A global consortium initiative on the association between Western diet and risk of bladder cancer

Western Diet and Bladder Cancer

Mostafa Dianati

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Abbreviations

Abbreviations Used in Chapter 1:
The BLadder cancer Epidemiology and Nutritional Determinants (BLEND), European Prospective Investigation into Cancer and Nutrition (EPIC), transurethral resection of bladder tumor (TURBT), computerized tomography (CT), TNM (Tumor, Nodes, and Metastases), non-muscle invasive bladder cancers (NMIBC) and muscle invasive bladder cancers (MIBC), The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR), Dietary Approaches to Stop Hypertension (DASH), the Dietary Inflammatory Index [DII], principal component analysis (PCA).

Abbreviations Used in Chapter 2:
Bladder cancer (BC), dietary-inflammatory-index (DII), Western diet (WD), Mediterranean diet (MD), Food-frequency questionnaire (FFQ), Relative risks (RRs), Hazard ratios (HRs), Odds ratios (ORs), Confidence intervals (CIs), Standard errors (SEs), Newcastle–Ottawa Scale (NOS).

Abbreviations Used in Chapter 3:
BLadder cancer Epidemiology and Nutritional Determinants (BLEND), body mass index (BMI), confidence intervals (CIs), Dietary patterns (DPs), food frequency questionnaire (FFQ), hazard ratios (HRs), heterocyclic amines (HCAs), muscle-invasive bladder cancer (MIBC), non-muscle-invasive bladder cancer (NMIBC), polycyclic aromatic hydrocarbons (PAHs), relative risk (RR), standard deviation (SD), and Western diet score (WDS).

Abbreviations Used in Chapter 4:
Bladder cancer (BC), Bladder cancer Epidemiology and Nutritional Determinants (BLEND), body mass index (BMI), confidence interval (CI), European Prospective Investigation into Cancer (EPIC), food frequency questionnaire (FFQ), hazard ratios (HRs), mono-unsaturated fatty acids (MUFAs), muscle-invasive BC (MIBC), non-muscle-invasive BC (NMIBC), The Netherlands Cohort Study (NLCS), poly-unsaturated fatty acids (PUFAs), relative risk (RR), saturated fatty acids (SFAs), standard deviation (SD), VITamins and Lifestyle study (VITAL).

Abbreviations Used in Chapter 5:
Bladder cancer (BC), Bladder cancer Epidemiology and Nutritional Determinants (BLEND), Body Mass Index (BMI), Confidence Interval (CI), European Prospective Investigation into Cancer (EPIC), Food Frequency Questionnaire (FFQ), Gram (g), Hazard Ratios (HRs), Heterocyclic Amines (HCAs), International Classification of Diseases for Oncology (ICD-O), kilocalorie (kcal), Milliliter (ml), Muscle-invasive BC (MIBC), N-nitroso

Compounds (NOC), Non-muscle-invasive BC (NMIBC), The Netherlands Cohort Study (NLCS), the Prostate, Lung, Colorectal, and Ovarian cohort study (PLCO), Polycyclic aromatic hydrocarbons (PAHs), Relative Risk (RR), Standard Deviation (SD), VITamins and Lifestyle study (VITAL), World Cancer Research Fund International (WCRF).

Abbreviations Used in Chapter 6:

The Bladder cancer Epidemiology and Nutritional Determinants (BLEND), dietary-inflammatory-index (DII), Monounsaturated fatty acids (MUFAs), Muscle-invasive BC (MIBC), Non-muscle-invasive BC (NMIBC), randomized clinical trials (RCTs), food frequency questionnaire (FFQ), carcinoma in situ (CIS), the International Classification of Diseases for Oncology (ICD-O), Glutathione S-Transferases (GSTs).

Chapter 1

General introduction

1.1 Cancer

1.1.a The definition of cancer

Cancer is a condition in which some cells in the body grow out of control and may spread to other regions of the body. Cancer is a broad word that encompasses a wide range of diseases that can affect any area of the body. Several main types of cancer exist, including; a) carcinoma; the most frequent type of cancer, originating from epithelial cells b) Leukemia, starting in the bone marrow's blood-forming tissue; c) Sarcoma, arising in the soft tissues of the body (e.g. muscle, fat, blood vessels, and lymph vessels) or in fibrous tissue (e.g. tendons and ligaments); d) lymphoma, starting in the lymphocytes (i.e. T- or B-cells) and can be divided in Hodgkin- and non-Hodgkin lymphoma; e) multiple myeloma, starting in the plasma cells of the body, and f) melanoma, arising in the melanocytes and develops into melanocytes (i.e. cells that produce melanin) [1, 2].

1.1.b Cancer development

Cancer can begin in nearly all of the billion cells that make up the human body. Human cells normally expand and multiply (via a process known as cell division) to create new cells as needed by the body. However, this ordered process can sometimes break down, resulting in aberrant or damaged cells. Cancer cells, unlike normal cells, do not cease growing and dividing, and this uncontrolled cell growth leads to the formation of a tumor. Multiplication of these damaged cells may lead to tumor development and growth [3]. Hence, tumors can be malignant or benign. Malignant tumors can invade surrounding tissues and spread to other parts of the body, resulting in the formation of new tumors (a process called metastasis). Benign tumors do not invade or spread into surrounding tissues and seldom reappear after being excised [4]. Generally, during the early stages of cancer, tumors are typically benign and remain confined within the normal boundaries of a tissue. As tumors grow and become malignant, however, they gain the ability to break through these boundaries and invade other tissues [5].

1.1.c General epidemiology of cancer

Cancer is a serious public health issue and a significant barrier to increase the life expectancy of people throughout the world. It is the leading cause of death in the United States with expected numbers of 1,898,160 new cancer cases and 608,570 cancer deaths by the end of 2021 [6]. The global cancer incidence rate was 19% higher in men (222.0 per 100,000) than in women (186 per 100,000), and rates varied greatly between areas. According to the IARC, since 2010 cancer is causing more dead's than cardiovascular diseases, making cancer the leading cause of death globally [7]. It is the foremost cause of mortality before the age of 70, in 86% of the world nations (**Figure 1.1**) [7]. It is expected that the cancer will double by 2020 and triple by 2030 [8]. Therefore, cancer

is not only a serious health concern, prevention of this disease represents a potential solution to a rising worldwide public health issues [6].

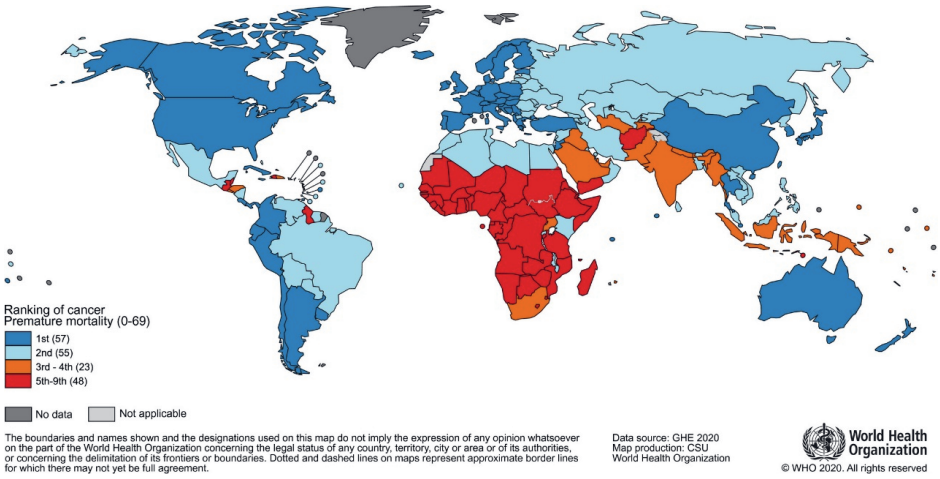

Figure 1.1. National ranking of cancer as a cause of death at ages <70 years in 2019. The numbers of countries represented in each ranking group are included in the legend. Source: World Health Organization. Available at: https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21660.

1.2 Bladder cancer

1.2.a Anatomy of the bladder

The urinary bladder is a temporary storage reservoir for urine. It is located in the pelvic cavity, posterior to the symphysis pubis, and below the parietal peritoneum, and more generally, it is located just below the kidneys and right behind the pubic bone [9]. In gross anatomy, the bladder can be divided into a broad fundus, a body, an apex, and a neck; a) the Fundus is located posteriorly, triangular-shaped with the tip of the triangle pointing backwards, b) the apex is located superiorly, pointing towards the pubic symphysis, connected to the umbilicus by the median umbilical ligament, c) the body is the main part of the bladder and is located between the apex and the fundus, and d) the neck is formed by the convergence of the fundus and the two inferolateral surfaces, and continuous with the urethra [9, 10]. The bladder is made of the many layers, including; a) urothelium or transitional epithelium. This is the layer of cells that lines the inside of bladder. Cells in this layer are called urothelial cells or transitional cells., b) lamina propria, the next layer around the urothelium, which contains blood vessels, nerves, and in some regions, glands, c) detrusor muscle or muscularispropria. This is the outer layer and it is well defined around the neck of the urinary bladder; however, in the rest of the bladder wall, they run randomly, without orientation, and d) fatty connective tissue, which covers and separates the bladder from other organs [9, 10]. Anatomical Features of the urinary bladder is presented in **Figure 1.2**.

