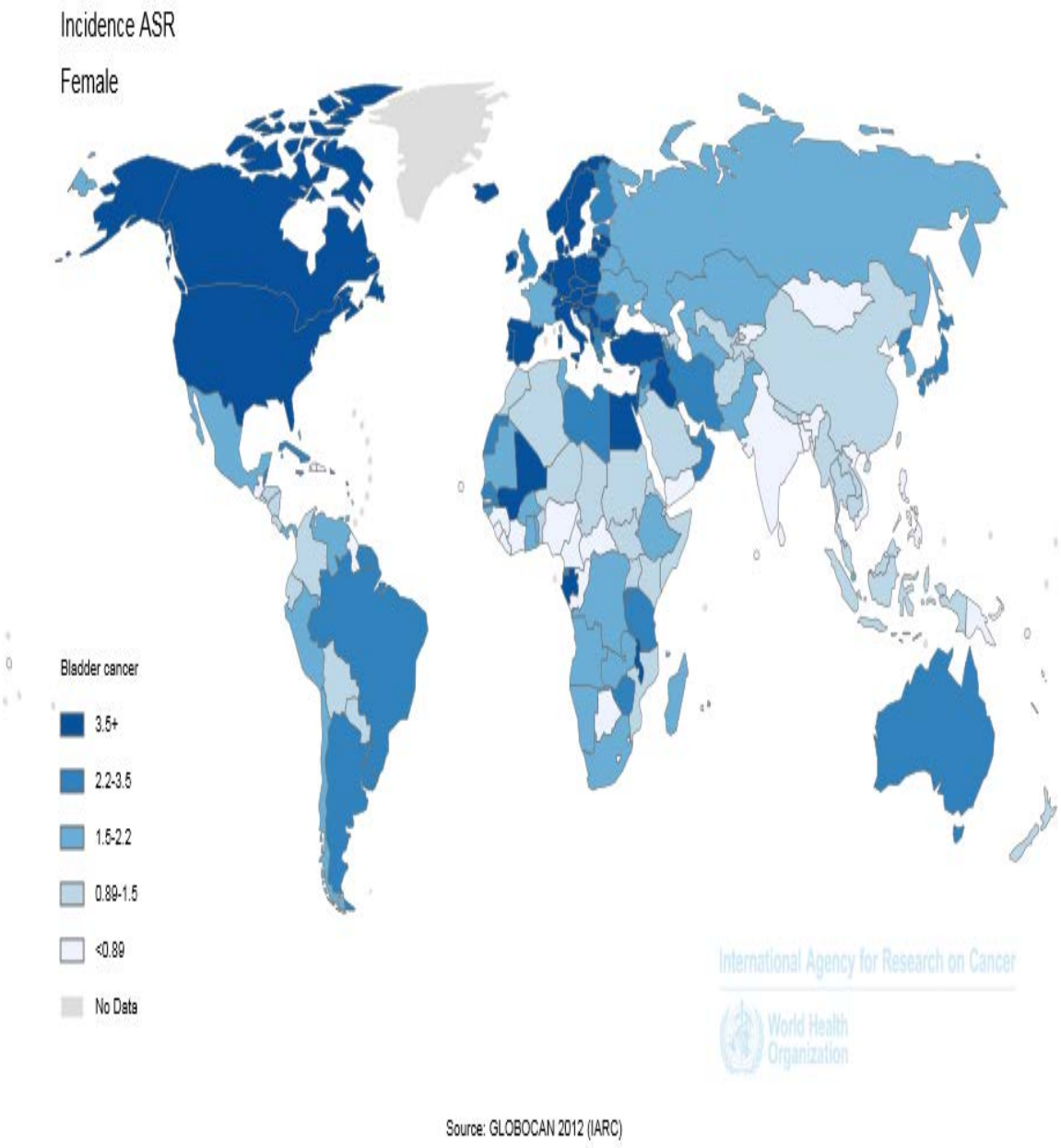
In terms of cancer incidence, bladder cancer is the ninth most frequently occurring cancer worldwide.[32] In 2012, approximately 429,000 new cases were diagnosed and 165,000 deaths occurred worldwide.[32] The incidence of bladder cancer varies across the world; the highest incidence rates are observed in countries in North America, Europe, North Africa and Middle East, while the lowest incidence rates are found within countries of Southeast Asia and West Africa (Figures 1.3 and 1.4).

Figure 1.3 Age-standardised Global incidence rates of bladder cancer per 100,000 men per year in 2012



Source: Globocan 2012. Available from: http://globocan.iarc.fr/Pages/Map.aspx

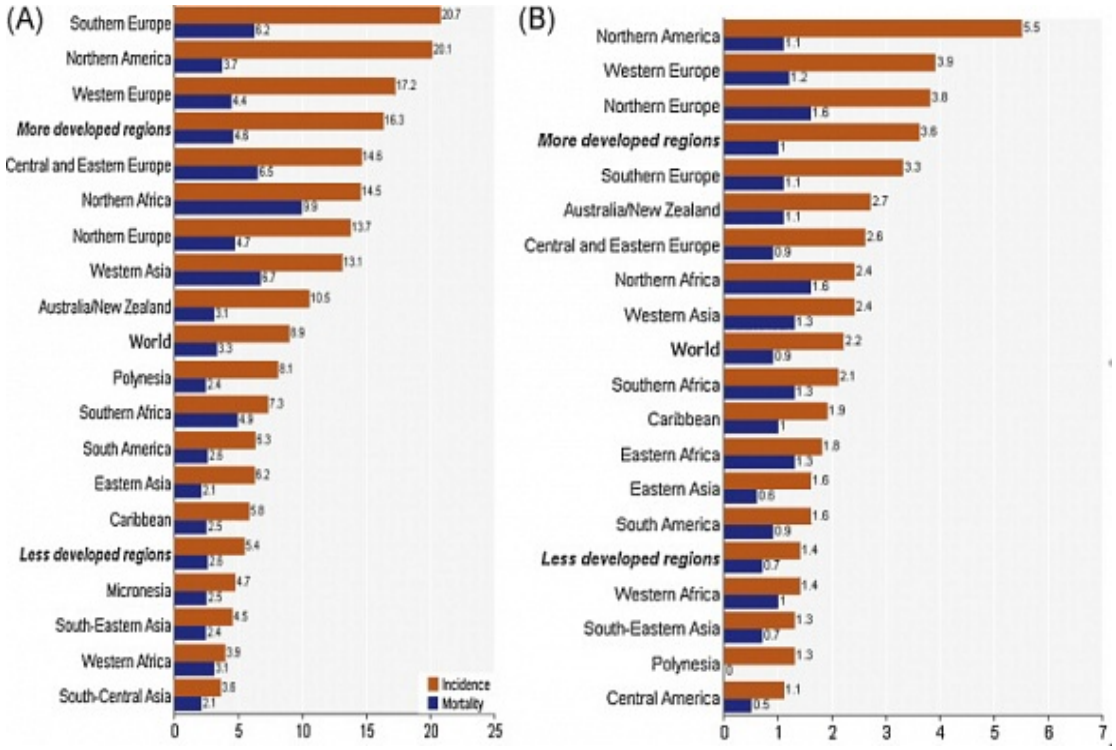
Figure 1.4 Age-standardised Global incidence rates of bladder cancer per 100,000 men per year in 2012



Source: Globocan 2012. Available from: http://globocan.iarc.fr/Pages/Map.aspx

In developed countries particularly North America and Southern and Western Europe, the incidence of bladder cancer is much higher (5.5 and 20.7 per 100,000 per year in women and men, respectively) when compared to Asia and West African countries (1.3 and 3.8 per 100,000 per year in women and men, respectively). In Europe and North America bladder cancer is the fourth most common cancer in men and ninth in women (Figure 1.5).

Figure 1.5 Age-standardised (world) incidence and mortality rates for bladder cancer per 100,000 in (A) men and (B) women (GLOBOCAN)



Source: Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr

The current estimated global prevalence of bladder cancer is 2.7 million cases.[33] The prevalence of bladder cancer is also the highest of all urological cancers, with the prevalence of individuals who have survival at least 5 years from diagnosis bladder cancer.[33]

Due to smoking cessation and reduction in occupational exposures to carcinogenic chemicals, the mortality rate of bladder cancer has declined in most European countries since the 1900's.[34] The mortality rate is stable in men currently, but has reduced considerably in women from 1997 through 2006 in the United States.[35] As of 2012, mortality rates were lower compared to incidence rates; the highest age standardised mortality rates was observed in Western Asia (mortality rate approximately 8.4 per 100,000 per year for men and 1.6 per 100,000 per year for women).[32]

1.9.2 Incidence of bladder cancer according to gender

Bladder cancer is the seventh most frequent cancer in men and 17th most frequent cancer in women worldwide. Globally, bladder cancer is three times more frequent in men than in women with an estimated male-female ratio of 3.8:1.0. In different geographical areas the male-female ratio of bladder cancer varies considerably: 5.1:1.0 in Southern Europe, 5.0:1.0 in North America, 1.1:1.0 in Eastern Africa and 2.1:1.0 in South Africa.[36] Although men are more likely to develop bladder cancer, women generally have worse prognosis and survival rates.[37]

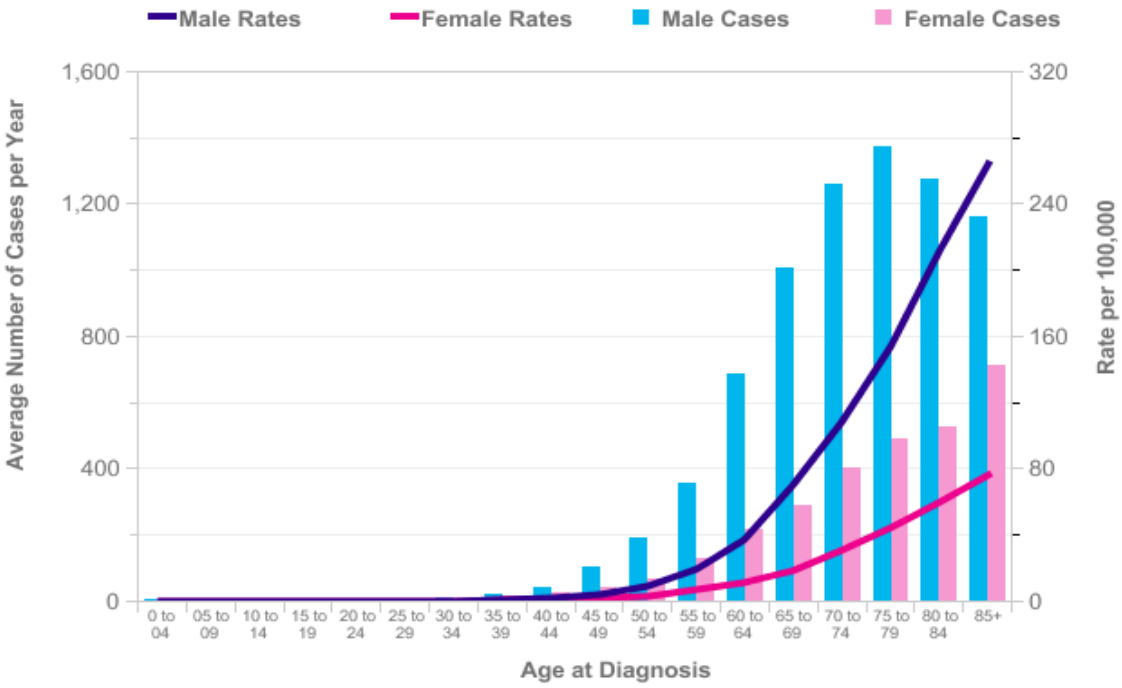
1.9.3 Incidence of bladder cancer according to age

Bladder cancer is more common in older people. Globally, the median age of developing bladder cancer for men is 69 years and 70 years for women.[38] Approximately 90% of bladder cancer cases occur in people who are over 55 years of age.[33] The incidence rate of

bladder cancer increases with increasing age. The incidence rate increases from 142 and 33 per 100,000 men and women per year, respectively aged 65-69 years, to 296 and 74 per 100,000 men and women per year, respectively aged 85 years and older, worldwide.[37]

In the United Kingdom, for both men and women, the age-specific incidence rate increases gradually from the age of 50-54 years with a sharp increase beyond the age 60-64 years. The highest incidence is observed for the age group of 85 years and older (Figure 1.6).[39]

Figure 1.6 Age-specific incidence rates per 100,000 population per year United Kingdom (2009-2011)



Sources: Cancer Research UK http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bladder/incidence/uk-bladder-cancer-incidence-statistics[39]

1.9.4 Incidence of bladder cancer according to ethnicity

The incidence and mortality rate of bladder cancer varies considerably according to ethnicity.[40] For example, the age standardised incidence rates is higher amongst the Caucasian population (19.9-20.5 per 100,000 per year in men and 5.7-6.0 per 100,000 per yearin women) in comparison to the black population (5.6-9.6 per 100,000 per year in men and 1.5–3.7 per 100,000 per year in women). However, it was reported that the black population have a higher mortality rate.[41]

1.10 The health and economic burden of bladder cancer

Bladder cancer remains a great challenge for clinicians because patients diagnosed with Ta/T1 bladder tumours have a recurrence rate of approximately 75%. Patients diagnosed with metastatic bladder cancer have a very poor prognosis with a median survival rate of approximately 12-15 months.[42] Bladder cancer is the most expensive cancer in terms of healthcare expenditure per patient because of lifetime ongoing cystoscopies and recurrent treatment episodes.[43] In developed countries like the USA, the annual cost of healthcare for patients with muscle invasive bladder cancer can surpass $35 million.[43]

1.11 Risk factors of bladder cancer

Environmental factors (such as tobacco, infectious organisms) and internal factors (such as inherited mutations, hormones, etc.) can cause cancer. The established environmental risk factors for bladder cancer include smoking, specific occupational exposures (e.g. aromatic amines) and infection with *Schistoma haematobium*.[44]

1.11.1 Smoking

Tobacco smoking is the principal risk factor of bladder cancer. Smoke from tobacco consists of different carcinogenic compounds such as arylamines, especially the carcinogenic agent 4-aminobiphenyl (4-ABP), N-nitroso mixes, heterocyclic amines, polycyclic aromatic hydrocarbons (PAHs), and epoxides.[45] It has been reported that the population attributable risk of bladder cancer for tobacco smoking in men is approximately 50-65% and 20-30% in women, since cigarette smoking is more common in men than in women.[46] The risk of developing bladder cancer increases with duration of smoking, number of cigarettes smoked per day, and extent of inhalation.[47] Long term exposure and high amount of smoking tobacco have been associated with the development of more aggressive tumours that can negatively affect prognosis.[29] The risk of developing bladder cancer can be reduced by 40% through smoking cessation.[48]

1.11.2 Occupational exposure

Occupational exposure to carcinogenic chemicals is a major risk factor of bladder cancer. Previous studies indicate that approximately 20% of bladder cancer cases are due to work related exposure to carcinogens.[49] Occupations such as industrial work in dye, rubber, textiles, paints, or leather factories have been indisputably associated with increased risk of developing bladder cancer.[50] Exposure to chemicals such as benzenes and arylamines typically used in these occupations might increase the risk of developing bladder cancer. Other chemicals associated with an increased risk of developing bladder cancer are polycyclic aromatic hydrocarbons (PAHs) used in manufacturing industries for the production of aluminium, carbon black and coal tar.

1.11.3 Schistosomiasis of the bladder

Schistosomiasis is caused by infection with a parasite known as *Schistosoma haematobium* and chronic infection can result in squamous cell carcinoma of the bladder. Chronic infection with *Schistosoma haematobium* is endemic in the Middle East and countries in North Africa with the highest prevalence in Egypt.[51] Previous studies conducted in Africa reported that a high prevalence of infection with *schistosoma haematobium* is associated with a high incidence of squamous cell carcinoma of the bladder in Egypt compared to areas with low prevalence. Approximately 31% of bladder cancer incidences in Egypt are squamous cell carcinoma of which approximately 90% are muscle invasive.[52] Squamous cell carcinoma is common in young and middle aged adults.

1.11.4 Other risk factors

There are other risks factors that might increase the risk of developing bladder cancer including family history of bladder cancer, treatment of prior tumours with chemotherapy and radiotherapy, and long-term or recurrent infections of the urinary tract.[53] Additionally, it has been reported that diet may be a potential risk factor however, there is need for further research to be conducted as previous results have been inconsistent.

1.12 Dietary consumption, fluid consumption and risk of developing bladder cancer

Research has suggested that diet may influence the risk of developing bladder cancer since most compounds ingested through most food are excreted via the urinary tract which might come in contact with the urothelium of the bladder.[49] A report from the International Agency for Research on Cancer (IARC) classified specific chemical compounds such as acrylamide,[54] which can be found in starchy foods (e.g. potato crisp, crisp bread), and

heterocyclic amines[55] found in cooked meat and fish, as potential human carcinogens. Total fluid consumption has been hypothesised to influence the risk of developing bladder. High consumption of total fluid may decrease the risk by diluting the urine and thereby reducing the time of exposure of carcinogens with the urothelium of the bladder through increased frequency of urination.[56] On the other hand, a high total fluid consumption of specific fluid items such as alcohol or chlorinated tap water may elevate the risk of developing bladder cancer because these fluids may contain compounds that are known to have carcinogenic properties, for example, acetaldehyde and trihalomethanes (THM).[57]

Findings from previous epidemiologic studies on the association between dietary consumption or fluid consumption in relation to bladder cancer risk have largely been inconsistent. Some studies reported that dietary factors or fluid consumption, such as higher consumption of meat or coffee, could increase the risk of developing bladder cancer,[58-62] but other studies have demonstrated that fruit or vegetables or tea consumption could have a protective effect.[63-67]

1.12.1 Meat consumption

The result of a recent systematic review showed that higher consumption of pork, barbecued meat, and canned meat were associated with increased risk of bladder cancer.[68] The pooled results of a meta-analysis on meat consumption and bladder cancer risk suggested a significant increased bladder cancer risk with high consumption of red or processed meat.[69]

1.12.2 Vegetables and fruits consumption

The effect of vegetable and fruit consumption on the risk of bladder cancer were summarised in systematic reviews and meta-analysis.

The results of a systematic review indicated that dietary consumption of carrots and cruciferous vegetables for example cauliflower, brocolli were associated with a decreased risk of bladder cancer.[70] A meta-analysis exploring the effect of consumption of vegetables such as cruciferous vegetables in relation to bladder cancer, found that consumption of cruciferous vegetables can reduce the risk of bladder cancer.[71]

1.12.3 Total fluid consumption

A pooled analysis of six case-control studies found that total fluid intake may also be associated with an increased risk of bladder cancer in men only.[72] In a recent meta-analysis of 17 case-control studies and four cohort studies, an odds ratio (OR) of 1.06 (95 confidence interval [95% CI]: 0.88-1.27) was found. In the Harvard Health Professional study, an inverse association between total fluid consumption and risk of developing bladder cancer was found. Only a few studies have investigated the effect of total fluid consumption on bladder cancer according to smoking; hence there is need to investigate this topic more comprehensively.

1.12.4 Dairy products consumption

Some studies have suggested that the consumption of skimmed milk is associated with a significantly reduced risk of bladder cancer,[73] but others have suggested that the consumption of fermented milk products, such as yoghurt and sour milk may play a role in reducing the risk of developing bladder cancer as these products contains lactic acid bacteria.[63, 74, 75] A recent meta-analysis suggested that high consumption of milk was significantly associated with a decreased risk of developing bladder cancer. However, in another meta-analysis it was reported that consumption of milk is not significantly associated with the risk of developing bladder cancer.[76]

1.12.5 Alcohol drinking

Studies that evaluated the association between alcohol consumption and risk of developing bladder cancer generally reported no significant association; some studies found positive associations whilst other studies found inverse associations.[77] A meta-analysis of 19 studies found no significant association between overall alcohol consumption and the risk of bladder cancer (OR=1.00, 95% CI: 0.89-1.10). However, when consumption of specific alcoholic drinks were investigated, beer consumption was inversely associated with the risk of developing bladder cancer (OR=0.86, 95% CI: 0.76-0.96) and the summary OR was 0.89 (95% CI: 0.71-1.00) for wine consumption.

1.12.6 Coffee consumption

A review on coffee consumption and risk of developing bladder cancer found that a moderately high relative risk was observed in coffee drinkers in comparison to non-drinkers.[77] In a dose-response meta-analysis it was reported that subjects who consumed 4 cups/day of coffee had an OR of 1.2 (95% CI: 1.12-1.48) when compared to non-drinkers of coffee.[78]

1.12.7 Water consumption

Consumption of chlorinated drinking water has been linked to bladder cancer risk. For example, tap water contains substances such as THM, which are known to have carcinogenic properties. A meta-analysis of eight studies found an elevated risk between consumption of chlorinated water and bladder cancer risk in men (summary OR=1.4, 95% CI: 1.2-1.7) and in women an increased but insignificant risk was found (OR=1.2, 95% CI: 0.7-1.8).[79]

1.12.8 Tea consumption

A recent meta-analysis based on 24 studies reported a decreased risk of bladder cancer with high tea consumption in females (summary OR=0.61, 95% CI: 0.38-0.98).[80] Another study found no significant association between tea consumption and bladder cancer risk, however, consumption of specific infusion drinks such as green tea showed a protective effect on bladder cancer.[81]

1.13 Justification for this research project

Previous research has suggested that 30% of all cancers could be prevented by dietary modifications.[82] Therefore, there is need for continuous research to understand potential risk factors such as dietary and fluid intake in order to prevent and reduce morbidity and mortality of bladder cancer. It is important to focus in detail on the effect of specific food groups in relation to bladder cancer to better understand the role dietary and fluid consumption has in the aetiology of bladder cancer.

The incidence of bladder cancer is much lower in China (1.5 and 3.6 per 100,000 in women and men, respectively) compared to developed countries in Europe and North America. The low incidence of bladder cancer observed in China relative to developed countries may be due to differences in dietary factors since the Chinese population generally has a different dietary pattern compared to the Western Caucasian population. The Western diet is known as the “meat-sweet diet” which typically comprises red meat, fried food and desserts compared with the Chinese diet which consists mainly of cooked vegetables, noodles, fruits and small amounts of meat. In spite of the potential effect of dietary components, little is known on the association between diet and bladder cancer in the Chinese population.

Previous epidemiological studies have reported inconsistent results regarding the relationship between diet and fluid consumption and risk of developing bladder cancer. The limitation of most previous individual studies has been the lack of statistical power to satisfactorily address the association between specific foods items and the risk of bladder cancer. There is a need to further conduct a comprehensive analysis to investigate the potential effect of dietary consumption and risk of developing bladder cancer.

1.14 PhD project work

The current thesis focuses on three different parts: (1) an analyses of dietary consumption, diet diversity and risk of developing bladder cancer within a case-control study in China, (2) a dose-response meta-analysis on the association between total fluid consumption and bladder cancer, and (3) a pooled analysis on fluid consumption and risk of developing bladder cancer using individual patient data from the Bladder Cancer Epidemiology and Nutritional Determinant consortium.

1.15 Aims

The principal aim of this thesis is to conduct a comprehensive investigation into the association between dietary consumption, fluid consumption and risk of developing bladder cancer.

1.15.1 Objectives

The specific objectives of the thesis were:

- To investigate the role of dietary consumption and diet diversity on the risk of developing bladder cancer in a Chinese population

- To provide an update of previously published reviews and to perform a dose-response meta-analysis summarizing the results from epidemiological studies on the association between total fluid consumption and risk of developing bladder cancer
- To use individual patient data from previous studies to investigate the association between fluid consumption and risk of developing bladder cancer

1.16 Outline of the thesis

After the general introduction, the second chapter reports on the results of the analyses of a case-control study on the association between dietary consumption, diet diversity and bladder cancer risk in China. The third chapter reports on a dose-response meta-analysis on fluid intake and risk of developing bladder cancer. Chapter four describes the Bladder cancer Epidemiology and Nutritional Determinant (BLEND) consortium and describes the methods used for collection of individual patient data (IPD) on dietary intake from studies participating in BLEND. The fifth chapter describes a pooled analysis of individual patient data on fluid consumption and the risk of developing bladder cancer using data from the BLEND consortium. The final chapter provides an overall discussion of the main findings of this research project and places these findings in a wider context.

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2.0 CHAPTER TWO

Dietary consumption and diet diversity and risk of developing bladder cancer: results from the South East China case-control study

Published in: Journal of Cancer Causes and Control

Isa F, Xie LP, Hu Z, Zhong Z, Hemelt M, Reulen RC, et al. *Dietary consumption and diet diversity and risk of developing bladder cancer: results from the South and East China case-control study.*

Cancer Causes Control. 2013 May; 24(5):885-95

2.1 Abstract

Background - The epidemiologic evidence on the role of dietary consumption on the risk of bladder cancer in the Chinese population is limited. We investigated the role of dietary consumption and diet diversity on the risk of developing bladder cancer within a Chinese population.

Method - A case-control study of 487 cases and 469 controls was conducted in four hospitals in China. A food frequency questionnaire was used to gather information on the consumption of 35 food items. Unconditional logistic regression models were used to derive odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the relationship between dietary factors, dietary diversity scores and bladder cancer.

Results - The OR of bladder cancer for red meat (OR=1.8, 95%CI: 1.1-3.0; P_{trend}=0.01), organ meat (OR=1.6, 95%CI: 0.9-2.9; P_{trend}=0.04), leafy vegetables (OR=2.9, 95%CI: 1.6-5.4; P_{trend}=0.003), bulb vegetables (OR=2.3, 95%CI: 1.3-4.0; P_{trend}=0.003) and preserved vegetables (OR=2.3, 95%CI: 1.2-4.2; P_{trend}=0.02) were significantly increased when comparing the highest to lowest level of consumption. The OR for white fresh fish (OR=0.5, 95%CI: 0.3-0.9; P_{trend}=0.004), citrus fruits (OR=0.4, 95%CI: 0.3-0.8; P_{trend}=0.007), stone fruits (OR=0.4, 95%CI: 0.2-0.6; P_{trend}<0.001), vine fruits (OR=0.5, 95%CI: 0.2-1.0; P_{trend}=0.02), flower vegetables (OR=0.3, 95%CI: 0.2-0.6; P_{trend}<0.001), potatoes (OR=0.4, 95%CI: 0.2-0.9; P_{trend}=0.005) or dairy products (OR=0.4, 95%CI: 0.3-0.7; P_{trend}<0.001) were significantly decreased when comparing the highest to lowest level of consumption. Subjects with the highest total diet diversity (OR=0.4, 95%CI: 0.2-1.1; P_{trend}=0.02) and fruit diversity (OR=0.1, 95%CI: 0.0-0.3; P_{trend}<0.001) had reduced OR compared to subjects with the lowest diversity.

Conclusion - Our results indicate that a diet with higher total diet diversity and in particular fruit diversity may reduce the risk of bladder cancer.

2.2 Introduction

Bladder cancer is the ninth most common cancer globally[1] accounting for approximately 386,000 new cases and 150,200 deaths worldwide in 2008.[2] The incidence of bladder cancer varies considerably across continents and countries. The age standardized incident rate of bladder cancer in China is lower (1.5 and 3.6 per 100,000 in females and males respectively) compared to Western regions such as Southern Europe and Northern America (6.4-4.1 and 27.1-24.1 per 100,000 in females and males, respectively).[3]

Established risk factors for bladder cancer include tobacco smoking, specific occupational exposures (e.g. aromatic amines) and infection with *Schistosoma haematobium*.[4] Diet may also influence the risk of developing bladder cancer since potential carcinogenic food compounds are metabolized and excreted as waste products through the urinary tract.[5]

The World Cancer Research Fund (WCRF) reported in 2007 that findings from previous epidemiologic studies on the association between diet and bladder cancer have been largely inconsistent.[6] Some epidemiologic studies reported that high intake of specific dietary factors such as meat (e.g. pork, processed meat),[7-8] egg,[9] or soy[10] increases the risk of developing bladder cancer. It has been suggested that specific dietary factors such as fruit,[11-12] vegetables,[11, 13] fish,[11] cereals,[14] and yoghurt[15] have a protective effect, whereas other studies reported no association.[16-20]

To our knowledge, the epidemiologic evidence on the role of dietary consumption and the risk of bladder cancer in the Chinese population is limited.[10, 21] Although some studies investigated the role of frequencies and quantities of dietary components and risk of developing bladder cancer in the Chinese population, to our knowledge, only one previous study investigated diet diversity[22] and none have examined the potential role of diet diversity in the Chinese population.

The Chinese diet mainly consists of vegetables, noodles and fruits combined with small amounts of meat, whereas the Western diet mainly consists of red meat, fried food and desserts. Diet diversity may be a useful indicator of nutrient adequacy and has been associated with several cancers[23] including those of the colon/rectum,[24] oesophagus,[25] and gastric,[26] oral and pharynx[27] areas. The principal aim of this study was to investigate the role of dietary consumption and diet diversity on the risk of developing bladder cancer in a Chinese population.

2.3 Methods

2.3.1 The South and East China case-control study

We carried out a case-control study on bladder cancer between October 2005 and June 2008 in four large public hospitals in South and East China. Each of the four hospitals provides services to large geographical areas-including metropolitan and rural regions. The methods of this study have been described in detail elsewhere.[28] All incident bladder cancer cases (ICD-10 C67) admitted to the hospitals were approached for inclusion into the study. Eligible cases were frequency matched on sex and age (5-year age bands) to eligible controls. The hospital controls were selected from patients whose main diagnosis excluded the risk factors like smoking which is associated with bladder cancer risk. Therefore, controls had to be admitted to the same hospital for non-urological, non-cancerous and non-smoking related diseases (Table 1). The cases were treated the same as controls, cases with smoking related co-morbidity were excluded to minimize bias. The hospital controls were selected from patients whose main diagnosis excluded the risk factors like smoking which is associated with bladder cancer risk. In total, 541 incident bladder cancer cases fulfilled the inclusion criteria. Of these, 12 (2%) refused to participate and 42 (8%) were excluded because of insufficient amount of data available for analyses resulting in a total of 487 (90% response rate) bladder cancer cases. In total, 585 controls fulfilled the inclusion criteria. Of these 5 (<1%) refused to participate and 111 (19%) were excluded due to insufficient amount of data for analyses resulting in a total of 469 controls (80% response rate) available for analyses. Urothelial carcinoma was the most common type of bladder cancer (94%) followed by adenocarcinoma (3%) and squamous cell carcinoma (2%). Two cases had another type of bladder cancer. The study was approved by the

Medical Ethics Committee of each participating hospital and the Medicine Information Profession Committee of China (中国医药信息专业委员会).

2.3.2 Method of dietary assessment

Trained interviewers who were aware of the case-control status of the subjects used a food frequency questionnaire to gather information on the consumption of 35 specific food items within eight food groups. The eight food groups were (specific food items in brackets): dairy products (cheese and yoghurt), egg (preserved egg, eggs), fish (dark fish, white fresh fish, sea food, river fish, preserved fish), fruit (citrus fruits, stone fruits, soft fruits, fleshy fruits and vine fruits), grain (rice, noodles, pasta, bread), meat (meat, organ meat, chicken, other poultry, preserved meat), soy (soybean, soymilk, other soy products) and vegetable (sweet corn, potato, fruit vegetable, flower vegetable, leafy vegetable, stem vegetable, mushroom, root vegetable, garlic, onions, preserved vegetables). The questions about dietary consumption reflected the period of one year before the interview. The dietary intake of each food item was categorised into six levels: no intake or < 1 a month; 1-3 times a month; once a week; 2-4 times a week, 5-6 times a week; or ≥ once a day. To derive the total number of food items consumed at least once a week, the diet diversity score was calculated as the sum of the total number of different food groups consumed, and the variety within a specific food group at least once a week.[24, 26,22] Diversity within the food items was calculated for each food group with five or more food items with different nutritional components. In this calculation we considered a consumption of less than once a week as “nil” and a consumption of at least once a week as “one”. Thus, five different diversity scores were calculated: total diet diversity score (range 0-35), which counts the total number of different food items consumed at least once in a week; diet diversity score for fruit (range 0-5), which counts the total number of different fruit subgroups consumed at least once in a week; diet diversity score for fish (range 0-5), which counts the total number of different fish subgroups consumed at least once in a

week; diet diversity score for meat (range 0-5), which counts the total number of different meat subgroups consumed at least once in a week; and diet diversity score for vegetable (0-11), which counts the total number of different vegetable subgroups consumed at least once in a week. In addition, data were collected on socio-economic status (including level of education, income and occupation), lifestyle factors (including smoking and physical activity), medical history and demographic factors.

2.4 Statistical analysis

Unconditional logistic regression models were used to derive odds ratios (OR) and corresponding 95% confidence intervals (95% CI) for the relationship between dietary factors, dietary diversity scores and bladder cancer. Adjustments were made for the potential confounding effects of: gender, age, smoking status (never, former, current smoking), smoking duration (continuous variable), smoking frequency (continuous variable) and other food groups. The variables level of education, income source and total calorie were initially included in all models, but since results were unchanged, these variables were not included in the final models. All covariates were included as categorical variables except for smoking duration and smoking frequency which were included as continuous variables. The data on food items and diversity score were analysed using cut off points to create categories for different levels of consumption for each food item. Each category consisted of at least 20 cases and 20 controls. The reference category for all ORs was the lowest consumption category.

For food items where the levels had ordinal properties, a likelihood-ratio test was used to derive a P-value for linear trend. To test for heterogeneity in the ORs across the four different hospitals, we also analysed the data using a random effects logistic regression

model. Similar results were obtained compared to the standard logistic regression model and therefore we only provide results relating to the standard logistic regression. Stata statistical software release 11 was used for all analyses.[29] Statistical significance was defined as a 2-sided P-value of less than 0.05.

2.5 Results

2.5.1 Case and control characteristics

The majority of the cases were male (80.7%) (Table 2.1). The mean age at recruitment was 63.5 years for both cases and controls. Most of the cases (50.5%) and controls (56.9%) were within the age range of 60-79 years. Cases were more likely to be current smokers (40.2%) than controls (27.1%). Cases smoked cigarettes more often than controls and also smoked more cigarettes per day for more years than controls. The proportion of cases and controls was similar for each level of education although a slightly greater proportion of cases (32.8%) than controls (30.6%) had a primary school education. The proportion of controls was slightly higher compared to cases for each level of the variable “income source”, although a slightly greater proportion of cases (33.4%) than controls (26.1%) had pension as source of income.

TABLE 2.1: Characteristics of bladder cancer cases and controls

CHARACTERISTICS		CASES (N=487)		CONTROLS (N=469)		
		No	%	No	%	P_{value}
Sex	Male	393	80.7	369	78.7	
	Female	94	19.3	100	21.3	0.45
City of residence	Guangzhou	215	44.1	223	47.4	
	Wuhan	71	14.6	105	22.3	
	Changsha	139	28.5	79	16.8	
	Hangzhou	62	12.7	63	13.4	<0.001
Age (years)[a]	<40	32	6.5	21	4.5	
	40-59	161	33.1	133	28.3	
	60-79	246	50.5	264	56.2	
	≥80	48	9.9	46	9.8	0.79
Smoking status	Non smoker	179	36.8	219	46.7	
	Former smoker	112	23.0	123	26.2	
	Current smoker	196	40.2	127	27.1	<0.001
Smoking duration[b] *(years)*	Never	179	36.8	219	46.6	
	<20	38	7.8	31	6.6	
	20-39	130	26.7	107	22.8	
	≥40	140	28.7	113	24.0	0.02
Amount of cigarettes (per day)	None	179	36.8	219	46.6	
	1-9	69	14.2	67	14.3	
	10-19	176	36.1	147	31.3	
	≥20	63	12.9	37	7.9	0.004
Education[c]	No formal schooling	22	4.5	42	8.9	
	Primary school	159	32.6	144	30.6	
	Junior school	120	24.6	123	26.2	
	Technical	104	21.4	85	18.1	
	Senior technical	36	7.4	41	8.7	
	University	44	9.0	34	7.2	0.07
Control admitted to hospital for	Disease of circulatory system			67	14.3	
	Disease of digestive system			147	31.3	
	Disease of musculoskeletal system			41	8.7	
	Disease of respiratory system			31	6.6	
	Other disease			184	39.1	
Income Source	Pension	154	33.4	122	26.1	
	Salary	58	12.6	44	9.4	
	Savings	31	6.7	43	9.2	
	Contributions from family	174	37.7	197	42.1	
	Other benefits	44	9.5	62	13.2	0.02

[a]data on age was missing for 5 controls
[b]data on smoking duration was missing for 5 controls
[c]data on education level was missing for 2 controls
[d]data on income source was missing for 1 control

2.5.2 Meat, fish and egg products

The OR of developing bladder cancer increased significantly with increasing consumption of red meat (P_{trend}=0.01) and organ meat (P_{trend}=0.04) (Table 2.2). Subjects who consumed red meat at least five times a week had a 2-fold increased OR compared to subjects who consumed meat less than once a week (OR=1.8, 95%CI: 1.1-3.0). Similarly, subjects who consumed organ meat at least three times a month or more had a nearly 2-fold increased OR of developing bladder cancer compared to subjects who never consumed organ meat (OR=1.6, 95%CI: 0.9-2.9). The consumption of white fresh fish was significantly associated with a decreased OR of bladder cancer (P_{trend}=0.004). Subjects who consumed white fresh fish had 40% lower odds of developing bladder cancer compared to those who never consumed white fish (OR=0.6, 95%CI: 0.3-0.9).

TABLE 2. 2: Odds ratios and 95% confidence intervals of bladder cancer for meat, fish, and egg products consumption

FOOD ITEM	FREQUENCY	$N_{CASE/CONTROL}$	OR[a] (95%CI)	P_{trend}
Red meat	≤1/week	67/71	1.0 (ref.)	
	2-4/week	260/270	1.2 (0.9-2.1)	
	≥5/week	160/128	1.8 (1.1-3.0)	0.01
Organ meat	Never	55/73	1.0 (ref.)	
	<1/month	236/225	1.3 (0.8-1.9)	
	1-3/month	196/171	1.9 (1.1-3.1)	
	≥1/week	61/60	1.6(0.9-2.9)	0.04
Preserved meat	Never	42/55	1.0 (ref.)	
	<1/month	313/281	1.6 (1.0-2.8)	
	1-3/month	131/133	1.7 (0.9-3.1)	
	1/week	37/38	2.2 (1.0-4.7)	0.09
Chicken	<1/month	118/85	1.0 (ref.)	
	1-3/month	239/238	0.7 (0.5-1.2)	
	≥1/week	129/146	0.9 (0.5-1.4)	0.69
Other Poultry	Never	20/24	1.0 (ref.)	
	<1/month	246/221	1.7 (0.9-3.6)	
	1-3/month	161/151	1.8 (0.8-3.9)	
	≥1/week	60/73	1.1 (0.5-2.5)	0.53
Dark fish[b]	Never	253/220	1.0 (ref.)	
	<1/month	121/124	1.2 (0.8-1.8)	
	1-3/month	40/46	1.2 (0.6-2.2)	
	≥1/week	72/79	1.2 (0.7-2.0)	0.51
White fresh fish[c]	Never	332/270	1.0 (ref.)	
	<1/month	105/125	0.6 (0.4-0.9)	
	≥3/month	49/74	0.5 (0.3-0.9)	0.004
Sea food[d]	Never	142/114	1.0 (ref.)	
	<1/month	217/201	1.0 (0.7-1.4)	
	1-3/month	122/96	0.8 (0.5-1.2)	
	≥1/week	30/31	1.1(0.5-2.2)	0.49
River fish	≤1 /week	243/237	1.0 (ref.)	
	≥2-4/week	242/232	1.2 (0.9-1.6)	0.27
Preserved fish	Never	47/60	1.0 (ref.)	
	<1/month	309/260	1.7 (1.0-2.7)	
	1-3/month	109/87	1.1 (0.6-2.0)	
	≥1/week	40/43	1.6 (0.9-1.6)	0.72
Preserved egg	Never	75/66	1.0 (ref.)	
	<1/month	296/269	1.2 (0.8-1.9)	
	1-3/month	84/90	1.2 (0.7-2.1)	

	≥1/week	31/44	0.9 (0.5-1.8)	0.932
Egg	1/week	178/140	1.0 (ref.)	
	2-4/week	243/247	0.8 (0.6-1.2)	
	≥5/week	66/82	0.6 (0.4-1.0)	0.06

OR=odds ratio; ref=reference group; CI=confidence interval
[a]adjusted for sex, age (categorical), smoking status (categorical), smoking duration (continuous), smoking amount (continuous) and other food groups
[b]e.g. mackerel, salmon, and tuna
[c]e.g. carp, cod, and eel
[d]e.g. crab, cockles, lobster, octopus, prawn, and squid

2.5.3 Fruit products

Significant inverse associations between bladder cancer and consumption of citrus fruits (P_{trend}=0.007), stone fruits (P_{trend}<0.001) and vine fruits (P_{trend}=0.02) were observed (Table 2.3). Subjects who consumed citrus fruits or stone fruits at least twice a week had a 60% reduction in the OR of bladder cancer relative to subjects who consumed citrus and stone fruits less than once a month (citrus fruits OR=0.4, 95%CI: 0.3-0.8; stone fruits OR=0.4, 95%CI: 0.2-0.6). Subjects who consumed vine fruits at least five times a week had a 50% reduction in the OR of bladder cancer relative to subjects who consumed vine fruits less than once a month (OR=0.5, 95%CI: 0.2-1.0).