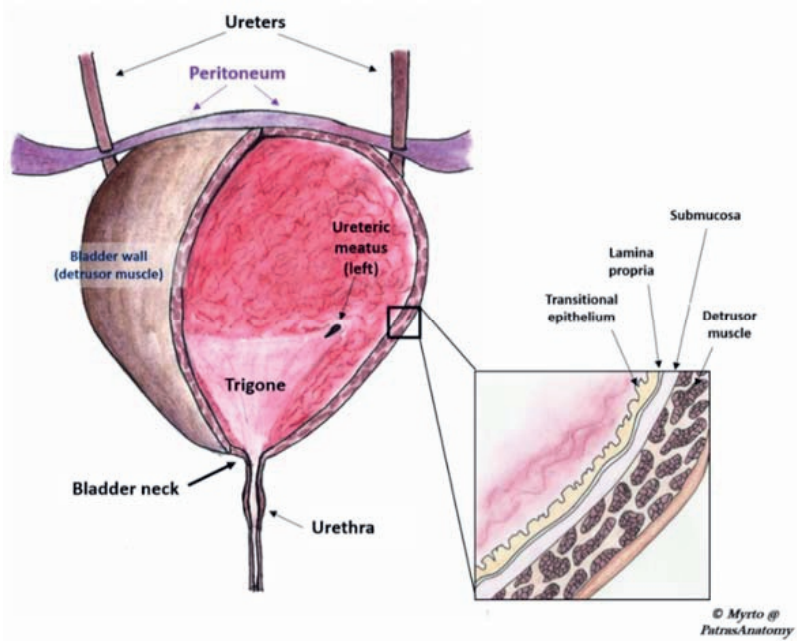

Figure 1.2. Anatomical Features of the Urinary Bladder. https://teachmeanatomy.info/pelvis/viscera/bladder/.

1.2.b Bladder cancer occurrence, diagnosis and tumor stages types

Bladder cancer develops when the DNA of bladder cells mutates or changes, disabling the functions that control cell growth [10]. Bladder cancer is a common type of urothelial carcinoma that begins in the urothelial cells that line the inside of the bladder [10].

Most often bladder cancer is diagnosed after an individual explains their doctor about blood in the urine, also called hematuria. Less common symptoms include a burning sensation when urinating, bladder pain, frequent urination or sudden urge, and frequent urinary tract infections. There are several tests that can determine the diagnosis of bladder cancer, including a) cystoscopy, in which the interior of the bladder is examined using a thin camera that is inserted into the urethra; b) voided urinary cytology, which is used to assess morphologic changes in intact cells in the urine; c) biopsy, which is used to remove a sample of tissue for testing that this procedure is sometimes called transurethral resection of bladder tumor (TURBT) and d) Imaging tests, such as computerized tomography (CT) urogram or retrograde pyelogram, which is used to examine the structures of the urinary tract [11, 12].

Most of the time, treatment of bladder cancer is based on the tumor's clinical stage when it's first diagnosed. This includes how deep it's thought to have grown into the bladder wall and whether it has spread beyond the bladder. Generally, five types of standard treatment are used for bladder cancer including surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy. After bladder cancer confirma-

tion, Transurethral resection of bladder tumor (TURBT) is the initial key step for treating a urothelial carcinoma of the bladder [21]. TURBT has two main goals: safe clearance of the tumour and the determination of the biological potential of the tumour. Bladder cancer is divided into prognostic stages based on TNM (Tumor, Nodes, and Metastases) classification. T- tumor is used to describe the size of the primary tumour and its invasion in neighboring tissue. N defines the presence and extent of regional nodal metastases, and M describes distant metastatic cancer [13] (**Table 1.1**).

Table 1.1. Tumor, Node, Metastasis (TNM) classification system for bladder cancer

T-primary tumor		N-regional lymph nodes	
T categories	T criteria	N categories	N criteria
Ta	Non-invasive papillary carcinoma	N0	No regional lymph node metastasis
Tis	Carcinoma in situ (CIS): "flat tumor"	N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
T1	Tumor invades subepithelial connective tissue	N2	Metastasis in multiple regional lymph nodes in the true pelvis (Hypogastric, obturator, external iliac, or presacral)
T2	Tumor invades muscle	N3	Metastasis in a common iliac lymph node(s)
T2a	Tumor invades superficial muscle (inner half)	NX	Regional lymph nodes cannot be assessed
T2b	Tumor invades deep muscle (outer half)	M-distant metastasis	
T3	Tumour invades peri vesical tissue:	M categories	M criteria
T3a	Microscopically	M0	No distant metastasis
T3b	Macroscopically (extravesical mass)	M1a	Non regional lymph nodes
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	M1b	Other distant metastases
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina	MX	Metastasis cannot be measured
T4b	Tumour invades pelvic wall or abdominal wall	Source: *Park, Jeong Hwan, and Kyung Chul Moon. "Tumor, Nodes, Metastases (TNM) Classification System for Bladder Cancer." In Bladder Cancer, pp. 181-184. Academic Press, 2018.*	
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		

1.2.c Bladder cancer subtypes

Bladder cancer can be divided in three main subtypes; a) urothelial carcinoma, b) squamous cell carcinoma and c) adenocarcinoma. Urothelial carcinoma (or transitional cell carcinoma) starts in the cells that line the interior of the bladder. In both the United States and Europe, urothelial carcinoma is the most prevalent type of bladder cancer, accounting for 90–95% cases of all bladder cancer cases [14, 15]. Squamous cell carcinomas that usually arises from the upper vesical hemisphere at the posterior wall or vault are more advanced stage carcinomas of the bladder and are aggressive and commonly invasive [16]. This bladder cancer type accounts for 5% of all bladder cancers. Adenocarcinomas is a rather uncommon malignancy in the bladder (around 1% of all bladder cancers), which may arise primarily in the bladder as well as secondarily from a number of other organs [14]. Like the squamous cell carcinomas, most of the adenocarcinomas are invasive [15, 17].

Bladder cancer can also be subdivided based on how far cancer cells have spread into the bladder wall (i.e. bladder muscle). The main subtypes are non-muscle invasive bladder cancers (**NMIBC**) and muscle invasive bladder cancers (**MIBC**). Although NMIBC and MIBC have similar topographies, there is enough evidence to suggest that they are distinct tumours. According to previous research, they may grow in two separate routes, papillary and non-papillary, that overlap to some extent but result in two different types of bladder cancer clinically [18, 19]. According to the American Cancer Society, NMIBCs account for around 70–80% of newly diagnosed bladder cancers, and include tumours in stages Ta (50–70%), T1 (20–40%), and Tis/CIS (5–10%) [14, 20]. Fifty to 70% of all NMIBCs will recur and 10–30% will progress into a MIBC [14, 21].

1.2.d Epidemiology of the bladder cancer (Incidence and death rates)

Bladder cancer is among the top ten most frequent cancer types in the world. While incidence rates of bladder cancer have declined, due to timely diagnosis, advanced surgical techniques, and the introduction of immunotherapy, bladder cancer is still the 4th most frequent cancer among men and the 7th most common cancer type among women [22]. Recent estimates by the Global Burden of Diseases (GBD 2019) shows that globally 524,000 bladder cancer cases (95% CI: 476,000 to 569,000) occur per year [23]. In addition, the American Cancer Society projects reported a predicted number of 83,730 new bladder cancer cases (64,280 men and 19,450 women) and 17,200 (12,260 men and 4,940 women) deaths in 2021 [6].

In general, 90% of patients diagnosed with bladder cancer are over 55 years old, with a typical average age of 73 years old at the time of diagnose [24]. Bladder cancer incidence rates for 2013–2017 showed a wide diversity in incidence rates by race and ethnicity. Per 100,000 individuals the age adjusted incidence rates are 22.4 for non-Hispanic white, 11.8 for non-Hispanic black, 11.2 for American Indian and Alaska Native, 10.7 for Hispanic and 8.4 for Asian and Pacific Islander [25].

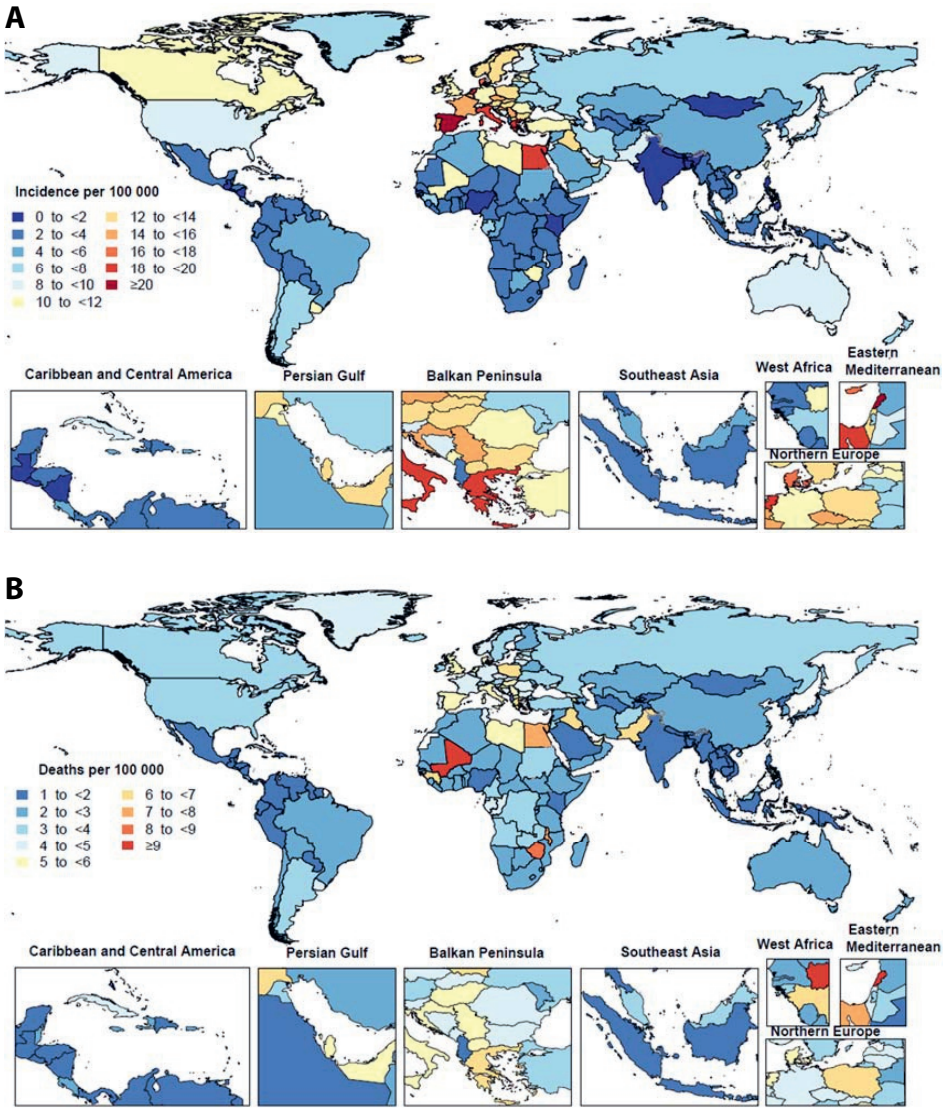

Figure 1.3. A. Age-standardised incidence rate of bladder cancer per 100,000 population by location for both sexes, 2019. **B.** Age-standardised death rate of bladder cancer per 100,000 population by location for both sexes, 2019. Global, regional, and national burden of bladder cancer and its attributable risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease study 2019. BMJ Global Health, 2021[http://dx.doi.org/10.1136/bmjgh-2020-004128].

1.2.e Bladder cancer survival and recurrence

According to the American Cancer Society, the overall 5-year survival rates for bladder cancer are high for in situ cancers (96%), moderate for localized tumours (69%), but low for both regional and distance tumours with 37% and 6%, respectively. Considering all the stages combined 5-year relative survival rates for bladder cancer is 77% [26]. A

significant diversity exists in the in 5- and 10-year bladder cancer survival rates between men and women. While 56.1% (95% CI: 55.2 to 57.1) of the men survive bladder cancer in the first 5 years after diagnosis, only 43.9% (95% CI: 42.4 to 45.4) of the women survive bladder cancer in the first five years. This disparity is mainly caused by the later stage of the tumour in men at the time of diagnosis [27]. Besides gender differences in incidence rates, also ethnicity is suggested to affect the 5- and 10-years survival, with white individuals having an 82.8 %, black a 70.2%, Hispanics a 80.7%, and Asian/Pacific Islanders a 81.9% five-year disease-specific survival rate [28].

Bladder cancer that returns after a successful initial treatment with surgery, radiation, chemotherapy, or immunotherapy is known as "*recurrent bladder cancer*". Despite significant advances in diagnostic methods and surgical and nonsurgical treatments in recent decades, bladder cancer has a significant recurrence rate, ranging from 50% to 90% [29, 30]. Many factors are associated with bladder cancer recurrence, including; high age, female sex, smoking, tumour size, multifocal tumours, higher tumour grade, end stage of the tumour, and previous recurrence. It is known that the risk of tumour recurrence in higher in NMIBC patients compared to MIBC patients.

1.2.f Economic burden of bladder cancer

Results of a comprehensive review revealed that, due to the high survival rate, high recurrence rate, and therefore, the necessity for lifetime regular monitoring and treatment, the cost per patient suffering from bladder cancer from diagnosis to death is the highest of all malignancies, ranging from $US96,000–187,000 (2001 values) in the United States. Likewise, another study across the European Union (EU) found that, this disease cost the EU €4.9 billion in 2012, with health care accounting for €2.991 billion (59%) of total cancer expenditures, or 5% of overall health care cancer costs. However, due to different cost-effective management approaches [31] there were large variations in the cost by country, with the lowest cost being found in Bulgaria (€8 for every 10 citizens) and the highest in Luxembourg (€93 for every 10 citizens) [32].

1.2.g Bladder cancer risk factors

It is reported that hereditary factors are thought to be responsible for around 7% of bladder cancer cases in developed countries [33], suggesting that risk factors such as lifestyle (i.e., smoking and diet), environmental, and occupational exposures might play a significant role in the development of this cancer [34]. To date, smoking has been identified as the major risk factor for bladder cancer, accounting for 50% of the cases [35]. Smokers have a 1.9 times higher risk for developing bladder cancer compared to never smokers [36]. Tobacco smoke causes bladder cancer by the accumulation of harmful chemicals (i.e., aromatic amines and polycyclic aromatic hydrocarbons) in the urine [37]. These chemicals affect the cells of the bladder, resulting in genetic mutations

that are irreversible [37]. The second well-established risk factor for bladder cancer is occupational exposure to carcinogens, particularly aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons. Exposure to these factors is thought to account for 20% of all new bladder cancers have [35]. Third, arsenic (higher than 300 µg/l) in drinking water is suggested as a cause of bladder cancer [34, 35]. Arsenic carcinogenesis is thought to be caused by oxidative damage, epi-genetic effects, and interference with DNA repair [38]. Besides these harmful chemicals, low physical activity (<600 metabolic equivalent (MET)-minutes per week) has been suggested as an important risk factor for bladder cancer [39].

1.3 Diet and bladder cancer

Since the bladder is an excretory organ, and is therefore constantly exposed to both harmful and favourable components of a person's diet that are excreted through the urinary tract, it is supposed that, besides the above-mentioned main risk factors, also diet likely plays an essential role in the development of bladder cancer [40, 41]. However, up to date evidence on the role of diet on bladder cancer development is insufficient and often controversial. As a result, the 2018 third expert report of the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) [42] reported that there is inadequate research on the relationship between particular diets and nutrients and the risk of bladder cancer. This insufficiency might be related to some challenges in conducting nutritional research.

1.3.a Difficulties in nutritional research.

Nutritional research played a pivotal role in establishing a relationship between dietary or nutrient intake and health outcomes. Many research identified specific food items and nutrient with a beneficial effect on health and determined dietary requirements and levels of supplementation to achieve specific health outcomes. However, within this field of research there are many difficulties and challenges. A first challenge in nutritional research is the research design. For example, as many diseases develop over time, trials studies are not appropriate for answering questions about longer-term dietary and chronic disease. Observational studies, on the other hand, are used to follow dietary intake in large number of individuals, and they are less expensive to run and have a lower burden on participants and investigators. However, unlike clinical trials, observational studies are not well controlled, thus the results may be less reliable. Second, the measurement of diet constitutes a difficult challenge. Each component of every food cannot be included in food and nutrition databases. For example, nutrients aren't the only components in foods, and nonnutritive components are frequently excluded from these databases. Third, Individuals are also complicated, for example, those who

self-select to consume either a healthy or unhealthy diet are compared in observational studies, and the two groups may differ in other factors that impact health outcomes and considering these mostly confounder factors with diet is challenging [43]. Lastly, low sample size and thus the lack of adequate statistical power to perform complex analyses to find causal associations is another important difficulty in nutritional research.

1.3.b Single food items and bladder cancer

Despites the above-mentioned difficulties in nutritional research to find strong evidence in the relation between diet and bladder cancer, previous research showed some promising results. It has been shown that high consumption of tea and high intake of fruits and vegetables may reduce bladder cancer risk [42, 44]. There are also limited evidence that greater consumption of tea, coffee and milk may decrease the risk of bladder cancer [34, 45, 46]. Previous studies reported the associations between the risk of bladder cancer with some of the main elements of the Western diet including consumption of read and processed meats [47, 48], egg [49], fat [47] and sugar intake and sweetened beverages [50].

1.3.c Nutrients and bladder cancer

Besides evidence on single food items, previous research also showed several significant results in the associations between nutrients and bladder cancer risk. It is suggested that, high intakes B-vitamins (B12, B6 and B2), and vitamin D is associated with a decrease in bladder cancer risk [51-53]. However, for most of the studied nutrients in relation to bladder cancer risk results remain unclear or contradictive. While several studies show a beneficial effect for high folate intake and bladder cancer risk [52, 54], results of a cohort study reported no significant effect of high folate intake and bladder cancer risk [55]. Similar contradictive results have been shown for vitamin C or E supplements and bladder cancer risk [55-57].