TABLE 2.3: Odds ratios and 95% confidence interval of bladder cancer for fruit intake

FOOD ITEM	FREQUENCY	$N_{CASE/CONTROL}$	OR [a](95%CI)	P_{trend}
Citrus fruit[b]	<1/month	106/48	1.0 (ref.)	
	1-3/months	212/198	0.6 (0.4-1.0)	
	1/week	75/76	0.7 (0.4-1.3)	
	≥2/week	92/147	0.4 (0.3-0.8)	0.007
Stone fruit[c]	≤1/month	168/90	1.0 (ref.)	
	1-3/months	210/194	0.8 (0.5-1.2)	
	1/week	57/65	0.6 (0.4-1.1)	
	≥2/week	51/120	0.4 (0.2-0.6)	<0.001
Vine fruit[d]	≤1/month	58/30	1.0 (ref.)	
	1-3/month	136/101	0.8 (0.4-1.4)	
	≤4/week	234/257	0.6 (0.3-1.0)	
	≥5/week	57/79	0.5 (0.2-1.0)	0.02
Soft fruit[e]	Never	231/175	1.0 (ref.)	
	<1/month	148/152	0.9 (0.6-1.3)	
	1-3/months	75/83	0.9 (0.6-1.5)	
	≥1/week	30/59	0.8 (0.4-1.4)	0.47
Fleshy fruit[f]	≤1/month	47/28	1.0 (ref.)	
	1-3/month	161/137	1.6 (0.8-3.2)	
	1/week	50/66	0.8 (0.4-1.8)	
	2-4/week	194/187	1.8 (0.9-3.6)	
	≥5/week	34/50	1.1 (0.5-2.5)	0.46

OR=odds ratio; ref=reference group; CI=confidence interval
[a]adjusted for sex, age (categorical), smoking status (categorical), smoking duration (continuous), smoking amount (continuous) and other food groups
[b]e.g. orange, lime, and grapefruit.
[c]e.g. apricot, peach, lychee, cherry, and mango.
[d]e.g. raspberry, blueberry, and strawberry.
[e]e.g. apple, papaya, pineapple, pear, and banana
[f]e.g. grape and watermelon

2.5.4 Vegetable products

The OR of developing bladder cancer decreased significantly with increasing consumption of flower vegetables (P_{trend}<0.001) and potatoes (P_{trend}=0.005) (Table 2.4). Subjects who consumed flower vegetables once or more per week had a 70% decreased OR of bladder cancer (OR=0.3, 95%CI: 0.2-0.6) compared to those who rarely consumed flower vegetables. The OR for subjects who consumed potatoes at least twice per week was 0.4 (95% CI: 0.2-0.9) relative to those who consumed less than once a month or never consumed potatoes. However, the OR of developing bladder cancer increased significantly with increasing consumption of leafy vegetables (P_{trend}=0.003), bulb vegetables (P_{trend}=0.003) and preserved vegetables (P_{trend}=0.02). The OR of bladder cancer for the highest category were 2.9 (95%CI: 1.6-5.4) for leafy vegetables, 2.3 (95%CI: 1.3-4.0) for bulb vegetables and 2.3 (95%CI: 1.2-4.2) for preserved vegetables.

TABLE 2.4: Odds ratios and 95% confidence interval of bladder cancer for vegetable intake

FOOD ITEM	FREQUENCY	$N_{CASE/CONTROL}$	OR [a](95%CI)	P_{trend}
Sweet corn	≤1/month	180/156	1.0 (ref.)	
	1-3/month	244/226	1.5 (0.9-2.4)	
	≥1/week	63/87	0.9 (0.5-1.6)	0.94
Flower vegetables[b]	<1/month	101/38	1.0 (ref.)	
	1-3/month	227/231	0.4 (0.2-0.8)	
	≥1/week	158/199	0.3 (0.2-0.6)	<0.001
Fruit vegetables[c]	≤3/months	212/208	1.0 (ref.)	
	1/week	62/49	1.3 (0.7-2.3)	
	2-4/week	155/144	1.0 (0.6-1.7)	
	≥5/week	57/68	0.9 (0.5-1.8)	0.72
Leafy vegetables[d]	≤3/months	191/214	1.0 (ref.)	
	1-4/week	151/132	2.8 (1.6-5.0)	
	≥5/week	142/123	2.9 (1.6-5.4)	0.003
Stem vegetables[e]	Never	121/110	1.0 (ref.)	
	<1/month	136/99	1.0 (0.6-1.5)	
	1-3/month	107/119	0.7 (0.5-1.2)	
	≥1/week	122/141	0.8 (0.4-1.3)	0.17
Mushroom	<1/month	115/85	1.0 (ref.)	
	1-3/month	227/211	1.3 (0.8-2.1)	
	1/week	105/100	1.3 (0.8-2.3)	
	≥4/week	39/73	0.7 (0.4-1.3)	0.56
Roots[f]	<1/month	95/56	1.0 (ref.)	
	1-3/month	226/209	1.0 (0.6-1.6)	
	≥1/week	163/204	0.8 (0.5-1.4)	0.44
Garlic	≤1/week	138/118	1.0 (ref.)	
	2-6/week	94/104	0.8 (0.5-1.3)	
	1/day	253/247	0.9 (0.5-1.4)	0.50
Bulb vegetables[g]	<1/month	124/120	1.0 (ref.)	
	1-3/month	210/203	1.4 (0.9-2.2)	
	1/week	70/69	1.5 (0.9-2.5)	
	≥2/week	82/77	2.3 (1.3-4.0)	0.003
Preserved vegetables	Never	49/78	1.0 (ref.)	
	<1/month	267/243	2.0 (1.2-3.2)	
	1-3/month	77/93	2.2 (1.2-4.0)	
	≥1/week	71/77	2.3 (1.2-4.2)	0.02

Potatoes	<1/month	116/73	1.0 (ref.)	
	1-3/month	282/262	1.3 (0.7-2.2)	
	1/week	53/65	0.8 (0.4-1.5)	
	≥2/week	36/69	0.4 (0.2-0.9)	0.005

OR=odds ratio; ref=reference group; CI=confidence interval
[a]adjusted for sex, age (categorical), smoking status (categorical), smoking duration (continuous), smoking amount (continuous) and other food groups
[b]e.g. broccoli and cauliflower
[c]e.g. cucumber and tomato
[d]e.g. cabbage, lettuce, and spinach
[e]e.g. asparagus and celery
[f]e.g. carrot and radish
[g]e.g. onion and leek

2.5.5 Grain, soy and dairy products

A significant inverse association was observed between increasing consumption of dairy products and bladder cancer (P_{trend}<0.001) (Table 2.5). Subjects who consumed dairy products at least once a week had a 60% reduction in the OR of bladder cancer compared to subjects who never consumed dairy products (OR=0.4, 95%CI: 0.3-0.7).

TABLE 2.5: Odds ratios and 95% confidence interval of bladder cancer for grain, soy, and dairy products consumption.

FOOD ITEM	FREQUENCY	$N_{CASE/CONTROL}$	OR[a] (95%CI)	P_{trend}
Rice noodle	<1/day	39/29	1.0 (ref.)	
	1/day	447/440	0.7 (0.4-1.3)	0.29
Pasta	Never	422/401	1.0 (ref.)	
	Consumption	65/68	1.1 (0.7-1.7)	0.59
Bread	Never	96/75	1.0 (ref.)	
	<1/month	97/75	1.2 (0.7-1.9)	
	≤1/week	96/98	0.8 (0.5-1.3)	
	≥4/week	198/221	0.7 (0.5-1.2)	0.12
Soy bean curd	<1/month	62/34	1.0 (ref.)	
	1-3/month	229/241	0.5 (0.3-1.0)	
	1/week	66/82	0.6 (0.3-1.4)	
	≥2-4/week	129/112	0.7 (0.3-1.7)	0.82
Soy bean milk	<1/month	178/122	1.0 (ref.)	
	1-3/month	219/236	0.7 (0.4-1.3)	
	≥1/week	89/111	0.5 (0.3-1.0)	0.13
Dairy Products	Never	87/66	1.0 (ref.)	
	<1/month	87/47	1.4 (0.8-2.4)	
	1/week	137/108	1.0 (0.7-1.7)	
	2-4/week	116/119	0.9 (0.6-1.5)	
	≥ 1/week	63/129	0.5 (0.3-0.7)	<0.001

OR=odds ratio; ref=reference group; CI=confidence interval
[a]adjusted for sex, age (categorical), smoking status (categorical), smoking duration (continuous), smoking amount (continuous) and other food groups

2.5.6 Diet Diversity

After adjustment for other food groups consumed, a strong inversely significant association was found between bladder cancer and total diet diversity (P_{trend}=0.02) and bladder cancer and fruit diversity (P_{trend}<0.001). Subjects who consumed at least 20 different food items a week had a 60% reduction in OR of bladder cancer compared to subjects who consumed at least four different food items a week (OR=0.4, 95%CI: 0.2-1.1). The OR of developing bladder cancer decreased substantially for subjects who consumed at least five different fruit items per week (OR=0.1, 95%CI: 0.0-0.3) (Table 2.6).

TABLE 2.6: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to cut-off points of diversity scores within specific food groups and total diet

FOOD ITEM	FREQUENCY	$N_{CASE/CONTROL}$	OR[a] (95%CI)	P_{trend}
Meat diversity	Never	45/38	1.0 (ref.)	
	1/week	273/249	0.5 (0.2-1.0)	
	2/week	93/98	0.5 (0.2-1.1)	
	≥3/week	74/85	0.3 (0.1-0.8)	0.07
Fish diversity	0/week	149/137	1.0 (ref.)	
	1/week	253/240	1.1 (0.8-1.6)	
	2/week	51/41	1.9 (1.0-3.5)	
	≥3/week	31/51	1.0 (0.5-2.0)	0.44
Vegetable diversity	≤2/week	147/152	1.0 (ref.)	
	2-3/week	85/39	2.0 (1.1-3.6)	
	4-5/week	103/97	0.9 (0.5-1.6)	
	6-7/week	91/98	1.1 (0.5-2.1)	
	≥8/week	55/83	0.8 (0.4-1.6)	0.21
Fruit diversity	Never	124/83	1.0 (ref.)	
	1/week	97/72	0.7 (0.4-1.2)	
	2/week	98/84	0.4 (0.2-0.8)	
	3/week	94/95	0.3 (0.1-0.6)	
	4/week	55/92	0.2 (0.1-0.4)	
	5/week	14/41	0.1 (0.0-0.3)	<0.001
Total diet diversity	≤4/week	138/126	1.0 (ref.)	
	5-8/week	95/66	0.9 (0.5-1.5)	

9-12/week	98/92	0.6 (0.3-1.1)	
13-16/week	106/68	0.4 (0.2-0.8)	
≥20/week	60/44	0.4 (0.2-1.1)	0.02

OR=odds ratio, ref=reference group; 95%CI=95% confidence interval
OR[a]= odds ratio adjusted for sex, age (categorical), smoking status (categorical), smoking duration(continuous), smoking amount (continuous) and other food groups (quantity)

2.6 Discussion

2.6.1 Main findings

In this study we found an inverse association between total diet diversity and bladder cancer risk and in particular between fruit diversity and bladder cancer. We demonstrated that consumption of citrus fruits, stone fruits, vine fruits, flower vegetables, white fresh fish, eggs, potatoes and dairy products may decrease the risk of bladder cancer in a Chinese population. We also found that consumption of red meat, organ meat, leafy vegetables, bulb vegetables and preserved vegetables may increase the risk of bladder cancer.

2.6.2 Comparison with previous studies

Our finding that diet diversity, and in particular fruit diversity, was associated with a lower risk of bladder cancer is in general agreement with the current literature on diet diversity and other cancers.[24-26] Diet diversity is a combination of different food items that contain different food micro nutrients and compounds; for example, carotenoids, vitamin C and E, flavonoids and phytosterols are all known to have strong antioxidant and anti-carcinogenic properties.[30] The only study that looked at the relationship between diet diversity, specifically vegetable and fruit diversity, and the risk of developing bladder cancer reported that there was no overall relationship between vegetable diversity or fruit diversity and risk of developing bladder cancer.[22]

The positive association between red meat, organ meat, preserved meat and the risk of bladder cancer is consistent with most previous studies.[11, 14, 31-33] In a recent meta-analysis including ten cohort studies and eleven case-control studies, an increased bladder cancer risk was observed with high consumption of red and preserved meat.[34] Red and preserved meats contain compounds that are carcinogenic. It has been reported

that cooking meat at a high temperature may produce carcinogenic compounds such as heterocyclic amines and polycyclic aromatic hydrocarbons.[35] Another constituent of red meat is heme (iron content) in red meat that produces free radicals in the colon that may damage DNA.[36] Salt used to process meat contains nitrates/nitrites and amides that contribute to the formation of nitrosamines, which are known to be mutagenic and carcinogenic in animals.[35]

Consistent with the current epidemiologic literature relating to fish consumption and bladder cancer risk, we observed a significant inverse association between consumption of white fresh fish and the risk of bladder cancer.[11,37] However, most previous studies did not specify what type of fish was consumed because these studies were not primarily designed to examine the effect of fish consumption on bladder cancer risk. Fish is the main source of omega-3 fatty acids and has been shown to inhibit tumour growth as well as modulate the expression of pro-inflammatory genes.[38]

Our findings in relation to fruits were generally consistent with previous studies.[14,39-40] A population-based case-control study of non-Asians in Los Angeles indicated a strong inverse association between consumption of citrus fruits and bladder cancer risk.[39] Another case-control study found that moderate consumption of stone fruits and vine fruits has a protective effect on bladder cancer risk.[14] One prospective study reported inverse associations between consumption of carotenoid β-cryptoxanthin (mainly found in citrus fruits) and bladder cancer risk.[40] In contrast with our findings, three previous studies found no association between citrus fruits or stone fruits consumption on bladder cancer risk.[41-43] Fruits are a rich source of vitamin C, mostly known for its antioxidant property. Vitamin C can inhibit nitrosamine formation in vivo, inhibits mutagenesis and carcinogenesis in vitro and lowers tumour cell growth and carcinogen-

induced DNA damage.[44] Additionally, other components of fruit include, phytochemicals, dietary fibres and carotenoids, which are also known to be antioxidants, and have been shown to have anti-carcinogenic effects on bladder cancer.[45]

Consistent with most previous literature, we observed an inverse association between consumption of flower vegetables (cruciferous vegetables) and bladder cancer risk. In a recent meta-analysis of five cohort and five case-control studies, a significant decreased risk was observed with overall consumption of flower vegetables (cruciferous vegetables).[46] Vegetables are rich sources of isothiocyanates and also other compounds such as phytochemicals, dietary fibres and carotenoids. They are known to be chemopreventive agents with anticancer mechanisms, including stimulation of apoptosis, induction of carcinogen detoxification and arrest of cell cycle progression.[47]

Besides flower vegetables, the consumption of potatoes was associated with a decreased risk of bladder cancer. The significantly decreased bladder cancer risk for consumption of potatoes has not been observed in other studies.[41] Some studies detected that consumption of fried potatoes was significantly associated with increased risk of bladder cancer[48] and our study reported a null association.[41]

The significant elevated bladder risk for consumption of leafy vegetables in our data has not been observed previously.[14,49] However, in China, the most common method of cooking leafy vegetables is lightly frying in little oil. High consumption of fried leafy vegetables has previously been associated with an increased risk of bladder cancer.[12,14] In the current study, subjects consumed leafy vegetables relatively commonly with an average consumption of three times a week. In addition, it has been reported that the high content of nitrate found in vegetables may play a role in the elevated risk of

developing cancer. Ingestion of nitrate compounds can be converted to nitrites via symbiotic bacteria of the oral cavity and this enhance the generation of N-nitroso compounds (e.g. nitrosamines), which are known to be carcinogenic in animals.[50] Consistent with two previous studies, the consumption of preserved vegetables (pickled vegetables) was associated with an increased risk of bladder cancer.[12,14]

We found a positive association between consumption of bulb vegetables and bladder cancer risk. A case-control study contradicts our findings; this study suggested that consumption of bulb vegetables such as leek and onion is inversely associated with risk of bladder cancer.[51] In another study it was reported that consumption of fried onions was positively associated with risk of bladder cancer.[14] However, it is possible that cooking may destroy or reduce the nutritional components of vegetables.[14]

Several studies have examined the relationship between the consumption of dairy products and the risk of bladder cancer,[28,52,53] but results of these studies were generally inconsistent. A recently published meta-analysis of 19 studies examined milk consumption and bladder cancer risk and found a decreased risk of bladder cancer in the highest category compared with the lowest category of milk consumption. Several mechanisms could explain the inverse association observed in our study. Dairy products are the main source of dietary calcium and it has been reported that the reduced risk of cancer is partly associated with consumption of calcium.[54] Another possible mechanism is that fermented dairy products contain lactic acid bacteria, which have been shown to suppress bladder cancer carcinogenesis.[55]

2.6.3 Strengths and Limitations

The strengths of this study include; a relatively large sample size and high response rate. To reduce interviewer bias, interviewers were rigorously trained in their interview

skills. An additional strength of our study was that we were able to control for potential confounders, such as smoking, that are known to influence bladder cancer risk. We cannot, however, entirely rule out the possibility of selection and non-response bias. However, since both the cases and controls came from the same underlying source population any selection bias should have been minimal. In fact, it is actually not necessary for cases and controls included in a case-control study to be representative of the general population as long as the controls represent the underlying source population that gave rise to the cases.[56] Also, if any selection bias would have been introduced, the fact that we controlled for attained age, sex and smoking in our regression models, should have minimised any potential effect of such selection bias. The 81% response rate among the controls is not uncommon among similar case-control studies investigating dietary factors and risk of cancer. There is no reason to assume that the 19% of the controls that refused to participate are systematically different, in terms of the exposure under investigation and/or potential unmeasured confounding factors, from those who actually participated. Unfortunately, we do not have more detailed information on the cases and controls that refused to participate, but we did record reasons for non-participation. The most common reasons that subjects gave for not participating were: no direct benefit; not being in the mood; duration of interview was too long; worries about privacy; and wanting to receive results. None of these reasons are likely to be associated with the exposure under investigation (i.e. dietary factors) and thus non-response bias should be minimal. The FFQ contained only 35 food items therefore a more detailed analysis was not possible. We cannot rule out the possibility of recall bias although we tried to minimize recall bias by asking study subjects about their usual food consumption a year before the interview.

To investigate the potential bias that could be caused by including hospital controls with digestive disease we conducted a sensitivity analysis. No appreciable effect on the OR estimates was observed after including or excluding these controls. The interviewers were aware of the case-control status of the subjects, but they were not aware of the relationship between diet and bladder cancer, thus this is unlikely to have caused bias. In addition, the interviewers were trained for patient recruitment, informed consent and structured interviews. This training was repeated every six months.

2.6.4 Conclusion

To our knowledge, this is the first study to investigate the relationship between diet and bladder cancer in detail in China. Our results indicate that higher diet diversity and particularly a diet varied in fruit may reduce the risk of developing bladder cancer. These findings add to epidemiologic evidence that support the dietary guidelines for a more diverse diet.[57] In addition, the consumption of citrus fruits, stone fruits, vine fruits, flower vegetables, fresh fish, potatoes and dairy products may decrease the risk of bladder cancer, whereas the consumption of red meat, organ meat, leafy vegetables, bulb vegetables or preserved vegetables may increase the risk of bladder cancer.

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3.0 CHAPTER THREE

Total fluid intake and the risk of developing bladder cancer: A dose-response meta-analysis

Submitted to: European Journal of Epidemiology

3.1 Abstract

Results from previous epidemiological studies evaluating the association between total fluid intake and bladder cancer (BC) risk have been inconsistent. We conducted a dose-response meta-analysis to investigate the association between total fluid intake and bladder cancer risk. Fifteen case-control studies and three cohort studies with a total of 10,678 BC cases were included. To quantify the dose-response relationship between fluid intake and bladder cancer risk, variance-weighted least squares and generalised least-squares trend estimation were used. Restricted cubic splines were used to investigate potential non-linearity in the dose-response. For men, significant non-linearity in the dose-response ($P<0.001$) was found between total fluid intake and BC risk. Compared to six cups (250 ml was assumed as a standard metric cup of fluid intake) per day, the estimated RRs from the cubic spline model were: 1.06 (95%CI: 1.03-1.09) for eight cups/day, 1.14 (95%CI: 1.08-1.21) for nine cups, 1.76 (95%CI: 1.37-2.26) for 12 cups and 1.9 (RR=3.36, 95%CI: 1.90-5.26) for 16 cups. For women, no-significant linear relationship was found the overall pooled relative risk of bladder cancer for each increment in total fluid intake of 250 ml/day was 1.02 (95%CI: 0.98-1.06). This meta-analysis suggests that in men the risk of bladder cancer increases steeply when fluid intake exceeds eight cups per day.

3.2 Introduction

Bladder cancer is the ninth most common cancer[1] worldwide with an estimated 386,000 incident cases and 150,200 deaths in 2008.[2] The incidence rate of bladder cancer varies by approximately 10-fold across countries or geographical regions.[3] The highest incidence rates of bladder cancer are found in developed countries of Southern Europe and Northern America compared to less developed regions such as Asia and Africa.[4] In both Europe and the USA, bladder cancer is the fifth most common cancer.[5] Bladder cancer is three to four times more common among men than in women.[6] Of all cancers, bladder cancer has the most expensive lifetime treatment per patient.[7, 8] Established risk factors for bladder cancer are tobacco smoking and exposures to occupational carcinogens. Tobacco smoking accounts for an estimated 50% of all bladder cancer cases.[9] Occupational exposure to carcinogens account for an estimated 20% of all bladder cancer cases.[10] Particularly, dye workers, aromatic amines manufacturers and rubber workers are at risk of developing bladder cancer.[11] Despite these established risk factors, the risk of bladder cancer cannot be fully explained; hence, it is important to identify additional potential risk factor of which total fluid intake is a potential candidate.

Results from previous epidemiological studies on the association between total fluid intake and risk of developing bladder cancer have generally been inconsistent. Several possible mechanisms have been suggested by which total fluid intake could affect the risk of developing bladder cancer. On one hand, a high total fluid intake may decrease the risk by diluting the urine and thereby decreasing the contact time of carcinogens with the bladder through increased frequency of urination.[12, 13] A high consumption of specific fluid items such as tea may also reduce the risk of bladder cancer as tea

contains polyphenolic compounds which are believed to have a protective effect.[14-16] On the other hand, a high total fluid intake of specific fluid items such as alcohol[17, 18] or chlorinated tap water[19] may increase the risk of bladder cancer because these fluids may contain compounds like acetaldehyde and trihalomethanes, which are known to have carcinogenic properties.[20, 21] In addition, high consumption of coffee may also increase the risk of bladder cancer as coffee has been classified as a possible carcinogenic agent (group 2A).[22] In 2008, the WHO consultancy report[23] on nutrition, fluid intake and bladder cancer concluded that out of 20 studies, six studies[14, 19, 20, 24-26] found a significantly elevated risk with increasing total fluid intake, four studies[12, 27-29] a significantly decreased risk, and 10 studies[18, 30-38] did not show any significant association. Since the consultancy report in 2008, eight more studies investigated the relationship between total fluid intake and risk of developing bladder cancer.[39-47] To our knowledge, the epidemiological evidence on the association between total fluid intake and the risk of developing bladder cancer has not been summarised quantitatively. The aim of this study was to perform a dose-response meta-analysis summarising the results from epidemiological studies on this topic.

3.3 Methods

The design, analysis and reporting of this meta-analysis was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[48] This meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO, Reg no: CRD42012002568).

3.3.1 Literature Search

We conducted a systematic literature search to identify relevant epidemiological studies on total fluid intake and bladder cancer. We searched the following databases: Medline (Ovid/Pubmed) and Embase (Ovid). The time frame for the search was: Medline 1946 to January 2014; Embase 1974 to January 2014; PubMed up to January 2014. No language restrictions were applied. We used the search terms: (Bladder cancer **OR** Bladder carcinoma **OR** Transitional cell carcinoma **OR** Urinary bladder neoplasm **OR** Urologic Neoplasm **OR** Urologic diseases **OR** Urologic Cancer **OR** Carcinoma **OR** Cancer **OR** Tumour) **AND** (Total fluid consumption **OR** Fluid consumption **OR** Total Fluid intake **OR** Fluid intake **OR** Drinking Behaviour **OR** Beverage Consumption **OR** Drinking) (Appendix 3.1). We reviewed the reference lists of identified research articles to identify other potentially relevant studies. We also searched for conference proceedings through the Biomed Central database, but no additional relevant abstracts were retrieved. We contacted some authors via email for further information and clarification if a study reported insufficient data to be included in the meta-analysis.

3.3.2 Inclusion and exclusion Criteria

Studies had to fulfil the following inclusion criteria for inclusion in this meta-analysis: a) case-control or cohort study design; b) exposure had to be total fluid consumption; c) participants or study population had to be adults of at least 18 years of age; d) the primary outcome measure had to be bladder cancer; and e) studies had to report risk estimates (e.g. Relative Risk (RR), Hazard Ratio (HR) or Odds Ratio (OR)) with corresponding 95% confidence intervals (95% CI) of developing bladder cancer in relation to total fluid intake for at least three different categories of total fluid intake. If numerous published reports from the same study were obtained, we included only the most recent study with the most comprehensive information for total fluid intake and bladder cancer risk.

3.3.3 Data extraction

A data extraction sheet was developed to extract the following information from each study article: first author's last name, year of publication, continent and country where the study was conducted, study design (case-control/cohort), number of cases and controls (for case-control studies), age range of subjects, covariates adjusted for in the analyses (e.g. smoking), measurement of total fluid intake (e.g. food frequency questionnaire), adjusted RR, HR or OR and corresponding 95% CI for the different levels of total fluid intake. Where these results were reported for males and females, both results were extracted. As bladder cancer is a rare disease, we assumed that ORs approximate RRs. Henceforth we used the phrase "relative risk (RR)" to synonymously refer to either an odds ratio (OR), hazard ratio (HR) or rate ratio.

3.4 Statistical analysis

In most identified study articles, total fluid intake was presented in categories with corresponding adjusted RR estimates for the different levels of fluid intake. Since various studies used different measurement units to report total fluid intake (e.g. oz, glasses, cups etc.) and to facilitate comparison of total fluid intake across studies, we converted the reported total fluid intake into millilitres (ml) per day as a standard measurement (assuming 250 ml as the standard metric cup) for each study. We then calculated the midpoint of the upper and lower boundaries in each category of fluid intake within each study. For open-ended categories, we assumed that the boundary had the same amplitude as the closest category. We then rescaled the midpoints of total fluid intake from millilitres to number of cups per day.

In order to summarise dose-response data from individual studies, a two-stage approach was used. The Variance-Weighted Least Square (VWLS) method[49, 50] was used to estimate, for each single study, a study specific regression slope through the (adjusted) log relative risks corresponding to the different levels of fluid intake, weighted by the variance of the log relative risk. At least three different categories of fluid intake were required from a single study to calculate a study specific regression slope and associated standard error with the VWLS method. The estimated study-specific regression slopes were then pooled into one overall slope using a random effects (inverse variance) meta-analysis model.

The advantage of the VWLS method is that it only requires adjusted RRs (and standard errors) from each study, however it assumes that the log RRs are independent (i.e. that the log RRs are not correlated with the reference group). To assess whether the results were sensitive to this assumption, we also used the Generalised Least-squares Trend

(GLST) estimation method[49, 50] in which the correlations between each of the log RRs (within each study) are not assumed to be zero. The GLST method requires, in addition to the adjusted RRs associated with the midpoints for each category of fluid intake, the number of cases in each category of fluid intake and for case-control studies the number of control subjects and for cohort studies the person-time. The GLST method estimates the study-specific slopes and then combines the study specific slopes into one overall slope using a random effects meta-analysis. In the GLST analysis, three studies[20, 39, 51] were excluded due to insufficient data on the number of cases and controls.

3.4.1 Potential effect modification, sub-group analyses, heterogeneity and sensitivity analysis

Between-study heterogeneity was assessed using the I^2 statistic, which quantifies the degree of variation attributable to between-studies. Sources of potential between-study heterogeneity were explored by stratifying analyses by gender, study design (i.e. case-control/cohort) and whether the control ascertainment source was hospital-based or population-based. In addition, heterogeneity by factors such as continent, types of questionnaire and year of publication, and methods of adjustment of smoking status in primary studies in four groups (i.e. never smoked/former smoker/current smoker, never smoked/former smoker/current smoker (pack years), never smoked/former smoker/current smoker (smoking duration and smoking frequency) and pack years) were explored by fitting these factors into one meta-regression model as effect modifiers.

3.4.2 Sensitivity analysis

A sensitivity analysis was conducted by excluding the study of Pohlabeln et al.[28] because in this study 89.6% of the cases were diagnosed with urinary bladder cancer and the remaining patients were diagnosed with cancer of other sites of the genito-urinary tract (ureter [n=3, 1.0%]; renal pelvis [n=11, 3.7%], urethra [n=5, 1.7%] and multiple localisations [n=12, 4.0%]).

3.4.3 Non-linearity in dose-response

Potential non-linearity in the dose-response relationship of total fluid intake and risk of bladder cancer was explored by applying a restricted cubic spline with four knots located at the 5^{th}, 35^{th}, 65^{th} and 95^{th} percentile of the distribution of total fluid intake derived from the GLST method. Deviations from non-linearity were tested using a Wald-test comparing the model with the restricted cubic spline to a model assuming a linear dose-response relationship (i.e. null model). The Food Standards Agency (FSA) recommended that, in terms of climate, people who live in countries such as the United Kingdom and other countries with similar climate should consume 6 to 8 glasses of fluid every day,[52] so we therefore used 6 cups (250ml) of fluid intake per day as the reference category.

3.4.3 Publication bias

Egger's regression test on the slopes derived from the VWLS method was used to assess potential publication bias.[53] All statistical analyses were conducted using Stata (version 12).[54]For the Egger's test, a two-sided P-value of 0.10 was considered

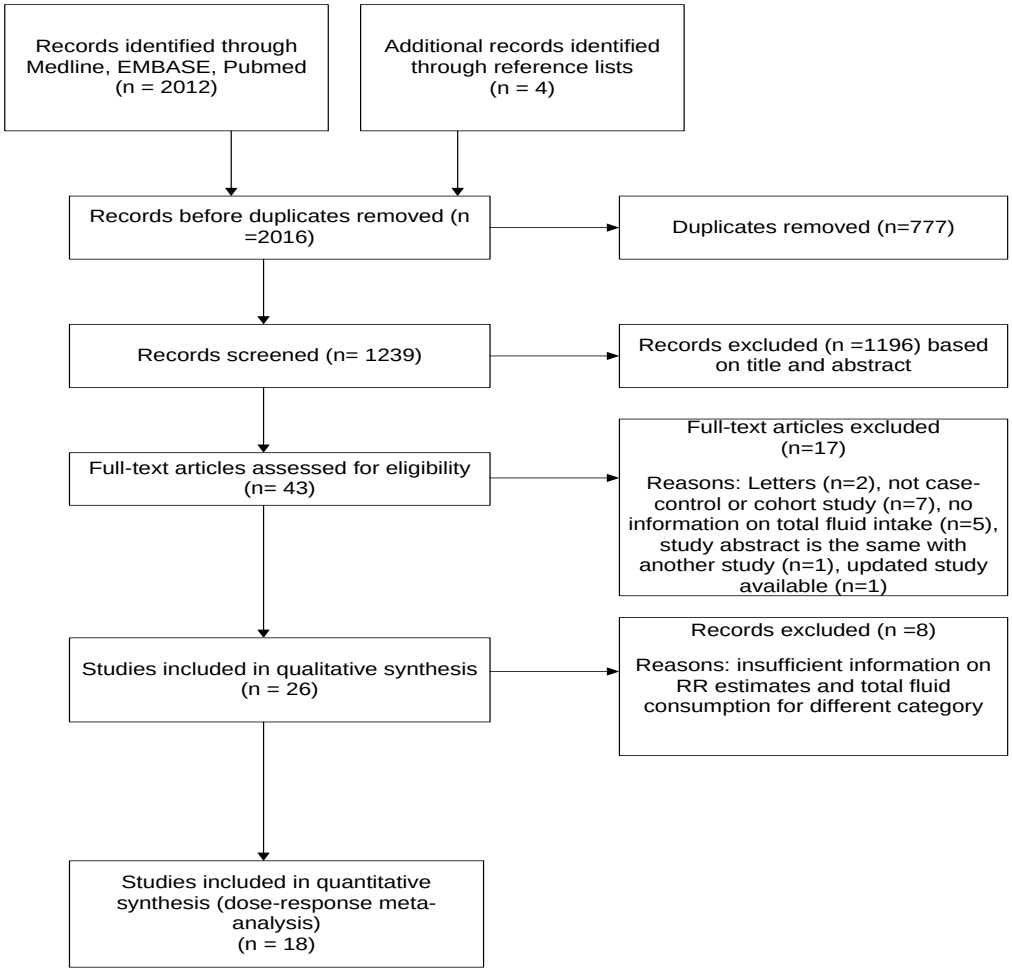
statistically significant since the Egger's test has low power; for all other tests a two-sided P-value of 0.05 was considered statistically significant.

3.5 Results

3.5.1 Study selection

Using the search strategy described, a total of 2,016 published articles were identified (Figure 3.1). Of these, 777 duplicate publications were excluded. The remaining 1,239 articles were reviewed and 43 articles were retrieved based on title and abstract. Full texts were retrieved for all 43 articles and of these, 17 articles were excluded for the following reasons: two articles[55, 56] were letters to a journal editor, six articles[18, 23, 38, 40, 57, 58] were systematic reviews, one article was a pooled analysis of six case-control studies[19], six articles reported no information on total fluid intake and risk of developing bladder cancer,[31, 59-62] and one article[63] was a duplicate of another study. The population of one study[12] was included in a recently published paper.

Figure 3.1: Flow chart for study selection for the dose-response meta-analysis on fluid intake and risk of developing bladder cancer



3.5.2 Characteristics of included studies

We identified 26 published studies[14, 20, 24, 26-37, 39, 41-47, 64] that assessed the relationship between total fluid intake and risk of developing bladder cancer. After examination, eight studies[29-31, 34, 35, 37, 44, 45] were excluded because data on RR estimates and the total fluid intake at different categories was not available for pooling. Of the 18 included studies, three were cohort studies[33, 39, 43] and 15 case-control studies.[14, 20, 24-28, 32, 36, 41, 42, 46, 47, 51, 64] Of the 15 case-control studies, seven were hospital-based[26-28, 42, 47, 51, 64] and eight population-based.[14, 20, 24, 25, 32, 36, 41, 46] Eight studies[25-28, 33, 39, 51, 64] were conducted in Europe, eight studies[14, 20, 24, 32, 36, 41, 43, 47] in USA and two studies in Asia[42, 46] (Table 1). One study[46] was published in Chinese only; a native speaker translated the article into English. Ten studies[24-26, 28, 36, 39, 41, 42, 51, 64] reported the association between total fluid intake and risk of developing bladder cancer for men and women separately, and two studies[20, 44] reported the association for men only.

Table 3.1 shows the selected basic characteristics of the included studies. A total of 10,678 bladder cancer cases were included in the current study. There were four times more male (n=8,740) bladder cancer patients than female (n=1,938) patients. In the included studies, total fluid intake comprised of consumption of various specific fluid items such as coffee, alcohol, juice, soft drinks etc. and varied across studies. Total fluid intake was generally higher in men than in women. All included studies controlled for the known risk factors tobacco smoking and age. Other confounders were adjusted for, but this varied across studies.

TABLE 3.1: Study characteristics for the included studies in the dose-response meta-analysis

Author (Year)	Continent	Country	Study design	Case	Control	Age (Years)	Fluid assessment	Gender	Fluid intake category	RR(95%CI)	Observations	Adjusted factors
1.Claude *et al* (1986)	Europe	Germany	Case-control	340 91	340 91	≥80	Interview & questionnaire	M F	>2.0 *vs* ≤2.0 (l/day) >2.0 *vs* ≤2.0 (l/day)	4.4 (2.3–8.2) 4.0 (0.50–30.3)	Total fluid intake includes coffee, tea, beer, wine and high-proof spirits	Smoking history: never smoked/ ever smoked (pack years)
2.Jensen *et al.* (1986)	Europe		Case-control	280 91	577 194	≤54-70	Interview & questionnaire	M F	0–0.99(Litres/day) 1-1.99 2-2.99 3-3.99 4+ 0–0.99(Litres/day) 1-1.99 2-2.99 3-3.99	1.0 0.9 (0.6–1.4) 1.3 (0.8–2.1) 2.0 (1.1–3.8) 3.3 (1.4–7.4) 1.0 1.1 (0.6–1.9) 1.3 (0.5–3.2) 1.8 (0.4–7.4)	Total fluid intake includes coffee, tea, beer, soft drinks.	Age, sex, smoking history: ever smoked/ current smoker (pack years)
3.Slattery *et al*. (1988)	North America	USA	Case-control	419	889	21-84	Interview & questionnaire	M/F	≤289(ozs/wk) 290-387 388-488 489-653 >653	1.00 0.91 (0.60–1.36) 0.84 (0.56–1.27) 1.20 (0.79–1.80) 1.36 (0.89–2.07)	Total fluid intake was calculated by adding together fluids from all sources	Age, sex, smoking history: Never smoked/ex-smoker/current smoker (pack years), history of diabetes and bladder cancer infections
4.Kunze *et al* (1992)	Europe	Germany	Case-control	416 75	360 71	55-84	Interview & questionnaire	M F	<1.1(Litres/day) 1.1–2.0 2.1-3.0 3.1+ <1.1(Litres/day) 1.1-2.0 2.1+	1.0 1.6 (1.2–2.3) 2.7 (1.6–4.4) 4.9(2.0–12.3) 1.0 1.2 (0.6–2.1) 0.9 (0.3–2.5)	Total fluid intake includes all non-alcoholic and alcoholic beverages.	Smoking history: Never smoked/ ex-smoker/current smoker(pack years)

Author (Year)	Continent	Country	Study design	Case	Control	Age (Years)	Fluid assessment	Gender	Fluid intake category	RR(95%CI)	Observations	Adjusted factors
5.Vena *et al.* (1993)	North America	USA	Case-control	351	855	35-90	Food frequency questionnaire	M	1(lowest quartile) 2 3 4(highest quartile)	1.00 2.60 (1.18–5.73) 3.68 (1.65–8.20) 6.30 (2.82–14.08)	Total fluid intake includes all alcoholic beverages, bottled beverages, soda, milk coffee, tea, all juices and glasses of tap water	Age, education, smoking history: pack years, coffee intake, carotene and sodium
6.Bruemmer *et al.* (1997)	North America	USA	Case-control	202 60	220 185	45-65	Interview	M F	≤7 (Cups/day) >7–9 >9–12 >12 ≤7 (Cups/day) >7–9 >9–12 >12	1.0 0.8 (0.4–1.5) 0.9 (0.5–1.6) 1.0 (0.5–1.7) 1.0 4.2(1.30-14.1) 5.6 (1.7–18.6) 4.7 (1.4–15.8)	Total fluid intake includes water, coffee, decaffeinated coffee, tea, diet, soft drinks, regular soft drinks, beer, wine and hard liquor	Age, county and smoking history: never smoked/ ex-smoker/ current smoker(pack years)
7.Cantor *et al.* (1998)	North America	USA	Case-control	1135 317	1601 833	40-85	Food frequency questionnaire	M F	< 2.08 (Litres/day) 2.08 to <2.72 2.72 to <3.46 ≥ 3.46 Unknown < 2.08 (Litres/day) 2.08 to <2.72 2.72 to <3.46 ≥ 3.46 Unknown	1.00 1.43(1.0-2.7) 1.08 (0.8–1.5) 1.13 (0.8–1.4) 1.0 1.61(1.0-2.7) 1.16(0.7-1.9) 1.08(0.6-1.9)	Total fluid intake includes beverages using tap water (water *per se*, coffee, hot and iced tea, reconstituted fruit juices, fruit drinks from powdered mixes and soups from concentrate or dry mix) and other beverages	Age, sex, smoking history: never smoked/ ex-smoker/ current smoker(smoking frequency and smoking duration), study period, education, high-risk occupation
8.Pohlabeln *et al.* (1999)	Germany	Europe	Case-control	239 61	239 61	36-91	Standardized questionnaire	M F	<1 (Litres/day) 1≤2 2≤3 >3 <1 (Litres/day) 1≤2 >2	1.00 1.21(0.68-2.15) 1.09(0.58-2.05) 1.52(0.64-3.59) 1.00 0.58(0.25-1.39) 0.28(0.11-0.99)	Total fluid intake includes coffee, tea, beer, wine, water and other beverages	Matched evaluation (sex, age ±5 year, area 1of residence), smoking history: never smoked/ cigar smoker, pipe smoker(pack years)

Author (Year)	Continent	Country	Study design	Case	Control	Age (Years)	Fluid assessment	Gender	Fluid intake category	RR(95%CI)	Observations	Adjusted factors
9.Bianchi *et al.* (2000)	North America	USA	Case-control	(See previous study Cantor)	(See previous study Cantor)	40-85	Food frequency questionnaire	M/F	<2.0(Litres/day) 2.0-2.5 2.6-3.3 >3.3	1.0 1.3(1.0-1.6) 1.4(1.1-1.7) 1.4(1.1-1.7)	Total fluid intake includes water, coffee, tea, fruit juices/drinks, soups, milk, soft drinks, and alcoholic beverages. Non-drinking water items (i.e., milk, soft drinks, and alcoholic beverages)	Age, smoking history: never smoked/ ex-smoker / current smoker (pack-years), education (<high school, high school, >high school), family history of bladder cancer, high risk occupation, years of chlorinated surface water, vegetable and coffee consumption
10.Geoffroy-Perez *et al.* (2001)	Europe	France	Case-control	658 107	658 107	≥18	Questionnaire	M F	≤8300(ml/week) 8301–10 400 10 401–12900 12 901–16800 >16 800 Unknown ≤7300(ml/week) 7301–9900 9901–12800 >12 800 Unknown	1.00 0.87 (0.58–1.30) 1.13 (0.76–1.67) 1.41 (0.96–2.08) 1.07 (0.72–1.59) 1.00 0.70 (0.30–1.65) 1.17 (0.51–2.72) 0.96 (0.42–2.22)	Total fluid intake includes non-alcoholic drinks such as tap water, coffee, tea, bottled water, juice, milk and alcoholic beverages such as wine and beer	Age, centre, and place of residence and smoking history: never smoked/ ex-smoker/current smoker (pack years)
11.Zeegers *et al* . (2001)	Europe	The Netherlands	Cohort	569		55-69 at baseline	Semi quantitative Food frequency questionnaire	M/F	1 (lowest quintile) 2 3 4 5 (highest quintile)	1.00 0.83 (0.55–1.25) 0.74 (0.48–1.13) 1.04 (0.69–1.56) 0.91 (0.65–1.29)	Total fluid intake includes fluids from 19 specific beverages	Age, sex, smoking history: never smoked/ ex-smoker/ current smoker(smoking duration and smoking frequency), coffee consumption(ml/day), and tea consumption(ml/day)
12.Michaud *et al* . (2007)	Europe	Spain	Case-control	397	664	20-80	Food frequency questionnaire	M/F	1 (lowest quintile) 2 3 4 5 (highest quintile	1.00 0.67 (0.44–1.02) 0.72 (0.48–1.09) 0.68 (0.45–1.04) 0.62 (0.40–0.95)	Total fluid intake includes beverages- coffee, beer, wine, liquor, champagne, soda, juices, tea, milk, and water	Age, sex, region, smoking history: never smoked/ ex-smoker/ current smoker / occasional smoker, high-risk occupation, night time urination frequency, THM levels, and non-tap fluid for water intake
13.Jiang *et al.* (2008)	North America	USA	Case-control	1196	1214	25-65	Structured questionnaire	M	1 (lowest quartile) 2 3 4(highest quartile)	1.00 0.89 (0.70–1.13) 0.94 (0.75–1.19) 0.98 (0.77–1.26)	Total fluid intake includes water, coffee, tea, alcohol, milk, juice, hot chocolate and soda	Matching factor(age sex and race), smoking history: never smoked/ ever smoked(smoking duration and smoking frequency), level of education,

Author (Year)	Continent	Country	Study design	Case	Control	Age (Years)	Fluid assessment	Gender	Fluid intake category	RR(95%CI)	Observations	Adjusted factors
				342	347			F	1 (lowest quartile) 2 3 4(highest quartile)	1.00 0.89 (0.70–1.13) 0.94 (0.75–1.19) 0.98 (0.77–1.26)		use of NSAIDs, intake of carotenoids, number of years as a hairdresser/barber
14.Hemelt *et al*. (2010)	Asia	China	Case-control	312 69	282 88	≥40	Food frequency questionnaire	M F	≤ 6.0 (cups/day) 6.0-7.4 7.4-9.0 >9.0 ≤5.0 (cups/day) 5.0-6.3 6.3-8.0 >8.0	1.00 0.50 (0.33–0.77) 0.71 (0.47–1.07) 0.65 (0.43–0.98) 1.00 0.51 (0.71-1.49) 1.20 (0.46-3.13) 2.19(0.89-5.38)	Total fluid intake includes six non-alcoholic drinks were covered: black tea (fermented tea), green tea (non-fermented tea), fruit juice, milk, soft drinks and water. Three alcoholic drinks were covered: beer, wine and liquor/spirits (including Chinese rice wine)	Age, sex, smoking history: never smoked/ ex-smoker/ current smoker (smoking frequency and smoking duration), level of education
15.Zhang *et al*. (2010)	Asia	China	Case-control	608	607	25-70	Questionnaire	M/F	≤750 (ml/day) >750 >1500	1.00 0.91(0.68-1.23) 0.89(0.65-1.22)	Total fluid intake includes coffee, tea, sparkling water, plain water, beer, cider and chinese liquor	Age, gender, smoking history: never smoked/ ever smoked, history of occupation with high risk, history of bladder infections, body mass index and alcohol intake
16.Ros *et al.* (2011)	Europe	Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden The United Kingdom	Cohort	362 151	N.A	20-70	Food frequency questionnaire	M F	<1735 (ml/day) 1735-2424 ≥2425 <1438 (ml/day) 1438-2045 ≥2046	1.00 1.07 (0.85–1.35) 1.12 (0.86–1.45) 1.00 0.92(0.60-1.42) 1.15(0.73-1.81)	Total fluid intake includes the specific fluid variables (alcoholic beverages, milk and other dairy beverages, coffee, tea, herbal tea, water, fruit and vegetable juices and soft drinks)	Age, sex, smoking history: never smoked/ ex-smoker/ current smoker (smoking frequency and smoking duration),centre, energy intake from fat and non-fat sources
17. Zhou *et al*. (2012)	North America	USA (Health Professional's study)	Cohort	823	N.A	40–75	Food frequency questionnaire	M	1 (lowest quintile) 2 3 4	1.00 1.37 (1.01, 1.85) 1.16 (0.84-1.59) 1.27 (0.92- 1.74)	Total fluid intake includes 22 beverage items	Age, smoking history: never smoked/ ever smoked (pack years), geographic region, total consumption of meat, energy

Author (Year)	Continent	Country	Study design	Case	Control	Age (Years)	Fluid assessment	Gender	Fluid intake category	RR(95%CI)	Observations	Adjusted factors
									5 (highest quintile)	1.34 (0.96-1.87)		intake, and intake of fruit and vegetables.
18. Wang *et al*. (2013)	North America	USA	Case-control	1007	1299	N.D	Food frequency questionnaire	M/F	<1696 (ml/day) 1696-2215 2215-2789 ≥2789	1.00 0.92(0.71-1.18) 0.81(0.62-1.05) 1.41(1.10-1.81)	Total fluid intake includes water, decaffeinated tea, black tea, green tea, other herbal tea, soft drinks, coffee, alcoholic beverage	Age, sex, smoking history: never smoked/ ex-smoker/ current smoker, ethnicity, energy intake
N.A — Not applicable N.D — Not described												

3.5.3 Dose-response meta-analysis

We compared the results of the two the methods: Generalised Least-squares Trend (GLST) estimation method and Variance-Weighted Least Square (VWLS) method used for conducting this dose-response meta-analysis and since results were similar, we report the results from the VWLS method only.