1.3.d Dietary patterns and bladder cancer

Since in our daily intake we consume foods and beverages, as well as the nutrients and dietary constituents they contain, together, studying single food items or nutrients might not result in lowering the number of bladder cancer cases. Especially, since most of the food and beverage items we consume correlate with each other and are likely interactive or have a synergistic effect. On the other hand, because people don't eat foods (or nutrients) in isolation, but rather in complicated combinations of several foods (or nutrients), this single food item method may be unable to capture the influence of food interactions on disease risk. It is therefore, that nowadays researchers are taking more and more a holistic dietary approach rather than looking at individual foods or nutrients when assessing diet and cancer risk. For this a number of different approaches

are suggested, including; a) "a priori approach", that refers to the method of defining dietary patterns based on pre-specified criteria. Well-known predefined diets are i. the Prudent Diet, ii. the Mediterranean Diet, iii. the Western Diet, iv. the Dietary Approaches to Stop Hypertension (DASH), v. the Dietary Inflammatory Index [DII] are b) "a posteriori technique", that uses principal component analysis (PCA), or cluster analysis to discover patterns experimentally based on observed dietary intake.

Evidence using an a priori approach show that the prudent diet, rich of fruit and vegetables, whole grains, poultry, and low-fat dairy products, and the Mediterranean diet, rich of high consumption of fruits, vegetables, legumes and cereals, fish, moderate intake of alcohol, low-to-moderate intake of milk and dairy products, and low intake of meat and meat products, are protective against bladder cancer risk, whereas the Western diet, high intakes of red and processed meat, refined grains, sweets and desserts, and high-fat dairy products is suggested to have detrimental effects on bladder cancer [58, 59]. Evidence using a posterior approach, however, on the associations between dietary patterns and bladder cancer risk is limited. Only one study suggested that the Western diet may increase the risk of bladder cancer [60]. Nevertheless, there is no enough evidence using this approach on other dietary patterns, including the Mediterranean diet, and bladder cancer risk [60, 61].

1.3.e The Western diet

As a consequence of the Neolithic revolution and industrial revolutions, the Western diet introduced to the world. Following this revolution, the staple foods of the western diet, such as processed meats, sugar, alcohol, and refined grains, became the main component of the diet of a people [62]. The contemporary Western diet originated during the industrial revolution, which brought new food processing technologies such as the inclusion of cereals, refined sugars, and refined vegetable oils to the Western diet, as well as boosted the fat content of domesticated meats.

We have known for years that the Western diet is potentially detrimental to our health. For example, the advent of the Western diet has been associated to an increase in the occurrence of chronic diseases that are peculiar to civilized "Western" culture. For example, this diet could increase the incidence of obesity, mortality from heart disease, type 2 diabetes, hypertension, cancer and other "Western"-related diseases [62-65]. Moreover, results of a meta-analysis of the observational studies in 2016, showed that a higher adherence to the Western dietary pattern was associated with 1.46 times increased risk of overall mortality (95% CI: 1.27–1.68) of cancer survivors [59]. Unfortunately, the western diet, which is the worst diet for one's health, has gained a lot of popularity across the world and in fact, the Western diet is spreading and negatively impacting individuals' health [62-65]. However, to date evidence for any association between a Western dietary pattern and bladder cancer risk is limited.

1.3.f Western diet and bladder cancer

Although several studies reported the associations between components of the Western diet and bladder cancer, there is limited evidence on the association between the Western diet as a whole and bladder cancer risk. To the best of our knowledge, only one study has examined this association, showing that individuals who adhered to the western diet had a 2.35 times greater risk of bladder cancer, compared to those with low adherence [60].

1.4 The BLEND study

The studies presented in this thesis were embedded in an international consortium of observational studies investigating bladder cancer risk (BLEND) [50]. BLadder cancer Epidemiology and Nutritional Determinants (BLEND) consortium. The BLadder cancer Epidemiology and Nutritional Determinants (BLEND) consortium currently consists of 19 case-control studies and 16 cohort studies, including data from the already pooled European Prospective Investigation into Cancer and Nutrition (EPIC) [66]. The BLEND consortium is still recruiting, but the database now has 13,112 cases, 21,307 controls, and 691,936 cohort members. In this thesis we used data from the cohort studies [66]. The goal of combining these observational studies is to discover more about the effects of dietary patterns, nutrients, and specific foods on bladder cancer risk. BLEND includes information on smoking habits, age, gender, family history of cancer, and tumor stage in addition to food consumption and disease status. Data was cleaned and recoded to the same codebook and added to construct the BLEND database after obtaining datasets from the participating research. The Eurocode 2 Core categorization version 99/2, which includes coding for 2,362 food products, was used to code the dietary items [67].

The consortium's large sample size allows for reliable estimation of relatively small effect sizes, which is to be expected when investigating the impact of single foods or dietary patterns on bladder cancer risk. Additionally, the large sample size allows for the application of complex statistical models that require sufficient power to obtain reliable results.

1.5 Outline of the thesis

This thesis aims to increase our current knowledge and gain better insights in the effect of the Western diet and its components on bladder cancer risk. For this, data from prospective cohort studies in the BLEND consortium were analysed. Our first aim was to conduct a meta-analysis to incorporate up-to-date evidence on the association of dietary patterns with bladder cancer risk (**chapter 2**). **Chapter 3** focus on the associations between the Western dietary pattern and risk of bladder cancer using 13

prospective cohort studies. In **chapter 4** and **5**, we described the role of meat and fat and their sources in bladder cancer development. Data from 11 prospective cohort studies was used to explore the associations between meat and fish and bladder cancer risk (**chapter 4**). **Chapter 5** describes the associations between dietary fats and oils and their sources and risk of bladder cancer. Finally, **chapter 6** summarizes all research done for this thesis by discussing; a) the results in general, b) the interpretation and implication of main findings, c) the methodological consideration, d) the statistical validity and limitations, e) the future aspects of cancer- and nutritional research. Lastly, Chapter 6 also provides final conclusions for the reader of this thesis.

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Chapter 2

Dietary patterns and risk of bladder cancer: A systematic review and meta-analysis

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Abstract

Background: Several studies have investigated the relationship between dietary patterns and the risk of bladder cancer (BC) in different regions including Europe, the United States, and Asia, with no conclusive evidence. A meta-analysis was undertaken to integrate the most recent information on the relationship between the Western diet (WD), Mediterranean diet (MD), and dietary-inflammatory-index (DII) and the risk of BC.

Methods: We looked for published research into the relationship between dietary patterns and the incidence of BC in the PubMed/Medline, Cochrane Library, Web of Science, and Scopus databases up until February 2021. Using a multivariate random-effects model, we compared the highest and lowest categories of WD, MD and DII patterns and provided the relative risk (RR) and 95 percent confidence intervals (CIs) for the relevant relationships.

Results: The analysis comprised 12 papers that were found to be suitable after scanning the databases. Both case-control (RR 0.73, 95% CI: 0.52, 0.94; I^2=49.9%, p=0.15) and cohort studies (RR 0.93, 95% CI: 0.88, 0.97; I^2=63%, p=0.04) found a substantial inverse association between MD and BC. In addition, although cohort studies (RR 1.53, 95% CI 1.37, 1.70) showed a direct association between WD and BC, case-control studies (RR 1.33, 95% CI: 0.81, 1.88; I^2= 68.5%, p=0.07) did not. In cohort studies, there found no significant association between DII and BC (RR 1.02, 95% CI: 0.93, 1.12). In case-control studies, however, a strong direct association between DII and BC was discovered (RR 2.04, 95% CI: 1.23, 2.85; I^2=0%, p=0.67).

Conclusion: The current meta-analysis supports this hypothesis that MD and WD have protective and detrimental effects on BC risk, respectively. No significant association between DII and the risk of BC was observed. More study is needed to better understand the etiological mechanisms underlying how different dietary patterns affect BC.

Key words: Western diet; Mediterranean diet; Bladder cancer; Meta-analysis

Introduction

Being among the top ten most common types of cancer in the world, cancer of the bladder (BC) causes approximately 550,000 new cases annually [1]. With regard to the geographical distribution the risk of bladder cancer is the highest in Southern and Eastern Europe, Africa, the Middle East, and North America [2]. About 75% of cases of BC are non-muscle-invasive bladder cancer (NMIBC), a type that frequently recur and requires intensive treatment and follow-up measures posing a large burden on any national health care budgets [3]. Epidemiological studies introduced several factors that potentially influence the risk of bladder cancer. These factors include, sex, age, occupation, and smoking [4, 5]. Urinary tract infections and exposures to arsenic or aromatic amines like heterocyclic amines (HCAs), and polycyclic aromatic hydrocarbons (PAHs) are also among the potential risk factors for BC [6]. Furthermore, more information is becoming available on the possible role of food in the development of BC [6]. However, according to the latest report from World Cancer Research Fund (WCRF), the evidence from epidemiologic studies on the above association is scarce and largely inconsistent [7].

Epidemiological studies suggested that several environmental and lifestyle related factors, e.g. pollutions and diet, might also play important roles in the risk of BC [8, 9]. In terms of diet, epidemiological studies have examined at the associations between certain foods and the risk of BC, with some intriguing results. As such, animal fat, a high red meat intake, and refined carbohydrate, that are the major component of the Western diet (WD), are associated to an elevated risk of BC [10-12]. In contrast, the Mediterranean diet's key components, fruits, vegetables, whole grains, and dietary fiber, have been associated to a lower incidence of BC [13-18]. The MD contains sufficient of fiber (found in fruits and vegetables), legumes and grains, fish, moderate wine intake, low-to-moderate milk and dairy products consumption, and minimal meat and meat products consumption [17, 19]. WD, on the other hand, is a dietary pattern that includes a lot of high-fat animal meat, processed products, red meat, and high-sugar foods [20-22]. Based on the existing evidence, MD is a significant protective factor for several non-communicable diseases [23-25].

Foods contain many interacting nutrients affecting body's function and well-being. Although several studies associated particular food items are with BC, the evidence is inconclusive [26, 27]. This is because, individuals do consume food items together and it is therefore rather than focusing at individual nutrients when analyzing food, it's critical to apply a holistic approach. Among the several methods in nutritional epidemiology, dietary pattern analysis is now often regarded as a more effective method for determining the overall impact of food consumption on health. Given the fact that the relationship between dietary pattern and BC has attained increasing attention, the evidence remains inconclusive. For example, a few studies reported hazardous effects of WD on the risk of BC [10-12], whereas others found an inverse association between

WD (or healthy diets) and BC [13-18]. To sum up, although the association of BC in association to dietary pattern, has been investigated by several researchers in Europe, United States, and Asia, no conclusive evidence over the subject has been made. We performed a meta-analysis to integrate the most recent evidence on the relationship between WD, MD, and DII and the risk of BC.

Methods

This study was carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) standard recommendations [28].

Protocol and registration

The aim of this study was to see if there was an association between dietary habits and the risk of developing BC. In August 2020, the study protocol was registered with the CRD42020155353 registration number in the international prospective register of systematic reviews database (PROSPERO).

Search strategy and selection criteria

Without restrictions, we searched PubMed/Medline, Web of Science (ISI), Cochrane library, Clinicaltrials.gov, and SCOPUS databases for papers that indicated a relation between dietary patterns and the risk of BC up to February 2021. The following search keywords or phrases were used to find relevant articles: ("neoplasm" OR "cancer" OR "carcinoma") AND ("bladder" OR "urinary bladder") AND ("dietary pattern" OR "eating pattern" OR "food pattern" OR "dietary habit" OR "diet" OR "dietary"). Additionally, the reference lists of the included papers and recent major reviews were carefully evaluated to find other relevant publications in order to prevent missing any related article.

Excluding review studies, If the retrieved publications fulfilled the following criteria, they were included in our study: Studies with a case-control or cohort design, reported the associations between dietary patterns and BC, included newly diagnosed cases of BC, diagnosed all cases using pathological biopsies or other standard methods, and provided relative risks (RRs), hazards ratios (HRs), or odds ratios (ORs) and their corresponding 95 percent confidence intervals for the dietary patterns. We included the most often identified dietary patterns across studies to reduce the possibility of misclassifications, and we made sure that the selected dietary patterns were specified consistently in terms of factor loadings of the most frequently consumed foods as much as feasible. The categorization of Western and Mediterranean dietary patterns was based on selected peer-reviewed publications. When several publications from the same data were found, the publication with the most participants/person-years was chosen. The selected articles and reading

the titles and abstracts of the searched papers independently were examined by two independent reviewers (NA and DB). If both reviewers agreed that a publication did not fulfill the above-mentioned inclusion criteria, it was excluded. Inconsistencies (if any) were to be solved by a consultation with a third author (MD).

Data extraction and quality assessment

Using a standardized data collection form, two reviewers independently extracted the required information. From each study, we gathered the following data: first author's last name; year of publication; study location; study design; sample size; duration of follow-up; method of analysis; diagnostic criteria; gender; average age of participants; dietary valuation methods; dietary patterns; RRs, HRs, or ORs and the corresponding 95% CIs for the highest vs. the lowest categories; of dietary patterns from the final adjusted models and potential confounders adjusted in the multivariate analysis. The authors were contacted by email at least twice, one week apart, when the full text of a paper was unavailable or if any essential information was missing in the provided data. The Newcastle–Ottawa Scale (NOS) was used to measure quality assessment of the included studies [29]. Concisely, we used a nine-score tool based on the NOS to assess the quality of the studies characterized by three broad criteria: (1) appropriate study population selection, (2) study group comparability, and (3) ascertainment of the exposure (for cohort studies) or outcome (for case control studies) of interest. Each study's quality was independently assessed by two reviewers (NA and DB). Disagreements were once again resolved by discussion among the reviewers. Studies having a score of 7 or above, with 9 being the maximum, were deemed to be of high quality.

Statistical analyses

The observed relationship between dietary patterns and the risk of BC was measured using RRs as the common scale. As RR estimators, HRs, ORs, and incidence rate ratios (IRRs) were also utilized [30]. We conducted random-effects meta-analysis to obtain the pooled RR and its 95% confidence intervals. Because of the potential heterogeneity in clinical and methodological characteristics within and between studies, the random-effects analysis was used [31]. To assess heterogeneity across studies, we utilized Q statistics with a significance level of $p<0.10$. We also used the I^2 statistic to indicate the variance between studies that may be attributed to heterogeneity rather than chance. Moderate heterogeneity was defined as an I^2 value larger than 50% [32].

To measure the impact of individual or a group of studies on the results e conducted a sensitivity analysis. We tested for publication bias by visual inspection of Begg's funnel plots presenting log RRs against their standard errors (SEs) [33, 34]. STATA version 15.0 was used for all analyses (Stata Corp LP, College Station, Texas). Except otherwise specified, statistical significance was defined as a p-value of less than 0.05.

Results

Study characteristics

Following the PRISMA flow diagram (**Figure 2.1**) of the study selection process, we found a total of 2,554 articles from the searched databases. Some were excluded because of duplication and being irrelevant articles. Eventually, seven cohort studies [11, 12, 15-18, 35], and five case control studies [10, 13, 14, 36, 37] were included in the present mete-analysis. Included cohort studies consisted of 12,679 cases and 1,952,859 non-cases. In addition, the case-control studies included 1,891 cases and 2,326 controls. The study selection procedure is illustrated in **Figure 2.1**.

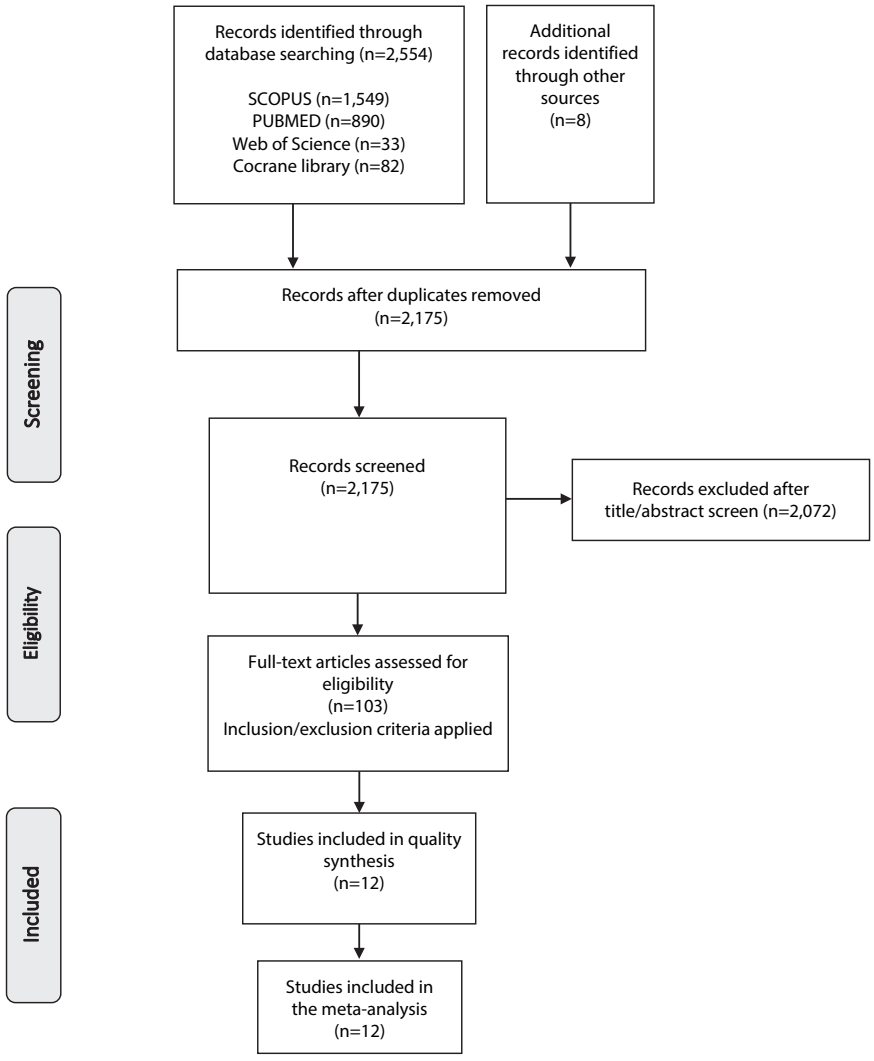

Figure 2.1. PRISMA flow diagram of the study selection process.