3.5.3.1 Overall analysis

Fifteen studies[14, 24-28, 32, 33, 39, 41, 42, 46, 47, 51, 64] reported the relative risks of bladder cancer for all subjects combined (i.e. males and females). Overall, a total of 10,678 bladder cancer cases were included in this dose-response meta-analysis. When we assumed that the relationship between fluid intake and bladder cancer was linear, but this was non-significant. The overall pooled RR of bladder cancer for each increment in total fluid intake of 250 ml/day was 1.02 (95% CI: 1.00-1.04; P_{value}=0.12) (Figure 3.2); i.e., the risk of developing bladder cancer increased by 2% for each additional 250 ml of total fluid intake per day.

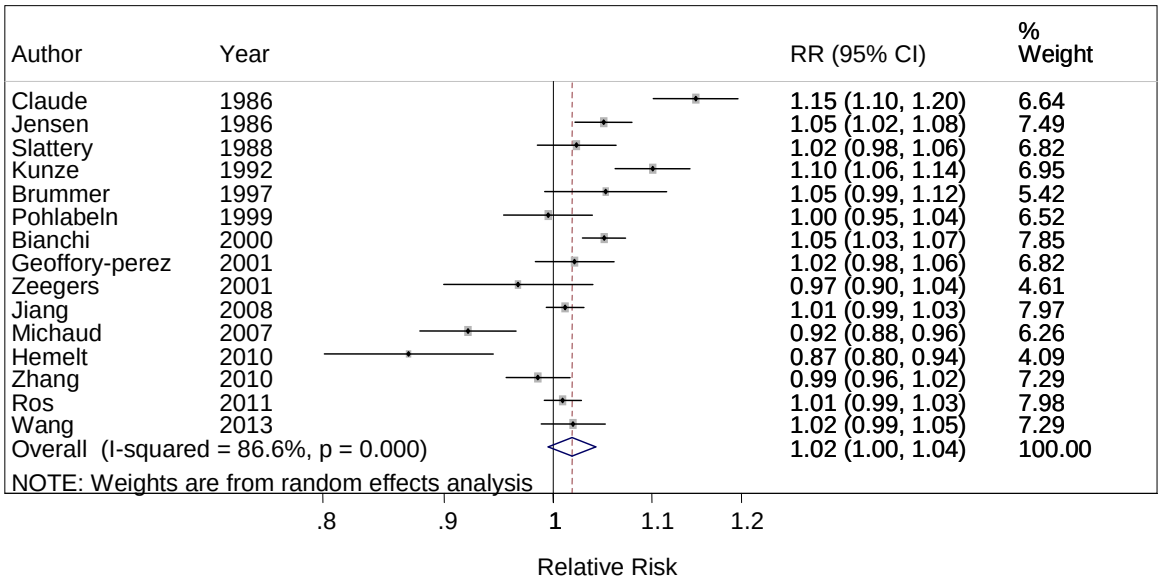
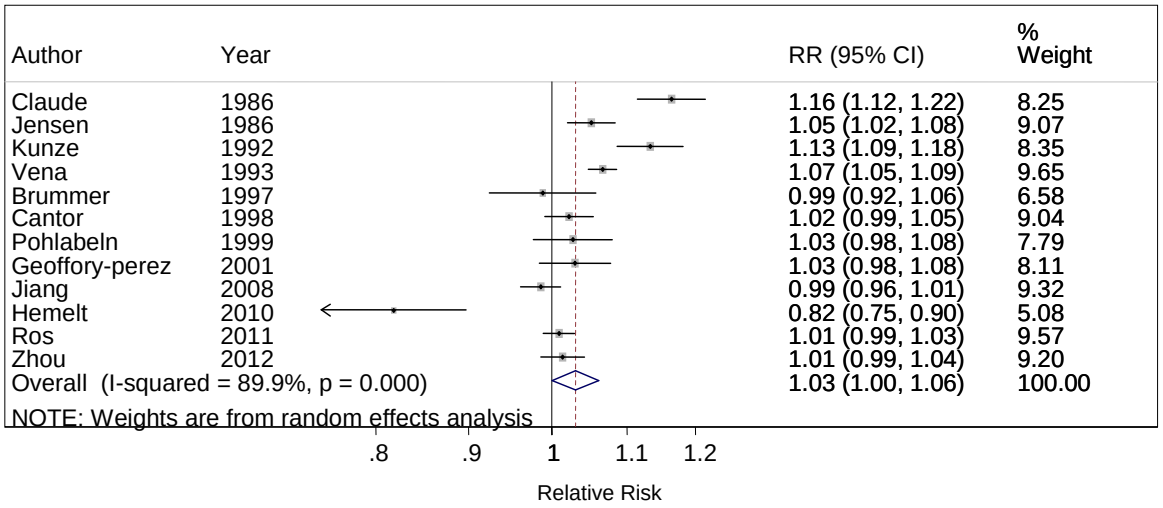


Figure 3.2 Forest plot of relative risks (RRs) of bladder cancer for each 250 ml/day increase in total fluid intake for men and women combined. Squares represent the relative risk estimates for each study; the area of squares reflects the weight of the study i.e., the inverse variance; horizontal lines through each square represent the 95% CI. The last columns include the estimated RRs and corresponding 95% CIs pooled across the levels of fluid intake estimated using VWLS (Variance-Weighted Least Square) method and their weights. The diamond represents the pooled RRs and 95% CI estimated using the random effects meta-analysis.

3.5.3.2 Subgroup analyses

Twelve studies[20, 24-26, 28, 36, 39, 41-43, 51, 64] investigated the association between total fluid intake and risk of developing bladder cancer for men separately. For men, the pooled RR of bladder cancer for each 250 ml/day increase of fluid intake was 1.03 (95% CI: 1.00-1.06; P_{value}=0.05) (Figure 3.3 (a)); i.e., the risk of developing bladder cancer increased by 3% for each additional 250 ml of total fluid intake per day. Ten studies[24-26, 28, 36, 39, 41, 42, 51, 64] examined the association between total fluid intake and risk of developing bladder cancer for women separately. The overall pooled RR of bladder cancer for women for each increase of 250 ml/day of fluid intake was 1.02 (95% CI: 0.98-1.06; P_{value}=0.23) (Figure 3.3 (b)), but this relationship was not significant.

A)



B)

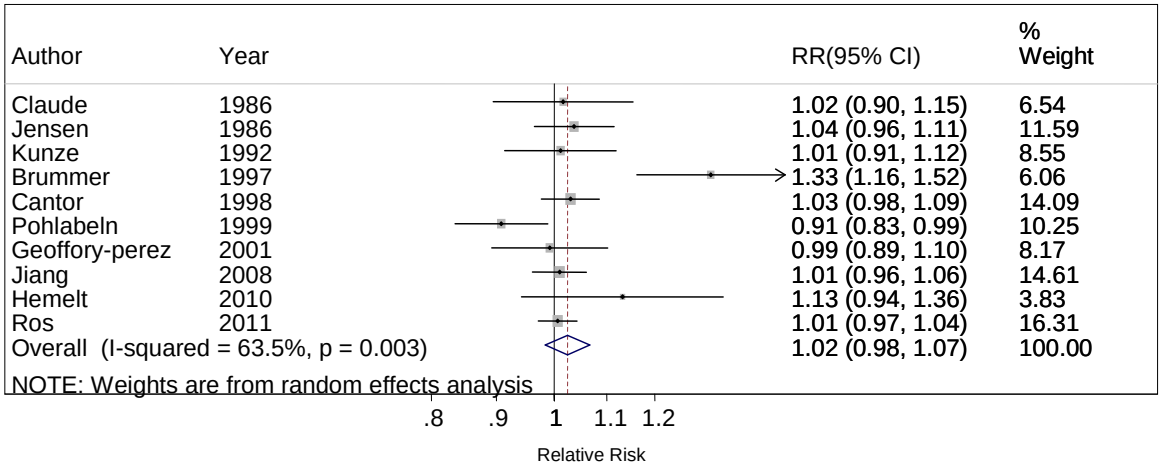


Figure 3.3 A) Forest plot of RRs of bladder cancer for each 250ml/day increases in total fluid intake in men. B) Forest plot of RRs of bladder cancer for a 250 ml/day increase in total fluid intake in women. Squares represent the relative risk estimates for each study; the area of squares reflects the weight of the study i.e., the inverse variance; horizontal lines through each square represent the 95% CI. The last columns include the estimated RRs and corresponding 95% CIs pooled across the levels of fluid intake estimated using VWLS (Variance-Weighted Least Square) method and their weights. The diamond represents the pooled RRs and 95% CI estimated using the random effects meta-analysis.

In subgroup analyses by study design, we observed a significant increase in bladder cancer risk for population-based case-control studies (RR=1.03, 95%CI: 1.01-1.05, P_{value}=0.016), but no significant association for hospital-based case-control studies (RR=1.01, 95%CI: 0.95-1.07, P_{value}=0.708) or cohort studies (RR=1.00, 95%CI: 0.97-1.03, P_{value}=0.877).

In subgroup analyses by study continent, we observed a significant increase in bladder cancer risk for North America (RR=1.03, 95%CI: 1.01-1.05, P_{value}=0.002), but no significant association for Europe (RR=1.03, 95%CI: 0.99-1.07, P_{value}=0.203) or Asia (RR=0.93, 95%CI: 0.82-1.05, P_{value}=0.252) (Figure 3.4).

A)

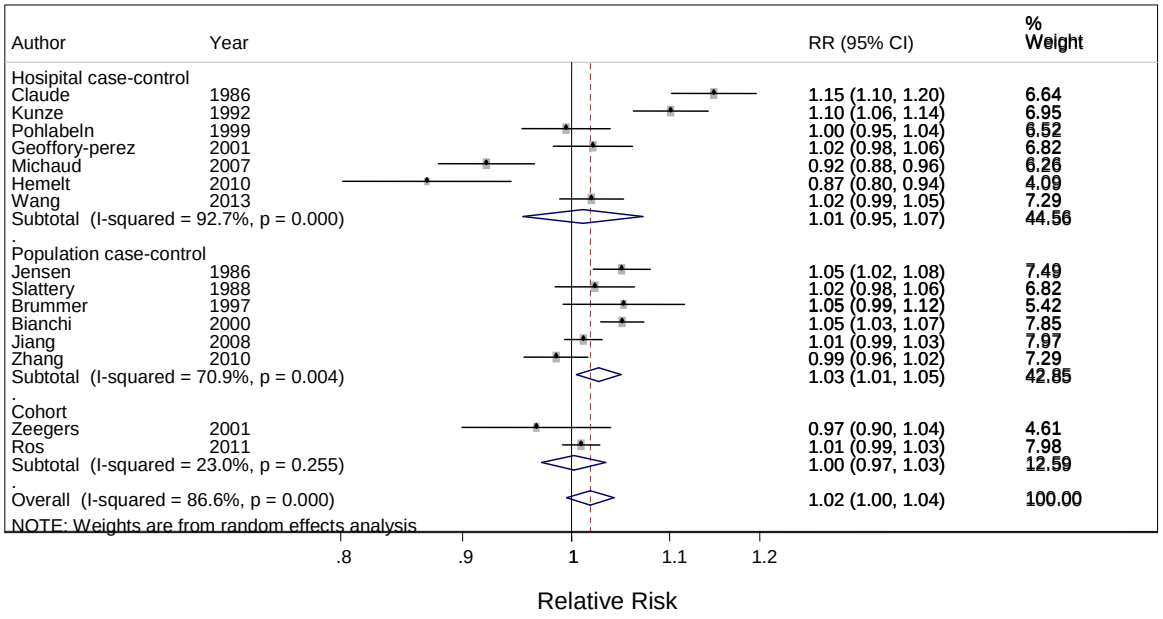


Figure 3.4 A) Subgroup analysis according to study design (hospital based and population based case-control studies, and cohort studies)—Relative risks (RRs) of bladder cancer for each 250ml/day increase in total fluid intake for men and women combined. Squares represent the relative risk estimates for each study; the area of squares reflects the weight of the study i.e., the inverse variance; horizontal lines through each square represent the 95% CI. The last columns include the estimated RRs and corresponding 95% CIs pooled across the levels of fluid intake estimated using VWLS (Variance-Weighted Least Square) method and their weights. The diamond represents the pooled RRs and 95% CI estimated using the random effects meta-analysis.

B)

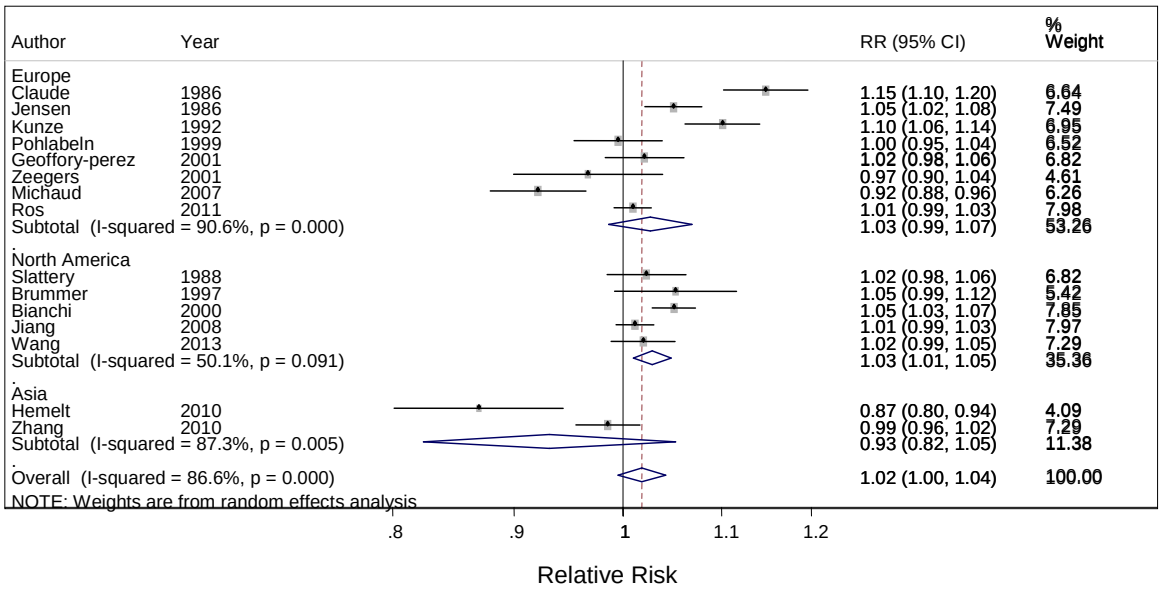


Figure 3.4 B) Subgroup analysis according to continent (Europe, North America and Asia) —Relative risks (RRs) of bladder cancer for each 250ml/day increase in total fluid intake for men and women combined. Squares represent the relative risk estimates for each study; the area of squares reflects the weight of the study i.e., the inverse variance; horizontal lines through each square represent the 95% CI. The last columns include the estimated RRs and corresponding 95% CIs pooled across the levels of fluid intake estimated using VWLS (Variance-Weighted Least Square) method and their weights. The diamond represents the pooled RRs and 95% CI estimated using the random effects meta-analysis.

3.5.3.3 Sensitivity analysis

We conducted a separate analysis excluding the study by Pohlabeln et al.[28] because in this study 89.6% of the cases were diagnosed with urinary bladder cancer and the remaining patients were diagnosed with cancer of other sites of the genito-urinary tract. Excluding this study did not affect the RR of developing bladder cancer appreciably (RR=1.02, 95%CI: 1.00-1.05; Pvalue=0.11).

3.5.4 Meta-regression

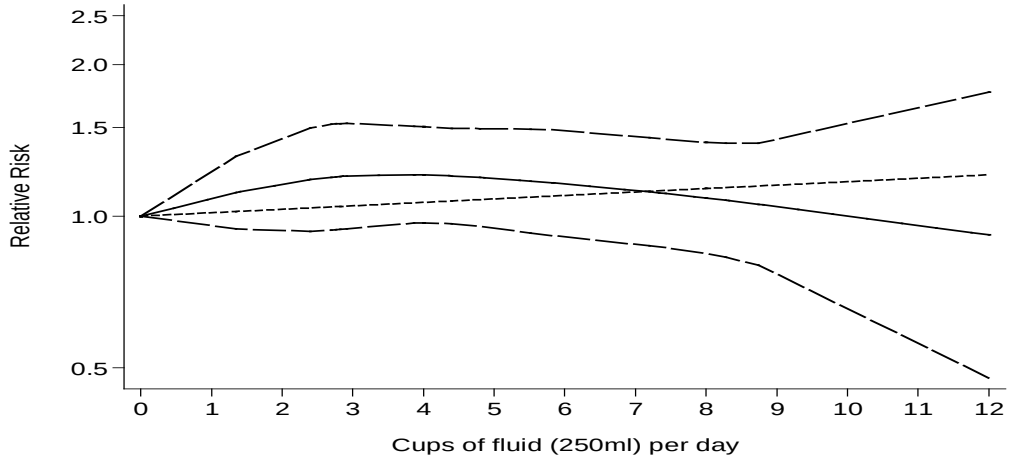
In meta-regression analysis, the association between total fluid intake and bladder cancer risk did not vary significantly when year of publication, method of fluid intake assessment, continent, study design and method of adjustment for smoking status in individual studies (i.e. never smoked/former smoker/current smoker, never smoked/former smoker/current smoker (pack years), never smoked/former smoker/current smoker (smoking duration and smoking frequency) and pack years) were explored by fitting these factors into a meta-regression model as effect modifiers (I^2=88.28%) (See Appendix 3.2).

3.5.5 Non-linear relationship between total fluid intake and bladder cancer risk

When investigating potential non-linearity in the dose-response relationship between total fluid intake and risk of developing bladder cancer, we observed a J-shaped association between total fluid intake and bladder cancer risk in men (Figure 3.5). The P-value for the non-linear dose-response model was significant for men (P<0.001). The cubic spline model suggested that for very low fluid intake (<five cups a day) the RR was slightly increased compared to six cups of fluid intake per day, and that men who consumed eight or more cups of total fluid intake per day, had a higher risk of developing bladder cancer compared to six cups a day. Compared to six cups per day, the estimated RRs from the cubic spline model were: 1.06 (95%CI: 1.03-1.09) for eight cups/day, 1.14 (95%CI: 1.08-1.21) for nine cups/day, 1.76 (95%CI: 1.37-2.26) for 12 cups/day, and 3.36 (95%CI: 1.90-5.26) for 16 cups/day. The non-linear dose-response relationship was not significant in women ($P_{value=}$0.260) (Figure 3.5). We did not examine the non-linear relationship in all subjects combined because seven studies did

not provide sufficient data such as the number of cases in each category of fluid intake, for case-control studies the number of control subjects, and for cohort studies the person-time.

A)



B)

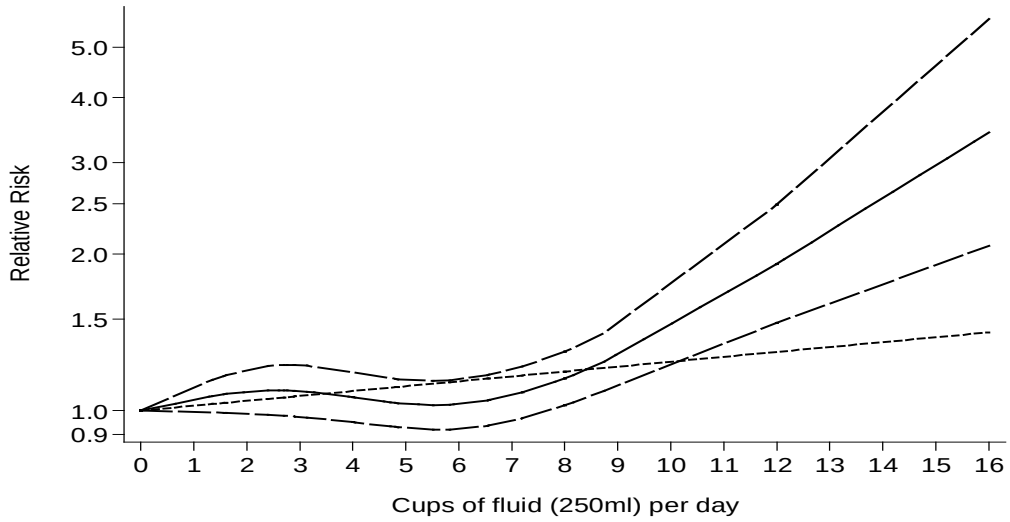


Figure 3.5 A) Dose-response modelled relationship between total fluid intake and risk of developing bladder cancer risk in women. B) Dose-response modelled relationship between total fluid intake and risk of developing bladder cancer risk in men. Total fluid intake was coded using restricted cubic spline with knots located at 5th, 35th, 65th and 95th percentiles of the distribution of total fluid intake. The solid line represents the RR estimate of the association between total fluid intake and risk of developing bladder cancer; long dashed line represents 95% CI; Short dashed line represents best fitting cubic spline. We used 6 cups (250ml) of fluid intake per day as the reference category. The P_{value} for non-linear dose-response model for women was 0.260. The P_{value} for non-linear dose-response model for men was 0.005.

3.5.6 Publication bias

There was no strong evidence of publication bias; P_{values} of Egger's regression asymmetry test were 0.614 for men and women combined, 0.988 for men and 0.380 for women.

3.6 Discussion

In this dose-response meta-analysis we investigated the association between total fluid intake and risk of developing bladder cancer based on 10,678 bladder cancer cases. Our result suggests a non-linear relationship between total fluid intake and bladder cancer risk in men. The lowest risk appears to be in those who consume about six cups (of 250 ml each) per day and the risk increases when fluid intake exceeds eight cups per day.

3.6.1 Summary of results of included studies

Several studies have suggested that total fluid intake is associated with increased risk of developing bladder cancer in men.[14, 20, 25, 26, 47, 51] The result from the EPIC study reported a slightly increased risk for each increase of 100 ml/day of total fluid intake per day which was slightly stronger in men than in women (HR=1.01, 95%CI: 1.00–1.02) , although the results were not statistically significant.[39] A previous pooled analysis of six case-control studies suggested that total fluid intake was associated with an elevated bladder cancer risk in men; the adjusted OR for one litre/day increase of intake was 1.08 (1.03-1.14).[19] In 2008, the WHO consultancy report concluded that there may be an association between total fluid intake and bladder cancer risk, but it was unclear on the direction of the association and for which gender.[23] All of the above mentioned previous studies are in agreement with the result of our meta-analysis although our meta-analysis is more up-to-date and no previous study explored potential non-linearity of the association.

To our knowledge, this study is the first meta-analysis that examined the non-linear relationship between total fluid intake and bladder cancer risk in men. We found a significant non-linear relationship between total fluid intake and bladder cancer risk in men. We also noted that in most studies included in this analysis, men consumed more

fluid than women. The recommendation for daily total fluid intake varies across continents and countries. The European Food Safety Authority proposed that women should consume 1.6 litres (about six cups) of fluid per day and men should consume 2.0 litres (eight cups) of fluid per day.[65] The Food Standards Agency (FSA) recommended that, in terms of climate, people who live in countries such as the United Kingdom and other countries with similar climate should consume six to eight glasses of fluid every day.[52] Whilst our work does not offer sufficient robust results to challenge these recommendations, it does suggest that further research is required before accepting that increasing fluid intake is part of healthy lifestyle advice.

3.6.2 Biological mechanisms

Our results should be interpreted cautiously; total fluid intake includes different fluid items such as water, alcohol, coffee, tea, soft drinks etc. Depending on what is contained in the fluid, it is difficult to pinpoint the carcinogenic role of total fluid intake on the risk of developing bladder cancer. Specific fluid items may contain different carcinogens and have different biological mechanisms that may play a role in the development of bladder cancer. Since the majority of carcinogens bind to DNA,[66] it is possible that exposure of the bladder wall to carcinogens lead to binding with epithelial DNA which forms DNA adducts that initiate carcinogenesis.

High intake of fluid has been hypothesised to increase the risk of bladder cancer by exposing the bladder to fluid items that have carcinogenic effects.[13, 27] For example, depending on the source of water, tap water contains chemical pollutants such as trihalomethanes. It was found in a prior study that tap water may contain carcinogens such as disinfection by-products and arsenic in drinking water.[20, 21, 27] High alcohol consumption might increase the risk of developing bladder cancer. Earlier studies

included in this meta-analysis have reported that high consumption of beer and coffee was associated with elevated bladder cancer risk.[26, 51] Alcoholic drinks contain compounds such as acetaldehyde that has been classified as a carcinogen as it has been shown to cause damage to DNA.[21, 67] Coffee contains compounds such as caffeine and it has been reported in animal studies that caffeine can stimulate or suppress tumours depending on the species and stages of administration.[68]

There are numerous plausible reasons for the stronger association between fluid intake and bladder cancer risk observed in men. Women are more likely to consume less fluid than men. The possible explanation for the observed J-shaped association between total fluid intake and bladder cancer in men may be due to the difference in the levels of drinking; men are more likely to drink more alcoholic drinks as compared to women.[69] The difference in gender may also be due to a lack of adequate data on total fluid intake and bladder cancer risk in women to establish an association.

3.6.3 Strengths and limitations

To conduct this dose-response meta-analysis, midpoints were assigned for each category of fluid intake within each study. It has been recommended by researchers that midpoints are the appropriate technique available for assigning exposure levels.[70] It has however been proposed by Shi and Copas (2004), that a dose value based on dose distribution (normal) should be assigned rather than the midpoints.[71] However, whilst potentially promising these methods are not without their drawbacks, primarily the assumption of normal distribution of the dose is untestifiable. These methods have not been adopted widely in applied applications (in part because they are not readily implementable in standard statistical packages).

The results between studies included in this dose-response analysis were heterogeneous and might not have been appropriate to pool in the overall analysis (even when using random effects analysis). The heterogeneity observed may be due to differences in population, geographical locations (USA, Europe and Asia), study designs, assessment method for smoking status and methods of fluid intake assessment. The different methods of fluid intake assessment used in most of the included studies were: food frequency questionnaire, standard questionnaire, semi-quantitative questionnaire, interviews and in-person interviews. Different measurement units were also used to report total fluid intake in various studies. For all studies, total fluid intake was converted into ml/day as the standard measurement to facilitate comparison between studies. A meta-regression was conducted to explore the effect of study design, method of adjustment of smoking status in primary studies, year of publication, geographical location and various methods of total fluid assessment on heterogeneity. However, none of these potential confounding factors could explain the variation observed. The presence of heterogeneity might be due to unknown confounders that were not adjusted for in the individual studies; for example, genetic susceptibility, energy intake, measurement error, and cultural and lifestyle differences in different populations. On the positive side, we found that the I^2 decreased in the subgroup analyses for women only, population case-control study only, cohort study only and studies conducted in North America only. It is possible that publication bias may have occurred however the results from Egger's test showed no strong evidence of publication bias.

The observed association between total fluid intake and bladder cancer risk may be affected by methodological biases. Such biases may also account for the inconsistencies observed between the hospital-based and population-based case-control studies, and

case-control studies and cohort studies. Recall bias may be a potential drawback in case-control studies; cases might tend to recall their fluid consumption differently compared to controls that are disease free and this may potentially bias the results of this study. However, it is unlikely that cases were aware or had knowledge about the hypothesis on the relationship between fluid intake and bladder cancer risk, hence any recall bias should have been minimal. Sensitivity analyses were also conducted; the use of hospital controls did not make any considerable variation on the odds ratios observed.

In general, more studies have reported that fluid intake was associated with an elevated bladder cancer risk in men and not in women. However, one study that was conducted in China reported a decreased bladder cancer risk in men and not in women. This may reflect a true inversion of the association, or it may be due to some sort of bias.[71] The quality of epidemiological studies has changed over time; therefore, it is possible that earlier studies might have poorer quality compared to recent studies. Also, the non-linear relationship observed in men might be due to other residual factors or other risk factors that were not adjusted for in individual studies. On the other hand, we found that the I^2 value decreased when the analysis included women only, population based case-control studies only, cohort studies only and North American studies only.

3.6.4 Conclusion

In conclusion, we found a positive association between total fluid intake and risk of bladder cancer in men. In men, whilst low to moderate fluid intake was not associated with an increased risk, fluid intake exceeding eight cups per day increases the risk substantially. To our knowledge our study is the first study to observe the non-linear relationship between total fluid intake and bladder cancer risk in men.

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4.0 CHAPTER FOUR

The methodology of the BLadder cancer Epidemiology and Nutritional Determinant (BLEND) Study

4.1 BLadder cancer Epidemiology and Nutritional Determinant (BLEND) Consortium

The BLadder cancer Epidemiology and Nutritional Determinant (BLEND) study is the world's largest consortium on dietary factors and risk of developing bladder cancer. This consortium promotes collaborative research by bringing together researchers with a background in bladder cancer and epidemiology from different parts of the world. The purpose of the consortium was to investigate comprehensively, the relationship between dietary factors and the risk of developing bladder cancer.

The main objectives of the BLEND consortium were to:

- pool individual patient data from previous observational studies on dietary nutritional factors and the risk of developing bladder cancer
- create a database on dietary, nutritional factors and the risk of developing bladder cancer that will act as a resource for potential future studies
- conduct comprehensive investigations into associations between dietary and nutritional factors and the risk of developing bladder cancer with the maximum amount of statistical power as is practically feasible

This chapter describes the steps undertaken to set up the BLEND consortium. The steps were:

- identifying available studies on dietary factors and bladder cancer
- contacting other international consortia
- define eligibility criteria for consortium participation
- identify potentially relevant studies and contact principal investigators

- organise transfer of data
- create a code book
- harmonisation of data
- combining data sets to form a single master data set

4.2 Identifying available studies on dietary factors and bladder cancer risk

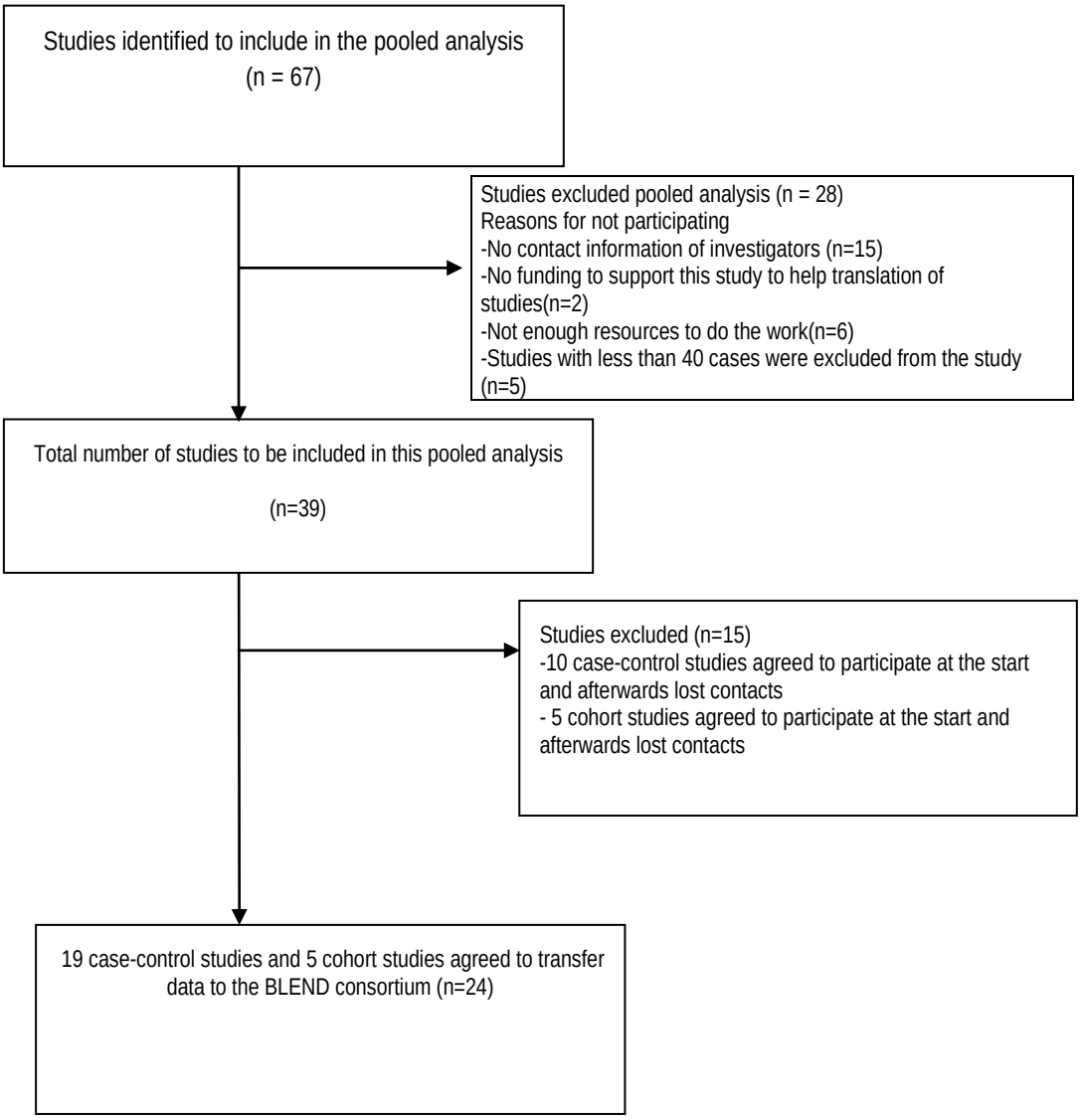
A computerised search through Pubmed (National Library of Medicine, Bethesda, Maryland) (1966–Sept 2009), and Embase (Elsevier B. V., Amderstam, the Netherlands (1974–Sept 2009), was conducted to identify published epidemiologic studies related to diet and bladder cancer. The search terms used to identify relevant articles were: (Bladder cancer **OR** Bladder carcinoma **OR** Transitional cell carcinoma **OR** Urinary bladder neoplasm **OR** Urologic Neoplasm **OR** Urologic diseases **OR** Urologic Cancer **OR** Carcinoma **OR** Cancer **OR** Tumour) **AND** (Dietary/diet consumption **OR** Total fluid consumption **OR** Fluid consumption **OR** Fruit consumption **OR** Vegetable consumption **OR** Fish consumption **OR** Fat or oil consumption **OR** Drinking behaviour **OR** Milk consumption OR Risk factors).

Researchers were contacted in networks such as the International Bladder Cancer Network (IBCN) and the US National Cancer Institute initiated International consortium on bladder cancer (ICBC) to help identify additional studies conducted on diet and bladder cancer.

4.3 Eligibility criteria for selection of studies

To be included in the BLEND consortium, studies had to meet the following criteria: a) the study design had to be case-control or cohort study; b) cases had to be bladder cancer patients; c) the source from which controls were ascertained had to be population-based or hospital-based for case-control studies only; d) hospital controls had to be free from bladder cancer; e) have reported data on dietary consumption; and f) subjects included had to be 18 years or over.

Figure 4.1 Flow diagram for relevant studies for the BLEND consortium



4.4 Study identification and contacting of principal investigators

A total of 67 studies were identified that examined the association between dietary factors and the risk of developing bladder cancer. The Principal Investigator of each potentially eligible study was invited to participate in the BLEND consortium and was asked to provide relevant data, study questionnaires and codebooks. Investigators of 39 studies agreed to participate, of which investigators of 24 studies provided complete data. Reasons why some investigators did not participate were: some investigators mentioned that their workload was already too high and with other investigators after the initial contact the communication was lost. (See appendix 4.1 for the list of studies not included in the BLEND consortium)

4.4.1 Participating studies

In total, investigators of 24 studies agreed to participate in the BLEND consortium, 12 studies[1-12] were from Europe, eight[10,13-19] from the USA and Canada, and four [20-22] from Asia. Six studies[2,5,8,13,16,17] have a population-based case-control design, 12 studies [14,4,6,9-11,15,18,20-23] have a hospital-based case-control design, and six [1,3,11,12,19,24] a population-based cohort design. The list of participating studies, location of studies, period of recruitment, study design, number of cases and control (for case-control studies) are presented in table 4.1. Also a full description of each study is reported below.

TABLE 4.1: Summary of participating studies in BLEND consortium

Participating Study	Country	Recruitment Period	Study Design	Cases n (%)	Controls n (%)	Food items assessed (n)
				In data each data set		
1.Swedish Mammography Cohort (SMC) & the Cohort of Swedish Men [1]	Sweden	1997-2008	Population based cohort	688	Non cases	96
2.Los-Angeles bladder cancer Case-control study [13]	USA	1987-1999	Population based case-control	1660 (51)	1586 (49)	49
3.Roswell Park Cancer Institute [14]	USA	1982-1998	Hospital-based case-control	275 (25)	825(75)	44
4.Belgian Case-control study on bladder cancer [2]	Belgium	1999-2004	Population based case-control	200 (34)	384 (66)	788
5.Netherlands Cohort Study on diet and cancer [3]	The Netherlands	1986-2003	Population based cohort	941	Non cases	150
6.Aichi Prefecture Case-control study [20]	Japan	1996-1999	Hospital-based case-control	40 (7)	568 (93)	107
7.Kaohsiung Study [21]	Taiwan	1996-1997	Hospital-based case-control	40 (20)	160 (80)	41
8.Hessen Case-control study on bladder cancer [4]	Germany	1989-1992	Hospital-based case-control	300 (50)	300 (50)	26
9.Stockholm Case-control study [5]	Sweden	1985-1987	Population based case-control	273 (33)	553 (67)	188
10.Roswell Park Memorial Institute Case-control study on bladder cancer [15]	USA	1957-1965	Hospital-based case-control	585 (6)	8460 (94)	64
11.Reina Sofia University [23]	Spain	1997	Hospital-based case-control	85 (40)	130 (60)	17
12.New England bladder cancer study [16]	USA	1994-2001	Population based case-control	398 (55)	326 (45)	121
13.Italian Case-control study on bladder cancer [6]	Italy	1985-1992	Hospital-based case-control	727 (41)	1067 (59)	21
14.Brescia bladder cancer study [7]	Italy	1992-1993	Hospital-based case-control	200 (48)	214 (52)	40
15.North Rhine Westphalia study [8]	Germany	1992-1995	Population based case-control	194 (45)	238 (55)	3
16.National Enhanced Cancer Surveillance System (NESCC) [17]	Canada	1994-1997	Population based case-control	1028 (17)	5030 (83)	69
17. Multicentre French case-control study	France	1984-1987	Hospital-based case-control	201	326	2

[9]				(38)	(62)	
18.South and East China Case-control study on bladder and prostate cancer [22]	China	2005-2008	Hospital-based case-control	483 (51)	464 (49)	52
19.Molecular Epidemiology of Bladder Cancer and Prostate Cancer [18]	USA	1993-1997	Hospital-based case-control	197 (39)	314 (61)	90
20.North Carolina case control study [10]	USA	1987-1991	Hospital-based case-control	245 (53)	215 (47)	9
21.Women's Lifestyle and Health Study [11]	Norway, Sweden	1991-2006	Population based cohort	49	Non cases	98
22.RERF atomic bomb survivors [24]	Japan	1950-2000	Population based cohort	311	Non cases	102
23.Vital study [19]	USA	2000-2008	Population based cohort	330	Non cases	126
24.European Prospective Investigation into Cancer and Nutrition (EPIC) [12]	Multiple centres in Europe	1993-2006	Population based cohort	513	Non cases	260

4.5 Brief description of each participating study

This section gives a brief description of the 24 participating studies.

Swedish Mammography Cohort (SMC) & the Cohort of Swedish Men (COSM) (Swedish study)

Subjects were recruited from the Swedish Mammography Cohort and Cohort of Swedish Men. In 1997, men and women between the ages of 45-85 years residing in central Sweden were asked to fill in a 96-item food frequency questionnaire. A total of 82,002 Swedish men and women who were cancer disease free were followed up for an average of 9.4 years and 485 incident bladder cancer cases were identified form the Swedish Cancer Registries. The Regional Ethics Committee of Karolinska Institute gave ethical approval to conduct the Swedish study.[1]

Los-Angeles bladder cancer case-control study

The Los-Angeles bladder cancer study was a population-based case-control study conducted from 1987 to 1999. The study involved a total of 1,660 cases and 1,586 controls The cases were newly histologically confirmed bladder cancer patients amongst non-Asians that were diagnosed between 1987 and 1999. The cases were selected from the Los Angeles County Cancer Surveillance Epidemiology and End Results Program (SEER registry). Controls were recruited from the same area of residence as the cases at the point in time when the cases were diagnosed with bladder cancer. Controls were frequency matched with cases based on gender, age (five year bands) and ethnicity (non-Hispanic white, Hispanic white or African American/others).[13]

Roswell Park Cancer Institute bladder cancer study

The Roswell Park Cancer Institute study was a hospital-based case-control study involving 275 incident bladder cancer cases and 825 controls. The cases were selected through the Roswell Park Center Institute Tumour Registry and 95% were transitional cell carcinoma and the remaining 5% were squamous cell carcinoma or adenocarcinoma. Controls subjects who were free from neoplastic conditions and treated for other diseases such as diseases of the circulatory system (12%), infectious and parasitic diseases (20%), disease of the genitourinary system (13%), ill-defined signs and symptoms (17%), benign neoplasms (8%), and other various conditions (28%), were recruited from the Roswell Park Cancer Institute. The participants were aged between 25-86 years and mostly Caucasians. To assess information about dietary intake, a 44-food frequency questionnaire was used.[14]

Belgian case-control study

The Belgian case-control study on bladder cancer was a population based unmatched case-control study carried out in the Belgian Province of Limburg and included 200 cases and 385 controls. Eligible cases were histologically confirmed with transitional cell carcinoma of the bladder between 1999 and 2004. The cases were identified from the Limburg Cancer Registry (LIKAR) and were contacted through general practitioners and urologists. To assess dietary consumption, a standard 788-item food frequency questionnaire was used.[2]

Netherlands cohort Study

The Netherlands cohort study was established in 1986 and included 120,852 men and women between the ages of 55-69 years who were followed up for 9.3 years (follow-up completeness was more than 95%). A total of 995 incident bladder cancer cases were identified through the cancer registries and the Dutch national database of pathology

reports (PALGA). Study participants were asked about their dietary consumption using a validated 150-item food frequency questionnaire.[3]

Aichi Cancer Centre Japan Case-control study

The Aichi cancer centre hospital case-control study was conducted in Japan between 1994 and 2000. The study included 124 histologically confirmed urinary tract cancers, of which 113 had cancer of the bladder, five renal pelvic cancer and six ureter cancer. A total of 620 controls that were cancer free were frequency matched to cases on age (five year bands) and sex. A food frequency questionnaire was used to obtain information about participant food consumption.[20]

Kaohsiung Taiwan study

The Kaohsiung study in Taiwan was a hospital-based case-control study conducted between 1997 and 1998. This study involved 103 eligible patients with histologically confirmed bladder cancer. One hundred and three ophthalmic patients free from non-neoplastic, non-urological renal and liver function diseases were recruited as controls. A structured questionnaire was used by trained interviewers to obtain information about dietary consumption.[21]

Hessen case-control study

The Hessen case-control study was a hospital-based case-control study carried out in Hessen, Germany, in 1989 to 1992. It involved 300 cases (61 females and 239 males) with histologically confirmed cancer of the lower urinary tract. The study included 300 controls that were matched with the cases based on sex, age and area of residence. Dietary consumption was measured using a food frequency questionnaire.[4]

Stockholm case-control study

The Stockholm case-control study was a population-based case-control study conducted in Stockholm, Sweden between 1985 and 1987. Eligible subjects were individuals with no history of neoplastic disease of the urothelium before the study was initiated. Four hundred and eighteen cases were histologically confirmed with the lower urinary tract cancer (bladder, renal pelvis, ureter and urethra) at the beginning of the study. Cases were ascertained from the regional cancer registry and urologic departments in the county of Stockholm. Controls were selected from a computerised registry in the same population using random sampling. A 56-item food frequency questionnaire was used to assess dietary consumption in this study.[5]

Roswell Park Memorial Institute bladder case-control study

The Roswell park memorial institute study was a hospital-based case-control study conducted in New York, USA between 1982 and 1998. Four hundred and ninety-nine patients with histologically confirmed bladder cancer and 1,922 control subjects matched for age were included. The controls were admitted for non-cancerous diseases of the digestive system, genitourinary system, respiratory system and circulatory system. The subjects were mainly Caucasians and aged between 19-94 years. A 29-item food frequency questionnaire was used to assess dietary consumption of the subjects a year before diagnoses.[15]

Reina Sofia University study

Reina Sofia University study was a hospital-based case-control study among men conducted in Corboda, Spain. It involved 74 bladder cancer patients and 89 controls subjects admitted for non-urological diseases. An administered interview questionnaire

was used to assess dietary consumption.[23]

New England bladder cancer study

This study was a population-based case-control study conducted in New Hampshire, USA between 1994 and 2004. A total of 857 newly diagnosed bladder cancer patients, aged 25 to 70 years were selected from the New Hampshire State Cancer Registry. Controls were matched with the cases based on sex and age. The controls were recruited from centres for medical services and the department of transport in New Hampshire.[16]

Milan and Pordenone case-control study

The Milan and Pordenone case-control study was a hospital-based case-control study conducted in Italy between 1985 and 1992. Cases were recruited from two areas in Italy: greater Milan and province of Pordenone. It involved 727 histologically confirmed bladder cancer patients and 1,067 controls treated for non-neoplastic conditions or urological diseases, aged between 25-79 years. A structured questionnaire was used by trained interviewers to assess the information on dietary consumption.[6]

Brescia bladder cancer study

The Brescia bladder cancer study was conducted in Italy between 1992 and 1993. A total of 934 subjects were recruited from the same hospital: 355 were histologically confirmed bladder cancer patients and 599 control subjects were admitted for non-neoplastic diseases. Dietary consumption of participants was assessed using a structured questionnaire.[7]

North Rhine Westphalia study

This was a case-control study carried out in North Rhine Westphalia, Germany between 1992 and 1995. Eligible participants were residents of North Rhine Westphalia, patients diagnosed with bladder cancer or prostate cancer, patients diagnosed before 1988 and with a specified year of first diagnosis. The cases were histologically confirmed bladder cancer patients (n=156) and the controls were prostate cancer patients who asked for after-care treatment (n=336).[8]

National Enhanced Cancer Surveillance System (NESCC) Study

The National Enhanced Cancer Surveillance System (NESCC) study was a population-based case-control study conducted in Canada between 1994 and 1997. The participants were recruited from seven provinces: Newfoundland, Manitoba, Alberta, Nova Scotia, Saskatchewan, Prince Edward Island, and British Columbia. A total of 887 incident cases histologically confirmed with bladder cancer aged between 20-74 years were included in this study. From the same provinces random sampling was used to select controls and frequency matched cases based on age and gender (n=2,897). Physician consent was obtained before contacting patients.[17]

Multicentre French case-control study

The Multicentre French study was a hospital case-control study conducted in France between 1984 and 1987. This study involved 690 incident histologically confirmed bladder cancer patients with 690 controls matched with cases by sex and age from the same hospital.[9]

South and East China Case-control study on bladder and prostate cancer

This South and East China case-control study was between 2005 and 2008. Participants were recruited in four hospitals: the first affiliated hospital in Hangzhou, Second Xiangya hospital in Changsha, the first municipal hospital Guangzhou and the Tongji hospital in Wuhan. This study recruited 432 cases histologically confirmed with bladder cancer aged 40 years and over. Three hundred and ninety-two controls were recruited and frequency matched to cases by age and sex. Information on dietary consumption was ascertained by trained interviewers using a computerised questionnaire.[25]

Molecular Epidemiology of Bladder Cancer and Prostate Cancer study

The Molecular Epidemiology of Bladder Cancer and Prostate Cancer was conducted in Memorial Sloan-Kettering Cancer Center (MSKCC) between 1994 and 1997 and was a hospital case-control study of 145 cases diagnosed with bladder cancer and 170 controls that were cancer free. A standardised questionnaire was used to measure food consumption.[18]

Duke University Medical Centre and University of North Carolina case-control study

The Duke University Medical Centre and University of North Carolina case-control study was conducted between 1987 and 1991. Two hundred thirty cases and 203 frequency matched controls based on sex and age were enrolled in this study. The controls had no history of cancer except for non-melanoma skin cancer.[10]

Women's Lifestyle and Health Study

The women's Lifestyle and Health Study was conducted in Sweden between 1991 and 2006. This study included 47,921 women between the ages of 30-49 years. The cohort members were followed up for 16 years.[11]

Atomic bomb survivors' cancer study

This was a cohort study of 120,321 participants that has been initiated since 1950 in Japan to examine the effect of atomic bomb radiation amongst survivors of atomic bombings. The participants were followed up and a total of 311 incident cases were identified.[24]

Vital cohort study

The Vital cohort study was conducted in Washington between 2000 and 2002. It involved 77,719 participants between the ages of 50-76 years recruited from 13 counties. A total 330 incident urothelial carcinoma cases were selected by SEER registry. A self-administered questionnaire was used to measure dietary consumption. The study was approved by the institutional review board of the Fred Hutchinson Cancer Research Center.[26]

European Prospective Investigation into Cancer and Nutrition (EPIC)

The European Prospective Investigation into Cancer and Nutrition study was a cohort study conducted in 23 centres in Europe. The centres were in 10 European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom. A total of 521,448 participants aged between 25-70 years were recruited in the study. The participants were followed for 9.3 years and 513 cases were

newly diagnosed with urothelial cell carcinoma. A 24 hour diet recall questionnaire was used to measure dietary consumption.[27]

4.6 Data transfer

The process of contacting principal investigators to obtain individual patient data from participating studies commenced in March 2009 (to date).

The Principal Investigator (PI) of each potentially eligible study was invited to participate in the BLEND consortium and asked to provide relevant individual patient data, study questionnaires and codebooks for their study. To ensure secure data transfer and compliance with data protection, principal investigators were asked to sign a data release agreement form. After signing of the agreement form by the principal investigator of each study, the electronic data files including data sets, codebooks, data dictionaries and questionnaires were received by the BLEND team. A database was then set up to collate all data sets received from principal investigators. Each data set included anonymous information on bladder cancer patients (case-control status for case-control study), age of participants, demographics (such as age, sex, ethnicity, smoking history of subjects), family history of bladder cancer patients and dietary consumption.

4.7 Number of cases and controls

For several studies, the numbers of cases and controls did not completely match those reported in the associated publications. In two studies[18,20] fewer cases were received, respectively 40 and 197 instead of 297 and 229. Four studies[10,15,17,23] had more cases (respectively 585, 85, 1028 and 245 instead of 569, 74, 887 and 228). Another four studies[15,17,18,20] received more controls (respectively 568, 8,460, 5,030 and 314 versus 295, 1,025, 2,847 and 204). One study[10] provided fewer controls (215 instead of 232). In total

we have 104 fewer cases less and 10,001 controls more compared to the numbers mentioned in the articles (Table 4.1).

4.8 Assessment of dietary/nutritional consumption

The food items assessed with the food frequency questionnaires (FFQs) varied widely. Whereas two studies[8,9] only asked respectively about three and two specific food items, others assessed a full dietary assessment of 788 food items. The use of a validated FFQ questionnaire was reported in seven studies.[1-3,11,12,16,19] Three studies[1-3] reported food items in a quantitative manner. The EPIC study[28] used a 24 hour recall questionnaire. After setting up a database, a codebook was developed which was used to help facilitate the management of the data sets (Figure 4.1).

4.9 Codebook

The codebook contained a list of variables such as study identification number, study design (cohort/case-control), bladder cancer cases-control status (for case-control studies), TNM classification of malignant tumour, gender, age at diagnosis of the participants, ethnicity, smoking status, smoking frequency and smoking duration, family history of bladder cancer patients and dietary consumption. All specific food (e.g. milk, egg, meat, fish, grains) and fluid (e.g. water, alcohol) items were categorised and coded based on the hierarchical Eurocode 2 Food Coding System which was developed by the project of Eurofoods Enfant. The Eurocode 2 Food Coding System was developed to serve as a standard instrument for nutritional surveys which improves comparability and quality in dietary consumption in Europe and studies on diet.

The codebook gives the description of what information is contained in the data sets. To combine and make the data sets in the database comparable, the codebook contained unique codes, and all data sets were re-coded based on the unique codes of the codebook. The codebook was created in an excel spread sheet and consisted of columns containing: a variable name, variable code, variable label and value label. A variable name was assigned to each variable with a variable label which shows the description of the variable and the content of each variable. For example, table 4.2 below shows the variable name was smoking with a unique variable code D01. The value label for D01 was tobacco smoking status, which was a categorical variable. Tobacco smoking had three value labels, 1=current tobacco smoker, 2=former smoker and 3=never smoked. For more clarity and completeness of the codebook, missing and unknown data were assigned a value label, e.g. for missing and unknown data on tobacco smoking ".a" and ".b" was assigned, respectively.

TABLE 4.2: Example of the codebook

VARIABLE NAME	VARIABLE CODE	VARIABLE LABEL	CODE	VALUE LABEL
SMOKING	D01	Tobacco smoking status	1	Current tobacco smoker
			2	Former tobacco smoker
			3	Never tobacco smoker
			.b	Not known - data not asked
-			.a	Missing data
	D02	Cigarette smoking status	1	Current cigarette smoker
			2	Former cigarette smoker
			3	Never cigarette smoker
			.b	Not known - data not asked
			.a	Missing data

The food items were grouped into 12 food categories in the Eurocode 2 food classification system:

- Milk and milk products
- Egg and egg products
- Meat and meat products
- Fish and fish products
- Fats and oils
- Grain and grain products
- Pulses, seeds, kernels and nuts products
- Vegetables
- Fruit and fruit products
- Sugar and sugar products
- Beverages (except milk)
- Miscellaneous (includes soups and sauces)

In the food classification system, each food group was further divided into subgroups and the subgroups into specific food items.

In the codebook food items, food subgroup and food group were recorded in a similar manner as in the Eurocode codebook, for example, milk products:

The food group was – milk and milk products

Subgroup – liquid milk

Food item – milk > 4% fat (whole milk)

For example, in table 4.3 below, the food group is milk and milk products and subgroup is liquid milk and food item whole milk has a unique variable code, variable label and value label in portions, grammes, millilitres per week. Then, for each food group, subgroup and

food item, the unique variable code was assigned which starts with two letters “EC (Eurocode)” and six numeric values and ended with a “P (portion)” or (grammes) or ML (millilitres). For example, the unique variable code for the food group milk and milk products was EC010000P (Milk and milk products in portions), EC010000G (Milk and milk products in grammes), EC010000P (Milk and milk products in millilitres).

Food items that were not in the codebook were indicated as a miscellaneous food item and were coded slightly differently with an extra letter “X (miscellaneous)” before the letter “P” or “G” or “ML”. For example, miscellaneous milk items were coded as EC010100XP. The codebook is documented in appendix 2.

TABLE 4.3: Example of milk and milk products coding in the codebook

VARIABLE NAME	VARIABLE CODE	VARIABLE LABEL		VALUE LABEL
Milk and milk products	EC010000P	Milk and milk products in portions		Portions per week
	EC010000G	Milk and milk products in grammes		Grammes per week
	EC010000ML	Milk and milk products in millilitres		Millilitres per week
	EC010100P	Liquid milks in portions		Portions per week
	EC010100ML	Liquid milks in millilitres		Millilitres per week
	EC010100XP	Liquid milks-MISCELLANEOUS-in portions		Portions per week
	EC010100XML	Liquid milks-MISCELLANEOUS-in millilitres		Millilitres per week
	EC010110P	Milk >4% fat in portions		Portions per week
	EC010110ML	Milk >4% fat in millilitres		Millilitres per week

4.10 Harmonization of data (Quality control and data cleaning)

After creating a codebook, the next step was carrying out harmonisation of data. The purpose of harmonisation of data was to improve comparability of different data collected from different independent sources to enable pooling of data.

The following steps were involved in harmonisation of data: quality control and data cleaning. All data management and cleaning was carried out using Stata software.

4.10.1 Quality control

Quality control is an important part in collaborative research; it is a process were data sets from each study are checked, monitored and maintained before the data sets are merged together into a single data set. Each data set was checked carefully and underwent extensive quality control to ensure that the data recorded are meaningful and reflect the actual details. The steps involved in quality control were: translations of data sets into English, decisions on missing or unknown values and data checking for errors.

4.10.1.1 Translations data questionnaire into English

A few data sets or questionnaire were not in English. The Reina Sofia University study reported the data set in Spanish; the principal investigator was contacted to help translate the data. The questionnaire of the Kaohsiung study in Taiwan was reported in Chinese; a native Chinese speaker was asked to translate the questionnaire to enable better understanding of the data.

4.10.1.2 Decisions on missing and unknown values

The data sets were checked to ensure completeness of values recorded. Missing and unknown data were occasionally missing in some data sets discussed with the BLEND team and principal investigators, and the data was updated accordingly for example in the Los Angeles Bladder Cancer Case-control Study the number "8" was coded as unknown and number "99" was coded as missing . Missing values were agreed by the BLEND team to be coded as ".a", unknown values ".b" and not applicable ".c" in all data sets. All these are Stata missing values in Stata.

4.10.1.3 Data checking

All data sets were double checked for possible coding errors. In two data sets, North Rhine Westphalia study and South and East China Case-control study two control subjects had data on bladder cancer staging, so it might have been actual bladder cancer cases. It was decided by the BLEND team to drop these controls from the data sets. Each data set and questionnaire was examined for inconsistencies, for example, the Multicentre French Case-control study coding was not consistent with the data dictionary.

4.10.2 Data cleaning

Data cleaning was carried out after each data set had undergone extensive quality control. The do file is a Stata program which contains syntax code. First, do files for each study were created and ensured that all variables were re-coded based on the codes in the BLEND codebook. Within each do file all the variables were re-coded, labelled and the food items were converted into portions per week, if necessary. Then, checks were conducted using specific Stata commands such as "assert" to verify the codes and true values of each variable (See full details of all do files in appendix 4.2).

4.11 Combining / appending data sets

Finally, all data sets that underwent extensive data cleaning and logical checks were merged into a single data set. The data set included data on 28,396 subjects where of which 7,514 were cases and 28,396 were non-cases.

4.12 BLEND team

Three reseachers were working on the BLEND study: Mieke Goossens, Fatima Isa and Anke Wesselius.

Mieke Goossens role was contacting the primary investigators for the transfer of individual patient data. My role (Fatima Isa) in the BLEND team was to help in creating the codebook and carrying out harmonisation of data for 19 case-control studies. I was involved in the day to day management of the data sets of the BLEND study. I made sure all 19 case-control studies underwent thorough quality control, data cleaning and combined data sets into a single data set. For quality control, I checked all data sets and questionniares for inconsistencies to ensure that the data set transferred to the BLEND study was accurate. I contacted native speakers to translate the questionnaires written in other languages to English. Finally, I combined the re-coded data sets into a single data set. Anke Wesselius is involved in data cleaning for the five cohort studies in the BLEND study.

4.13 Part of my PhD Project work on BLEND study

For the purpose of this PhD I focused on conducting a pooled analysis of 19 case-control studies. Therefore, the next chapter will focus on the investigation on the association between fluid consumption and risk of developing bladder cancer using data from the BLEND consortium. Also, only case-control studies have been included in this pooled analysis because individual patient data from cohort studies are still yet to be transferred completely to the BLEND study from principal investigators.

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5.0 CHAPTER FIVE

Fluid consumption and risk of developing bladder cancer: an international pooled analysis of case-control studies

The Bladder Cancer Epidemiology and Nutritional Determinant (BLEND) Study

5.1 Introduction

In terms of cancer incidence, bladder cancer is the ninth most frequently diagnosed cancer worldwide.[1] The main established risk factors for bladder cancer include smoking, specific occupational exposures (e.g. aromatic amines) and *Schistosoma haematobium*,[2] although it has been postulated that fluid consumption may also be a possible risk factor implicated in the development of bladder cancer.[3] Beverages such as alcohol, coffee and hot mate tea have been classified as potential carcinogenic agents (group1, group 2A and group 2B).[4]

Findings from previous epidemiological studies that investigated the relationship between specific fluids or total fluid intake and the risk of bladder cancer have largely been inconsistent. In some studies, fluid consumption was associated with an elevated risk of bladder cancer;[5-19] despite the overall elevated risk, not all previous studies showed a clear dose-response relationship, and the risk in women remains unclear. However, in other studies fluid intake was associated with a decreased risk of bladder cancer[20-30] and some studies showed no significant association.[31-37]

A pooled analysis of six previous case-control studies demonstrated that total fluid intake may be associated with an increased risk of bladder cancer but in men only.[38] Another systematic review could not identify any significant association between total fluid intake and risk of bladder cancer.[39] However, in a recent updated systematic review and dose-response meta-analysis, it was concluded that the risk of bladder cancer is increased in men if total fluid intake exceeds eight cups per day. [40]

In most reviews and pooled analyses conducted to date, specific fluids such as coffee consumption were generally not significantly associated with an increased risk of

bladder cancer, although some studies did find that heavy consumption of coffee (more than five or 10 cups of coffee per day) modestly increased the risk of bladder cancer.[41-43] In another meta-analysis, no significant association between overall alcohol consumption and bladder cancer risk was found, although consumption of wine and beer significantly decreased the risk of bladder cancer.[44]

Some pooled analysis tends to have high statistical power and allows for subgroup analyses to be performed which would otherwise not be possible in individual studies. It also allows investigation of consumption of specific fluid items that cannot be investigated in individual studies.

The Bladder Epidemiology and Nutritional Determinant (BLEND) study was established to comprehensively investigate the association between dietary intake and the risk of developing bladder cancer. The Principal Investigators of 19 individual case-control studies provided individual patient data and one study was excluded from the analysis because there was no data on fluid consumption. Therefore, the principal aim of the current study was to characterise the association between fluid intake and risk of developing bladder cancer by pooling individual patient data on 7,514 bladder cancer patients and 20,882 controls from the BLEND study. The study pooled individual patient data from 18 case-control studies.

5.2 Methods and materials

5.2.1 The Bladder Cancer Epidemiology and Nutritional Determinant (BLEND) Study

A systematic literature search was conducted to identify observational studies on dietary intake and risk of bladder cancer and potential for participation in the BLEND study. The databases Medline (National Library of Medicine, Bethesda, Maryland) (1966–Sept 2009), and Embase (Elsevier B. V., Amderstam, the Netherlands (1974–Sept 2009) were searched. The search terms used to identify relevant articles were:
(Bladder cancer **OR** Bladder carcinoma **OR** Transitional cell carcinoma **OR** Urinary bladder neoplasm **OR** Urologic Neoplasm **OR** Urologic diseases **OR** Urologic Cancer **OR** Carcinoma **OR** Cancer **OR** Tumour) **AND** (Dietary/diet consumption **OR** Total fluid consumption **OR** Fluid consumption **OR** Fruit consumption **OR** Vegetable consumption **OR** Fish consumption **OR** Fat or oil consumption **OR** Drinking behaviour **OR** Milk consumption OR Risk factors).

Additionally, researchers were contacted via the personal contacts in existing bladder cancer consortia such as the *International Bladder Cancer Network* and *US National Cancer Institute* led consortium of molecular case-control studies on bladder cancer.

For inclusion in the BLEND consortium, studies had to meet the following inclusion criteria: a) case-control design, b) cases had to be incident bladder cancer patients, c) the source from which controls were ascertained had to be population-based or hospital-based, d) hospital controls should be free from bladder cancer, e) reported data on dietary intake, and f) the cases and controls should be 18 years or over.

The Principal Investigator (PI) of each potentially eligible study was invited to participate in the BLEND consortium and asked to provide relevant individual patient data, study questionnaires and codebooks for their study. To ensure secure data transfer and compliance with data protection, principal investigators were asked to sign a data release agreement form.

5.2.2 Fluid intake assessment

In all studies, a food frequency questionnaire (FFQ) was used to collect information on fluid intake. The fluid items assessed varied widely across studies. For each study, total fluid intake was calculated as the total sum of all different fluid items assessed. Additional information on socio-demographic variables, such as age, gender, smoking history (smoking status, smoking duration and smoking frequency) was obtained from each study if available. To standardise measures of fluid intake across studies, all fluid items were converted from the portion size used (e.g. cup, pint) in each study to millilitres. A standard cup of a non-alcoholic beverage such as coffee, tea or a glass of soft drink (e.g. cola) was considered to be 250 millilitres. Alcoholic drinks such as a pint of beer was measured as 360 millilitres, a glass of wine as 120 millilitres and a glass of liquor as 45 millilitres. Missing and unknown data were discussed with the BLEND team and principal investigators, and the data were updated accordingly. After satisfactory quality control, data cleaning and checking errors and inconsistencies, the individual study data sets were merged into one overall pooled data set.

5.2.3 Statistical analysis

Fluid intake was originally measured as a continuous variable. It was subsequently transformed into easy interpretable cut-off points. The lowest category was used as the reference group in all analyses. A multilevel mixed-effects logistic regression model was used to calculate odds ratios (OR) and corresponding 95% confidence intervals (CIs) for the association between fluid intake and risk of developing bladder cancer.[45] This model was used because of the hierarchical structure of the pooled data set, therefore both variations between studies and clustering within studies was examined. The data set consists of two clusters: the first hierarchy of clustering is the individual studies included in the pooled data set. The second hierarchy is the centres or hospitals where cases and controls were recruited from within each study. Additionally, an interaction between the clustered variable and exposure variable (fluid consumption) as a random effect (i.e. random slope) was included in the model to allow the potential for variation in ORs between studies. Potential confounders such as smoking status (non-smoker, former smoker and current smoker), age (continuous, in years), and gender were included in the logistic regression model for all analyses unless otherwise specified. To test for linear trend, a Wald-test was used to derive a p-value for trend by including fluid intake as a non-negative consecutive integer variable in each model. Subgroup analyses were conducted stratifying by gender and smoking status of case and control population.

All statistical analyses were conducted using Stata version 13 and a two-sided p-value less than 0.05 was used as statistical significance.

5.3 Results

The Principal Investigators of 19 individual case-control studies agreed to participate, and provided individual patient data. One study was excluded from the analysis because there was no data on fluid consumption.[46] Therefore, individual patient data from 18 case-control studies were included in this analysis.

Of the 18 individual case-control studies in the BLEND study, six studies were population-based and 12 were hospital based. The studies were conducted between the periods of 1957-2008 in twelve different countries: Belgium (1), Canada (1), China (1), France (1), Germany (1), Japan (1), Italy (2), USA (6), Spain (1), Sweden (1) and Taiwan (1). Studies were from three continents: Europe (8), North America (7) and Asia (3) (Table 5.1).

TABLE 5.1: Characteristics of the 18 case-control studies included into the Bladder Cancer Epidemiology and Nutritional Determinant (BLEND) study

First author	Continent	Country	Recruitment Period	Study design	Cases n (%)	Controls n (%)
Jiang[47]	North America	USA	1987-1999	Population-based	1660	1586
Tang[48]	North America	USA	1982-1998	Hospital-based	275	825
Mettlin[49]	North America	USA	1957-1965	Hospital-based	585	8546
Wallace[50]	North America	USA	1994-2001	Population based	398	326
Zhang[51]	North America	USA	1993-1997	Hospital-based	197	314
Taylor[46]	North America	USA	1987-1991	Hospital-based	245	215
Gaertner[52]	North America	Canada	1994-1997	Population-based	1028	5039
Wakai[53]	Asia	Japan	1996-1999	Hospital-based	40	568
Lu[14]	Asia	Taiwan	1996-1997	Hospital-based	40	160
Hemelt[24]	Asia	China	2005-2008	Hospital-based	483	469
Kellen[54]	Europe	Belgium	1999-2004	Population-based	200	384
Pohlabeln [29]	Europe	Germany	1989-1992	Hospital-based	300	300
Steineck[55]	Europe	Sweden	1985-1987	Population-based	273	553
Randi[56]	Europe	Italy	1985-1992	Hospital-based	727	1067
Baena[6]	Europe	Spain	1997	Hospital-based	85	130
Porru[57]	Europe	Italy	1992-1993	Hospital-based	200	214
Golka[58]	Europe	Germany	1992-1995	Population-based	194	238
Clavel[59]	Europe	France	1984-1987	Hospital-based	201	326
				Total	7514 (27)	20882 (73)

Table 5.2 shows a detailed description of the characteristics of cases and control subjects in each of the studies included in BLEND study. The master data set comprised of 7,514 bladder cancer cases and 20,882 control subjects. Cases were more likely to be males; a total of 76.1% of the cases and 54.7% of the controls were male. The mean age was 60 years for cases and 57 years for controls. For smoking status, 43.1% cases and 32.8% of the controls were current smokers and 37.6% of the cases and 27.9% of the controls were former smokers. Cases who were smokers or former smokers tend to smoke for longer duration when compared to controls.

TABLE 5.2: Characteristics of bladder cancer cases and controls from 18 case-control studies included in BLEND study

		Cases (N=7514)		Controls (N=20882)	
		No	%	No	%
Sex	Male	5719	76.1	11413	54.7
	Female	1795	23.9	9469	45.3
Age (years)	<40	214	2.8	2947	14.2
	40-44	252	3.4	1464	7.0
	45-49	408	5.4	1706	8.2
	50-54	738	9.8	2104	10.1
	55-59	1162	15.5	2525	12.2
	60-64	1471	19.6	2836	13.6
	65-69	1233	16.4	2907	14.0
	70-74	1187	15.8	2645	12.7
	≥75	846	14.1	1645	7.9
Smoking status	Non smoker	1418	19.3	7918	39.4
	Former smoker	2757	37.6	5612	27.9
	Current smoker	3160	43.1	6589	32.8
Smoking Duration (years)	<1	1449	20.6	7778	41.0
	1-9	256	3.6	1477	7.8
	10-19	554	7.9	2194	11.6
	20-29	990	14.1	2553	13.4
	30-39	1467	20.8	2328	12.3
	40-49	1512	21.5	1691	8.9
	≥50	817	11.6	964	5.1
Amount of Cigarettes (per day)	<1	1727	24.6	9547	49.5
	1-4	273	3.9	646	3.3
	5-14	1242	17.7	4255	22.1
	15-24	2031	28.9	2536	13.1
	25-34	841	12.0	1498	7.8
	35-44	588	8.4	582	3.0
	≥45	322	4.6	229	1.2

Subjects less than 18 years old were excluded from the analysis

Table 5.3 presents median fluid consumption of controls and cases within each individual study. Fluid consumption varied across studies, with coffee as the major contributor of fluid consumption in almost all studies, particularly those studies conducted in Europe and America. The second source of fluid consumption was water in all studies, although in studies conducted in Asia the major source of fluid consumption was tea.

Table 5.3: Fluid consumption for controls and cases by studies included in the BLEND study

1st Author (Location)	Total Fluid Intake includes:	Controls consumption (ml/week)			Cases consumption (ml/week)		
		Mean	Median	(25th-75th) Percentiles	Mean	Median	(25th-75th)
Jiang (USA)	Coffee	5514	3600	(1680-6720)	6426	5040	(3360- 8400)
	Tea (miscel.)	1339	0	(0-1680)	1414	0	(0- 1680)
	Soda water	1866	720	(0- 1680)	2398	960	(0- 3360)
	Tomato juice	168	55	(2-240)	180	28	(0-166)
	Orange juice	699	480	(111- 1200)	602	240	(55- 960)
	Grape fruit juice	167	28	(0-111)	145	9	(0-111)
	Fruit juice	866	591	(231-1551)	747	480	(111-1200)
	Other fruit juice	90	0	(0-9)	117	0	(0-5)
	Beer	2577	360	(0-2160)	2861	0	(0-2160)
	Wine	379	0	(0-240)	291	0	(0-120)
	Liquor	245	0	(0-180)	357	0	(0-270)
	Water	5284	5040	(1680-6720)	4903	3360	(1680-6720)
Tang (USA)	Coffee	5234	4375	(2188-7437.5)	5562	4375	(2188-7438)
	Tea (miscel.)	1715	875	(438-1750)	1426	438	(438-1750)
	Herbal tea	786	438	(438-438)	533.75	438	(438- 438)
	Carbonated soft drink	1301	438	(0-875)	1515	438	(0-1750)
	Beer	513	360	(0-720)	940	360	(0-1080)
	Wine	110	120	(0- 240)	164	0	(0-120)
	Liquor	62	45	(0-90)	103	45	(0-90)
Stieneck (Europe)	Lemonade	371	63	(63-500)	520	63	(63- 500)
	Fruit Juices	478	125	(63-500)	556	125	(63-1125)
	Carbonated soft drinks	584	188	(125-563)	717	188	(125-1000)
	Beer	1638	1080	(360-2520)	1987	1800	(720- 2520)
	Wine	424	360	(120-480)	517	360	(240-720)
	Beverages (miscel.)	979	500	(250-1250)	1182	750	(500-1750)
	Coffee	5073	4667	(3208-6417)	5727	5250	(3500- 7583)
	Tea (miscel.)	1455	1167	(292-1750)	1308	875	(0-1750)
Wallace (USA)	Carbonated soft drinks	1737	625	(438-1750)	2038	1063	(438-2813)
	Apple juice	158	60	(60-120)	211	60	(60-120)
	Liquor	82	11	(11- 23)	86	11	(11-23)
	Wine	321	60	(60-150)	207	60	(60- 90)
	Beer	620	90	(90-180)	750	90	(90-180)
	Tea (miscel.)	1006	125	(63-750)	703	63	(63-250)
	Coffee	3832	4125	(844 -5313)	3995	2625	(1436- 5313)
	Punch drinks	216	63	(63-125)	356	63	(63-125)
	Tomato juice	153	63	(63-125)	185	63	(63-125)
	Other fruit	464	63	(63-250)	493	63	(63- 250)
	Grape juice	184	63	(63- 63)	170	63	(63- 63)
	Orange juice	1061	250	(63-2500)	805	125	(63-1375)
Zhang (USA)	Coffee	5496	5250	(1750-7000)	5620	3500	(1750-7000)
	Tea (miscel.)	2793	1750	(1750- 3500)	2746	1750	(750-3500)
	Orange Juice	1555	1750	(500-1750)	1366	1750	(500-1750)
	Grape Juice	763	500	(250- 750)	754	500	(63-1750)
	Tomato Juice	498	188	(65-500)	492	135	(63-500)
	Fruit Juice	1426	1250	(500-1750)	1446	875	(375-1750)
	Carbonated soft drink	1620	1000	(500-1750)	1385	1250	(438-1750)
	Beer	1322	720	(270-1440)	1065	360	(90-1080)
	Wine	284	180	(60-360)	352	150	(30-600)
	Liquor	106	45	(11-135)	135	90	(6-225)
Randi (Italy)	Coffee	3274	3150	(1575-4725)	3603	3150	(1575-4725)
	Tea (miscel.)	384	0	(0-0)	399	0	(0-0)
	Cola	101	0	(0-0)	38	0	(0-0)

Table 5.3: Fluid consumption for controls and cases by studies included in the BLEND study (Continued)

1st Author (Location)	Total Fluid Intake includes:	Controls consumption (ml/week)			Cases consumption (ml/week)		
		Mean	Median	(25th-75th)	Mean	Median	(25th-75th)
Pohlabeln (Germany)	Coffee	5594	5250	(3500-7000)	4577	3500	(1750-7000)
	Tea (miscel.)	2335	1750	(0-3500)	2442	1750	(0-3500)
	Water	5256	3500	(1750-7000)	5379	5250	(1750- 7000)
	Beer	1788	0	(0-2520)	1408	0	(0- 2520)
	Wine	153	0	(0-0)	111	0	(0-0)
Kellen (Belgium)	Soft drink	481	37	(0-488)	697	74	(0-1050)
	Coffee	3594	3640	(1820-4633)	3934	3640	(1820- 5460)
	Herbal tea	259	0	(0- 96)	174	0	(0-0)
	Infusion drink	197	0	(0-0)	215	0	(0-0)
	Tea (miscel.)	383	0	(0- 127)	221	0	(0-0)
	Water	3546	2998	(1050-4715)	3541	3071	(1050- 5250)
	Wine	423	245	(0-566)	374	62	(0-368)
	Liquor	379	0	(0- 37)	310	0	(0-0)
	Beer	1087	245	(0-1246)	1083	208	(0-1111)
	Spirits	170	0	(0-0)	60	0	(0-0)
Golka (Germany)	Coffee	3275	2250	(2250-2250)	3424	2250	(2250-6300)
Wakai (Japan)	Coffee	3175	2750	(1750-4500)	2868	2500	(1750- 3500)
	Oolon tea	930	0	(0 – 219)	723	0	(0-0)
	Beverages (miscel)	4340	2750	(0-6250)	2752	813	(0-4875)
	Tea (miscel)	7603	5531	(4500 – 10500)	6769	5250	(3594-10500)
	Fruit juice	337	0	(0-188)	248	0	(0-250)
	Soft drink	242	0	(0-50)	173	0	(0-100)
	Water	2869	1750	(0-4500)	2991	1563	(0-3500)
Lu (Taiwan)	Tea (miscel.)	624	0	(0-1750)	836	625	(0-1750)
	Oolong tea	495	0	(0-1750)	755	63	(0-1750)
	Wine	104	0	(0-0)	165	0	(0-300)
Porru (Italy)	Coffee	6476	7000	(0-10500)	9104	7000	(3500-10500)
	Tea (miscel.)	2100	1750	(1750-1750)	2285	1750	(875-1750)
	Wine	2590	2352	(1176-3528)	2473	2352	(0-3528)
	Beer	79	0	(0-0)	103	0	(0-0)
	Aperitif	16	0	(0-0)	0	0	(0-0)
	Liquor	66	0	(0-0)	83	0	(0-0)
	Water	1241	1400	(1050-1400)	1276	1400	(525-1575)
	Carbonated soft drink	2154	1750	(1750-1750)	2625	1750	(1750-3500)
Hemelt (China)	Red tea	2038	0	(0- 4667)	2064	153	(0- 4667)
	Green tea	2626	806	(0- 4667)	2604	750	(0- 4667)
	Water	7111	7000	(3500-11667)	7189.431	7000	(3500- 11667)
	Fruit juice	118	0	(0-77)	92	0	(0-77)
	Carbonated soft drink	15	0	(0-0)	63	0	(0-0)
	Beer	501	0	(0-0)	599	0	(0- 55)
	Wine	21	0	(0-0)	34	0	(0-0)
	Liquor	52	0	(0-7)	50	0	(0-0)
	Beverages (miscel.)	30	0	(0-0)	84	0	(0-0)
Clavel (France)	Coffee	3276	3500	(1750-3500)	2803	1750	(1750-3500)

Table 5 3: Fluid consumption for controls and cases by studies included in the BLEND study (Continued)

1st Author (Location)	Total Fluid Intake includes:	Controls consumption (ml/week)			Cases consumption (ml/week)		
		Mean	Median	(25th-75th) Percentiles	Mean	Median	(25th-75th)
Gartner (Canada)	Coffee	3701	4500	(750-4500)	4754	4500	(1750-8000)
Baena (Spain)	Water	6165	6125	(3500-8750)	6609	6125	(6125-8750)
	Coffee	2214	2625	(0-2625)	2666	2625	(0-2625)
Taylor (USA)	Beer	966	0	(0-720)	1064	0	(0-720)
	Wine	108	0	(0-0)	132	0	(0-0)
	Liquor	145	0	(0-0)	203	0	(0-0)
	Coffee	4729	3500	(1750- 7000)	6053	3500	(1750-7000)
	Tea (miscel.)	1950	1750	(0- 3500)	2257	1750	(0-3500)
	Carbonated Soft drink	1661	0	(0-1750)	2407	0	(0-1750)
Mettlin (USA)	Beer	436	90	(0-540)	559	90	(0-540)
	Wine	45	0	(0-30)	45	0	(0-30)
	Spirit	38	0	(0-23)	41	0	(0- 23)
	Tea	1885	1313	(1313-1750)	1695	1313	(1313-1750)
	Coffee	4376	5250	(1750-7000)	4389	5250	(1750-7000)
	Alcohol mix	541	147	(0- 898)	415	74	(0-452)
	Liquor	52	0	(0-7)	50	0	(0-0)
	Beverages (miscel.)	30	0	(0-0)	84	0	(0-0)

To facilitate interpretation of results of fluid items in relation to bladder cancer risk, 250 millilitres was assumed as the standard metric cup.