The characteristics of the included studies are presented in **Table 2.1**. Of the Included articles that were published between 2008 and 2020, six studies assessed the effect of MD on BC risk [13-18], three articles investigated the associations between WD and BC [10-12], and three studied on DII and BC [35-37]. Two of them were conducted in Italy [13, 36] and others were conducted in Netherlands [16], two from EPIC study [15, 17], Belgium [14], Australia [18], Uruguay [10], Iran [37], united states [12, 35], and one from Australia, European countries and united states [11]. Dietary intake was assessed using food-frequency questionnaire (FFQ) in almost all the included studies. Adjustment-variables were mostly age, sex, smoking, total energy intake, body mass index, alcohol consumption, physical activity, and family history of BC.

Association between a Western dietary patterns and risk of BC

The combined RR for the highest compared with the lowest category of a WD and risk of BC was 1.52 (95% CI: 1.36, 1.67), with no significant heterogeneity (I^2=19.5%, p=0.29) (**Figure 2.2**). A similar pattern of association was observed in cohort studies (RR 1.53, 95% CI: 1.37, 1.70), again with no heterogeneity (I^2= 0%, p=0.82). In contrast, no significant association was found between a WD and risk of BC in case-control studies (RR 1.33, 95% CI: 0.81, 1.88; I^2=68.5%, p=0.07).

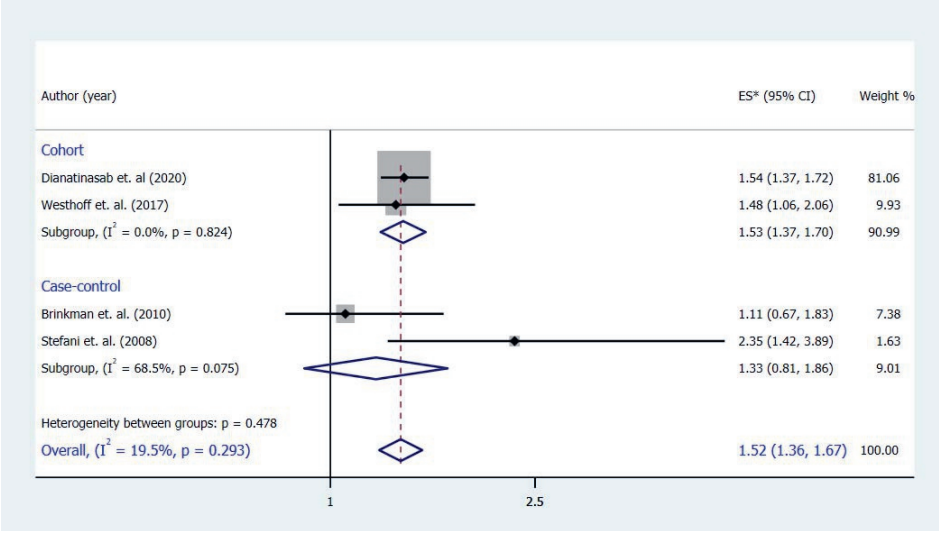

Figure 2.2. Forest plot shows the association between the highest category of a WD and risk of BC.

Association between Mediterranean diet and risk of BC

As shown in **Figure 2.3**, six studies (4 cohorts and 2 case-control) conducted on the association between a MD and risk of BC, and their results were inconsistent. As **Figure 2.3** presents, the pooled RR of the association between risk of BC for the highest

compared with the lowest category of MD was protective (RR 0.92, 95% CI: 0.87, 0.96), with a significant heterogeneity (I^2=62.5%, p=0.02). We found the same pattern with pooled estimate, in both cohorts (RR 0.93, 95% CI: 0.88, 0.97; I^2=63%, p=0.04) and case control studies (RR 0.73, 95% CI: 0.52, 0.94; I^2=49.9%, p=0.15).

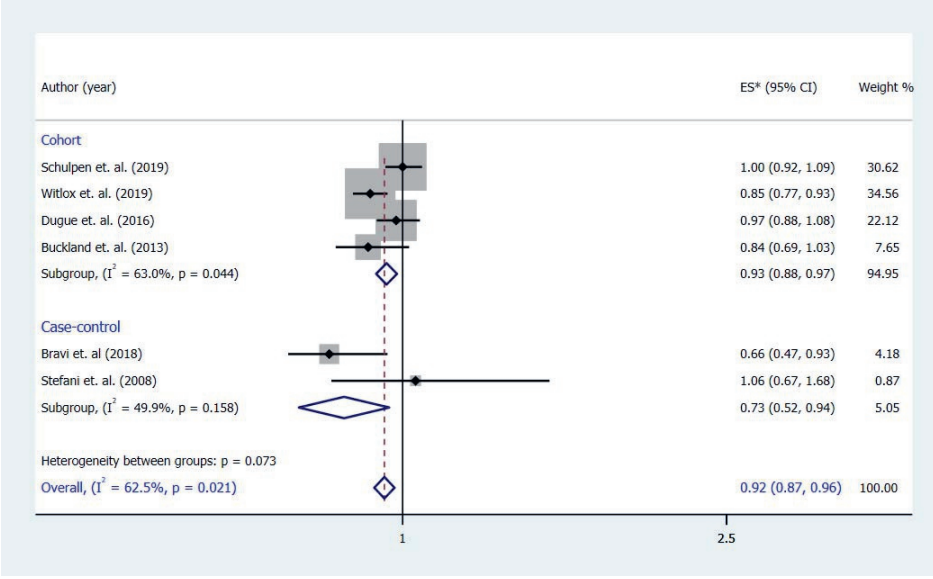

Figure 2.3. Forest plot shows the association between the highest category of a MD and the risk of BC.

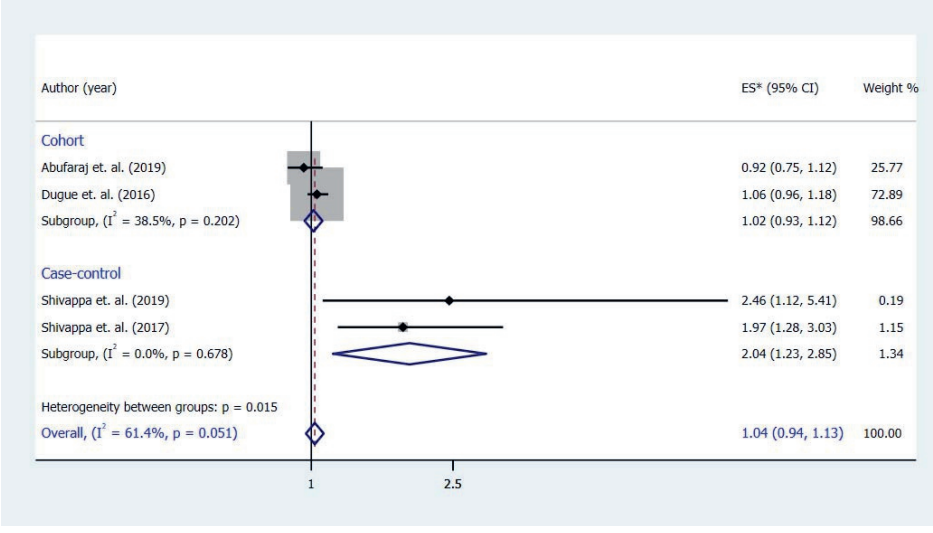

Figure 2.4. Forest plot shows the association between the highest category of DII and risk of BC.

Table 2.1. The characteristics of the included studies in the meta-analysis

Author	Year	Location	Study design	Sex (n%)	Follow up duration	Sample size and characteristics	Mean age	Method of analysis	invasive or non-invasive	diet components	Dietary patterns investigated and associated risk
Schulpen, et al.	2019	Netherlands	Cohort	Men 48% Women 52%	20.3 years	2,049 cases 4,084 sub cohort members	55–69	Trichopoulou	996 invasive/1,053 non-invasive	Proxy of MD: vegetables, legumes, fruits, nuts, whole grains, fish, the ratio of MUFA to saturated fatty acids.	MD (HR=1.00, 95% CI: 0.92–1.09) total
Witlox, et al.	2019	European countries	Cohort	Men 47% Women 53%	6,577,179 person-years	3,639 cases/642,583 non-case	younger than 70 years	Trichopoulou	1,480 non-invasive/945 invasive	fruits, vegetables, legumes and cereals, moderate-to-high consumption of fish, moderate consumption of alcohol (mostly wine), low-to-moderate consumption of milk and dairy products, and low consumption of meat and meat products	MD (HR=0.85, 95% CI: 0.77–0.93)
Bravi, et al.	2018	Italy	Case-control	Men 85% Women 15%	NA	690 cases/665 controls	25–84	Trichopoulou	268 non-invasive/ 192 pT1/ 159 invasive/ 307 moderately or well differentiated/ 312undifferentiated or poorly differentiated	olive oil, fruits, vegetables, legumes, and whole grain cereals	MD (OR=0.66, 95% CI: 0.47–0.93)

Table 2.1 continues on next page.