5.3.1 Overall analysis with all subjects combined

Table 5.4 reports the ORs of developing bladder cancer and corresponding 95% confidence intervals in relation to total fluid intake and specific fluid items for all subjects combined. A borderline significant association was found between coffee consumption and bladder cancer risk for all subjects combined (P_{trend}=0.082). Subjects that consumed 10 or more cups ($\geq$ 2,500 ml/day) of coffee had an estimated 3-fold increase in ORs (OR=3.0, 95% CI: 1.3-7.0) compared to subjects who drank one cup (250 ml/day) or less than one cup of coffee.

Table 5.4: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to total fluid intake for all subjects combined

Fluid item	Cups (250 ml) /day	N_{CASE}	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Total fluid	<1	381	2,067	1.0 (ref.)	
	1	619	2,026	0.8 (0.5-1.4)	
	2-3	1,696	5,353	1.0 (0.6-1.7)	
	4-8	3,042	7,310	1.1 (0.7-1.9)	
	≥9	1,507	1,402	1.3 (0.8-2.3)	0.142
Coffee	0-1	1,940	6,235	1.0 (ref.)	
	2	2,459	6,157	1.1 (0.7-1.8)	
	3-9	1,697	4,428	1.3 (0.7-1.8)	
	≥10	205	116	3.0 (1.3-7.0)	0.082
Water	0	682	678	1.0 (ref.)	
	1-2	1,049	1,130	1.0 (0.7-1.3)	
	3-5	912	1,033	1.0 (0.8-1.4)	
	≥6	438	452	1.0 (0.7-1.5)	0.757
Cola	0	1,351	2,028	1.0 (ref.)	
	1	158	219	0.8 (0.5-1.3)	
	3	35	35	0.9 (0.4-1.8)	
	≥4	39	47	1.0 (0.5-1.9)	0.838
Tea	0	2924	7253	1.0 (ref.)	
	1-2	899	2660	0.9 (0.8-1.2)	
	3-5	235	889	0.8 (0.6-1.0)	
	≥6	77	71	0.9 (0.7-1.2)	0.218
Green tea	0	286	295	1.0 (ref.)	
	1-2	77	59	0.9 (0.4-1.8)	
	3-5	75	84	1.2 (0.6-2.5)	
	≥6	27	23	0.9 (0.6-1.5)	0.897
Liquor	0	1,953	2,116	1.0 (ref.)	
	½	76	66	0.8 (0.4-1.3)	
	≥1	62	34	1.3 (0.7-2.5)	0.735
Beer	0	3,066	7,501	1.0 (ref.)	
	¼	246	1,112	0.8 (0.6-1.0)	
	½	224	621	0.7 (0.6-1.0)	
	1	446	1,198	0.8 (0.6-1.1)	
	≥2	505	545	1.1 (0.8-1.4)	0.798
Wine	0	3,398	9,287	1.0 (ref.)	
	¼	203	574	0.7 (0.5-0.9)	
	½	140	218	0.8 (0.6-1.2)	
	1	152	216	0.9 (0.6-1.3)	
	≥2	628	846	1.0 (0.7-1.5)	0.687

OR=odds ratio from model with random effect and random slope, ref=reference group; CI=confidence interval
[a]adjusted for sex, age (continuous), smoking status (categorical), smoking duration(continuous), cigarette amount (continuous)

Table 5.4: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to total fluid intake for all subjects combined (Continued)

Fluid item	Cups (250 ml) /day	N_{CASE}	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Soda water	0	826	1082	1.0(ref.)	
	1-2	299	295	1.0(0.9-1.3)	
	3-5	95	96	1.0(0.8-1.4)	
	≥6	71	37	1.5(0.9-2.2)	0.167
Carbonated soft drinks	0	2,924	7,253	1.0(ref.)	
	1-2	899	2660	0.9(0.8-1.2)	
	3-4	204	845	0.8(0.6-1.0)	
	≥5	108	115	0.9(0.7-1.2)	0.210
Fruit juice	0	2508	2534	1.0(ref)	
	1-2	527	591	0.9(0.7-1.2)	
	≥3	29	31	0.8(0.4-1.4)	0.291

OR=odds ratio from model with random effect and random slope, ref=reference group; CI=confidence interval
[a]adjusted for sex, age (continuous), smoking status, smoking duration(continuous), cigarette amount (continuous)

5.3.2 Subgroup analysis according to gender

The association between coffee consumption and bladder cancer risk varied amongst gender. A significant increased association between coffee consumption and the risk of developing bladder cancer was observed (P_{trend}= 0.030) when the analyses was restricted to men only. Men that consumed 10 or more cups (≥ 2,500 ml/day) of coffee per day had an estimated 3-fold increased OR of developing bladder cancer (RR=2.9, 95% CI: 1.2-6.9) compared to men who drank one cup (250 ml/day) or less than one cup of coffee (Table 5.5). For women, the OR of drinking at least six or more cups (≥ 1,500 ml/day) of coffee was 0.9 (95% CI: 0.5-1.8; P_{trend}=0.867) when compared to women who never drank coffee (Table 5.6).

Table 5.5: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to fluid intake for males only

Fluid item	Cups (250 ml) /day	$N_{CASE/}$	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Total fluid	<1	215	1,011	1.0 (ref.)	
	1-2	813	2,484	1.1 (0.7-1.7)	
	3-5	1,593	3,346	1.3 (0.8-2.1)	
	6-8	1,291	1,724	1.2 (0.8-1.9)	
	≥9	1,396	1,376	1.4 (0.8-2.3)	0.200
Coffee	0-1	1,408	3,394	1.0 (ref.)	
	2-3	1,909	3,480	1.2 (0.8-1.8)	
	4-9	1,328	2,419	1.3 (0.9-2.0)	
	≥10	172	98	2.9 (1.2-6.9)	0.030
Water	0	560	569	1.0 (ref.)	
	1	425	430	1.1 (0.8-1.5)	
	2	416	421	1.1 (0.8-1.6)	
	3-5	756	769	1.2 (0.9-1.7)	
	≥6	331	338	1.2 (0.8-1.9)	0.184
Cola	0	995	1,380	1.0 (ref.)	
	1	92	144	0.7 (0.4-1.2)	
	≥3	42	46	1.0 (0.5-1.8)	0.597
Tea	<1	2,282	4,137	1.0 (ref.)	
	1-2	638	1,291	0.9 (0.8-1.2)	
	3-4	196	378	0.8 (0.6-1.1)	
	≥5	225	243	0.9 (0.6-1.2)	0.227
Green tea	0	175	168	1.0 (ref.)	
	½	45	52	1.1 (0.4-3.3)	
	1	31	23	1.1 (0.4-2.7)	
	2	34	25	1.1 (0.4-2.8)	
	3	90	89	0.8 (0.4-1.7)	0.601
Beer	0	2,225	3,475	1.0 (ref.)	
	¼	215	706	0.8 (0.5-1.1)	
	½	189	1461	0.7 (0.5-0.9)	
	1	395	957	0.7 (0.5-1.0)	
	≥2	469	506	1.0(0.7-1.4)	0.492
Carbonated soft drink	0	2,282	4,137	1.0 (ref.)	
	1-2	638	1,291	0.9 (0.8-1.2)	
	3-4	196	378	0.8 (0.6-1.1)	
	≥5	225	243	0.9 (0.6-1.2)	0.227
Wine	0	2,523	4,816	1.0 (ref.)	
	¼	154	368	0.6 (0.4-0.9)	
	½	115	156	0.9 (0.6-1.3)	
	≥1	705	860	0.9 (0.6-1.3)	0.355

OR=odds ratio from model with random effect and random slope, ref=reference group; CI=confidence interval

[a]adjusted for age (continuous), smoking status(categorical), smoking duration(continuous), cigarette amount (continuous)

Table 5.6: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to total fluid intake for females only

Fluid item	Cups (250 ml) /day	N_{CASE}	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Total fluid	<1	123	988	1.0 (ref.)	
	1	109	767	0.9 (0.4-1.8)	
	2-3	420	2,392	1.2 (0.6-2.2)	
	4-8	696	3,286	1.1 (0.6-2.2)	
	≥9	276	282	1.3 (0.6-2.8)	0.389
Coffee	<1	273	1,547	1.0 (ref.)	
	1	259	1,294	0.9 (0.5-1.6)	
	2-3	550	2,677	1.0 (0.6-1.7)	
	4-5	257	1,791	0.9 (0.5-1.7)	
	≥6	145	236	0.9 (0.5-1.8)	0.867
Water	0	121	105	1.0 (ref.)	
	1-2	208	278	0.7 (0.4-1.1)	
	3-5	156	263	0.6 (0.4-1.0)	
	≥6	107	114	0.8 (0.5-1.3)	0.323
Cola	0	353	647	1.0 (ref.)	
	1-2	66	75	0.7 (0.4-1.2)	
	≥3	32	36	1.0 (0.5-1.8)	0.597
Tea	<1	594	2,988	1.0 (ref.)	
	1-2	275	1,366	1.1 (0.7-1.5)	
	3-4	75	517	0.8 (0.5-1.2)	
	≥5	68	68	1.3 (0.7-2.2)	0.891
Beer	< ¼	841	4,026	1.0 (ref)	
	¼	31	406	0.7 (0.4-1.3)	
	½	35	160	0.9 (0.5-1.7)	
	1	87	281	1.3 (0.8-2.1)	0.473
Carbonated soft drink	0	594	2,988	1.0 (ref.)	
	1-2	275	1,366	1.1 (0.7-1.5)	
	3-4	75	517	0.8 (0.5-1.2)	
	≥5	68	68	1.3 (0.7-2.2)	0.891
Wine	0	875	875/4,471	1.0 (ref.)	
	¼	49	49/207	0.8 (0.5-1.3)	
	½	25	25/62	0.7 (0.3-1.3)	
	≥1	75	75/202	1.2 (0.6-2.2)	0.793
Soda water	<1	187	377	1.0 (ref.)	
	1	42	56	0.8 (0.6-1.1)	
	≥2	56	53	1.3 (1.0-1.7)	0.178

OR=odds ratio from model with random effect and random slope, ref=reference group; CI=confidence interval

[a]adjusted for age (continuous), smoking status(categorical), smoking duration(continuous), cigarette amount (continuous)

5.3.3 Subgroup analysis according to smoking status

The association between total fluid intake or specific fluid items and bladder risk among men according to smoking status was examined. A borderline significant association was found between coffee consumption and bladder cancer risk for all subjects who were ever smokers (P_{trend}=0.063). Ever smokers who consumed 10 or more cups (≥ 2,500 ml/day) of coffee had an estimated 2.6 increased ORs (OR=2.6, 95% CI: 1.1-5.9) compared to subjects who drank one cup (250 ml/day) or less than one cup of coffee. A significant positive association was observed between coffee consumption and bladder cancer risk amongst men who were ever smokers (P_{trend}=0.043). Men who were ever smokers who consumed at least 10 or more cups (≥2,500 ml/day) of coffee per day had a 2.5 increased OR of developing bladder cancer (OR=2.5, 95% CI: 1.1-5.8) compared to men who were ever smokers and drank one cup (250 ml/day) or less than one cup of coffee (Table 5.8). In addition, no evidence of interaction between smoking and coffee consumption effect on the risk of developing bladder cancer.(Pvalue=0.614) For men who were never smokers and drank at least six or more cups (1,500 ml/day) of coffee per day had an estimated 50% increased risk of developing bladder cancer (OR=1.5, 95% CI: 0.8-2.5) compared to men who were never smokers and never drank coffee (Table 5.9), although this effect was borderline significant (P_{trend}=0.089).

Table 5.7: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to fluid intake for ever smokers only

Fluid item	Cups (250 ml) /day	N_{CASE}	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Total fluid	<1	230	894	1.0 (ref.)	
	1-2	239	850	0.8 (0.4-1.4)	
	3-5	1,088	2,783	1.0 (0.6-1.8)	
	6-8	2,573	5,012	1.0 (0.6-1.7)	
	≥9	1,465	1,275	1.3 (0.7-2.3)	0.293
Coffee	0-1	1,421	3,207	1.0 (ref.)	
	2-3	2,047	3,808	1.1 (0.7-1.7)	
	4-9	1,529	3,334	1.2 (0.8-1.9)	
	≥10	198	105	2.6 (1.1-5.9)	0.063
Water	0	566	490	1.0 (ref.)	
	1-2	865	707	1.1 (0.8-1.5)	
	3-5	700	673	1.0 (0.8-1.4)	
	≥6	336	260	1.3 (0.8-1.9)	0.379
Cola	0	1,116	1,258	1.0 (ref.)	
	1-2	124	136	0.9 (0.6-1.4)	
	3	33	25	1.0 (0.5-1.9)	
	≥4	32	32	1.0 (0.5-1.8)	0.861
Tea	<1	4559	2345	1.0 (ref.)	
	1-2	1,452	1,721	1.0 (0.8-1.1)	
	3-4	504	209	0.8 (0.6-1.0)	
	≥5	225	242	0.9 (0.7-1.2)	0.214
Green tea	0	111	131	1.0 (ref.)	
	½	42	39	1.1 (0.4-3.0)	
	≥1	125	92	1.1 (0.5-2.2)	0.848
Beer	0	2,544	4,781	1.0 (ref.)	
	¼	191	459	0.8 (0.6-1.1)	
	½	388	973	0.8 (0.6-1.1)	
	1	149	176	0.9 (0.7-1.3)	
	≥2	315	274	1.2 (0.9-1.7)	0.461
Wine	0	2,804	5,874	1.0 (ref.)	
	¼	118	153	0.8 (0.6-1.2)	
	½	119	119	0.8 (0.5-1.3)	
	1	157	157	1.3 (0.8-2.2)	
	≥2	404	404	1.0 (0.6-1.6)	0.761
Liquor	0	1,407	1,212	1.0 (ref.)	
	¼	107	72	1.1 (0.8-1.7)	
	½	72	61	0.9 (0.6-1.4)	
	≥1	60	27	1.8(1.0-3.1)	0.231

Table 5.7 Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to fluid intake for ever smokers only (Continued)

Fluid item	Cups (250 ml) /day	N_{CASE}	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Fruit juice	0	1,754	1,422	1.0 (ref.)	
	½	253	210	0.9 (0.7-1.3)	
	1	385	331	0.9 (0.7-1.2)	
	2	56	48	0.8 (0.5-1.2)	0.243
Carbonated soft drink	0	2,345	4,559	1.0 (ref.)	
	1-2	721	1,452	1.0 (0.8-1.1)	
	3-4	209	504	0.8 (0.6-1.0)	
	≥5	242	225	0.9 (0.7-1.2)	0.214
Soda water	<1	679	658	1.0 (ref.)	
	1-2	249	204	1.0 (0.8-1.3)	
	3-5	73	53	1.1 (0.8-1.6)	
	≥6	64	27	1.6 (1.0-2.5)	0.129

OR=odds ratio from model with random effect and random slope, ref=reference group; CI= confidence interval
[a]adjusted for sex, age (continuous),smoking duration(continuous), cigarette amount (continuous)

Table 5.8: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to fluid intake for ever smokers in males only

Fluid item	Cups (250 ml) /day	N_{CASE}	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Total fluid	<1	169	575	1.0 (ref.)	
	1-2	674	1,800	1.1 (0.7-1.8)	
	3-5	1,348	2,640	1.2 (0.7-2.0)	
	6-8	1,137	1,302	1.2 (0.7-1.9)	
	≥9	1,272	1,131	1.4 (0.8-2.4)	0.251
Coffee	0-1	1,148	2,250	1.0 (1.0-1.0)	
	2-3	1,687	2,705	1.1 (0.8-1.7)	
	4-9	1,232	2,074	1.3 (0.9-2.0)	
	≥10	167	90	2.5 (1.1-5.8)	0.043
Water	0	497	442	1.0 (ref.)	
	1	382	311	1.2 (0.8-1.6)	
	2	348	290	1.1 (0.8-1.6)	
	3-5	623	567	1.1 (0.8-1.5)	
	≥6	284	222	1.3 (0.9-2.0)	0.234
Cola	0	878	999	1.0 (ref.)	
	1	72	94	0.7 (0.4-1.2)	
	≥3	35	33	0.9 (0.4-1.8)	0.429
Tea	<1	1,967	3,209	1.0 (ref.)	
	1-2	557	966	1.0 (0.8-1.2)	
	3-4	163	299	0.8 (0.6-1.0)	
	≥5	214	202	1.0 (0.7-1.4)	0.480
Green tea	0	126	106	1.0 (ref.)	
	½	41	37	1.0 (0.3-3.6)	
	1	89	122	1.0 (0.4-2.4)	0.971
Beer	0	1,870	2,445	1.0 (ref.)	
	¼	185	580	0.8 (0.5-1.1)	
	½	165	367	0.7 (0.5-1.0)	
	1	348	824	0.7 (0.5-1.0)	
	2	43	422	1.0 (0.7-1.4)	0.481
Wine	0	2,123	3,642	1.0 (ref.)	
	¼	133/ 281	133/ 281	0.7 (0.5-1.0)	
	½	99/114	99/114	0.9 (0.6-1.3)	
	≥1	639/672	639/672	0.8 (0.6-1.2)	0.275

Table 5.8: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to fluid intake for ever smokers in males only (Continued)

Fluid item	Cups (250 ml) /day	N_{CASE}	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Liquor	0	1,100	926	1.0 (ref.)	
	¼	77	60	0.8 (0.4-1.4)	
	½	57	46	0.7 (0.4-1.4)	
	1	47	24	1.1 (0.5-2.3)	0.619
Carbonated soft drink	0	1,967	3,209	1.0 (ref.)	
	1-2	557	966	1.0 (0.8-1.2)	
	3-4	163	299	0.8 (0.6-1.0)	
	≥5	214	202	1.0 (0.7-1.4)	0.480
Fruit juice	0	1,476	1,171	1.0 (ref.)	
	½	198	164	1.0 (0.7-1.4)	
	1	312	252	1.0 (0.7-1.4)	
	2	42	34	0.8 (0.5-1.3)	0.602
Soda water	0	449	411	1.0 (ref.)	
	½	83	73	1.0 (0.7-1.5)	
	1	124	112	0.9 (0.7-1.2)	
	2	186	104	1.4 (1.0-1.9)	0.124

OR=odds ratio from model with random effect and random slope, ref=reference group, CI= confidence interval
[a]adjusted for age (continuous), smoking duration(continuous), cigarette amount (continuous)

Table 5.9: Odds ratios (OR) and 95% confidence interval (95% CI) of bladder cancer in relation to fluid intake for never smokers in males only

Fluid item	Cups (250 ml) /day	N_{CASE}	$N_{CONTROL}$	OR[a] (95%CI)	P_{trend}
Total fluid	<1	46	436	1.0 (1.0-1.0)	
	1-2	139	684	1.5 (0.9-2.5)	
	3-5	245	706	2.1 (1.2-3.7)	
	6-8	154	422	1.7 (0.9-3.0)	
	≥9	124	245	1.9 (1.0-3.5)	0.098
Coffee	0	134	706	1.0 (ref.)	
	1	126	438	1.3 (0.8-2.0)	
	2-3	146	561	1.5 (1.0-2.3)	
	4-5	130	431	1.4 (0.9-2.3)	
	≥6	47	136	1.5 (0.8-2.6)	0.089
Water	0	63	127	1.0 (ref.)	
	1	43	119	0.7 (0.5-1.2)	
	2	68	131	0.9 (0.6-1.4)	
	3-5	133	202	1.2 (0.8-1.8)	
	≥6	47	116	0.6 (0.4-1.0)	0.796
Tea	<1	315	928	1.0(ref.)	
	1	54	208	0.8(0.5-1.2)	
	2	27	117	0.7(0.4-1.2)	
	≥3	44	120	0.9(0.5-1.6)	0.468
Beer	0	355	1,030	1.0 (ref.)	
	¼	30	126	0.8 (0.5-1.5)	
	½	24	94	0.6 (0.3-1.2)	
	1	47	133	1.0 (0.6-1.7)	
	≥2	38	84	1.1 (0.6-2.1)	0.884
Carbonated soft drink	0	315	928	1.0(ref.)	
	1	54	208	0.8(0.5-1.2)	
	2	27	117	0.7(0.4-1.2)	
	≥3	44	120	0.9(0.5-1.6)	0.468
Wine	0	400	1,174	1.0(ref.)	
	¼	21	87	0.6(0.3-1.2)	
	≥½	82	230	1.0(0.5-1.9)	0.693
Fruit juice	0	247	446	1.0(ref.)	
	½	73	48	1.0(0.6-1.9)	
	≥1	139	81	0.9(0.5-1.6)	0.762
Soda water	0	84/186	84/186	1.0 (1.0-1.0)	
	½	23/35	23/35	1.4 (0.7-2.7)	
	1	21/51	21/51	0.9 (0.4-1.9)	
	≥2	36/52	36/52	1.4 (0.8-2.7)	0.361

OR=odds ratio from model with random effect and random slope, ref=reference group, CI=Confidence interval
[a]adjusted for age (continuous)

5.4 Discussion

5.4.1 Summary of key findings

To my knowledge, this is the largest ever pooled analysis to date to comprehensively investigate the association between total fluid intake and risk of developing bladder cancer with a total of 7,514 bladder cancer cases and 20,882 control subjects. The result of this study shows a 3-fold increased risk of developing bladder cancer in men who consumed at least 10 or more cups (≥2500 ml/day) of coffee per day. In addition, the positive association between coffee consumption and bladder cancer risk in men was observed both in ever smokers, after adjusting for amount of cigarettes smoked and smoking duration, and never smokers.

5.4.2 Comparison findings with previous studies

A previous pooled analysis of 10 European case-control studies involving a total of 564 cases and 2,929 controls suggested that never smokers who consumed 10 or more cups of coffee per day had an excess significant risk of developing bladder cancer (RR=1.80, 95% CI: 1.00-3.30) compared to those who never drank coffee.[60] These results are consistent with our findings, but our analysis included 10 times the number of cases and takes into account clustering within the dataset. Another previous pooled analysis of six case-control studies consisting of 2,729 bladder cancer cases and 5,150 control subjects have showed that heavy consumption of coffee i.e. more than five cups of coffee per day increased the risk of developing bladder cancer, mainly in ever smokers.[61] Additionally, the pooled analysis of six case-control studies also suggested that total fluid consumption was associated with an increased bladder cancer risk in men; after

controlling for confounders the OR for 1 litre/day increased consumption was 1.08 (95%CI: 1.03-1.14). Results of a previous cohort study conducted in the Netherlands indicated that there may be a positive association between high coffee consumption and bladder cancer risk in men.[62] Another prospective study conducted in Japan has suggested that high coffee consumption increases the risk of developing bladder cancer in never or former smokers (RR=2.24, 95% CI: 1.21-4.16; or RR=2.05, 95% CI: 1.15-3.65).[63]

5.4.3 Biological mechanisms

There are plausible biological mechanisms that have been suggested by researchers for the association of coffee on cancer development. Coffee is amongst the most widely consumed beverages in the world. It is one of the main sources of caffeine in the western diet and has been reported to be potentially carcinogenic. Caffeine may induce the production of cytochrome P450 enzymes that promote carcinogenesis.[64] In addition, caffeine can inhibit DNA repair and stimulate cell division before DNA replication is completed.

Researchers have evaluated the effect of coffee consumption and on health and other forms of cancers such as lung cancer. Some studies have shown that caffeine inhibits genes, for example, the tumour suppressor gene P53 and ataxia telangiectasia mutated (ATM) genes that respond to DNA damage. These genes have been associated with increased risk of developing childhood leukaemia[65] and lung cancer.[66] Furthermore, higher consumption of caffeine has been associated with low birth weight or miscarriage in pregnant women.[67]

5.4.4 Implication for practice

Despite the limitation of this study, findings from this study are consistent with previous research which shows that higher consumption of coffee may increase the risk of developing bladder cancer in men. Furthermore, there are possible mechanisms suggesting that caffeine may have carcinogenic properties at higher levels of consumption. Therefore, based on these findings it is useful to refine and improve dietary guidance on higher coffee consumption and bladder cancer risk. Also, individuals should be aware that excessive consumption of coffee might have an impact on the development of bladder cancer. However, to my knowledge dietary guidelines on coffee consumption advised that pregnant women should consume 200mg per day of caffeine (that is 2 cups of coffee per day) based on the Food standard agency.[68]

5.4.5 Study strengths and limitations

The large sample size is one of the strengths of this study. Individual studies used food frequency questionnaires (FFQ) to record how often the subjects consume fluid intake over a period of time. FFQ has been demonstrated to be reliable and easy to complete for subjects in a large population setting. All datasets were re-coded using standard rules and fluid items were standardised from portion sizes (e.g. cups, pints) to millilitres to ensure consistency across all studies. Adjustment was made for the principal confounders such as smoking history (smoking status, smoking duration and smoking frequency), age and gender.

This study may have several limitations, firstly only case-control studies were included in this pooled analysis. Case-control study designs are more susceptible to recall bias and selection bias. In selection bias, the process of selection of controls might bias the

result observed in this study. However to reduce selection bias, for each study the controls subjects were selected from the same source population were the cases were derived from. Recall bias might be a limitation because subjects with the disease might report fluid consumption differently compared to subjects with no disease. However, it is unlikely that recall bias can distort the results of this study because cases and controls generally were not aware of the association between coffee consumption and bladder cancer.

Studies were conducted in three continents: Europe, North America and Asia. Studies conducted in the African continent were not included because of limited evidence on bladder cancer risk and dietary consumption.

None of the included studies in this study provided information on the method of preparation or brewing of coffee. In different populations, brewing and method of preparation of coffee varies considerably.[69] The concentration of coffee consumed or exposure of coffee may vary across countries. However, potential variation in exposure variable (fluid item) between studies was taken into account by including a random slope in the multilevel logistic regression model (an interaction between the cluster variable i.e. hospital or centre within the study and fluid item).

Despite the available biological mechanism on the effect of coffee consumption and risk of developing bladder cancer, it is possible the results might be confounded by smoking. Therefore, in this study, subgroup analysis by smoking status in men was conducted and adjustment was made for smoking duration and cigarette smoking per day for ever smokers. The result shows a positive association in both ever smokers and never smokers. In addition, no evidence of interaction between smoking and coffee

consumption effect on the risk of developing bladder cancer. Furthermore, other possible unknown confounders that might play a role in bladder cancer risk were not adjusted for due to lack of information or data.

In conclusion, this pooled analysis of 18 individual case-control studies suggests that consumption of at least 10 or more cups (≥2500 ml/day) of coffee per day may increase the risk of developing bladder cancer in men.

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6.0 CHAPTER SIX

General discussion and conclusion

6.1 Principal findings

Chapter 2 focused on investigating the role of dietary consumption and diet diversity on the risk of developing bladder cancer in a Chinese population. This thesis showed that a high diet diversity— particularly a diet varied in fruit— may reduce the risk of developing bladder cancer. The consumption of citrus fruits, stone fruits, vine fruits, flower vegetables, fresh fish, potatoes and dairy products may decrease the risk of developing bladder cancer, whereas the consumption of red meat, organ meat, leafy vegetables, bulb vegetables or preserved vegetables may increase the risk of bladder cancer.

In chapter 3, an update of previous published reviews and a dose-response meta-analysis summarizing the results from epidemiological studies on overall fluid consumption and risk of developing bladder cancer was presented. The results indicate that low to moderate fluid consumption is not associated with an increased risk of developing bladder cancer but that fluid consumption exceeding eight cups per day increases the risk of developing bladder cancer substantially in men only. The results of this study suggest a non-linear relationship between total fluid intake and bladder cancer risk in men.

In Chapter 5 the association between fluid consumption and risk of developing bladder cancer was investigated by pooling individual patient data from the BLEND consortium. A non-linear relationship was observed in the pooled analysis, but the overall trend was not significant.

The results presented in this thesis suggest that the consumption of 10 or more cups (≥2500 ml/day) of coffee per day increases the risk of developing bladder cancer by 3-fold in men. Additionally, the association between coffee consumption and bladder cancer risk did not differ substantially between ever smokers and never smokers in men which suggest that the found association is not confounded by smoking.

6.2 Discussion

To my knowledge, only chapter two is the second study to examine the association between diet diversity and risk of developing bladder cancer. Contrary to the findings, the other previous study that examined fruit and vegetable diversity and risk of developing bladder cancer reported that there was no overall relationship between vegetable diversity or fruit diversity and risk of developing bladder cancer.[1] The inconsistencies observed between both studies might be due to differences in methods of dietary assessment. The previous study was a multicentre cohort study, consisting of subjects from 23 centres in 10 European countries. In the previous study the method of dietary assessment differed between countries, for example different questionnaires such as food frequency questionnaire, semi quantitative questionnaire and extensive self-administered questionnaire. Also, in the dietary questionnaires the number of fruits and vegetables consumed differed by country. In the study population of the case-control study conducted in this thesis, the study population was from China and a food frequency questionnaire was used to obtain information on dietary consumption. Because of the differences in study design and methods of dietary assessment it is difficult to compare findings between studies.

Additionally, other studies have investigated the relationship between diet diversity and other forms of cancer. For example, an Italian a case-control study reported that total diet

diversity is associated with decrease risk of developing colorectal cancer.[2] Another study concluded that a diet that is diverse in vegetable and fruit was significantly associated with decrease risk of developing pharyngeal cancer.[3] All these findings are consistent with the findings in this thesis on diet diversity and risk of developing bladder cancer. Also the results of this thesis supports the recommended dietary guideline on more varied diet.[4] The American dietary guideline supports a more diverse diet particularly in fruits and vegetables.[4]

Other findings from chapter 2 confirm the results of previous studies that the consumption of citrus fruits, stone fruits, vine fruits, flower vegetables, fresh fish, potatoes and dairy products may decrease the risk of developing bladder cancer, whereas the consumption of red meat, organ meat, leafy vegetables, bulb vegetables or preserved vegetables may increase the risk of bladder cancer. These findings support the World Health Organization guidelines which recommend 5 a day, that is, eating 400 grams of fruits and vegetables a day to reduce the risk of developing chronic diseases like cancer and diabetes. [5]

In chapter 3 and 5, the effect of total fluid consumption on the risk of developing bladder cancer was investigated using two different approaches (meta-analysis and pooled analysis). The result in both chapters indicated a non-linear relationship between total fluid consumption and risk of developing bladder cancer in men. The European Food Safety Authority and Food standard Agency proposed that individuals should consume 6 to 8 glasses of fluid every day.[6,7] In this thesis, it is possible the increased bladder cancer risk in relation to total fluid consumption observed might be due high consumption of specific fluids since total fluid consumed is the combination of specific fluid items such as alcohol,

coffee, water, tea and soda water etc. The major limitation in the dose response meta-analysis conducted in this thesis is that only data on total fluid consumption was available and further analysis into specific fluid consumption in relation to bladder cancer risk was not conducted. An advantage of using the pooled analysis approach is that specific fluid items could be investigated in relation to bladder cancer and subgroup analyses could be conducted for smoking and gender. Additionally, the result from chapter 5 suggests that excess consumption of coffee may increase the risk of developing bladder cancer by 3 fold in men. This result is consistent with the American medical association council on scientific affairs which recommends that 10 cups of coffee per day is excessive and people should consume two to three cups of coffee per day.[8] Excess consumption of coffee has been associated with increased risk of diseases such as osteoporosis, fibrocystic disease.[8]

6.3 Strengths and Limitations of conducting research on dietary consumption and fluid consumption in relation to bladder cancer risk

6.3.1 Assessment of dietary and fluid consumption

A challenge in many epidemiological studies that aim to investigate the relationship between dietary consumption and fluid consumption and a specific disease is that dietary assessment is extremely difficult to measure.[9] Usually, a food frequency questionnaire is the tool used in epidemiological studies to measure dietary consumption.[10] Other used methods of dietary assessment are: 24 hour recall questionnaires or food diaries.

Food frequency questionnaire

Food frequency questionnaires are used to assess individuals' habitual food and beverages consumption over a given period of time (for example one year).[10] The food frequency questionnaire (FFQ) is an appropriate tool used for large scale epidemiological studies on dietary consumption and disease risk.[11] In this thesis, a food frequency questionnaire was used in the study conducted in chapter 2 and all case-control studies included in the BLEND consortium. In addition, it has been suggested that food frequency questionnaire is the most appropriate tool to use for case-control study design because it assess the food and drink over a longer period time. The reliability of the FFQ has been tested previously and measures the frequency of food consumed in individuals. However, the FFQ does not ask for details on how the food was prepared and the portion size consumed. Other alternative methods such as the food diary and 24 hour recall can be used obtain the portion size of food consumed. The food frequency questionnaire takes into account the day to day variability of food consumed by individuals. The FFQ is relatively less expensive tool used in measuring food, nutritional and beverage consumption when compared to other alternative methods of food assessment such as 24 hour recall questionnaires and food diary.[10] Hence, the FFQ in the SEARCH study as described in chapter 2.

24 hour recall questionnaire

The 24 hour recall questionnaire involves trained interviewers asking individuals about their food and drink consumption in the preceding 24 hours. This method can be used to obtain detailed information of food and drink consumed such as methods of cooking, portion size and quantity of food consumed.[9]

Food diary / record

This method of dietary assessment requires individuals to record food and drink consumption for 3, 4, 5 or 7 days at home in a food diary. The food diary consists of coloured photographs of different food items and their portion sizes. One benefit of the food diary is that it gives comprehensive information on the food consumed in portion sizes and weight of food items can be recorded before consumption.[12] Furthermore, some food items consumed can be eaten raw or cooked for example tomatoes, fish etc. The FFQ might not have detailed information on such food items.

Therefore, future studies on the association between fluid consumption and risk of developing bladder cancer should also focus on assessing the quantity or portion sizes of food consumed using combination alternative questionnaires such as food diaries, 24 hour recall questionnaires. Illustrated in table 6.1 are the advantages and disadvantages of the commonly used methods of dietary assessment in epidemiological studies.[12]

Table 6.1 Advantages and disadvantages of the commonly used methods of dietary assessment

Methods of dietary assessment	Advantages	Disadvantages
Food frequency questionnaire	• Does not alter eating behaviours • Captures frequency or usual consumption over a long period of time • It is cheap	• Relies on the recall of subjects food or fluid consumption • FFQ does not give precise quantity of food consumed by subjects • Dietary pattern cannot be recorded • Cannot be used over short period of time
24 hour recall	• Consumption is measured in portion size or weighed, gives more detail • Eating behaviour is not altered • Can be used over a short period of time	• Expensive when compared to food frequency questionnaire • Rely on subjects recall on fluid and food consumption • Requires multiple recalls over several months to capture the usual consumption
Food diary / record	• Do not rely on subjects recall • Gives detailed information of portion size and estimates of food and drink eaten • Suitable for assessment of food or drink eaten often	• Time consuming • Expensive compared to food frequency questionnaire • Individuals might forget to record food items

6.3.2 Multicollinearity

A potential issue in the analysis of diet and cancer is extreme correlations, that is collinearity, between similar food items complicating determining the net effect of a specific food item on an outcome.[14] Food items from the same food group might consist of similar nutrients, for example citrus fruits such as orange, satsuma and grapefruit might have high degree of collinearity. An example of multicollinearity problem is when a particular variable is added to a regression model that is correlated with other explanatory variables of interest and this will increase the variance. Therefore, the added variable to the regression model do not explain the variation in the outcome variable. In this thesis, to detect the degree of multicollinearity of the food items in the case-control study from chapter 2, a correlation test was conducted to confirm if two or more food items were correlated.

6.4 Implication of conducting meta-analysis versus pooled analysis in dietary consumption and bladder cancer research

Some individual studies had small sample sizes and lacked statistical power to yield conclusive results on the association between fluid consumption and risk of developing bladder cancer. In chapter 3 and 5 of this thesis, a meta-analysis and a pooled analysis procedure was used to investigate the association between fluid consumption and risk of developing bladder cancer. Meta-analysis and a pooled analysis methods are extensively used in epidemiological research when results from individual studies are inconclusive.[15] The meta-analysis required pooling of results of individual studies to produce an overall summary effect. The pooled analysis involved pooling individual patient data from prior studies to produce a single data set and the effect of exposure on disease is then

investigated.[15] Both a meta-analysis and pooled analysis methods have usually greater statistical power and give more precise estimates when compared to individual studies.[16] Despite the benefits of using meta-analysis and pooled analysis in term of gaining statistical power, both methods have advantages and disadvantages. In the dose-response meta-analysis in this thesis, a subgroup analysis according to smoking could not be conducted because most individual studies did not report the association between total fluid consumption and risk of developing bladder cancer stratified by smoking. However, in the pooled analysis individual patient data was available on smoking history, gender and age for studies included in the BLEND consortium.

Furthermore, the studies included in both the meta-analysis and pooled analysis were conducted in different populations, there is a chance that there will be variations between studies hence is critically important to choose a model that will take account of these variations. The random effect model was used in the dose-response meta-analysis which takes into account the variations in terms population across the studies. In the pooled analysis a more complex model (multilevel mixed-effects logistic regression model) was used which takes into account the variation across the studies but also potential clustering within studies. An example of a clustering within a study is when subjects are recruited from different centers or hospitals.

In the meta-analysis, information on the overall total fluid intake was available in the relevant articles. Therefore, the pooled analysis was a more appropriate approach to be adopted when compared to the meta-analysis because it gave the opportunity to: explore variation within study for example clustering and investigate the association between consumption of specific fluid item (for example water, coffee) and risk of developing

bladder cancer. All these analyses were not possible in a meta-analysis because only data on overall fluid consumption and risk of developing bladder was available.[16]

Table 6.2 Strengths and limitations of meta-analysis and pooled analysis[15]

Methods	Strengths	Limitations
Meta-analysis	• Gives a further comprehensive summary of literature than narrative systematic review • Gives a precise estimate of the average effect from all available studies • Increases statistical power • Examine between study heterogeneity	• Heterogeneity across included studies • Difficult to examine subgroup analyses or conduct stratified analysis • Errors cannot be checked in individual studies because of lack of availability of individual patient data
Pooled analysis	• Increase statistical power • Permits subgroup analyses • Allows better adjustment of confounders • Gives a precise estimates of the average effect from all available studies	• Time consuming • Involves collaboration with many principal investigators • Unavailability of data and some principal investigators might not be willing to participate

6.5 Case-control studies

In a case-control study the cases are identified with a particular disease in a given population and the controls are generally free of disease of interest.[17] Details on exposures are collected retrospectively. In chapter two of this thesis, a hospital based case-control design was used to investigate the association between dietary consumption and diet diversity and risk of developing bladder cancer. Cases were histologically confirmed bladder cancer patient and the controls were recruited from the same hospital as the cases and were free from cancer. The case-control design was used in this study because it is more appropriate to study diseases that are rare, for example bladder cancer and inexpensive in terms of cost of data collection and processing. However, compared to a

prospective cohort, case-control studies may be subject to recall bias and selection bias.[17] Strengths of case-control studies are: case-control studies are less expensive and quicker to conduct compared to other study designs such as cohort study. Also, they are suitable for examining rare diseases such as bladder cancer. Case-control studies can be used to investigate multiple risk factors and smaller sample sizes are necessary compared to cohort studies.

Further limitations of case-control studies include: this study design is limited to examining one outcome. Also, case-control studies are subject to recall and selection bias, and rare exposures are difficult to investigate. In chapter 2, 3, and 5 of this thesis, the limitations of recall and selection bias have been discussed for each chapter.

In this study, both hospital and population controls were included and both controls have numerous strengths and limitation. Although the hospital controls are not healthy and may have diseases with the same risk factors. In this study controls were hospitalized for digestive, cardiovascular and respiratory diseases therefore I conducted a sensitivity analysis excluding controls that have digestive problem. No substantial effect on the OR estimates was observed after including or excluding these controls. Using hospital controls in case-control studies have some advantages for example: the hospital controls are easy to find and more co-operative and have similar tendency to remember past exposure and other factors (such as ethnic and socioeconomic status). In addition, when hospital controls are used, recall bias and selection bias are minimized because the hospital controls are from the same source population and are sick but have different diagnosis.

6.6 Implication for practice

According to the findings in this thesis, diet diversity may reduce the risk of developing bladder cancer, particularly fruit diversity. Therefore, the policy makers and general public should be aware of importance of variety in diet and should be encouraged to consume diverse diet particularly a diet diverse in fruit. Although this is the second study on this topic area therefore more investigation. The World Health Organization (WHO) dietary guidelines advice the general public to increase intake of variety of different foods through and within food groups to encourage good health and for consumption of sufficient essential nutrients.[18] In addition, individuals should be aware that consumption of citrus fruits, stone fruits, vine fruits, flower vegetables (broccoli, cauliflower), white fresh fish, eggs, potatoes and dairy products could prevent bladder cancer. While high consumption of red meat, organ meat, bulb vegetables and preserved vegetables could increase the risk of bladder cancer. Also, it has been recommended by experts that diet consisting of low fat from meat might reduce the risk of chronic diseases such as cardiovascular diseases.[19] The World Cancer Research Fund (WCRF)/ American Institute for Cancer Research (AICR) suggested that a diverse diet consisting of protein-rich and starch plant based foods might be a better diet when compared to diets high in meat, alcohol, fat and sugar.[19]

The results of this thesis emphasize that eight cups of fluid per day should be consumed; this finding is consistent with the normal recommended fluid consumption per day. Therefore, general public should be advised by health professionals and doctors to consume the recommended 6 cups of total fluid per day and in relation to bladder cancer risk. Findings of this thesis suggest that consumption of ten or more cups of coffee is associated with on elevated risk of developing bladder cancer. Hence, general public

should be advised on the effect of excessive consumption of coffee and the risk of developing bladder cancer. Although, the relative risk of 2.9 was observed for coffee consumption, 3% of cases who consumed 10 or more cups of coffee could be attributed to having bladder cancer. So in essence, a case number of bladder cancers could potentially be prevented if people who consume a lot of coffee would decrease their coffee consumption.

6.7 Recommendation for future research on dietary consumption and bladder cancer

People eat meals consisting of different food groups (for example fish, grains and vegetables etc.) with combination of nutrients. To my knowledge, this is the second study that explicitly investigated the effect of diet diversity and risk of developing bladder cancer risk. Therefore, it is important for researchers to further examine diet diversity and risk of developing bladder cancer in detail using combination of alternative tools such as diet diversity questionnaire as proposed by Food and Agriculture Organization (FAO) or 24 hour recall questionnaire. [20]

Since most individuals consume different variety of food items and drinks each day, therefore, future research should explore the effect of dietary patterns and risk of developing bladder cancer. To my knowledge only one study has investigated the association between dietary pattern and risk of developing bladder cancer. [21]

To date, most epidemiological studies have focused mainly on dietary consumption and risk of developing bladder cancer and there is a need to further investigate the prognosis of bladder cancer in relation to dietary consumption. Additionally, the effect of dietary consumption in different stages of bladder cancer such as progression of non-muscle

invasive bladder cancer to muscle invasive bladder cancer should be investigated in detail. To my knowledge, only one study investigated the relationship between cruciferous vegetables and among bladder cancer survivors. The findings of the study suggest that broccoli consumption may reduce bladder cancer mortality.

Most studies conducted on dietary consumption in relation to bladder cancer were conducted in Europe, North America and few in Asia. Therefore, results observed in this thesis reflect the association between dietary consumption and fluid consumption and risk of developing bladder cancer in developed countries.[22,23] As a result, well-designed epidemiological studies are needed in Africa and Asia to investigate the dietary factors and diet diversity and risk of developing bladder cancer.

Future studies should report the different methods of cooking, preservation and processing of dietary and fluid items; to better understand the relationship between dietary consumption, fluid consumption and risk of developing bladder cancer.
The association between cooking method or method of food preparation and risk of developing bladder cancer was reported in three previous epidemiological studies. Findings from two of the previous studies have suggested that food items such as red meat when cooked in high temperature forms compounds like heterocycline amines that may increase the risk of developing bladder cancer. Another previous study suggested no significant association between cooking method and risk of developing bladder cancer. Also, deep fried foods are associated with elevated risk of diseases; hence according to World Health Organization (WHO) a safe way of preparation of food to reduce fat is by steaming, boiling, grilling and baking.[5] Additionally, evidence on the method of

preservation and processing of food and fluid items on the risk of developing cancer are limited.

6.8 General conclusion

The general conclusions of this thesis are: higher diet diversity, particularly a diet varied in fruit may reduce the risk of developing bladder cancer. A low to moderate fluid consumption was not associated with an increased risk of developing bladder cancer; although fluid consumption exceeding 8 cups per day increases the risk of developing bladder cancer substantially in men. A J shape association between total fluid intake and bladder cancer risk in men was observed. An increased risk of developing bladder cancer by 3 folds in men who consumed at least 10 or more cups (≥2500 ml/day) of coffee per day was found. In addition, the positive association between coffee consumption and bladder cancer risk in men was observed both in ever smokers— after adjusting for amount of cigarette smoked and smoking duration —and never smokers.

6.9 References

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Appendices

Appendix 2.1: Published Article in Journal of Cancer Causes and Control: Dietary consumption and diet diversity and risk of developing bladder cancer: results from the South East China case-control study

Appendix 3.1: Search strategy for dose response meta-analysis on fluid intake and risk of developing bladder cancer

Ovid MEDLINE(R) 1946 to November Week 3 2012
Search Strategy:

#	Searches	Results
1	bladder cancer$.mp. or exp Urinary Bladder Neoplasms/	43742
2	ucc.mp.	322
3	exp Carcinoma, Transitional Cell/ or tcc.mp.	16698
4	((bladder or urinary) adj2 (neoplasm$ or cancer$ or carcinoma$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	45530
5	or/1-4	50704
6	((fluid$ or liquid$ or beverage$) adj2 (intake or consumption)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	4978
7	drink$.mp.	121247
8	drinking behavior.mp. or exp Drinking Behavior/	53693
9	or/6-8	124064
10	5 and 9	725

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations January 02, 2013
Search Strategy:

#	Searches	Results
1	bladder cancer$.mp. or exp Urinary Bladder Neoplasms/	1313
2	ucc.mp.	20
3	tcc.mp. or exp Carcinoma, Transitional Cell/	243
4	((bladder or urinary) adj2 (neoplasm$ or cancer$ or carcinoma$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	1525
5	or/1-4	1679
6	((fluid$ or liquid$ or beverage$) adj2 (intake or consumption)).mp. [mp=title, abstract, original title, name	265

	of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	
7	drink$.mp.	4765
8	drinking behavior.mp. or exp Drinking Behavior/	399
9	or/6-8	4955
10	5 and 9	

Embase 1974 to 2012 December 19

Search Strategy:

#	Searches	Results
1	bladder cancer$.mp. or exp bladder cancer/	45625
2	ucc.mp.	475
3	transitional cell carcinoma/ or tcc.mp.	17287
4	((bladder or urinary) adj2 (neoplasm$ or cancer$ or carcinoma$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	56204
5	or/1-4	64959
6	((fluid$ or liquid$ or beverage$) adj2 (intake or consumption)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18041
7	drink$.mp.	137681
8	drinking behavior.mp. or exp drinking behavior/	33919
9	or/6-8	150175
10	5 and 9	957

Pubmed

"Urinary Bladder Neoplasms"[Mesh] AND "Beverages"[Mesh] AND (Journal Article[ptyp] AND hasabstract[text] AND "humans"[MeSH Terms])

Appendix 3.2: Appendix 3.2: Meta-regression for total fluid intake and risk of developing bladder cancer

CHARACTERISTIC	SUMMARY RR (95%CI)	STANDARD ERROR
Year of publication		
Old studies	1.00	
New studies	1.00(0.87-1.14)	.05538
Method of fluid assessment		
Interview and questionnaire	1.00	
Food frequency questionnaire	0.94 (0.82-1.08)	.05119
Type of study design		
Hospital based case-control study	1.00	
Population based case-control study	0.99(0.87-1.12)	.04962
Cohort study	1.08(0.88-1.32)	.09035
Continent		
North America	1.00	
Europe	0.97(0.84-1.11)	.05413
Asia	0.93(0.80-1.08)	.05596
Smoking		
Never smoked/former smoker/current smoker	1.00	
Never smoked/former smoker/current smoker (pack years)	1.03(0.90-1.20)	.06202
Never smoked/former smoker/current smoker (smoking frequency and smoking duration)	0.96(0.82-1.11)	.05745

Appendix 4.1 Studies not included in The Bladder Cancer Epidemiology and Nutritional Determinant (BLEND) Consortium

First author	Country	Year	Design	Number Case	Number Controls	Recruitment period	Study name
Sun [1]	China	2004	Cohort	61	18244	1986-1989	Shanghai Cohort Study
Sun[2]	China	2002	Cohort	61	63257	1993-1998	Singapore Chinese Health Study
Serra [3]	Spain	2008	Case-Control	1219	1271	1998-2001	Spanish Bladder Cancer Study
Ciccone [4]	Italy	1988	Case-Control	567	794	1978-1983	Turin Study
Carel [5]	Israël	1999	Case-Control	92	92	1989-1993	Israël Study
Lynch [6]	USA	1987	Case-Control	49	956	N/A	Omaha, Nebraska Study
Schabath [7]	USA	2005	Case-Control	409	451	1999-2003	The University of Texas M.D. Anderson Cancer Center
Loffredo	Egypt	Ongoing at time of systematic literature search		-	-	2006-ongoing	Egypt Bladder Cancer Case-Control Study
Kiemeney[8]	Hungary, Romania, Slovakia		Case-Control	214	540	2002-2004	Eastern European Bladder Cancer Study
Rohan [9]	Canada	2007	Cohort	140	4800	1995-1998	Canadian Study of Diet and Health
Aben[10]	The Netherlands	2008	Case-Control	1453	6468	1995-2006	Nijmegen Bladder Cancer Study
Baris[11]	USA	2009	Case-Control	1170	1413	2001-2004	New England Study
Radosavljevic[12]	Serbia	2005	Case-Control	130	130	1997-199	Serbia Case-Control Study
Riboli[13]	Spain	1991	Case-Control	432	792	1985-1986	Spanish Multi-centre Case-Control Study
Sakauchi	Japan	2005	Cohort	123	-	1988-1997	Japan collaborative Cohort Study
Zhao[14]	USA	2007	Case-Control	697	708	1999-2007	The University of Texas M.D. Anderson Cancer Centre Study
Wilkens[15]	Hawaii	1996	Case-Control	261	522	1979-1986	Hawaii Study
Mucci[16]	Sweden	2003	Case-Control	263	538	1992-1994	Stockholm cancer Study
Aune[17]	Uraguay	2009	Case-Control	254	2117	1996-2004	Uraguay cancer Study
Balbi [18]	Uraguay	2001	Case-Control	144	516	1998-1999	Montevideo Study
Michaud [19]	Spain	2007	Case-Control	397	664	1998-2001	Bladder cancer Spain Study
Greffroy-perez[20]	France	2001	Case-Control	765	765	1984-1987	France Case-Control Study
Cantor[21]	USA	1998	Case-Control	1452	2434	1986-1989	Iowa Case-Control Study
Brummer[22]	USA	1996	Case-Control	202	220	1987-1990	Western Washington Case-Control Study

Kunze[23]	Germany	1992	Case-Control	491	431	1977-1985	South Lower Saxony Case-control Study
Slattery[24]	USA	1988	Case-Control	419	889	1977-1982	Utah Case-Control Study
Jensen[25]	Denmark	1986	Case-Control	371	771	1979-1981	Cophenghen Case-Control Study
Claude[26]	Germany	1986	Case-Control	431	431	1977-1982	Southern Lower Saxony Case-Control Study
Michaud [27]	Finland	2002	Cohort	344	-	1985-1998	Alpha-tocopherol beta-carotene cancer prevention Study
Michaud [28]	USA	2000	Cohort	320	-	1986-Ongoing	Health professional follow up study
La Vecchia[29]	Italy	1989	Case-Control	163	181	1985-Ongoing	Northern Italy Case-Control Study
Keszei[30]	The Netherlands	2009	Case-Control	1549	-	1986-2003	Netherlands Cohort Study on Diet and Cancer
Demiral [31]	Turkey	2008	Case-Control	164	324	2001-2006	Urology Clinic of Ankara Diskapi Training Hospital Study
Destefani[32]	Uraguay	2007	Case-Control	255	501	1996-2006	Uraguay Bladder Cancer Case-Control study
Chyou[33]	Hawaii	1993	Case-Control	96	96	1965-1968	Oahu Hawaii Case-Control Study
Mills[34]	USA	1991	Cohort	52	-	1976-1982	Seventh-day Adventist Study
Risch[35]	Canada	1988	Case-Control	826	792	1979-1982	Canada Case-Control Study
Wynder[36]	USA	1980	Case-Control	367	367	1957-1960	New York Case-Control Study
Garcia-closas[37]	Spain	2007	1219	1219	1271	1998-2001	Spanish Bladder Cancer Study
Dunham[38]	USA	1968	Case-Control	702	NA	1958-1964	New Orleans Bladder Cancer Study
Bate[39]	Argentina	2007	Case-Control	114	114	N/A	Argentina Case-control Study
Castelao[40]	America	2004	Case-Control	1592	1592	1987-1996	Non-Asians Los Angeles Study
Sacerdote[41]	Italy	2007	Case-Control	266	193	1994-2003	Torino Study
Lin[42]	USA	2009	Case-Control	884	878	1999-Ongoing	Texas Cancer Centre Study
Kurashi[43]	Japan	2009	Cohort	206	-	1990-2005	Japanese bladder cancer Cohort

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Appendix 4.2 The Bladder Cancer Epidemiology and Nutritional Determinant (BLEND) Study codebook

VARIABLE CODE	VARIABLE LABEL	CODE	VALUE LABEL
A01	Study ID	101	Cohort of Swedish Men (Larsson et al)
		102	Jiang et al (Los Angeles)
		103	Tang et al (New York)
		104	Spanish Bladder Cancer Study (Garcia-Closas et al)
		105	Kellen et al (Limberg - Belgium)
		106	Singapore Chinese Health Study (Sun et al)
		107	Shanghai Cohort Study (Sun et al)
		108	Netherlands Cohort Study (Zeegers et al)
		109	Wakai et al (Japan)
		110	Lu et al (Taiwan)
		111	Pohlabeln et al (West Germany - Hessen)
		112	Hartge et al (US)
		113	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Wright et al)
		114	-
		115	Steineck et al (Stockholm)
		116	Quirk et al (New York)
		117	Spanish Bladder Cancer Study (Serra et al)
		118	Baena et al (Spain)
		119	-
		120	Turino Bladder Cancer Study (Sacerdote et al)
		121	Wallace et al (New Hampshire)
		122	-
		123	Randi et al (Italy)
		124	Carel et al (Israel)
		125	Porru et al
		126	Lynch et al (Omaha)
		127	Lutherstadt Wittenberg Bladder Cancer Study (Golka et al)
		128	Canadian Study (Gaertner et al)
		129	French Bladder Cancer Study
		130	SEARCH
		131	Anderson
		132	Zhang
		133	Fletcher
		134	Cantor
		135	Bosetti
		136	Kiemeney
		137	Taylor
		138	-
		139	New England
		140	Leeds
		141	Women's Health Study (Zhang et al)
		142	Swedish Women's Lifestyle and Health Study (Wiederpass et al)
		143	Canadian Study of Diet, Lifestyle, and Health (Rohan et al)
		144	Park
		145	Grant

A02	Primary Subject ID		Assigned subject number
A03	Study Subject ID		Study subject ID
A04	Study Design	10	Case-Control Study
		20	Cohort Study
		21	Retrospective Cohort Study
		22	Prospective Cohort Study
		30	Cross-sectional Study
A05	Assessment Method	10	Questionnaire
		11	Self-administered questionnaire
		12	Interview-administered questionnaire
		20	Registry
A06	Length of time investigated by questionnaire before diagnosis (categorical)	0	usual habit/currently
		1	habits before current illness
		2	< 1 year
		3	>= 1 year
A07	Country of study location	1	Argentina
		2	Belgium
		3	Canada
		4	China
		5	Singapore
		6	Denmark
		7	France
		8	Germany
		9	Greece
		10	Hawaii
		11	Israel
		12	Italy
		13	Japan
		14	Lebanon
		15	Pakistan
		16	Russia
		17	Serbia
		18	Spain
		19	Sweden
		20	Taiwan
		21	The Netherlands
		22	Tunisia
		23	Turkey
		24	UK
		25	Uruguay
		26	USA
A08	Subject Status	1	Case subject
		2	Control subject
		3	Cohort Subject
A09	Cluster	1	First centre or pair
		2	Second centre or pair
		3	Third centre or pair

		4	Fourth centre or pair
		5	Fifth centre or pair
		6	Sixth centre or pair
		7	Seven centre or pair
		8	Eigth centre or pair
B01	Age at time of bladder cancer diagnosis (years)		Age in years at time of diagnosis of bladder cancer
B02	Age at time of study/questionnaire (years)		Age in years at time of questioning/study
B03	Gender	1	Male
		2	Female
		.b	Not known - data not asked
		.a	Missing data
B04	Ethnic group	10	Caucasian
		20	Mixed
		21	White and Black Caribbean
		22	White and Black African
		23	Any other mixed background
		30	Asian
		31	Indian
		32	Pakistani
		33	Bangladeshi
		34	Any other Asian background
		40	Black
		41	Caribbean
		42	African
		43	Any other Black background
		50	Chinese
		60	Any other ethnic group
		.b	Not known - data not asked
		.a	Missing data
C01	Bladder Cancer Stage	10	Non-muscle invasive
		11	CIS
		12	Ta
		13	T1
		20	Muscle-invasive
		21	T2
		22	T3
		23	T4
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
C02	Nodal disease	1	No nodal disease
		2	Nodal disease
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
C03	Metastatic disease	1	No metastatic disease
		2	Metastatic disease

		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
C04	Bladder Cancer Grade	10	Low grade
		11	G1
		12	G2
		20	High grade (G3)
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
D01	Tobacco smoking status	1	Current tobacco smoker
		2	Former tobacco smoker
		3	Never tobacco smoker
		.b	Not known - data not asked
		.a	Missing data
D02	Cigarette smoking status	1	Current cigarette smoker
		2	Former cigarette smoker
		3	Never cigarette smoker
		.b	Not known - data not asked
		.a	Missing data
D03	Passive smoking status	1	No
		2	Yes
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
D04	Length of time smoking cigarettes (pack years)		Smoking pack years
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
D05	Number of cigarette smoked per day	.b	Not known - data not asked
		.a	Missing data
D06	Number of years of smoking cigarettes	.b	Not known - data not asked
		.a	Missing data
E01	Number of siblings	.b	Not known - data not asked
		.a	Missing data
E02	Number of brothers		Brothers
E03	Number of sisters		Sisters
E04	Number of offspring	.b	Not known - data not asked
		.a	Missing data
E05	Number of sons		Sons
E06	Number of daughters		Daughters
F01	1st degree relative with bladder cancer	1	Yes
		2	No
		.b	Not known - data not asked

		.a	Missing data
F02	No. of 1st degree relatives with bladder cancer		Number of 1st degree relatives with bladder cancer
F03	Classification of 1st degree relative with bladder cancer - Relative 1	10	Parent
		11	Father
		12	Mother
		20	Sibling
		21	Sister
		22	Brother
		30	Offspring
		31	Daughter
		32	Son
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F04	Classification of 1st degree relative with bladder cancer - Relative 2	10	Parent
		11	Father
		12	Mother
		20	Sibling
		21	Sister
		22	Brother
		30	Offspring
		31	Daughter
		32	Son
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F05	Classification of 1st degree relative with bladder cancer - Relative 3	10	Parent
		11	Father
		12	Mother
		20	Sibling
		21	Sister
		22	Brother
		30	Offspring
		31	Daughter
		32	Son
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F06	Classification of 1st degree relative with bladder cancer - Relative 4	10	Parent

		11	Father
		12	Mother
		20	Sibling
		21	Sister
		22	Brother
		30	Offspring
		31	Daughter
		32	Son
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F07	Classification of 1st degree relative with bladder cancer - Relative 5	10	Parent
		11	Father
		12	Mother
		20	Sibling
		21	Sister
		22	Brother
		30	Offspring
		31	Daughter
		32	Son
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F08	2nd degree relative with bladder cancer	1	Yes
		2	No
		.b	Not known - data not asked
		.a	Missing data
F09	No. of 2nd degree relatives with bladder cancer		Number of 2nd degree relatives with bladder cancer
F10	Classification of 2nd degree relative with bladder cancer - Relative 1	1	Paternal relative
		2	Maternal relative
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F11	Classification of 2nd degree relative with bladder cancer - Relative 2	1	Paternal relative
		2	Maternal relative
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F12	Classification of 2nd degree relative with bladder cancer -	1	Paternal relative

	Relative 3		
		2	Maternal relative
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F13	Classification of 2nd degree relative with bladder cancer - Relative 4	1	Paternal relative
		2	Maternal relative
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
F14	Classification of 2nd degree relative with bladder cancer - Relative 5	1	Paternal relative
		2	Maternal relative
		.c	Not applicable
		.b	Not known - data not asked
		.a	Missing data
EC010000P	Milk and milk products in portions		Portions per week
EC010000G	Milk and milk products in grammes		Grammes per week
EC010000ML	Milk and milk products in millilitres		Millilitres per week
EC010000XP	Milk and milk products - MISCELLANEOUS - in portions		Portions per week
EC010000XG	Milk and milk products - MISCELLANEOUS - in grammes		Grammes per week
EC010000XML	Milk and milk products - MISCELLANEOUS - in millilitres		Millilitres per week
EC010100P	Liquid milks in portions		Portions per week
EC010100ML	Liquid milks in millilitres		Millilitres per week
EC010100P	Liquid milks - MISCELLANEOUS- in portions		Portions per week
EC010100ML	Liquid milks - MISCELLANEOUS- in millilitres		Millilitres per week
EC010110P	Milk >4% fat in portions		Portions per week
EC010110ML	Milk >4% fat in millilitres		Millilitres per week
EC010120P	Milk 3-4% fat in portions		Portions per week
EC010120ML	Milk 3-4% fat in		Millilitres per week

	millilitres		
EC010130P	Milk 1-2.9% fat in portions		Portions per week
EC010130ML	Milk 1-2.9% fat in millilitres		Millilitres per week
EC010140P	Milk <1% fat in portions		Portions per week
EC010140ML	Milk <1% fat in millilitres		Millilitres per week
EC010200P	Processed milks in portions		Portions per week
EC010200ML	Processed milks in millilitres		Millilitres per week
EC010210P	Chocolate-flavoured milk in portions		Portions per week
EC010210ML	Chocolate-flavoured milk in millilitres		Millilitres per week
EC010220P	Fruit-flavoured milk in portions		Portions per week
EC010220ML	Fruit-flavoured milk in millilitres		Millilitres per week
EC010230P	Evaporated milk in portions		Portions per week
EC010230G	Evaporated milk in grammes		Grammes per week
EC010230ML	Evaporated milk in millilitres		Millilitres per week
EC010240P	Condensed milk in portions		Portions per week
EC010240G	Condensed milk in grammes		Grammes per week
EC010240ML	Condensed milk in millilitres		Millilitres per week
EC010250P	Dried milk in portions		Portions per week
EC010250G	Dried milk in grammes		Grammes per week
EC010250ML	Dried milk in millilitres		Millilitres per week
EC010260P	Filled milk in portions		Portions per week
EC010260G	Filled milk in grammes		Grammes per week
EC010260ML	Filled milk in millilitres		Millilitres per week
EC010270P	Buttermilk in portions		Portions per week
EC010270G	Buttermilk in grammes		Grammes per week
EC010270ML	Buttermilk in millilitres		Millilitres per week
EC010280P	Acidophilus milk in portions		Portions per week
EC010280G	Acidophilus milk in grammes		Grammes per week
EC010280ML	Acidophilus milk in millilitres		Millilitres per week
EC010290P	Whey in portions		Portions per week
EC010290G	Whey in grammes		Grammes per week
EC010290ML	Whey in millilitres		Millilitres per week
EC010300P	Cream in portions		Portions per week
EC010300G	Cream in grammes		Grammes per week
EC010300ML	Cream in millilitres		Millilitres per week
EC010310P	Cream >50% fat in		Portions per week

	portions		
EC010310G	Cream >50% fat in grammes		Grammes per week
EC010310ML	Cream >50% fat in millilitres		Millilitres per week
EC010320P	Cream 31-50% fat in portions		Portions per week
EC010320G	Cream 31-50% fat in grammes		Grammes per week
EC010320ML	Cream 31-50% fat in millilitres		Millilitres per week
EC010330P	Cream 15-30% fat in portions		Portions per week
EC010330G	Cream 15-30% fat in grammes		Grammes per week
EC010330ML	Cream 15-30% fat in millilitres		Millilitres per week
EC010340P	Cream <15% fat in portions		Portions per week
EC010340G	Cream <15% fat in grammes		Grammes per week
EC010340ML	Cream <15% fat in millilitres		Millilitres per week
EC010400P	Yoghurt in portions		Portions per week
EC010400G	Yoghurt in grammes		Grammes per week
EC010400ML	Yoghurt in millilitres		Millilitres per week
EC010410P	Yoghurt >3% fat in portions		Portions per week
EC010410G	Yoghurt >3% fat in grammes		Grammes per week
EC010410ML	Yoghurt >3% fat in millilitres		Millilitres per week
EC010420P	Yoghurt 1-3% fat in portions		Portions per week
EC010420G	Yoghurt 1-3% fat in grammes		Grammes per week
EC010240ML	Yoghurt 1-3% fat in millilitres		Millilitres per week
EC010430P	Yoghurt <1% fat in portions		Portions per week
EC010430G	Yoghurt <1% fat in grammes		Grammes per week
EC010430ML	Yoghurt <1% fat in millilitres		Millilitres per week
EC010500P	Cheese in portions		Portions per week
EC010500G	Cheese in grammes		Grammes per week
EC010510P	Fresh cheese in portions		Portions per week
EC010510G	Fresh cheese in grammes		Grammes per week
EC010511P	Fresh cheese >60% fat in portions		Portions per week
EC010511G	Fresh cheese >60% fat in grammes		Grammes per week
EC010512P	Fresh cheese 46-60% fat in portions		Portions per week

EC010512G	Fresh cheese 46-60% fat in grammes		Grammes per week
EC010513P	Fresh cheese 31-45% fat in portions		Portions per week
EC010513G	Fresh cheese 31-45% fat in grammes		Grammes per week
EC010514P	Fresh cheese 15-30% fat in portions		Portions per week
EC010514G	Fresh cheese 15-30% fat in grammes		Grammes per week
EC010515P	Fresh cheese <15% fat in portions		Portions per week
EC010515G	Fresh cheese <15% fat in grammes		Grammes per week
EC010520P	Soft cheese in portions		Portions per week
EC010520G	Soft cheese in grammes		Grammes per week
EC010521P	Soft cheese >60% fat in portions		Portions per week
EC010521G	Soft cheese >60% fat in grammes		Grammes per week
EC010522P	Soft cheese 46-60% fat in portions		Portions per week
EC010522G	Soft cheese 46-60% fat in grammes		Grammes per week
EC010523P	Soft cheese 30-45% fat in portions		Portions per week
EC010523G	Soft cheese 30-45% fat in grammes		Grammes per week
EC010524P	Soft cheese <30% fat in portions		Portions per week
EC010524G	Soft cheese <30% fat in grammes		Grammes per week
EC010530P	Semi-hard cheese in portions		Portions per week
EC010530G	Semi-hard cheese in grammes		Grammes per week
EC010531P	Semi-hard cheese >60% fat in portions		Portions per week
EC010531G	Semi-hard cheese >60% fat in grammes		Grammes per week
EC010532P	Semi-hard cheese 46-60% fat in portions		Portions per week
EC010532G	Semi-hard cheese 46-60% fat in grammes		Grammes per week
EC010533P	Semi-hard cheese 30-45% Fat in portions		Portions per week
EC010533G	Semi-hard cheese 30-45% Fat in grammes		Grammes per week
EC010534P	Semi-hard cheese <30% fat in portions		Portions per week
EC010534G	Semi-hard cheese <30% fat in grammes		Grammes per week
EC010540P	Hard cheese in portions		Portions per week
EC010540G	Hard cheese in grammes		Grammes per week

EC010541P	Hard cheese >50% fat in portions		Portions per week
EC010541G	Hard cheese >50% fat in grammes		Grammes per week
EC010542P	Hard cheese 30-50% fat in portions		Portions per week
EC010542G	Hard cheese 30-50% fat in grammes		Grammes per week
EC010543P	Hard cheese <30% fat in portions		Portions per week
EC010543G	Hard cheese <30% fat in grammes		Grammes per week
EC010550P	Blue cheese in portions		Portions per week
EC010550G	Blue cheese in grammes		Grammes per week
EC010551P	Blue cheese >50% fat in portions		Portions per week
EC010551G	Blue cheese >50% fat in grammes		Grammes per week
EC010552P	Blue cheese 30-50% fat in portions		Portions per week
EC010552G	Blue cheese 30-50% fat in grammes		Grammes per week
EC010553P	Blue cheese <30% fat in portions		Portions per week
EC010553G	Blue cheese <30% fat in grammes		Grammes per week
EC010560P	Smoked cheese in portions		Portions per week
EC010560G	Smoked cheese in grammes		Grammes per week
EC010570P	Processed cheese in portions		Portions per week
EC010570G	Processed cheese in grammes		Grammes per week
EC010580P	Whey cheese in portions		Portions per week
EC010580G	Whey cheese in grammes		Grammes per week
EC010600P	Imitation milk and cream in portions		Portions per week
EC010600G	Imitation milk and cream in grammes		Grammes per week
EC010610P	Soya milk in portions		Portions per week
EC010610ML	Soya milk in millilitres		Millilitres per week
EC010620P	Non-dairy coffee creamer in portions		Portions per week
EC010620ML	Non-dairy coffee creamer in millilitres		Millilitres per week
EC010630P	Imitation cream >20% fat in portions		Portions per week
EC010630ML	Imitation cream >20% fat in millilitres		Millilitres per week
EC010640P	Imitation cream < 20% fat in portions		Portions per week

EC010640ML	Imitation cream < 20% fat in millilitres		Millilitres per week
EC010650P	Soya yoghurt in grammes		Grammes per week
EC010650G	Soya yoghurt in portions		Portions per week
EC010650ML	Soya yoghurt in millilitres		Millilitres per week
EC010660P	Soya cheese in portions		Portions per week
EC010660G	Soya cheese in grammes		Millilitres per week
EC010700P	Milk beverage powders in portions		Portions per week
EC010700G	Milk beverage powders in millilitres		Millilitres per week
EC010710P	Milk shake powder in portions		Portions per week
EC010710G	Milk shake powder in grammes		Millilitres per week
EC010720P	Malt beverage powder in portions		Portions per week
EC010720G	Malt beverage powder in grammes		Millilitres per week
EC010730P	Drinking chocolate powder in portions		Portions per week
EC010730G	Drinking chocolate powder in grammes		Millilitres per week
EC010800P	Ices in portions		Portions per week
EC010800G	Ices in grammes		Grammes per week
EC010800ML	Ices in millilitres		Millilitres per week
EC010810P	Dairy ice cream in portions		Portions per week
EC010810G	Dairy ice cream in grammes		Grammes per week
EC010810ML	Dairy ice cream in millilitres		Millilitres per week
EC010820P	Non-dairy ice cream in portions		Portions per week
EC010820G	Non-dairy ice cream in grammes		Grammes per week
EC010820ML	Non-dairy ice cream in millilitres		Millilitres per week
EC010830P	Water ice in portions		Portions per week
EC010830G	Water ice in grammes		Grammes per week
EC010830ML	Water ice in millilitres		Millilitres per week
EC010840P	Garnita in portions		Portions per week
EC010840G	Garnita in grammes		Grammes per week
EC010840ML	Garnita in millilitres		Millilitres per week
EC010850P	Sorbet in portions		Portions per week
EC010850G	Sorbet in grammes		Grammes per week
EC010850ML	Sorbet in mililitres		Millilitres per week
EC020000P	Eggs in portions		Portions per week
EC020000G	Eggs in grammes		Grammes per week
EC020000XP	Eggs -		Portions per week

	MISCELLANEOUS - in portions		
EC020000XG	Eggs - MISCELLANEOUS - in grammes		Grammes per week
EC020100P	Chicken eggs in portions		Portions per week
EC020100G	Chicken eggs in grammes		Grammes per week
EC020110P	Whole chicken egg in portions		Portions per week
EC020110G	Whole chicken egg in grammes		Grammes per week
EC020120P	Chicken egg yolk in portions		Portions per week
EC020120G	Chicken egg yolk in grammes		Grammes per week
EC020130P	Chicken egg white in portions		Portions per week
EC020130G	Chicken egg white in grammes		Grammes per week
EC020200P	Turkey eggs in portions		Portions per week
EC020200G	Turkey eggs in grammes		Grammes per week
EC020300P	Duck eggs in portions		Portions per week
EC020300G	Duck eggs in grammes		Grammes per week
EC020400P	Goose eggs in portions		Portions per week
EC020400G	Goose eggs in grammes		Grammes per week
EC020500P	Quail eggs in portions		Portions per week
EC020500G	Quail eggs in grammes		Grammes per week
EC020600P	Ostrich eggs in portions		Portions per week
EC020600G	Ostrich eggs in grammes		Grammes per week
EC020700P	Seagull eggs in portions		Portions per week
EC020700G	Seagull eggs in grammes		Grammes per week
EC020800P	Egg products in portions		Portions per week
EC020800G	Egg products in grammes		Grammes per week
EC020810P	Scotch egg in portions		Portions per week
EC020810G	Scotch egg in grammes		Grammes per week
EC020900P	Egg dishes in portions		Portions per week
EC020900G	Egg dishes in grammes		Grammes per week
EC020910P	Omelette in portions		Portions per week
EC020910G	Omelette in grammes		Grammes per week
EC020920P	Soufflé Meringue in		Portions per week

	portions		
EC020920G	Soufflé Meringue in grammes		Grammes per week
EC020930P	Egg nog in portions		Portions per week
EC020930G	Egg nog in grammes		Grammes per week
EC030000P	Meat and meat products in portions		Portions per week
EC030000G	Meat and meat products in grammes		Grammes per week
EC030000XP	Meat and meat products - MISCELLANEOUS - in portions		Portions per week
EC030000XG	Meat and meat products - MISCELLANEOUS - in grammes		Grammes per week
EC030100P	Beef in portions		Portions per week
EC030100G	Beef in grammes		Grammes per week
EC030110P	Beef Tenderloin in portions		Portions per week
EC030110G	Beef Tenderloin in grammes		Grammes per week
EC030120P	Beef Striploin in portions		Portions per week
EC030120G	Beef Striploin in grammes		Grammes per week
EC030130P	Beef Fore-rib in portions		Portions per week
EC030130G	Beef Fore-rib in grammes		Grammes per week
EC030140P	Beef Topside in portions		Portions per week
EC030140G	Beef Topside in grammes		Grammes per week
EC030150P	Beef Silverside in portions		Portions per week
EC030150G	Beef Silverside in grammes		Grammes per week
EC030160P	Beef Shoulder clod in portions		Portions per week
EC030160G	Beef Shoulder clod in grammes		Grammes per week
EC030170P	Beef Chuck tender in portions		Portions per week
EC030170G	Beef Chuck tender in grammes		Grammes per week
EC030200P	Veal in portions		Portions per week
EC030200G	Veal in grammes		Grammes per week
EC030300P	Pork in portions		Portions per week
EC030300G	Pork in grammes		Grammes per week
EC030310P	Pork Loin in portions		Portions per week
EC030310G	Pork Loin in grammes		Grammes per week
EC030320P	Pork Tenderloin in portions		Portions per week

EC030320G	Pork Tenderloin in grammes		Grammes per week
EC030330P	Pork Neck in portions		Portions per week
EC030330G	Pork Neck in grammes		Grammes per week
EC030340P	Pork Belly in portions		Portions per week
EC030340G	Pork Belly in grammes		Grammes per week
EC030350P	Pork Chump in portions		Portions per week
EC030350G	Pork Chump in grammes		Grammes per week
EC030360P	Pork Leg in portions		Portions per week
EC030360G	Pork Leg in grammes		Grammes per week
EC030400P	Mutton/Lamb in portions		Portions per week
EC030400G	Mutton/Lamb in grammes		Grammes per week
EC030500P	Mammals in portions		Portions per week
EC030500G	Mammals in grammes		Grammes per week
EC030510P	Horse in portions		Portions per week
EC030510G	Horse in grammes		Grammes per week
EC030520P	Goat in portions		Portions per week
EC030520G	Goat in grammes		Grammes per week
EC030530P	Rabbit in portions		Portions per week
EC030530G	Rabbit in grammes		Grammes per week
EC030540P	Wild pig/boar in portions		Portions per week
EC030540G	Wild pig/boar in grammes		Grammes per week
EC030550P	Venison in portions		Portions per week
EC030550G	Venison in grammes		Grammes per week
EC030560P	Elk in portions		Portions per week
EC030560G	Elk in grammes		Grammes per week
EC030570P	Reindeer in portions		Portions per week
EC030570G	Reindeer in grammes		Grammes per week
EC030580P	Chamois in portions		Portions per week
EC030580G	Chamois in grammes		Grammes per week
EC030590P	Kangaroo in portions		Portions per week
EC030590G	Kangaroo in grammes		Grammes per week
EC030600P	Poultry in portions		Portions per week
EC030600G	Poultry in grammes		Grammes per week
EC030610P	Chicken in portions		Portions per week
EC030610G	Chicken in grammes		Grammes per week
EC030611P	Chicken breast in portions		Portions per week
EC030611G	Chicken breast in grammes		Grammes per week
EC030612P	Chicken leg in portions		Portions per week
EC030612G	Chicken leg in grammes		Grammes per week
EC030613P	Chicken wing in portions		Portions per week
EC030613G	Chicken wing in grammes		Grammes per week

EC030620P	Turkey in portions		Portions per week
EC030620G	Turkey in grammes		Grammes per week
EC030621P	Turkey breast in portions		Portions per week
EC030621G	Turkey breast in grammes		Grammes per week
EC030622P	Turkey leg in portions		Portions per week
EC030622G	Turkey leg in grammes		Grammes per week
EC030623P	Turkey wing in portions		Portions per week
EC030623G	Turkey wing in grammes		Grammes per week
EC030700P	Birds in portions		Portions per week
EC030700G	Birds in grammes		Grammes per week
EC030710P	Duck in portions		Portions per week
EC030710G	Duck in grammes		Grammes per week
EC030720P	Goose in portions		Portions per week
EC030720G	Goose in grammes		Grammes per week
EC030730P	Pigeon in portions		Portions per week
EC030730G	Pigeon in grammes		Grammes per week
EC030740P	Guinea fowl in portions		Portions per week
EC030740G	Guinea fowl in grammes		Grammes per week
EC030750P	Pheasant in portions		Portions per week
EC030750G	Pheasant in grammes		Grammes per week
EC030760P	Partridge in portions		Portions per week
EC030760G	Partridge in grammes		Grammes per week
EC030770P	Quail in portions		Portions per week
EC030770G	Quail in grammes		Grammes per week
EC030780P	Grouse in portions		Portions per week
EC030780G	Grouse in grammes		Grammes per week
EC030790P	Ostrich in portions		Portions per week
EC030790G	Ostrich in grammes		Grammes per week
EC030800P	Liver in portions		Portions per week
EC030800G	Liver in grammes		Grammes per week
EC030810P	Beef liver in portions		Portions per week
EC030810G	Beef liver in grammes		Grammes per week
EC030820P	Veal liver in portions		Portions per week
EC030820G	Veal liver in grammes		Grammes per week
EC030830P	Pork liver in portions		Portions per week
EC030830G	Pork liver in grammes		Grammes per week
EC030840P	Mutton/Lamb liver in portions		Portions per week
EC030840G	Mutton/Lamb liver in grammes		Grammes per week
EC030850P	Chicken liver in portions		Portions per week
EC030850G	Chicken liver in grammes		Grammes per week
EC030860P	Turkey liver in portions		Portions per week
EC030860G	Turkey liver in grammes		Grammes per week