Table 2.1. *Continued*

Author	Year	Location	Study design	Sex (n%)	Follow up duration	Sample size and characteristics	Mean age	Method of analysis	invasive or non-invasive	diet components	Dietary patterns investigated and associated risk
Buckland, et al.	2013	EPIC	Cohort	Men 30% Women 70%	11 years	1,575 cases 475,737 non cases	51.2 6±9.9	Trichopoulou	430 were aggressive and 413 were non-aggressive UCC tumors and for 582 subject's tumor aggressiveness was unknown (n 5 52) or not validated (n 5 530)	fruit, nuts and seeds, vegetables, legumes, fish, olive oil and cereals (dairy products and meat, calculated as a function of energy)	MD (HR=0.84, 95% CI: 0.69, 1.03)
Brinkman, et al.	2010	Belgium	Case-control	Men 69% Women 31%	NA	200 cases/386 controls	cases 67.6 ± 9.9 controls 64.2 ± 9.6	PCA	No data	dietary fat, meat, olive oil, fish, eggs, milk, cheese, margarine	WD (OR: 1.11, 95% CI: 0.67–1.83)
Dugué, et al.	2016	Australia	Cohort	Men 41% Women 59%	21.3 years	379 Cases/37063 Non-cases	27 to 76	Trichopoulou	165 invasive/ 214 superficial	Alternate Healthy Eating Index (AHEI): vegetables, fruit, whole grains, nuts and legumes, long chain omega-3 fats, and polyunsaturated fatty acids/MD: vegetables, fruits, cereals, legumes, and fish/DII:	MDS: HR=0.97, 95% CI: 0.88–1.08); Alternate Healthy Eating Index (AHEI)-2010: (HR=1.03, 95% CI: 0.92–1.15); DII: (HR=1.06, 95% CI: 0.96–1.18)/ AHEI-2010 for superficial UCC (HR=1.17, 95% CI: 1.01–1.34)
Dianatinasab, et al.	2020	Australia, European Countries and united states	Cohort	Men 33% Women 67%	11.4 years	3,401 cases /577 367 non-cases	52.7 years (±10.2) for cases and 60.5 (±7.3) 52.6 (±10.1) for controls	Priori	1,365 no muscle-invasive / 874 muscle-invasive	Cream, Egg, Red and processed meet, Butter, Margarine, Animal fat, Pasta, Sugar, Dressing, Dips, Vegetables, Fruits, Fluid	WD (HR=1.54, 95% CI: 1.37-1.72)

Table 2.1. *Continued*

Author	Year	Location	Study design	Sex (n%)	Follow up duration	Sample size and characteristics	Mean age	Method of analysis	invasive or non-invasive	diet components	Dietary patterns investigated and associated risk
Westhoff, et al.	2017	Texas	Cohort	Men 80% Women 20%	median of 65.7 months	595 case	No restrictions on age	Factor analysis	Only 595 non-invasive selected then 120 progressed to muscle-invasive bladder cancer during study	Western: Cornbread, Black eyed peas, Fried chicken, Fried fish, Okra, Gravy, Canned chili, Green beans, French fries, bacon, corn, hamburgers, beef, pork, potato, sausages, wine/ fruit and vegetables	WD (HR=1.48, 95% CI: 1.06–2.06)
Stefani, et al.	2008	Uruguay	Case-control	Men 88% Women 12%	NA	255 cases/501 controls	30–89	Factor analysis	no data	Sweet beverage: coffee, tea, and added sugar/ western patter: red meat, fried eggs, potatoes, and red wine/prudent pattern: fresh vegetables, cooked vegetables, and fruits	WD (OR=2.35, 95% CI: 1.42–3.89 MD (OR=1.06, 95% CI: 0.67–1.68)
Shivappa, et al.	2019	Iran	Case-control	Men 92% Women 8%	NA	56 cases/109 controls	48–73	Multivariate analyses	no data	Bread, rice, meat, fish and…	Dietary inflammatory index (DII) score >–0.12 (OR=2.46; 95% CI: 1.12–5.41) among current/ex-smokers (OR DII (>–0.12/ –0.12) 3.30; 95% CI: 1.07–10.16

Table 2.1 continues on next page.

Table 2.1. *Continued*

Author	Year	Location	Study design	Sex (n%)	Follow up duration	Sample size and characteristics	Mean age	Method of analysis	invasive or non-invasive	diet components	Dietary patterns investigated and associated risk
Abufaraj, et al.	2019	United States	Cohort	Men 20% Women 80%	23 years	1,042 cases/ 218074 non-case	25–75	EDIP score assessment	no data	Red meat, processed meat, all vegetables, fish, high energy beverages, carbonated beverages, low energy beverages, tomatoes, beer; wine; tea; coffee; dark yellow vegetables, snacks; fruit juice; and pizza	Dietary patterns with pro-inflammatory potential (RR=0.92, 95% CI: 0.75–1.12)
Shivappa, et al.	2017	Italy	Case-control	Men 84% Women 16%	NA	690 cases/665 controls	25–80	Factor analysis	460 noninvasive/ 159 invasive/ 307 moderately or well differentiated/ 312undifferentiated or poorly differentiated	Carbohydrates, proteins, fats, alcohol, fibers, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, niacin, thiamin, riboflavin, vitamin B6, iron, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, anthocyanidins, flavan3ols, flavonols, flavanones, flavones, isoflavones, caffeine, and tea	DII (OR Continuous=1.11, 95% CI=1.03, 1.20)/ (OR Quartile4vs1=1.97, 95% CI=1.28–3.03)

Table 2.1. *Continued*

Author	Year	Events followed	Diagnostic criteria	MD/WD compliance assessment method	Variables for adjustment
Schulpen, et al.	2019	Bladder cancer risk	Rrecord linkage with the Netherlands cancer Registry and the nationwide Dutch Pathology Registry	FFQ	Age, sex
Witlox, et al.	2019	Bladder cancer risk	Pathology confirmed cases	FFQ	Ssex, age, smoking, total energy intake
Bravi, et al.	2018	Bladder cancer risk	Incident diagnosis of urothelial carcinoma of the bladder (93%histologically confirmed)	FFQ	Age, sex, BMI, study center, year of interview, Education, Smoking, non-alcohol energy intake, History of Diabetes, History of Cystitis, Family history of bladder cancer
Buckland, et al.	2013	Bladder cancer risk	All newly diagnosed by pathology reports	Dietary questionnaires	Smoking, dietary energy
Brinkman, et al.	2010	Bladder cancer risk	histologically confirmed with transitional cell carcinoma	FFQ	Age, sex, smoking characteristics, occupational exposures, calorie intake.
Dugué, et al.	2016	Bladder cancer risk	identified from Victorian cancer registry and the Australian Cancer Database	FFQ	Sex, country of birth, smoking, alcohol consumption, body mass index physical activity, education, and socioeconomic status
Dianatinasab, et al.	2020	Bladder cancer risk	The International Classification of Diseases for Oncology (ICD-O-3 code C67) using population-based cancer registries, health insurance records or medical records	FFQ	Total energy intake in kilocalories, sex, smoking status (never, former or current smoker) and smoking intensity, fluid, vegetables and fruits intake

Table 2.1 continues on next page.

Table 2.1. *Continued*

Author	Year	Events followed	Diagnostic criteria	MD/WD compliance assessment method	Variables for adjustment
Westhoff, et al.	2017	Risk of recurrence and progression in non- muscle-invasive bladder cancer	Newly histologically confirmed NMIBC	FFQ	Age, sex, education, income, body mass index, smoking status and intensity, total energy intake, grade, tumor multiplicity, concomi- tant carcinoma in situ, and treatment
Stefani, et al.	2008	Bladder cancer risk	Newly diagnosed and micro- scopically confirmed cases of transitional cell carcinoma of the bladder with hospitalized controls	FFQ	Age, sex, residence, urban/rural status, education, family history of bladder cancer, high-risk occupation, body mass index, years smoked, and total energy intake
Shivappa, et al.	2019	Bladder cancer risk	Histologically confirmed cases	FFQ	Age, sex, body mass index (BMI), physical activity, smoking status, alcohol use and family history of cancer
Abufaraj, et al.	2019	Bladder cancer risk	Confirmed by retrieving relevant medical records	FFQ	Aage, energy intake, smoking status, fluid intake, nonsteroidal anti-inflammatory drug use, pregnancy, menopausal status, age at menopause
Shivappa, et al.	2017	Bladder cancer risk	Histologically confirmed cases of BC	FFQ	Age, sex, year of interview, study center, and total energy intake, education, smoking

Association between DII and risk of BC

The combined RR for the highest compared with the lowest category of a DII and risk of BC was 1.04 (95% CI: 0.94, 1.13), with a significant heterogeneity (I^2=61.4%, p=0.05) (**Figure 2.4**). A similar pattern of association was found in cohort studies (RR 1.02, 95% CI: 0.93, 1.12), with no significant heterogeneity (I^2=38.5%, p=0.20). In contrast, a significant direct association was found between a DII and risk of BC in case-control studies (RR 2.04, 95% CI: 1.23, 2.85; I^2=0%, p=0.67).

Quality assessment in individual studies and sensitivity analysis

Table 2.2 shows the methodological quality of the included articles according to NOS. The NOS scores for the included studies ranged from 6 to 8, with 11 high [10, 11, 13-18, 35-37] and one medium-quality [12]. Sensitivity analyses were also conducted to determine whether the results would change when one study was removed at a time. The results were fairly robust after removing the individual studies from the meta-analyses, except for studies on DII and risk of BC.