EC030870P	Duck liver in portions		Portions per week
EC030870G	Duck liver in grammes		Grammes per week
EC030880P	Goose liver in portions		Portions per week
EC030880G	Goose liver in grammes		Grammes per week
EC030900P	Kidney in portions		Portions per week
EC030900G	Kidney in grammes		Grammes per week
EC030910P	Beef kidney in portions		Portions per week
EC030910G	Beef kidney in grammes		Grammes per week
EC030920P	Veal kidney in portions		Portions per week
EC030920G	Veal kidney in grammes		Grammes per week
EC030930P	Pork kidney in portions		Portions per week
EC030930G	Pork kidney in grammes		Grammes per week
EC030940P	Mutton/lamb kidney in portions		Portions per week
EC030940G	Mutton/lamb kidney in grammes		Grammes per week
EC031000P	Other offal in portions		Portions per week
EC031000G	Other offal in grammes		Grammes per week
EC031010P	Tongue in portions		Portions per week
EC031010G	Tongue in grammes		Grammes per week
EC031020P	Heart in portions		Portions per week
EC031020G	Heart in grammes		Grammes per week
EC031030P	Lungs in portions		Portions per week
EC031030G	Lungs in grammes		Grammes per week
EC031040P	Stomach in portions		Portions per week
EC031040G	Stomach in grammes		Grammes per week
EC031050P	Intestines in portions		Portions per week
EC031050G	Intestines in grammes		Grammes per week
EC031060P	Marrowbone in portions		Portions per week
EC031060G	Marrowbone in grammes		Grammes per week
EC031070P	Tail in portions		Portions per week
EC031070G	Tail in grammes		Grammes per week
EC031080P	Trotters and feet in portions		Portions per week
EC031080G	Trotters and feet in grammes		Grammes per week
EC031090P	Giblets in portions		Portions per week
EC031090G	Giblets in grammes		Grammes per week
EC031100P	Preserved meats in portions		Portions per week
EC031100G	Preserved meats in grammes		Grammes per week
EC031110P	Ham in portions		Portions per week
EC031110G	Ham in grammes		Grammes per week
EC031120P	Bacon in portions		Portions per week
EC031120G	Bacon in grammes		Grammes per week
EC031130P	Preserved beef in		Portions per week

	portions		
EC031130G	Preserved beef in grammes		Grammes per week
EC031140P	Preserved poultry in portions		Portions per week
EC031140G	Preserved poultry in grammes		Grammes per week
EC040000P	Fish and fish products in portions		Portions per week
EC040000G	Fish and fish products in grammes		Grammes per week
EC040000XP	Fish and fish products - MISCELLANEOUS - in portions		Portions per week
EC040000XG	Fish and fish products - MISCELLANEOUS - in grammes		Grammes per week
EC040100P	Clupeiformes in portions		Portions per week
EC040100G	Clupeiformes in grammes		Grammes per week
EC040110P	Herring in portions		Portions per week
EC040110G	Herring in grammes		Grammes per week
EC040120P	Sprat in portions		Portions per week
EC040120G	Sprat in grammes		Grammes per week
EC040130P	Sardine and pilchard in portions		Portions per week
EC040130G	Sardine and pilchard in grammes		Grammes per week
EC040140P	Anchovy in portions		Portions per week
EC040140G	Anchovy in grammes		Grammes per week
EC040150P	Shad in portions		Portions per week
EC040150G	Shad in grammes		Grammes per week
EC040160P	Salmon and trout in portions		Portions per week
EC040160G	Salmon and trout in grammes		Grammes per week
EC040170P	Char in portions		Portions per week
EC040170G	Char in grammes		Grammes per week
EC040180P	Smelt in portions		Portions per week
EC040180G	Smelt in grammes		Grammes per week
EC040190P	Whitefish in portions		Portions per week
EC040190G	Whitefish in grammes		Grammes per week
EC040200P	Perciformes in portions		Portions per week
EC040200G	Perciformes in grammes		Grammes per week
EC040210P	Perch in portions		Portions per week
EC040210G	Perch in grammes		Grammes per week
EC040220P	Bass Surgeon-fish in portions		Portions per week
EC040220G	Bass Surgeon-fish in grammes		Grammes per week

EC040230P	Mackerel in portions		Portions per week
EC040230G	Mackerel in grammes		Grammes per week
EC040240P	Tuna in portions		Portions per week
EC040240G	Tuna in grammes		Grammes per week
EC040250P	Sea catfish and wolf-fish in portions		Portions per week
EC040250G	Sea catfish and wolf-fish in grammes		Grammes per week
EC040260P	Grey mullet in portions		Portions per week
EC040260G	Grey mullet in grammes		Grammes per week
EC040300P	Gadiformes in portions		Portions per week
EC040300G	Gadiformes in grammes		Grammes per week
EC040310P	Cod and whiting in portions		Portions per week
EC040310G	Cod and whiting in grammes		Grammes per week
EC040320P	Hake in portions		Portions per week
EC040320G	Hake in grammes		Grammes per week
EC040400P	Pleuronectiformes in portions		Portions per week
EC040400G	Pleuronectiformes in grammes		Grammes per week
EC040410P	Flounder in portions		Portions per week
EC040410G	Flounder in grammes		Grammes per week
EC040420P	Halibut in portions		Portions per week
EC040420G	Halibut in grammes		Grammes per week
EC040430P	Plaice in portions		Portions per week
EC040430G	Plaice in grammes		Grammes per week
EC040440P	Sole in portions		Portions per week
EC040440G	Sole in grammes		Grammes per week
EC040500P	Cypriniformes in portions		Portions per week
EC040500G	Cypriniformes in grammes		Grammes per week
EC040510P	Roach in portions		Portions per week
EC040510G	Roach in grammes		Grammes per week
EC040520P	Carp in portions		Portions per week
EC040520G	Carp in grammes		Grammes per week
EC040530P	Babel in portions		Portions per week
EC040530G	Babel in grammes		Grammes per week
EC040540P	Bream in portions		Portions per week
EC040540G	Bream in grammes		Grammes per week
EC040600P	Other fish in portions		Portions per week
EC040600G	Other fish in grammes		Grammes per week
EC040610P	Eels in portions		Portions per week
EC040610G	Eels in grammes		Grammes per week
EC040620P	Zeomorphi in portions		Portions per week
EC040620G	Zeomorphi in grammes		Grammes per week
EC040630P	Lophiiformes in portions		Portions per week

EC040630G	Lophiiformes in grammes		Grammes per week
EC040640P	Selachoidei in portions		Portions per week
EC040640G	Selachoidei in grammes		Grammes per week
EC040650P	Rays in portions		Portions per week
EC040650G	Rays in grammes		Grammes per week
EC040660P	Acipenseriformes in portions		Portions per week
EC040660G	Acipenseriformes in grammes		Grammes per week
EC040700P	Crustaceans in portions		Portions per week
EC040700G	Crustaceans in grammes		Grammes per week
EC040710P	Crab in portions		Portions per week
EC040710G	Crab in grammes		Grammes per week
EC040720P	Lobster in portions		Portions per week
EC040720G	Lobster in grammes		Grammes per week
EC040730P	Prawns in portions		Portions per week
EC040730G	Prawns in grammes		Grammes per week
EC040740P	Shrimps in portions		Portions per week
EC040740G	Shrimps in grammes		Grammes per week
EC040750P	Crayfish in portions		Portions per week
EC040750G	Crayfish in grammes		Grammes per week
EC040800P	Molluscs in portions		Portions per week
EC040800G	Molluscs in grammes		Grammes per week
EC040810P	Quid in portions		Portions per week
EC040810G	Quid in grammes		Grammes per week
EC040820P	Octopus in portions		Portions per week
EC040820G	Octopus in grammes		Grammes per week
EC040830P	Cuttlefish in portions		Portions per week
EC040830G	Cuttlefish in grammes		Grammes per week
EC040840P	Abalone in portions		Portions per week
EC040840G	Abalone in grammes		Grammes per week
EC040850P	Clam in portions		Portions per week
EC040850G	Clam in grammes		Grammes per week
EC040860P	Cockle in portions		Portions per week
EC040860G	Cockle in grammes		Grammes per week
EC040870P	Mussel in portions		Portions per week
EC040870G	Mussel in grammes		Grammes per week
EC040880P	Oyster in portions		Portions per week
EC040880G	Oyster in grammes		Grammes per week
EC040890P	Scallop in portions		Portions per week
EC040890G	Scallop in grammes		Grammes per week
EC040900P	Fish offal in portions		Portions per week
EC040900G	Fish offal in grammes		Grammes per week
EC040910P	Herring roe in portions		Portions per week
EC040910G	Herring roe in grammes		Grammes per week
EC040920P	Salmon roe in portions		Portions per week
EC040920G	Salmon roe in		Grammes per week

	grammes		
EC040930P	Cod roe in portions		Portions per week
EC040930G	Cod roe in grammes		Grammes per week
EC040940P	Mullet roe in portions		Portions per week
EC040940G	Mullet roe in grammes		Grammes per week
EC040950P	Caviar in portions		Portions per week
EC040950G	Caviar in grammes		Grammes per week
EC041000P	Dried and salted fish in portions		Portions per week
EC041000G	Dried and salted fish in grammes		Grammes per week
EC041010P	Dried cod in portions		Portions per week
EC041010G	Dried cod in grammes		Grammes per week
EC041020P	Bombay duck in portions		Portions per week
EC041020G	Bombay duck in grammes		Grammes per week
EC041030P	Shark's fin in portions		Portions per week
EC041030G	Shark's fin in grammes		Grammes per week
EC041040P	Jellyfish/seaweed in portions		Portions per week
EC041040G	Jellyfish/seaweed in grammes		Grammes per week
EC041100P	Smoked fish in portions		Portions per week
EC041100G	Smoked fish in grammes		Grammes per week
EC041110P	Smoked herring in portions		Portions per week
EC041110G	Smoked herring in grammes		Grammes per week
EC041120P	Smoked sprat in portions		Portions per week
EC041120G	Smoked sprat in grammes		Grammes per week
EC041130P	Smoked haddock in portions		Portions per week
EC041130G	Smoked haddock in grammes		Grammes per week
EC041140P	Smoked salmon and trout in portions		Portions per week
EC041140G	Smoked salmon and trout in grammes		Grammes per week
EC041150P	Smoked mackerel in portions		Portions per week
EC041150G	Smoked mackerel in grammes		Grammes per week
EC041160P	Smoked halibut in portions		Portions per week
EC041160G	Smoked halibut in grammes		Grammes per week
EC041170P	Smoked eel in portions		Portions per week
EC041170G	Smoked eel in grammes		Grammes per week
EC041180P	Smoked sturgeon in		Portions per week

	portions		
EC041180G	Smoked sturgeon in grammes		Grammes per week
EC041200P	Canned fish in portions		Portions per week
EC041200G	Canned fish in grammes		Grammes per week
EC041210P	Canned herring in portions		Portions per week
EC041210G	Canned herring in grammes		Grammes per week
EC041220P	Canned sardine in portions		Portions per week
EC041220G	Canned sardine in grammes		Grammes per week
EC041230P	Canned mussels in portions		Portions per week
EC041230G	Canned mussels in grammes		Grammes per week
EC041240P	Canned anchovy in portions		Portions per week
EC041240G	Canned anchovy in grammes		Grammes per week
EC041250P	Canned salmon in portions		Portions per week
EC041250G	Canned salmon in grammes		Grammes per week
EC041260P	Canned mackerel in portions		Portions per week
EC041260G	Canned mackerel in grammes		Grammes per week
EC041270P	Canned tuna in portions		Portions per week
EC041270G	Canned tuna in grammes		Grammes per week
EC041280P	Canned crab in portions		Portions per week
EC041280G	Canned crab in grammes		Grammes per week
EC041290P	Cabend abalone in portions		Portions per week
EC041290G	Cabend abalone in grammes		Grammes per week
EC041300P	Pickled fish in portions		Portions per week
EC041300G	Pickled fish in grammes		Grammes per week
EC041400P	Restructed fish - Crabsticks in portions		Portions per week
EC041400G	Restructed fish - Crabsticks in grammes		Grammes per week
EC041500P	Fish products in portions		Portions per week
EC041500G	Fish products in grammes		Grammes per week
EC041510P	Fishballs in portions		Portions per week
EC041510G	Fishballs in grammes		Grammes per week

EC041520P	Fishcakes in portions		Portions per week
EC041520G	Fishcakes in grammes		Grammes per week
EC041530P	Fish fingers in portions		Portions per week
EC041530G	Fish fingers in grammes		Grammes per week
EC041540P	Fish past in portions		Portions per week
EC041540G	Fish past in grammes		Grammes per week
EC041550P	Taramasalata in portions		Portions per week
EC041550G	Taramasalata in grammes		Grammes per week
EC041600P	Marine mammals in portions		Portions per week
EC041600G	Marine mammals in grammes		Grammes per week
EC041700P	Amphibians in portions		Portions per week
EC041700G	Amphibians in grammes		Grammes per week
EC041800P	Reptiles in portions		Portions per week
EC041800G	Reptiles in grammes		Grammes per week
EC041900P	Insects in portions		Portions per week
EC041900G	Insects in grammes		Grammes per week
EC050000P	Fats and oils in portions		Portions per week
EC050000G	Fats and oils in grammes		Grammes per week
EC050000XP	Fats and oils - MISCELLANEOUS - in portions		Portions per week
EC050000XG	Fats and oils - MISCELLANEOUS - in grammes		Grammes per week
EC050100P	Butter in portions		Portions per week
EC050100G	Butter in grammes		Grammes per week
EC050110P	Salted butter in portions		Portions per week
EC050110G	Salted butter in grammes		Grammes per week
EC050120P	Unsalted butter in portions		Portions per week
EC050120G	Unsalted butter in grammes		Grammes per week
EC050130P	Butter spread >50%fat in portions		Portions per week
EC050130G	Butter spread >50%fat in grammes		Grammes per week
EC050140P	Butter spread < 50% fat in portions		Portions per week
EC050140G	Butter spread < 50% fat in grammes		Grammes per week
EC050150P	Butter ghee in portions		Portions per week
EC050150G	Butter ghee in grammes		Grammes per week
EC050200P	Margarine in portions		Portions per week
EC050200G	Margarine in grammes		Grammes per week

EC050210P	Margarine >25% saturates in portions		Portions per week
EC050210G	Margarine >25% saturates in grammes		Grammes per week
EC050220P	Margarine <25% saturates in portions		Portions per week
EC050220G	Margarine <25% saturates in grammes		Grammes per week
EC050300P	Fat spread in portions		Portions per week
EC050300G	Fat spread in grammes		Grammes per week
EC050310P	Fat spread >65% fat >25 % saturates in portions		Portions per week
EC050310G	Fat spread >65% fat >25 % saturates in grammes		Grammes per week
EC050320P	Fat spread >65% fat <25% saturates in portions		Portions per week
EC050320G	Fat spread >65% fat <25% saturates in grammes		Grammes per week
EC050330P	Fat spread 45-65% fat, >25% saturates in portions		Portions per week
EC050330G	Fat spread 45-65% fat, >25% saturates in grammes		Grammes per week
EC050340P	Fat spread 45-65% fat <25% saturates in portions		Portions per week
EC050340G	Fat spread 45-65% fat <25% saturates in grammes		Grammes per week
EC050350P	Fat spread 30-45 % fat in portions		Portions per week
EC050350G	Fat spread 30-45 % fat in grammes		Grammes per week
EC050360P	Fat spread <30% fat in portions		Portions per week
EC050360G	Fat spread <30% fat in grammes		Grammes per week
EC050400P	Animal fat in portions		Portions per week
EC050400G	Animal fat in grammes		Grammes per week
EC050410P	Beef fat in portions		Portions per week
EC050410G	Beef fat in grammes		Grammes per week
EC050420P	Pork fat in portions		Portions per week
EC050420G	Pork fat in grammes		Grammes per week
EC050430P	Sheep fat in portions		Portions per week
EC050430G	Sheep fat in grammes		Grammes per week
EC050440P	Goose fat in portions		Portions per week
EC050440G	Goose fat in grammes		Grammes per week
EC050450P	Duck fat in portions		Portions per week
EC050450G	Duck fat in grammes		Grammes per week

EC050460P	Other animal fat in portions		Portions per week
EC050460G	Other animal fat in grammes		Grammes per week
EC050500P	Marine oil in portions		Portions per week
EC050500G	Marine oil in grammes		Grammes per week
EC050500ML	Marine oil in millilitres		Millilitres per week
EC050510P	Herring oil in portions		Portions per week
EC050510G	Herring oil in grammes		Grammes per week
EC050510ML	Herring oil in millilitres		Millilitres per week
EC050520P	Whale oil in portions		Portions per week
EC050520G	Whale oil in grammes		Grammes per week
EC050520ML	Whale oil in millilitres		Millilitres per week
EC050530P	Shark oil in portions		Portions per week
EC050530G	Shark oil in grammes		Grammes per week
EC050530ML	Shark oil in millilitres		Millilitres per week
EC050540P	Sardine oil in portions		Portions per week
EC050540G	Sardine oil in grammes		Grammes per week
EC050540ML	Sardine oil in millilitres		Millilitres per week
EC050550P	Other marine oil in portions		Portions per week
EC050550G	Other marine oil in grammes		Grammes per week
EC050550ML	Other marine oil in millilitres		Millilitres per week
EC050600P	Vegetable fats and oils in portions		Portions per week
EC050600G	Vegetable fats and oils in grammes		Grammes per week
EC050600ML	Vegetable fats and oils in millilitres		Millilitres per week
EC050610P	Cocoa butter in portions		Portions per week
EC050610G	Cocoa butter in grammes		Grammes per week
EC050610ML	Cocoa butter in millilitres		Millilitres per week
EC050620P	Coconut oil in portions		Portions per week
EC050620G	Coconut oil in grammes		Grammes per week
EC050620ML	Coconut oil in millilitres		Millilitres per week
EC050630P	Olive oil/Sunflower oil in portions		Portions per week
EC050630G	Olive oil/Sunflower oil in grammes		Grammes per week
EC050630ML	Olive oilSunflower oil in millilitres		Millilitres per week
EC050640P	Corn oil in portions		Portions per week
EC050640G	Corn oil in grammes		Grammes per week
EC050640ML	Corn oil in millilitres		Millilitres per week
EC050650P	Soya bean oil in portions		Portions per week
EC050650G	Soya bean oil in		Grammes per week

	grammes		
EC050650ML	Soya bean oil in millilitres		Millilitres per week
EC050660P	Rapesee oil in portions		Portions per week
EC050660G	Rapesee oil in grammes		Grammes per week
EC050661ML	Rapesee oil in millilitres		Millilitres per week
EC050670P	Sesame oil in portions		Portions per week
EC050670G	Sesame oil in grammes		Grammes per week
EC050670ML	Sesame oil in millilitres		Millilitres per week
EC050680P	Peanut oil in portions		Portions per week
EC050680G	Peanut oil in grammes		Grammes per week
EC050680ML	Peanut oil in millilitres		Millilitres per week
EC050700P	Compound fats and oils in portions		Portions per week
EC050700G	Compound fats and oils in grammes		Grammes per week
EC050700ML	Compound fats and oils in millilitres		Millilitres per week
EC060000P	Grain and grain products in portions		Portions per week
EC060000G	Grain and grain products in grammes		Grammes per week
EC060000XP	Grain and grain products - MISCELLANEOUS - in portions		Portions per week
EC060000XG	Grain and grain products - MISCELLANEOUS - in grammes		Grammes per week
EC060100P	Wheat basic products in portions		Portions per week
EC060100G	Wheat basic products in grammes		Grammes per week
EC060110P	Whole grain wheat in portions		Portions per week
EC060110G	Whole grain wheat in grammes		Grammes per week
EC060120P	Bulgar in portions		Portions per week
EC060120G	Bulgar in grammes		Grammes per week
EC060130P	Wheat flour - wholemeal in portions		Portions per week
EC060130G	Wheat flour - wholemeal in grammes		Grammes per week
EC060140P	Wheat flour - 80% extraction rate in portions		Portions per week
EC060140G	Wheat flour - 80% extraction rate in grammes		Grammes per week
EC060150P	Wheat flour - 72% extraction rate in		Portions per week

	portions		
EC060150G	Wheat flour - 72% extraction rate in grammes		Grammes per week
EC060160P	Wheat flour - patent in portions		Portions per week
EC060160G	Wheat flour - patent in grammes		Grammes per week
EC060170P	Wheat flour - brown in portions		Portions per week
EC060170G	Wheat flour - brown in grammes		Grammes per week
EC060180P	Semolina in portions		Portions per week
EC060180G	Semolina in grammes		Grammes per week
EC060200P	Rye flour in portions		Portions per week
EC060200G	Rye flour in grammes		Grammes per week
EC060300P	Oats basic products in portions		Portions per week
EC060300G	Oats basic products in grammes		Grammes per week
EC060310P	Groats in portions		Portions per week
EC060310G	Groats in grammes		Grammes per week
EC060320P	Rolled oats in portions		Portions per week
EC060320G	Rolled oats in grammes		Grammes per week
EC060330P	Oatmeal in portions		Portions per week
EC060330G	Oatmeal in grammes		Grammes per week
EC060340P	Oatflour in portions		Portions per week
EC060340G	Oatflour in grammes		Grammes per week
EC060400P	Barley basic products in portions		Portions per week
EC060400G	Barley basic products in grammes		Grammes per week
EC060410P	Whole grain barley in portions		Portions per week
EC060410G	Whole grain barley in grammes		Grammes per week
EC060420P	Pearl barley in portions		Portions per week
EC060420G	Pearl barley in grammes		Grammes per week
EC060430P	Barley flakes in portions		Portions per week
EC060430G	Barley flakes in grammes		Grammes per week
EC060440P	Barley meal in portions		Portions per week
EC060440G	Barley meal in grammes		Grammes per week
EC060450P	Barley flour in portions		Portions per week
EC060450G	Barley flour in grammes		Grammes per week
EC060500P	Maize basic products in portions		Portions per week
EC060500G	Maize basic products in grammes		Grammes per week

EC060510P	Maize rice in portions		Portions per week
EC060510G	Maize rice in grammes		Grammes per week
EC060520P	Cornmeal in portions		Portions per week
EC060520G	Cornmeal in grammes		Grammes per week
EC060530P	Maize flour in portions		Portions per week
EC060530G	Maize flour in grammes		Grammes per week
EC060540P	Cornflour in portions		Portions per week
EC060540G	Cornflour in grammes		Grammes per week
EC060550P	Custard powder in portions		Portions per week
EC060550G	Custard powder in grammes		Grammes per week
EC060600P	Rice basic products in portions		Portions per week
EC060600G	Rice basic products in grammes		Grammes per week
EC060610P	Rice flour in portions		Portions per week
EC060610G	Rice flour in grammes		Grammes per week
EC060620P	Rice flakes in portions		Portions per week
EC060620G	Rice flakes in grammes		Grammes per week
EC060630P	Brown rice in portions		Portions per week
EC060630G	Brown rice in grammes		Grammes per week
EC060640P	Basmati rice in portions		Portions per week
EC060640G	Basmati rice in grammes		Grammes per week
EC060650P	Glutinous rice in portions		Portions per week
EC060650G	Glutinous rice in grammes		Grammes per week
EC060660P	Polished rice in portions		Portions per week
EC060660G	Polished rice in grammes		Grammes per week
EC060700P	Basic products of other cereals in portions		Portions per week
EC060700G	Basic products of other cereals in grammes		Grammes per week
EC060710P	Buckwheat in portions		Portions per week
EC060710G	Buckwheat in grammes		Grammes per week
EC060720P	Buckwheat flour in portions		Portions per week
EC060720G	Buckwheat flour in grammes		Grammes per week
EC060730P	Millet in portions		Portions per week
EC060730G	Millet in grammes		Grammes per week
EC060740P	Millet flour in portions		Portions per week
EC060740G	Millet flour in grammes		Grammes per week
EC060800P	Substitute flours and		Portions per week

	starches in portions		
EC060800G	Substitute flours and starches in grammes		Grammes per week
EC060810P	Soya flour in portions		Portions per week
EC060810G	Soya flour in grammes		Grammes per week
EC060820P	Potato flour in portions		Portions per week
EC060820G	Potato flour in grammes		Grammes per week
EC060830P	Lotus root flour in portions		Portions per week
EC060830G	Lotus root flour in grammes		Grammes per week
EC060840P	Arrowroot in portions		Portions per week
EC060840G	Arrowroot in grammes		Grammes per week
EC060850P	Sago in portions		Portions per week
EC060850G	Sago in grammes		Grammes per week
EC060860P	Tapioca in portions		Portions per week
EC060860G	Tapioca in grammes		Grammes per week
EC060900P	Pasta and noodles in portions		Portions per week
EC060900G	Pasta and noodles in grammes		Grammes per week
EC060910P	Dried main-dish pasta in portions		Portions per week
EC060910G	Dried main-dish pasta in grammes		Grammes per week
EC060920P	Dried miniature pasta in portions		Portions per week
EC060920G	Dried miniature pasta in grammes		Grammes per week
EC060930P	Fresh main-dish pasta in portions		Portions per week
EC060930G	Fresh main-dish pasta in grammes		Grammes per week
EC060940P	Fresh miniature pasta in portions		Portions per week
EC060940G	Fresh miniature pasta in grammes		Grammes per week
EC060950P	Egg noodles in portions		Portions per week
EC060950G	Egg noodles in grammes		Grammes per week
EC060960P	Plain noodles in portions		Portions per week
EC060960G	Plain noodles in grammes		Grammes per week
EC060970P	Rice noodles in portions		Portions per week
EC060970G	Rice noodles in grammes		Grammes per week
EC060980P	Transparent noodles in portions		Portions per week
EC060980G	Transparent noodles in grammes		Grammes per week
EC061000P	Leavened breads in		Portions per week

	portions		
EC061000G	Leavened breads in grammes		Grammes per week
EC061010P	Wheat bread - wholemeal in portions		Portions per week
EC061010G	Wheat bread - wholemeal in grammes		Grammes per week
EC061020P	Wheat bread - white in portions		Portions per week
EC061020G	Wheat bread - white in grammes		Grammes per week
EC061030P	Wheat bread - brown in portions		Portions per week
EC061030G	Wheat bread - brown in grammes		Grammes per week
EC061040P	Naan bread in portions		Portions per week
EC061040G	Naan bread in grammes		Grammes per week
EC061050P	Soda bread in portions		Portions per week
EC061050G	Soda bread in grammes		Grammes per week
EC061060P	Rye bread in portions		Portions per week
EC061060G	Rye bread in grammes		Grammes per week
EC061070P	Potato bread in portions		Portions per week
EC061070G	Potato bread in grammes		Grammes per week
EC061080P	Bread - other flour in portions		Portions per week
EC061080G	Bread - other flour in grammes		Grammes per week
EC061090P	Bread - mixed flour in portions		Portions per week
EC061090G	Bread - mixed flour in grammes		Grammes per week
EC061100P	Unleavened breads and crispbreads in portions		Portions per week
EC061100G	Unleavened breads and crispbreads in grammes		Grammes per week
EC061110P	Bannock in portions		Portions per week
EC061110G	Bannock in grammes		Grammes per week
EC061120P	Pitta bread in portions		Portions per week
EC061120G	Pitta bread in grammes		Grammes per week
EC061130P	Matzo in portions		Portions per week
EC061130G	Matzo in grammes		Grammes per week
EC061140P	Tortilla in portions		Portions per week
EC061140G	Tortilla in grammes		Grammes per week
EC061150P	Crispbread in portions		Portions per week
EC061150G	Crispbread in grammes		Grammes per week
EC061200P	Bread products in		Portions per week

	portions		
EC061200G	Bread products in grammes		Grammes per week
EC061210P	Breadcrumbs in portions		Portions per week
EC061210G	Breadcrumbs in grammes		Grammes per week
EC061220P	Bread stuffing in portions		Portions per week
EC061220G	Bread stuffing in grammes		Grammes per week
EC061230P	Bread pudding in portions		Portions per week
EC061230G	Bread pudding in grammes		Grammes per week
EC061300P	Fine bakery wares in portions		Portions per week
EC061300G	Fine bakery wares in grammes		Grammes per week
EC061310P	Savoury biscuits in portions		Portions per week
EC061310G	Savoury biscuits in grammes		Grammes per week
EC061320P	Sweet biscuits and cookies in portions		Portions per week
EC061320G	Sweet biscuits and cookies in grammes		Grammes per week
EC061330P	Croissants in portions		Portions per week
EC061330G	Croissants in grammes		Grammes per week
EC061340P	Currant bun in portions		Portions per week
EC061340G	Currant bun in grammes		Grammes per week
EC061350P	Dough cakes in portions		Portions per week
EC061350G	Dough cakes in grammes		Grammes per week
EC061360P	Scone in portions		Portions per week
EC061360G	Scone in grammes		Grammes per week
EC061370P	Doughnut in portions		Portions per week
EC061370G	Doughnut in grammes		Grammes per week
EC061380P	Danish pastry in portions		Portions per week
EC061380G	Danish pastry in grammes		Grammes per week
EC061390P	Cake in portions		Portions per week
EC061390G	Cake in grammes		Grammes per week
EC061400P	Savoury cereal dishes in portions		Portions per week
EC061400G	Savoury cereal dishes in grammes		Grammes per week
EC061410P	Dumpling in portions		Portions per week
EC061410G	Dumpling in grammes		Grammes per week
EC061420P	Savoury pancake in portions		Portions per week

EC061420G	Savoury pancake in grammes		Grammes per week
EC061430P	Couscous in portions		Portions per week
EC061430G	Couscous in grammes		Grammes per week
EC061440P	Risotto in portions		Portions per week
EC061440G	Risotto in grammes		Grammes per week
EC061450P	Pizza in portions		Portions per week
EC061450G	Pizza in grammes		Grammes per week
EC061460P	Savoury pie in portions		Portions per week
EC061460G	Savoury pie in grammes		Grammes per week
EC061500P	Sweet puddings in portions		Portions per week
EC061500G	Sweet puddings in grammes		Grammes per week
EC061510P	Custard in portions		Portions per week
EC061510G	Custard in grammes		Grammes per week
EC061520P	Trifle in portions		Portions per week
EC061520G	Trifle in grammes		Grammes per week
EC061530P	Fruit crumble in portions		Portions per week
EC061530G	Fruit crumble in grammes		Grammes per week
EC061540P	Fruit pie in portions		Portions per week
EC061540G	Fruit pie in grammes		Grammes per week
EC061550P	Milk pudding in portions		Portions per week
EC061550G	Milk pudding in grammes		Grammes per week
EC061560P	Rice pudding in portions		Portions per week
EC061560G	Rice pudding in grammes		Grammes per week
EC061570P	Sponge pudding in portions		Portions per week
EC061570G	Sponge pudding in grammes		Grammes per week
EC061580P	Suet pudding in portions		Portions per week
EC061580G	Suet pudding in grammes		Grammes per week
EC061600P	Breakfast cereals in portions		Portions per week
EC061600G	Breakfast cereals in grammes		Grammes per week
EC061610P	Cereals - wheat based in portions		Portions per week
EC061610G	Cereals - wheat based in grammes		Grammes per week
EC061620P	Cereals - rye based in portions		Portions per week
EC061620G	Cereals - rye based in grammes		Grammes per week
EC061630P	Cereals oats based in portions		Portions per week

EC061630G	Cereals oats based in grammes		Grammes per week
EC061640P	Cereals rice based in portions		Portions per week
EC061640G	Cereals rice based in grammes		Grammes per week
EC061650P	Cereals mixed grain in portions		Portions per week
EC061650G	Cereals mixed grain in grammes		Grammes per week
EC061660P	Muesli in portions		Portions per week
EC061660G	Muesli in grammes		Grammes per week
EC070000P	Pulses, seeds, kernels and nut products in portions		Portions per week
EC070000G	Pulses, seeds, kernels and nut products in grammes		Grammes per week
EC070000XP	Pulses, seeds, kernels and nut products - MISCELLANEOUS - in portions		Portions per week
EC070000XG	Pulses, seeds, kernels and nut products - MISCELLANEOUS - in grammes		Grammes per week
EC070100P	Pulses in portions		Portions per week
EC070100G	Pulses in grammes		Grammes per week
EC070110P	Dried pea in portions		Portions per week
EC070110G	Dried pea in grammes		Grammes per week
EC070120P	Chick pea in portions		Portions per week
EC070120G	Chick pea in grammes		Grammes per week
EC070130P	Dried broad bean in portions		Portions per week
EC070130G	Dried broad bean in grammes		Grammes per week
EC070140P	Lentil in portions		Portions per week
EC070140G	Lentil in grammes		Grammes per week
EC070150P	Common bean in portions		Portions per week
EC070150G	Common bean in grammes		Grammes per week
EC070160P	Dried lima bean in portions		Portions per week
EC070160G	Dried lima bean in grammes		Grammes per week
EC070170P	Mung bean in portions		Portions per week
EC070170G	Mung bean in grammes		Grammes per week
EC070180P	Black eye bean in portions		Portions per week
EC070180G	Black eye bean in grammes		Grammes per week

EC070190P	Soya beans in portions		Portions per week
EC070190G	Soya beans in grammes		Grammes per week
EC070200P	Underground pulses - peanut in portions		Portions per week
EC070200G	Underground pulses - peanut in grammes		Grammes per week
EC070300P	Seeds and kernels in portions		Portions per week
EC070300G	Seeds and kernels in grammes		Grammes per week
EC070310P	Linseed in portions		Portions per week
EC070310G	Linseed in grammes		Grammes per week
EC070320P	Sunflower seed in portions		Portions per week
EC070320G	Sunflower seed in grammes		Grammes per week
EC070330P	Poppy seed in portions		Portions per week
EC070330G	Poppy seed in grammes		Grammes per week
EC070340P	Cotton seed in portions		Portions per week
EC070340G	Cotton seed in grammes		Grammes per week
EC070350P	Rape seed in portions		Portions per week
EC070350G	Rape seed in grammes		Grammes per week
EC070360P	Beechnut seed in portions		Portions per week
EC070360G	Beechnut seed in grammes		Grammes per week
EC070370P	Sesame seed in portions		Portions per week
EC070370G	Sesame seed in grammes		Grammes per week
EC070380P	Olive seed in portions		Portions per week
EC070380G	Olive seed in grammes		Grammes per week
EC070390P	Pumpkin seed in portions		Portions per week
EC070390G	Pumpkin seed in grammes		Grammes per week
EC070400P	Nuts in portions		Portions per week
EC070400G	Nuts in grammes		Grammes per week
EC070410P	Walnut in portions		Portions per week
EC070410G	Walnut in grammes		Grammes per week
EC070420P	Hazelnut in portions		Portions per week
EC070420G	Hazelnut in grammes		Grammes per week
EC070430P	Coconut in portions		Portions per week
EC070430G	Coconut in grammes		Grammes per week
EC070440P	Brazil nut in portions		Portions per week
EC070440G	Brazil nut in grammes		Grammes per week
EC070450P	Cashew nut in portions		Portions per week
EC070450G	Cashew nut in grammes		Grammes per week

EC070460P	Almond in portions		Portions per week
EC070460G	Almond in grammes		Grammes per week
EC070470P	Pistachio in portions		Portions per week
EC070470G	Pistachio in grammes		Grammes per week
EC070480P	Chestnut in portions		Portions per week
EC070480G	Chestnut in grammes		Grammes per week
EC070500P	Pulse products in portions		Portions per week
EC070500G	Pulse products in grammes		Grammes per week
EC070510P	Soya paste in portions		Portions per week
EC070510G	Soya paste in grammes		Grammes per week
EC070520P	Peanut butter in portions		Portions per week
EC070520G	Peanut butter in grammes		Grammes per week
EC070600P	Nut and seed products in portions		Portions per week
EC070600G	Nut and seed products in grammes		Grammes per week
EC070610P	Coconut milk in portions		Portions per week
EC070610G	Coconut milk in grammes		Grammes per week
EC070620P	Chestnut puree in portions		Portions per week
EC070620G	Chestnut puree in grammes		Grammes per week
EC070630P	Tahini paste in portions		Portions per week
EC070630G	Tahini paste in grammes		Grammes per week
EC080000P	Vegetables in portions		Portions per week
EC080000G	Vegetables in grammes		Grammes per week
EC080000XP	Vegetables - MISCELLANEOUS - in portions		Portions per week
EC080000XG	Vegetables - MISCELLANEOUS - in grammes		Grammes per week
EC080100P	Leaf vegetables in portions		Portions per week
EC080100G	Leaf vegetables in grammes		Grammes per week
EC080110P	Lettuce in portions		Portions per week
EC080110G	Lettuce in grammes		Grammes per week
EC080120P	Spinach in portions		Portions per week
EC080120G	Spinach in grammes		Grammes per week
EC080130P	Watercress in portions		Portions per week
EC080130G	Watercress in grammes		Grammes per week
EC080140P	Mustard seedling in		Portions per week

	portions		
EC080140G	Mustard seedling in grammes		Grammes per week
EC080150P	Cress seedling in portions		Portions per week
EC080150G	Cress seedling in grammes		Grammes per week
EC080160P	Vine leaf in portions		Portions per week
EC080160G	Vine leaf in grammes		Grammes per week
EC080170P	Nettle in portions		Portions per week
EC080170G	Nettle in grammes		Grammes per week
EC080180P	Sorrel in portions		Portions per week
EC080180G	Sorrel in grammes		Grammes per week
EC080190P	Parsley in portions		Portions per week
EC080190G	Parsley in grammes		Grammes per week
EC080200P	Brassicas in portions		Portions per week
EC080200G	Brassicas in grammes		Grammes per week
EC080210P	Broccoli in portions		Portions per week
EC080210G	Broccoli in grammes		Grammes per week
EC080220P	Cauliflower in portions		Portions per week
EC080220G	Cauliflower in grammes		Grammes per week
EC080230P	Cabbage in portions		Portions per week
EC080230G	Cabbage in grammes		Grammes per week
EC080240P	Red cabbage in portions		Portions per week
EC080240G	Red cabbage in grammes		Grammes per week
EC080250P	Chinese cabbage in portions		Portions per week
EC080250G	Chinese cabbage in grammes		Grammes per week
EC080260P	Brussel sprouts in portions		Portions per week
EC080260G	Brussel sprouts in grammes		Grammes per week
EC080270P	Turnip in portions		Portions per week
EC080270G	Turnip in grammes		Grammes per week
EC080280P	Curly kale in portions		Portions per week
EC080280G	Curly kale in grammes		Grammes per week
EC080300P	Stalk vegetables in portions		Portions per week
EC080300G	Stalk vegetables in grammes		Grammes per week
EC080310P	Celery in portions		Portions per week
EC080310G	Celery in grammes		Grammes per week
EC080320P	Fennel in portions		Portions per week
EC080320G	Fennel in grammes		Grammes per week
EC080330P	Sea kale in portions		Portions per week
EC080330G	Sea kale in grammes		Grammes per week
EC080340P	Rhubarb in portions		Portions per week
EC080340G	Rhubarb in grammes		Grammes per week
EC080400P	Shoot vegetables in		Portions per week

	portions		
EC080400G	Shoot vegetables in grammes		Grammes per week
EC080410P	Asparagus in portions		Portions per week
EC080410G	Asparagus in grammes		Grammes per week
EC080420P	Chicory in portions		Portions per week
EC080420G	Chicory in grammes		Grammes per week
EC080430P	Artichoke in portions		Portions per week
EC080430G	Artichoke in grammes		Grammes per week
EC080440P	Bamboo shoot in portions		Portions per week
EC080440G	Bamboo shoot in grammes		Grammes per week
EC080450P	Palm heart in portions		Portions per week
EC080450G	Palm heart in grammes		Grammes per week
EC080500P	Onion-family vegetables in portions		Portions per week
EC080500G	Onion-family vegetables in grammes		Grammes per week
EC080510P	Onion in portions		Portions per week
EC080510G	Onion in grammes		Grammes per week
EC080520P	Spring onion in portions		Portions per week
EC080520G	Spring onion in grammes		Grammes per week
EC080530P	Shallot in portions		Portions per week
EC080530G	Shallot in grammes		Grammes per week
EC080540P	Leek in portions		Portions per week
EC080540G	Leek in grammes		Grammes per week
EC080550P	Garlic in portions		Portions per week
EC080550G	Garlic in grammes		Grammes per week
EC080560P	Chives in portions		Portions per week
EC080560G	Chives in grammes		Grammes per week
EC080600P	Tubers in portions		Portions per week
EC080600G	Tubers in grammes		Grammes per week
EC080610P	New potato in portions		Portions per week
EC080610G	New potato in grammes		Grammes per week
EC080620P	Main crop potato in portions		Portions per week
EC080620G	Main crop potato in grammes		Grammes per week
EC080630P	Jerusalem artichoke in portions		Portions per week
EC080630G	Jerusalem artichoke in grammes		Grammes per week
EC080640P	Sweet potato in portions		Portions per week
EC080640G	Sweet potato in grammes		Grammes per week
EC080650P	Yam in portions		Portions per week

EC080650G	Yam in grammes		Grammes per week
EC080660P	Taro in portions		Portions per week
EC080660G	Taro in grammes		Grammes per week
EC080700P	Root vegetables in portions		Portions per week
EC080700G	Root vegetables in grammes		Grammes per week
EC080710P	Carrot in portions		Portions per week
EC080710G	Carrot in grammes		Grammes per week
EC080720P	Celeriac in portions		Portions per week
EC080720G	Celeriac in grammes		Grammes per week
EC080730P	Parsnip in portions		Portions per week
EC080730G	Parsnip in grammes		Grammes per week
EC080740P	Turnip in portions		Portions per week
EC080740G	Turnip in grammes		Grammes per week
EC080750P	Swede in portions		Portions per week
EC080750G	Swede in grammes		Grammes per week
EC080760P	Radish in portions		Portions per week
EC080760G	Radish in grammes		Grammes per week
EC080770P	Beetroot in portions		Portions per week
EC080770G	Beetroot in grammes		Grammes per week
EC080800P	Fruit vegetables in portions		Portions per week
EC080800G	Fruit vegetables in grammes		Grammes per week
EC080810P	Tomato in portions		Portions per week
EC080810G	Tomato in grammes		Grammes per week
EC080811P	Raw tomatoes in portions		Portions per week
EC080811G	Raw tomatoes in grammes		Grammes per week
EC080812P	Cooked tomatoes in portions		Portions per week
EC080812G	Cooked tomoatoes in grammes		Grammes per week
EC080820P	Aubergine in portions		Portions per week
EC080820G	Aubergine in grammes		Grammes per week
EC080830P	Sweet pepper in portions		Portions per week
EC080830G	Sweet pepper in grammes		Grammes per week
EC080840P	Chilli pepper in portions		Portions per week
EC080840G	Chilli pepper in grammes		Grammes per week
EC080850P	Cucumber in portions		Portions per week
EC080850G	Cucumber in grammes		Grammes per week
EC080860P	Courgette in portions		Portions per week
EC080860G	Courgette in grammes		Grammes per week
EC080870P	Plantain in portions		Portions per week
EC080870G	Plantain in grammes		Grammes per week
EC080880P	Avocado in portions		Portions per week
EC080880G	Avocado in grammes		Grammes per week

EC080890P	Olive in portions		Portions per week
EC080890G	Olive in grammes		Grammes per week
EC080900P	Pod and seed vegetables in portions		Portions per week
EC080900G	Pod and seed vegetables in grammes		Grammes per week
EC080910P	Pea in portions		Portions per week
EC080910G	Pea in grammes		Grammes per week
EC080920P	Broad bean in portions		Portions per week
EC080920G	Broad bean in grammes		Grammes per week
EC080930P	Wax beans in portions		Portions per week
EC080930G	Wax beans in grammes		Grammes per week
EC080940P	French bean in portions		Portions per week
EC080940G	French bean in grammes		Grammes per week
EC080950P	Runner beans in portions		Portions per week
EC080950G	Runner beans in grammes		Grammes per week
EC080960P	Sweet corn in portions		Portions per week
EC080960G	Sweet corn in grammes		Grammes per week
EC080970P	Okra in portions		Portions per week
EC080970G	Okra in grammes		Grammes per week
EC081000P	Edible fungi in portions		Portions per week
EC081000G	Edible fungi in grammes		Grammes per week
EC081010P	Cultivated mushroom in portions		Portions per week
EC081010G	Cultivated mushroom in grammes		Grammes per week
EC081020P	Field mushroom in portions		Portions per week
EC081020G	Field mushroom in grammes		Grammes per week
EC081030P	Honey mushroom in portions		Portions per week
EC081030G	Honey mushroom in grammes		Grammes per week
EC081040P	Truffle in portions		Portions per week
EC081040G	Truffle in grammes		Grammes per week
EC081050P	Morel in portions		Portions per week
EC081050G	Morel in grammes		Grammes per week
EC081060P	Cantharelle in portions		Portions per week
EC081060G	Cantharelle in grammes		Grammes per week
EC081070P	Oyster mushroom in portions		Portions per week
EC081070G	Oyster mushroom in grammes		Grammes per week
EC081080P	Shitake mushroom in		Portions per week

	portions		
EC081080G	Shitake mushroom in grammes		Grammes per week
EC081090P	Straw mushroom in portions		Portions per week
EC081090G	Straw mushroom in grammes		Grammes per week
EC081100P	Seaweeds in portions		Portions per week
EC081100G	Seaweeds in grammes		Grammes per week
EC081200P	Vegetable mixes in portions		Portions per week
EC081200G	Vegetable mixes in grammes		Grammes per week
EC081300P	Vegetable products in portions		Portions per week
EC081300G	Vegetable products in grammes		Grammes per week
EC081310P	Mushy peas in portions		Portions per week
EC081310G	Mushy peas in grammes		Grammes per week
EC081320P	Garlic puree in portions		Portions per week
EC081320G	Garlic puree in grammes		Grammes per week
EC081330P	Tomato puree in portions		Portions per week
EC081330G	Tomato puree in grammes		Grammes per week
EC081340P	Vegetable puree in portions		Portions per week
EC081340G	Vegetable puree in grammes		Grammes per week
EC081350P	Pickled gherkins in portions		Portions per week
EC081350G	Pickled gherkins in grammes		Grammes per week
EC081360P	Pickled onion in portions		Portions per week
EC081360G	Pickled onion in grammes		Grammes per week
EC081370P	Pickled red cabbage in portions		Portions per week
EC081370G	Pickled red cabbage in grammes		Grammes per week
EC081380P	Sauerkraut in portions		Portions per week
EC081380G	Sauerkraut in grammes		Grammes per week
EC090000P	Fruits and fruit products in portions		Portions per week
EC090000G	Fruits and fruit products in grammes		Grammes per week
EC090000XP	Fruits and fruit products - MISCELLANEOUS - in portions		Portions per week

EC090000XG	Fruits and fruit products - MISCELLANEOUS - in grammes		Grammes per week
EC090100P	Malaceious fruit in portions		Portions per week
EC090100G	Malaceious fruit in grammes		Grammes per week
EC090110P	Dessert apple in portions		Portions per week
EC090110G	Dessert apple in grammes		Grammes per week
EC090120P	Cooking apple in portions		Portions per week
EC090120G	Cooking apple in grammes		Grammes per week
EC090130P	Pear in portions		Portions per week
EC090130G	Pear in grammes		Grammes per week
EC090200P	Prunus species fruit in portions		Portions per week
EC090200G	Prunus species fruit in grammes		Grammes per week
EC090210P	Apricot in portions		Portions per week
EC090210G	Apricot in grammes		Grammes per week
EC090220P	Peach in portions		Portions per week
EC090220G	Peach in grammes		Grammes per week
EC090230P	Nectarine in portions		Portions per week
EC090230G	Nectarine in grammes		Grammes per week
EC090240P	Plum in portions		Portions per week
EC090240G	Plum in grammes		Grammes per week
EC090250P	Cherry in portions		Portions per week
EC090250G	Cherry in grammes		Grammes per week
EC090260P	Plum in portions		Portions per week
EC090260G	Plum in grammes		Grammes per week
EC090300P	Other stone fruit in portions		Portions per week
EC090300G	Other stone fruit in grammes		Grammes per week
EC090310P	Date in portions		Portions per week
EC090310G	Date in grammes		Grammes per week
EC090320P	Lychee in portions		Portions per week
EC090320G	Lychee in grammes		Grammes per week
EC090400P	Berries in portions		Portions per week
EC090400G	Berries in grammes		Grammes per week
EC090410P	Grapes in portions		Portions per week
EC090410G	Grapes in grammes		Grammes per week
EC090420P	Strawberries in portions		Portions per week
EC090420G	Strawberries in grammes		Grammes per week
EC090430P	Raspberries in portions		Portions per week
EC090430G	Raspberries in grammes		Grammes per week

EC090440P	Blackberries in portions		Portions per week
EC090440G	Blackberries in grammes		Grammes per week
EC090450P	Gooseberries in portions		Portions per week
EC090450G	Gooseberries in grammes		Grammes per week
EC090460P	Elderberries in portions		Portions per week
EC090460G	Elderberries in grammes		Grammes per week
EC090470P	Currants in portions		Portions per week
EC090470G	Currants in grammes		Grammes per week
EC090480P	Cranberries in portions		Portions per week
EC090480G	Cranberries in grammes		Grammes per week
EC090490P	Blueberries in portions		Portions per week
EC090490G	Blueberries in grammes		Grammes per week
EC090500P	Citrus fruit in portions		Portions per week
EC090500G	Citrus fruit in grammes		Grammes per week
EC090510P	Lemon in portions		Portions per week
EC090510G	Lemon in grammes		Grammes per week
EC090520P	Orange in portions		Portions per week
EC090520G	Orange in grammes		Grammes per week
EC090530P	Tangerine in portions		Portions per week
EC090530G	Tangerine in grammes		Grammes per week
EC090540P	Grapefruit in portions		Portions per week
EC090540G	Grapefruit in grammes		Grammes per week
EC090550P	Pomelo in portions		Portions per week
EC090550G	Pomelo in grammes		Grammes per week
EC090560P	Lime in portions		Portions per week
EC090560G	Lime in grammes		Grammes per week
EC090570P	Kumquat in portions		Portions per week
EC090570G	Kumquat in grammes		Grammes per week
EC090600P	Miscellaneous fruit in portions		Portions per week
EC090600G	Miscellaneous fruit in grammes		Grammes per week
EC090610P	Banana in portions		Portions per week
EC090610G	Banana in grammes		Grammes per week
EC090620P	Pineapple in portions		Portions per week
EC090620G	Pineapple in grammes		Grammes per week
EC090630P	Kiwi fruit in portions		Portions per week
EC090630G	Kiwi fruit in grammes		Grammes per week
EC090640P	Melon in portions		Portions per week
EC090640G	Melon in grammes		Grammes per week
EC090650P	Water melon in portions		Portions per week
EC090650G	Water melon in grammes		Grammes per week
EC090660P	Fig in portions		Portions per week

EC090660G	Fig in grammes		Grammes per week
EC090670P	Mango in portions		Portions per week
EC090670G	Mango in grammes		Grammes per week
EC090680P	Pomegranate in portions		Portions per week
EC090680G	Pomegranate in grammes		Grammes per week
EC090690P	Passion fruit in portions		Portions per week
EC090690G	Passion fruit in grammes		Grammes per week
EC090700P	Fruit mixtures in portions		Portions per week
EC090700G	Fruit mixtures in grammes		Grammes per week
EC090710P	Fruit cocktail in portions		Portions per week
EC090710G	Fruit cocktail in grammes		Grammes per week
EC090720P	Fruit salad in portions		Portions per week
EC090720G	Fruit salad in grammes		Grammes per week
EC090800P	Fruit products in portions		Portions per week
EC090800G	Fruit products in grammes		Grammes per week
EC090810P	Dried mixed fruit in portions		Portions per week
EC090810G	Dried mixed fruit in grammes		Grammes per week
EC090820P	Mixed peel in portions		Portions per week
EC090820G	Mixed peel in grammes		Grammes per week
EC090830P	Glace cherry in portions		Portions per week
EC090830G	Glace cherry in grammes		Grammes per week
EC090840P	Apple sauce in portions		Portions per week
EC090840G	Apple sauce in grammes		Grammes per week
EC090850P	Cranberry sauce in portions		Portions per week
EC090850G	Cranberry sauce in grammes		Grammes per week
EC100000P	Sugar and sugar products in portions		Portions per week
EC100000G	Sugar and sugar products in grammes		Grammes per week
EC100000XP	Sugar and sugar products - MISCELLANEOUS - in portions		Portions per week
EC100000XG	Sugar and sugar products - MISCELLANEOUS - in grammes		Grammes per week

EC100100P	Sugar in portions		Portions per week
EC100100G	Sugar in grammes		Grammes per week
EC100101P	White sugar in portions		Portions per week
EC100101G	White sugar in grammes		Grammes per week
EC100102P	Brown sugar in portions		Portions per week
EC100102G	Brown sugar in grammes		Grammes per week
EC100200P	Other sugars in portions		Portions per week
EC100200G	Other sugars in grammes		Grammes per week
EC100210P	Glucose in portions		Portions per week
EC100210G	Glucose in grammes		Grammes per week
EC100210ML	Glucose in millilitres		Millilitres per week
EC100220P	Fructose in portions		Portions per week
EC100220G	Fructose in grammes		Grammes per week
EC100220ML	Fructose in millilitres		Millilitres per week
EC100230P	Malt sugar in portions		Portions per week
EC100230G	Malt sugar in grammes		Grammes per week
EC100240P	Milk sugar in portions		Portions per week
EC100240G	Milk sugar in grammes		Grammes per week
EC100240ML	Milk sugar in millilitres		Millilitres per week
EC100300P	Sugar substitutes in portions		Portions per week
EC100300G	Sugar substitutes in grammes		Grammes per week
EC100310P	Non-nutritive sweeteners in portions		Portions per week
EC100310G	Non-nutritive sweeteners in grammes		Grammes per week
EC100320P	Nutritive sweeteners in portions		Portions per week
EC100320G	Nutritive sweeteners in grammes		Grammes per week
EC100400P	Honey in portions		Portions per week
EC100400G	Honey in grammes		Grammes per week
EC100400ML	Honey in millilitres		Millilitres per week
EC100500P	Syrups in portions		Portions per week
EC100500G	Syrups in grammes		Grammes per week
EC100500ML	Syrups in millilitres		Millilitres per week
EC100510P	Molasses in portions		Portions per week
EC100510G	Molasses in grammes		Grammes per week
EC100510ML	Molasses in millilitres		Millilitres per week
EC100520P	Black treacle in portions		Portions per week
EC100520G	Black treacle in grammes		Grammes per week
EC100520ML	Black treacle in millilitres		Millilitres per week
EC100530P	Golden syrup in		Portions per week

	portions		
EC100530G	Golden syrup in grammes		Grammes per week
EC100530ML	Golden syrup in millilitres		Millilitres per week
EC100540P	Maple syrup in portions		Portions per week
EC100540G	Maple syrup in grammes		Grammes per week
EC100540ML	Maple syrup in millilitres		Millilitres per week
EC100550P	Fruit syrup in portions		Portions per week
EC100550G	Fruit syrup in grammes		Grammes per week
EC100550ML	Fruit syrup in millilitres		Millilitres per week
EC100560P	Glucose syrup in portions		Portions per week
EC100560G	Glucose syrup in grammes		Grammes per week
EC100560ML	Glucose syrup in millilitres		Millilitres per week
EC100570P	Sugar syrup in portions		Portions per week
EC100570G	Sugar syrup in grammes		Grammes per week
EC100570ML	Sugar syrup in millilitres		Millilitres per week
EC100600P	Jams, marmalades and spreads in portions		Portions per week
EC100600G	Jams, marmalades and spreads in grammes		Grammes per week
EC100610P	Fruit jam in portions		Portions per week
EC100610G	Fruit jam in grammes		Grammes per week
EC100620P	Fruit jelly preserve in portions		Portions per week
EC100620G	Fruit jelly preserve in grammes		Grammes per week
EC100630P	Marmalade in portions		Portions per week
EC100630G	Marmalade in grammes		Grammes per week
EC100700P	Jelly in portions		Portions per week
EC100700G	Jelly in grammes		Grammes per week
EC100800P	Non-chocolate dessert topping in portions		Portions per week
EC100800G	Non-chocolate dessert topping in grammes		Grammes per week
EC100900P	Chocolate and chocolate products in portions		Portions per week
EC100900G	Chocolate and chocolate products in grammes		Grammes per week
EC100910P	Cocoa powder in portions		Portions per week

EC100910G	Cocoa powder in grammes		Grammes per week
EC100920P	Milk chocolate bar in portions		Portions per week
EC100920G	Milk chocolate bar in grammes		Grammes per week
EC100930P	Plain chocolate bar in portions		Portions per week
EC100930G	Plain chocolate bar in grammes		Grammes per week
EC100940P	Other chocolate goods in portions		Portions per week
EC100940G	Other chocolate goods in grammes		Grammes per week
EC101000P	Chocolate-coated confectionery bars in portions		Portions per week
EC101000G	Chocolate-coated confectionery bars in grammes		Grammes per week
EC101100P	Non-chocolate confectionery in portions		Portions per week
EC101100G	Non-chocolate confectionery in grammes		Grammes per week
EC101110P	Sweet in portions		Portions per week
EC101110G	Sweet in grammes		Grammes per week
EC101120P	Liquorice in portions		Portions per week
EC101120G	Liquorice in grammes		Grammes per week
EC101130P	Fudge in portions		Portions per week
EC101130G	Fudge in grammes		Grammes per week
EC101140P	Toffee in portions		Portions per week
EC101140G	Toffee in grammes		Grammes per week
EC101150P	Marshmallow in portions		Portions per week
EC101150G	Marshmallow in grammes		Grammes per week
EC101160P	Nougat in portions		Portions per week
EC101160G	Nougat in grammes		Grammes per week
EC101170P	Turkish delight in portions		Portions per week
EC101170G	Turkish delight in grammes		Grammes per week
EC101180P	Cereal bar in portions		Portions per week
EC101180G	Cereal bar in grammes		Grammes per week
EC101190P	Chewing gum in portions		Portions per week
EC101190G	Chewing gum in grammes		Grammes per week
EC101200P	Sugar products in portions		Portions per week
EC101200G	Sugar products in grammes		Grammes per week
EC101210P	Marzipan in portions		Portions per week

EC101210G	Marzipan in grammes		Grammes per week
EC101220P	Candied fruit in portions		Portions per week
EC101220G	Candied fruit in grammes		Grammes per week
EC101230P	Preserved ginger in portions		Portions per week
EC101230G	Preserved ginger in grammes		Grammes per week
EC110000P	Beverages in portions		Portions per week
EC110000ML	Beverages in millilitres		Millilitres per week
EC110000XP	Beverages - MISCELLANEOUS - in portions		Portions per week
EC110000XML	Beverages - MISCELLANEOUS - in millilitres		Millilitres per week
EC110100P	Beers and malt beverages in portions		Portions per week
EC110100ML	Beers and malt beverages in millilitres		Millilitres per week
EC110110P	Beer - alcohol >5% in portions		Portions per week
EC110110ML	Beer - alcohol >5% in millilitres		Millilitres per week
EC110120P	Beer - alcohol 3.1-5% in portions		Portions per week
EC110120ML	Beer - alcohol 3.1-5% in millilitres		Millilitres per week
EC110130P	Beer - alcohol 1-3% in portions		Portions per week
EC110130ML	Beer - alcohol 1-3% in millilitres		Millilitres per week
EC110140P	Beer - alcohol <1% in portions		Portions per week
EC110140ML	Beer - alcohol <1% in millilitres		Millilitres per week
EC110150P	Barley beer in portions		Portions per week
EC110150ML	Barley beer in millilitres		Millilitres per week
EC110200P	Ciders in portions		Portions per week
EC110200ML	Ciders in millilitres		Millilitres per week
EC110210P	Cider in portions		Portions per week
EC110210ML	Cider in millilitres		Millilitres per week
EC110220P	Perry in portions		Portions per week
EC110220ML	Perry in millilitres		Millilitres per week
EC110230P	Ginger beer in portions		Portions per week
EC110230ML	Ginger beer in millilitres		Millilitres per week
EC110240P	Elderflower in portions		Portions per week
EC110240ML	Elderflower in millilitres		Millilitres per week
EC110300P	Wines in portions		Portions per week
EC110300ML	Wines in millilitres		Millilitres per week

EC110310P	Wine - alcohol >9% in portions		Portions per week
EC110310ML	Wine - alcohol >9% in millilitres		Millilitres per week
EC110320P	Wine - alcohol 5.1.a% in portions		Portions per week
EC110320ML	Wine - alcohol 5.1.a% in millilitres		Millilitres per week
EC110330P	Wine - alcohol 1-5% in portions		Portions per week
EC110330ML	Wine - alcohol 1-5% in millilitres		Millilitres per week
EC110340P	Wine - alcohol <1% in portions		Portions per week
EC110340ML	Wine - alcohol <1% in millilitres		Millilitres per week
EC110350P	Dessert wine in portions		Portions per week
EC110350ML	Dessert wine in millilitres		Millilitres per week
EC110360P	Homemade wine in portions		Portions per week
EC110360ML	Homemade wine in millilitres		Millilitres per week
EC110400P	Fortified and liqueur wines in portions		Portions per week
EC110400ML	Fortified and liqueur wines in millilitres		Millilitres per week
EC110410P	Port in portions		Portions per week
EC110410ML	Port in millilitres		Millilitres per week
EC110420P	Sherry in portions		Portions per week
EC110420ML	Sherry in millilitres		Millilitres per week
EC110430P	Madeira in portions		Portions per week
EC110430ML	Madeira in millilitres		Millilitres per week
EC110440P	Marsala in portions		Portions per week
EC110440ML	Marsala in millilitres		Millilitres per week
EC110450P	Vermouth in portions		Portions per week
EC110450ML	Vermouth in millilitres		Millilitres per week
EC110460P	Ginger wine in portions		Portions per week
EC110460ML	Ginger wine in millilitres		Millilitres per week
EC110500P	Liqueurs in portions		Portions per week
EC110500ML	Liqueurs in millilitres		Millilitres per week
EC110510P	Fruit liqueurs in portions		Portions per week
EC110510ML	Fruit liqueurs in millilitres		Millilitres per week
EC110520P	Herb liqueurs in portions		Portions per week
EC110520ML	Herb liqueurs in millilitres		Millilitres per week
EC110530P	Seed liqueurs in portions		Portions per week
EC110530ML	Seed liqueurs in		Millilitres per week

	millilitres		
EC110540P	Chocolate liqueurs in portions		Portions per week
EC110540ML	Chocolate liqueurs in millilitres		Millilitres per week
EC110550P	Coffee liqueurs in portions		Portions per week
EC110550ML	Coffee liqueurs in millilitres		Millilitres per week
EC110560P	Egg liqueurs in portions		Portions per week
EC110560ML	Egg liqueurs in millilitres		Millilitres per week
EC110600P	Spirits in portions		Portions per week
EC110600ML	Spirits in millilitres		Millilitres per week
EC110610P	Brandy in portions		Portions per week
EC110610ML	Brandy in millilitres		Millilitres per week
EC110620P	Whisky in portions		Portions per week
EC110620ML	Whisky in millilitres		Millilitres per week
EC110630P	Gin in portions		Portions per week
EC110630ML	Gin in millilitres		Millilitres per week
EC110640P	Vodka in portions		Portions per week
EC110640ML	Vodka in millilitres		Millilitres per week
EC110650P	Rum in portions		Portions per week
EC110650ML	Rum in millilitres		Millilitres per week
EC110700P	Alcoholic mixed drinks in portions		Portions per week
EC110700ML	Alcoholic mixed drinks in millilitres		Millilitres per week
EC110710P	Cocktails in portions		Portions per week
EC110710ML	Cocktails in millilitres		Millilitres per week
EC110720P	Punch - alcohol >1% in portions		Portions per week
EC110720ML	Punch - alcohol >1% in millilitres		Millilitres per week
EC110730P	Punch - alcohol <1% in portions		Portions per week
EC110730ML	Punch - alcohol <1% in millilitres		Millilitres per week
EC110740P	Shandy in portions		Portions per week
EC110740ML	Shandy in millilitres		Millilitres per week
EC110750P	Laced coffee in portions		Portions per week
EC110750ML	Laced coffee in millilitres		Millilitres per week
EC110800P	Carbonated soft drinks in portions		Portions per week
EC110800ML	Carbonated soft drinks in millilitres		Millilitres per week
EC110810P	Tonic water in portions		Portions per week
EC110810ML	Tonic water in millilitres		Millilitres per week
EC110820P	Soda water in portions		Portions per week
EC110820ML	Soda water in		Millilitres per week

	millilitres		
EC110830P	Carbonated lemonade in portions		Portions per week
EC110830ML	Carbonated lemonade in millilitres		Millilitres per week
EC110840P	Carbonated fruit drink in portions		Portions per week
EC110840ML	Carbonated fruit drink in millilitres		Millilitres per week
EC110850P	Cola in portions		Portions per week
EC110850ML	Cola in millilitres		Millilitres per week
EC110860P	Root beer in portions		Portions per week
EC110860ML	Root beer in millilitres		Millilitres per week
EC110870P	Cream soda in portions		Portions per week
EC110870ML	Cream soda in millilitres		Millilitres per week
EC110880P	Dr Pepper in portions		Portions per week
EC110880ML	Dr Pepper in millilitres		Millilitres per week
EC110890P	Lucozade in portions		Portions per week
EC110890ML	Lucozade in millilitres		Millilitres per week
EC110900P	Non-dilution still drinks in portions		Portions per week
EC110900ML	Non-dilution still drinks in millilitres		Millilitres per week
EC110910P	Still lemonade in portions		Portions per week
EC110910ML	Still lemonade in millilitres		Millilitres per week
EC111000P	Dilution drinks in portions		Portions per week
EC111000ML	Dilution drinks in millilitres		Millilitres per week
EC111010P	Blackcurrant drink in portions		Portions per week
EC111010ML	Blackcurrant drink in millilitres		Millilitres per week
EC111020P	Fruit squash in portions		Portions per week
EC111020ML	Fruit squash in millilitres		Millilitres per week
EC111030P	Fruit cordial in portions		Portions per week
EC111030ML	Fruit cordial in millilitres		Millilitres per week
EC112000P	Infusion drinks in portions		Portions per week
EC112000ML	Infusion drinks in millilitres		Millilitres per week
EC112010P	Black tea in portions		Portions per week
EC112010ML	Black tea in millilitres		Millilitres per week
EC112020P	Oolon tea in portions		Portions per week
EC112020ML	Oolon tea in millilitres		Millilitres per week
EC112030P	Green tea in portions		Portions per week
EC112030ML	Green tea in millilitres		Millilitres per week
EC112040P	Herbal tea in portions		Portions per week

EC112040ML	Herbal tea in millilitres		Millilitres per week
EC112050P	White tea in portions		Portions per week
EC112050ML	White tea in millilitres		Millilitres per week
EC112060P	Instant tea powder in portions		Portions per week
EC112060ML	Instant tea powder in millilitres		Millilitres per week
EC112070P	Coffee in portions		Portions per week
EC112070ML	Coffee in millilitres		Millilitres per week
EC112071P	Decaffeinated coffee in portions		Portions per week
EC112071ML	Decaffeinated coffee in millilitres		Millilitres per week
EC112072P	Caffeinated coffee in portions		Portions per week
EC112072ML	Caffeinated coffee in millilitres		Millilitres per week
EC112080P	Instant coffee in portions		Portions per week
EC112080ML	Instant coffee in millilitres		Millilitres per week
EC112081P	Instant decaffeinated coffee in portions		Portions per week
EC112081ML	Instant decaffeinated coffee in millilitres		Millilitres per week
EC112082P	Instant caffeinated coffee in portions		Portions per week
EC112082ML	Instant caffeinated coffee in millilitres		Millilitres per week
EC113000P	Water in portions		Portions per week
EC113000ML	Water in millilitres		Millilitres per week
EC113010P	Tap water in portions		Portions per week
EC113010ML	Tap water in millilitres		Millilitres per week
EC113020P	Demineralised tap water in portions		Portions per week
EC113020ML	Demineralised tap water in millilitres		Millilitres per week
EC113030P	Carbonated mineral water in portions		Portions per week
EC113030ML	Carbonated mineral water in millilitres		Millilitres per week
EC113040P	Still mineral water in portions		Portions per week
EC113040ML	Still mineral water in millilitres		Millilitres per week
EC114000P	Fruit juices in portions		Portions per week
EC114000ML	Fruit juices in millilitres		Millilitres per week
EC114010P	Orange juice in portions		Portions per week
EC114010ML	Orange juice in millilitres		Millilitres per week
EC114020P	Grapefruit juice in portions		Portions per week
EC114020ML	Grapefruit juice in millilitres		Millilitres per week

EC114030P	Lemon juice in portions		Portions per week
EC114030ML	Lemon juice in millilitres		Millilitres per week
EC114040P	Apple juice in portions		Portions per week
EC114040ML	Apple juice in millilitres		Millilitres per week
EC114050P	Prune juice in portions		Portions per week
EC114050ML	Prune juice in millilitres		Millilitres per week
EC114060P	Grape juice in portions		Portions per week
EC114060ML	Grape juice in millilitres		Millilitres per week
EC114070P	Mango juice in portions		Portions per week
EC114070ML	Mango juice in millilitres		Millilitres per week
EC114080P	Mixed fruit juice in portions		Portions per week
EC114080ML	Mixed fruit juice in millilitres		Millilitres per week
EC115000P	Vegetable juices in portions		Portions per week
EC115000ML	Vegetable juices in millilitres		Millilitres per week
EC115010P	Tomato juices in portions		Portions per week
EC115010ML	Tomato juices in millilitres		Millilitres per week
EC115020P	Carrot juices in portions		Portions per week
EC115020ML	Carrot juices in millilitres		Millilitres per week
EC116000P	Fruit and vegetable nectars in portions		Portions per week
EC116000ML	Fruit and vegetable nectars in millilitres		Millilitres per week
EC117000P	Other juices in portions		Portions per week
EC117000ML	Other juices in millilitres		Millilitres per week
EC117010P	Coconut milk in portions		Portions per week
EC117010ML	Coconut milk in millilitres		Millilitres per week
EC120000P	Miscellaneous in portions		Portions per week
EC120000G	Miscellaneous in grammes		Grammes per week
EC120000XP	Miscellaneous in portions		Portions per week
EC120000XG	Miscellaneous in grammes		Grammes per week
EC120100P	Baking goods in portions		Portions per week
EC120100G	Baking goods in grammes		Grammes per week
EC120110P	Sodium bicarbonate in		Portions per week

	portions		
EC120110G	Sodium bicarbonate in grammes		Grammes per week
EC120120P	Cream of tartar in portions		Portions per week
EC120120G	Cream of tartar in grammes		Grammes per week
EC120130P	Baking powder in portions		Portions per week
EC120130G	Baking powder in grammes		Grammes per week
EC120140P	Gelatine in portions		Portions per week
EC120140G	Gelatine in grammes		Grammes per week
EC120150P	Gum in portions		Portions per week
EC120150G	Gum in grammes		Grammes per week
EC120160P	Yeast in portions		Portions per week
EC120160G	Yeast in grammes		Grammes per week
EC120200P	Flavourings and essences in portions		Portions per week
EC120200G	Flavourings and essences in grammes		Grammes per week
EC120210P	Almond essence in portions		Portions per week
EC120210G	Almond essence in grammes		Grammes per week
EC120220P	Vanilla pods in portions		Portions per week
EC120220G	Vanilla pods in grammes		Grammes per week
EC120300P	Seasoning in portions		Portions per week
EC120300G	Seasoning in grammes		Grammes per week
EC120310P	Salt in portions		Portions per week
EC120310G	Salt in grammes		Grammes per week
EC120320P	Monosodium glutamate in portions		Portions per week
EC120320G	Monosodium glutamate in grammes		Grammes per week
EC120330P	Stock cubes/powder in portions		Portions per week
EC120330G	Stock cubes/powder in grammes		Grammes per week
EC120340P	Gravy in portions		Portions per week
EC120340ML	Gravy in millilitres		Millilitres per week
EC120350P	Vinegar in portions		Portions per week
EC120350ML	Vinegar in millilitres		Millilitres per week
EC120400P	Herbs in portions		Portions per week
EC120400G	Herbs in grammes		Grammes per week
EC120500P	Spices in portions		Portions per week
EC120500G	Spices in grammes		Grammes per week
EC120600P	Condiments in portions		Portions per week
EC120600G	Condiments in grammes		Grammes per week

EC120610P	Mustard in portions		Portions per week
EC120610G	Mustard in grammes		Grammes per week
EC120620P	Tomato ketchup in portions		Portions per week
EC120620G	Tomato ketchup in grammes		Grammes per week
EC120620ML	Tomato ketchup in millilitres		Millilitres per week
EC120630P	Brown sauce in portions		Portions per week
EC120630G	Brown sauce in grammes		Grammes per week
EC120630ML	Brown sauce in millilitres		Millilitres per week
EC120640P	Worcestershire sauce in portions		Portions per week
EC120640G	Worcestershire sauce in grammes		Grammes per week
EC120640ML	Worcestershire sauce in millilitres		Millilitres per week
EC120650P	Tabasco sauce in portions		Portions per week
EC120650G	Tabasco sauce in grammes		Grammes per week
EC120650ML	Tabasco sauce in millilitres		Millilitres per week
EC120660P	Horseradish sauce in portions		Portions per week
EC120660G	Horseradish sauce in grammes		Grammes per week
EC120660ML	Horseradish sauce in millilitres		Millilitres per week
EC120670P	Mint sauce in portions		Portions per week
EC120670G	Mint sauce in grammes		Grammes per week
EC120670ML	Mint sauce in millilitres		Millilitres per week
EC120680P	Tartare sauce in portions		Portions per week
EC120680G	Tartare sauce in grammes		Grammes per week
EC120680ML	Tartare sauce in millilitres		Millilitres per week
EC120700P	Dressings in portions		Portions per week
EC120700G	Dressings in grammes		Grammes per week
EC120710P	Salad dressing in portions		Portions per week
EC120710G	Salad dressing in grammes		Grammes per week
EC120720P	Mayonnaise in portions		Portions per week
EC120720G	Mayonnaise in grammes		Grammes per week
EC120800P	Chutney and pickles in portions		Portions per week
EC120800G	Chutney and pickles in grammes		Grammes per week

EC120810P	Mixed chutney in portions		Portions per week
EC120810G	Mixed chutney in grammes		Grammes per week
EC120820P	Apple chutney in portions		Portions per week
EC120820G	Apple chutney in grammes		Grammes per week
EC120830P	Cucumber chutney in portions		Portions per week
EC120830G	Cucumber chutney in grammes		Grammes per week
EC120840P	Tomato chutney in portions		Portions per week
EC120840G	Tomato chutney in grammes		Grammes per week
EC120850P	Relish in portions		Portions per week
EC120850G	Relish in grammes		Grammes per week
EC120860P	Pickle in portions		Portions per week
EC120860G	Pickle in grammes		Grammes per week
EC120900P	Savoury sauces in portions		Portions per week
EC120900G	Savoury sauces in grammes		Grammes per week
EC120900ML	Savoury sauces in millilitres		Millilitres per week
EC120910P	White sauce in portions		Portions per week
EC120910G	White sauce in grammes		Grammes per week
EC120910ML	White sauce in millilitres		Millilitres per week
EC120920P	Butter sauce in portions		Portions per week
EC120920G	Butter sauce in grammes		Grammes per week
EC120920ML	Butter sauce in millilitres		Millilitres per week
EC120930P	Fish sauce in portions		Portions per week
EC120930G	Fish sauce in grammes		Grammes per week
EC120930ML	Fish sauce in millilitres		Millilitres per week
EC120940P	Tomato sauce in portions		Portions per week
EC120940G	Tomato sauce in grammes		Grammes per week
EC120940ML	Tomato sauce in millilitres		Millilitres per week
EC121000P	Dessert sauces in portions		Portions per week
EC121000G	Dessert sauces in grammes		Grammes per week
EC121000ML	Dessert sauces in millilitres		Millilitres per week
EC121010P	Fruit sauce in portions		Portions per week
EC121010G	Fruit sauce in		Grammes per week

	grammes		
EC121010ML	Fruit sauce in millilitres		Millilitres per week
EC121020P	Chocolate sauce in portions		Portions per week
EC121020G	Chocolate sauce in grammes		Grammes per week
EC121020ML	Chocolate sauce in millilitres		Millilitres per week
EC122000P	Soups in portions		Portions per week
EC122000ML	Soups in millilitres		Millilitres per week
EC122010P	Milk/egg soup in portions		Portions per week
EC122010ML	Milk/egg soup in millilitres		Millilitres per week
EC122020P	Meat/poultry soup in portions		Portions per week
EC122020ML	Meat/poultry soup in millilitres		Millilitres per week
EC122030P	Fish soup in portions		Portions per week
EC122030ML	Fish soup in millilitres		Millilitres per week
EC122040P	Vegetable soup in portions		Portions per week
EC122040ML	Vegetable soup in millilitres		Millilitres per week
EC123000P	Savoury snacks in portions		Portions per week
EC123000G	Savoury snacks in grammes		Grammes per week
EC123010P	Potato-based snacks in portions		Portions per week
EC123010G	Potato-based snacks in grammes		Grammes per week
EC123020P	Maize-based snacks in portions		Portions per week
EC123020G	Maize-based snacks in grammes		Grammes per week
EC123030P	Wheat-based snacks in portions		Portions per week
EC123030G	Wheat-based snacks in grammes		Grammes per week
EC123040P	Rice-based snacks in portions		Portions per week
EC123040G	Rice-based snacks in grammes		Grammes per week

Appendix 4.3 Sample of do file
PORDENONE STUDY

```
**-read in data as DTA FILE--*
use "$path/data/pordenone", clear

*---check whether anything has changed since last time data was read
save "$path/temp/pordenone", replace
cf _all using "$path/temp/pordenone"

*-check whether data has changed-*
datasignature
assert r(datasignature)== "1794:52(60900):877230665:365421863"

*RENAME/CODE VARIABLES*
gen A01 = 123

recode v2 (.=.a)
tostring v2, replace
gen str15 A02=v2

gen A04 = 10
gen A05 = 12
gen A06 = .b
gen A07 = 12
gen A08 = v3
gen A09 = centro
gen B01 = .b
gen B02 = v11
gen B03 = v6
gen B04 = .b
gen C01 = cond(A08==2, .c , .b)
gen C02 = cond(A08==2, .c , .b)
gen C03 = .b
recode C03 (.b=.c) if A08==2
gen C04 = .b
recode C04 (.b=.c) if A08==2
gen D01 = v24
recode D01 (1=3) (2=1) (3=2)
gen D02 = v24
recode D02 (1=3) (2=1) (3=2)
gen D03 = .b
gen D04 = (v26*v29)/20
replace D04 = 0 if D01 == 3
recode D04 (.=.a)
gen D05 = v26
recode D05 (.=0) if D01==3
recode D05 (.=0) if D02==3
recode D05 (.=.a)
```

```
gen D06 = v29
recode D06 (.=0) if D01==3
recode D06 (.=0) if D02==3
recode D06 (.=.a)

gen E01 = v118
gen E02 = v124
gen E03 = .a
gen E04 = .b
gen E05 = .b
gen E06 = .b
gen F01 = .
replace F01 =1 if  v120==2
replace F01 = 1 if  v122==2
replace F01 =2 if v120 ==1
replace F01 =2 if v120 ==1
recode F01 (.=.a)
egen F02= anyvalue(F01),values(1)
recode F02 (.=.a)
gen F03 = .a
gen G01 = .a
gen G02 = .a
gen G03 = .a
gen H01 = .a
gen H02 = .a
gen H03 = .a

*================================================
============================
*GENERATE NEW STUDY ID*
*================================================
============================
set seed 22782938
generate random = runiform()

*CHECK WHETHER UNIQUE*
egen group = group (A02 A08 random)
isid group
drop group

sort A02 A08 random, stable
egen A03 = seq()
tostring A03, replace
replace A03 = "123_" + A03

isid A03
drop random
```

```
*================================================================
*1. MILK AND MILK PRODUCTS (EC010000)*
*================================================================
*CHEESE*
gen EC010500P = v6

*LIQUID MILK*
gen EC010100P = v51



*================================================================
*2. EGG AND EGG PRODUCTS (EC020000)*
*================================================================
gen EC020000XP = v57


*================================================================
*3. MEAT AND MEAT PRODUCTS (EC030000)*
*================================================================
egen EC030000XP =rowtotal(v52  v58) , missing
gen EC030800P = v53


*================================================================
*4. FISH AND FISH PRODUCTS (EC040000)*
*================================================================
gen EC040000XP = v59

*================================================================
*8. VEGETABLES (EC080000)*
*================================================================
gen EC080710P = v54
gen EC080100P = v55


*================================================================
```

```
*9. FRUITS AND FRUIT PRODUCTS (EC090000)*
*================================================
============================
gen EC090000XP = v56

*10. Bread
gen EC061030P = v61
recode EC061030P (1=0) (3=4)

*================================================
============================
*11. BEVERAGES (EC110000)*
*================================================
============================
*MISCELLANEOUS COFFEE*
gen EC112002XP = v31 * 7
gen EC112002XML = EC112002XP * 250

*DECAF COFFEE*
gen EC112071P = v33 * 7
gen EC112071ML = EC112071P * 250

egen EC112070P = rowtotal (EC112071P EC112002XP), missing
egen EC112070ML = rowtotal (EC112071ML EC112002XML), missing

*TEA*
gen EC112001XP = v35 * 7
gen EC112001XML = EC112001XP * 250

*COLA*
gen EC110850P = v37 * 7
gen EC110850ML = EC110850P * 250

*BEER
destring beermed , generate (beer) dpcomma force
gen EC110100P = beer*7
gen EC110100ML = EC110100P * 360

*WINE
destring winemed , generate (wine) dpcomma force
gen EC110300P = wine*7
gen  EC110300ML = EC110300P * 250


*liquor
destring liqmed , generate (liq) dpcomma force
gen EC110500P = liq*7
gen EC110500ML = EC110500P * 45
```

```
*TOTAL FLUID*
egen EC110000ML = rowtotal(EC112070ML  EC112001XML
EC110850ML EC110100ML EC110300ML EC110500ML), missing
egen EC110000P  = rowtotal(EC112070P  EC112001XP  EC110850P
EC110100P EC110300P EC110500P), missing

/*label variable A08 "Subject status"
label define casecontrol 1 "Case (1)" 2 " Control (2)" 3 "Cohort (3)"
label values A08 casecontrol
tabstat EC112070ML  EC112001XML  EC110850ML EC110100ML
EC110300ML EC110300ML, by (A08) statistics( mean median p25
p75)*/

*================================================
============================
*LABEL NAME, DEFINE & VALUES & RECODE VARIABLES*
*================================================
============================

include labeling.doi

*ORDER*
order A01 A02 A03 A04 A05 A06 A07 A08 A09 B01 B02 B03 B04 D01
D02 D03 D04  ///
D05 D06 E01 E02 E04 E05 E06 F01 F02 F03 G01 G02 G03 H01 H02
H03 EC*

*RECODING MISSING VALUES FOR CONTINUOUS
VARIABLES*
foreach var of varlist EC010500P-EC110500P {
label values `var' miss
recode `var' (.=.a)
}



keep A01 A02 A03 A04 A05 A06 A07 A08 A09 B01 B02 B03 B04 C01
C02 C03 C04 ///
D0* E01 E02 E04 E05 E06 F01 F02 F03 G01 G02 G03 H01 H02 H03
EC*


*================================================
============================
* ASSERTIONS- CHECK DATA FOR INCONSISTENTIES -
CATEGORICAL VARIABLES
```

```
*(CASECON, SMOKING STATUS, AGE, GENDER, BROWN
BREAD,OIL, MARGARINE)*
*================================================
============================
assert _N==1794
assert inlist(D01, 1,2,3,.a,.b)
assert inrange(B02, 20, 79)
assert inlist(A08, 1,2,3,.a)

*================================================
============================
*ASSERTION FOR CONTINUOUS VARIABLES*
*================================================
============================

foreach var of varlist EC010500P-EC110500P {
cap: assert inrange(`var', 0, 100)
local x = `var'
if _rc di as err "Values for `var' not between 0 and 100.; value is: `x'!"
}

list D01 if D04==0 & D01==2
list D01 if D04==0 & D01==1
list B03 if B03 > 2
list B03 if B03 < 0
list D01 if D04 < 0 & D01==3
list D01 if D04 > 0 & D01==3
list D01 if D04 == .a
list D02 if D04 < 0 & D02==3
list D02 if D04 > 0 & D02==3

recode D02 (2=.a) if A03 == "123_952"
recode D02 (1=.a) if A03 == "123_390"
recode D02 (2=.a) if A03 == "123_1254"
recode D02 (2=.a) if A03 == "123_1643"
recode D02 (2=.a) if A03 == "123_1693"
recode D02 (1=.a) if A03 == "123_196"
recode D02 (1=.a) if A03 == "123_243"
recode D02 (1=.a) if A03 == "123_245"
recode D02 (1=.a) if A03 == "123_522"
list D02 if D04==0 & D02==2
list D02 if D04==0 & D02==1

recode D04 (0=.a) if A03 == "123_1402"
recode D04 (0=.a) if A03 == "123_1754"
recode D04 (0=.a) if A03 == "123_347"
recode D04 (0=.a) if A03 == "123_645"
recode D05 (0=.a) if A03 == "123_522"
```

```
list D01 if D05==0 & D01==1

*RANDOM CHECK*

*--Check all missings are either .a or .b and not .
ds , has(type numeric)
foreach var of varlist `r(varlist)' {
//assert `var' !=.
list `var' if `var' ==.

}
save "$path/output/pordenone", replace
exit
```