Publication bias

Although the funnel plot was slightly asymmetric, after using the trim-and-fill method, visual inspection of Begg's funnel plot did not identify substantial asymmetry for WD studies (Begg's test p=0.08, Egger's test p=0.32). In addition, Begg's and Egger's tests showed no evidence of publication bias for MD studies (Begg's test p=0.26, Egger's test p=0.57), though, publication bias was significant for DII studies after using the trim-and-fill method (Begg's test p=0.002, Egger's test p=0.04).

Discussion

In the meta-analysis, we reviewed the investigated associations between adherence to major dietary patterns and risk of BC. We observed a direct association between WD and risk of BC, and an inverse association between MD and risk of developing BC. However, there was no association between DII and BC risk.

Several systematic review and meta-analyses have investigated the association between dietary patterns and the risk of cancer of other organs, WD was associated with increased risk of colorectal [38, 39], stomach [40], and prostate cancers [41]. Similar to our results, a meta-analysis with 12 observational studies reported that WD is related to an increased risk of prostate cancer but no association between healthy pattern and prostate cancer risk [41]. However, to date no pooled estimate is available on the association between dietary patterns and BC. The results published from studies that have examined the relationship between WD and risk of BC are in accordance with our findings [10-12]. For

Table 2.2. Results of the Newcastle-Ottawa Scale (NOS) for assessing the quality of case-control and cohort studies in the meta-analyses

	Selection				Comparability	Exposure			
Case-control studies	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	Control for most important factor and Control for any additional factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total score
Bravi 2018	a (1)	a (1)	b(0)	a (1)	a , b (2)	c(0)	a (1)	a (1)	7
Brinkman 2010	a (1)	a (1)	a (1)	a (1)	a , b (2)	c (0)	a (1)	a (1)	8
Shivappa 2017	a (1)	a (1)	b (0)	a (1)	a , b (2)	c (0)	a (1)	a (1)	7
Shivappa 2019	a (1)	a (1)	b (0)	a (1)	a , b (2)	c (0)	a (1)	a(1)	7
Stefani 2008	a (1)	a (1)	b (0)	a (1)	a , b (2)	c (0)	a (1)	a (1)	7

Table 2.2. *Continued*

	Selection			Comparability		Outcome			
Cohort studies	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome was not present as baseline	Control for most important factor and Control for any additional factor	Assessment of outcome	Adequate follow-up period for outcome	Adequacy of follow up of cohorts	Total score
Abufaraj 2019	a (1)	a (1)	c(0)	a (1)	a , b (2)	c(0)	a (1)	a (1)	7
Buckland 2013	a (1)	a (1)	c (0)	a (1)	a , b (2)	b (1)	a (1)	a (1)	8
Dianatinasab 2020	a (1)	a (1)	a (1)	a (1)	a (1)	a (1)	a (1)	a (1)	8
Dugu 2016	a (1)	a (1)	c (0)	b (0)	a , b (2)	b (1)	a (1)	a(1)	7
Schulpen 2019	a (1)	a (1)	c (0)	a (1)	a , b (2)	b (1)	a (1)	a (1)	8
Westhoff 2017	a (1)	a (1)	c(0)	b (0)	a , b (2)	d (0)	a (1)	a(1)	6
Witlox 2019	a (1)	a (1)	a (1)	a (1)	a (1)	a (1)	a (1)	a (1)	8

example, the results of a recently published pooled analysis on 13 cohorts suggested that adherence to a WD pattern is associated with an increased risk of BC [11]. Also, Westhoff et al. found that greater adherence to a WD was associated with a higher risk of BC recurrence [12]. This finding supports the hypothesis that WD plays a role in the etiology and prognosis of BC. According to the results, although a strong association was observed between higher adherence to a WD and BC in cohort studies (RR 1.55, 95% CI: 1.37, 1.70), we found no significant association between WD and risk of BC in case-control studies (RR 1.30, 95% CI: 0.81, 1.88). This might be due to recall bias in these studies and even small sample size of the included case control studies.

Epidemiological studies have concentrated on some key elements of WD and reported a positive association between red and processed meat, refined grain and saturated fats and risk of BC [42]. Red and processed meat is one of the important key elements of this dietary pattern and it is positively associated with the risk of BC [43]. Potentially hazardous materials present in the WD, such as N-nitroso-compounds, heterocyclic aromatic amines and polycyclic aromatic hydrocarbons in red meat, are excreted in the urine. As a result, they come into direct contact with the inner lining of the bladder wall, potentially causing cancer in urothelial cells [44]. Moreover, it is suggested that red and processed meats contain saturated fat and heme iron, potential inducers of oxidative stress and DNA damage [45]. Also, more mutagenic substitutes during the cooking procedure of these nutrients takes place. As mentioned by Matteo et al., cooking meat or fats, main components of WD, at higher temperatures (roasting) or for prolonged times (e.g., stewing) were associated with an increased BC risk [46]. According to the previous studies, components produced during food processing, particularly when meat is cooked at higher temperatures or for longer periods of time, can damage DNA and increase the risk of cancer [46-48]. However, the lack of information on cooking and preparing food in the included studies prevented us to conduct a subgroup analysis according to the cooking methods.

Regarding adherence to MD and cancer risk, results of a systematic review reported that MD was inversely associated with cancer mortality and risk of colorectal, breast, gastric, liver, head and neck, gallbladder, and biliary tract cancers [49]. However, a meta-analysis of 10 epidemiological studies provided evidence that MD is not related with prostate cancer risk [50]. In our meta-analysis the association between MD and risk of BC was reported by 6 studies [13-18]. We found a stronger association between MD and BC in cohort studies rather than case-control studies. A pooled analysis of 13 cohort studies showed that adherence to the MD was associated with a reduced risk of developing BC (HR: 0.85; 95% CI: 0.77, 0.93), suggesting a positive effect of a MD on BC risk [17]. In addition, Dugué et al. discovered a moderate inverse relationship between MD adherence and urothelial cell cancer [18]. Also, Buckland et al. found an inverse association between adherence to the MD and occurrence of overall, aggressive or non-aggressive, BC for both gender [15]. It is suggested that, among key elements of this

diet, some of them had beneficial effects on the prevention of BC. For example, it has been shown that the consumption of vegetables and fruits, as the main components of the WD, are inversely associated with the risk of BC [51, 52]. It is suggested that, polyphenols, carotenoids, and vitamins C and E are abundant in both vegetables and fruits, and they serve as antioxidants, preventing DNA damage by neutralizing reactive oxygen species [53]. Olive oil is another significant component of the MD that has been examined as a single dietary item in relation to bladder cancer. Brinkman et al. showed that a higher consumption of olive oil was inversely related to the risk of BC [14].

Regarding DII, A meta-analysis found that higher pro-inflammatory diets are linked to an increased risk of prostate, kidney, and bladder cancer [54], results that are different with our finding. In this study, we investigated 2 case-control and 2 cohort studies [18, 35-37] on the association of DII and BC. Our pooled estimates show that DII was not significantly associated with the BC risk. Null association between a DII and BC in cohort studies suggests that the significant association found in case-control studies may be due to recall bias rather than a real association. The discrepancies between the individual studies could be attributed to the small sample sizes, study design or population substructure. Chronic inflammation causes oxidative and nitrative DNA damage in stem cells, which might be one of the processes behind the observed positive relationship between DII and BC [55].

There are probably differences in the definitions of diets in different studies, so we used the most common definition. However, there are some limitations to this meta-analysis, as such, the results are combined from studies conducted with different methods in different populations, resulting in heterogeneity. Among several potential explanations, recall bias occurs a lot in case control studies rather than cohort studies. Moreover, a possible misclassification within the considered dietary patterns may existed. We cannot generalize our results to the whole world because the most studies that we found were from European and developed countries. As a result, more studies are needed, especially in Asian and African countries, to support these findings.

Conclusions

Our results specified a direct association between WD and risk of BC, and an inverse association between MD and risk of developing BC. Also, there was no association between DII and BC risk. According to our findings dietary patterns might play an important role in BC prevention and guidelines might provide more attention to recommend consuming MD components and reducing WD components. However, further researches are needed to confirm our findings and to study the possible mechanisms for the WD effects on carcinogenesis of BC and MD and their effects on BC prevention.

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Chapter 3

Adherence to a Western dietary pattern and risk of bladder cancer: A pooled analysis of 13 cohort studies of the Bladder Cancer Epidemiology and Nutritional Determinants international study

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Abstract

Objective: Little is known about the association of diet with risk of bladder cancer. This might be due to the fact that the majority of studies have focused on single food items, rather than dietary patterns, which may better capture any influence of diet on bladder cancer risk. We aimed to investigate the association between a measure of Western dietary pattern and bladder cancer risk.

Methods: Associations between adherence to a Western dietary pattern and risk of developing bladder cancer were assessed by pooling data from 13 prospective cohort studies in the "BLadder cancer Epidemiology and Nutritional Determinants" (BLEND) study and applying Cox regression analysis. Dietary data from 580,768 study participants, including 3,401 incident cases, and 577,367 non-cases were analysed.

Results: A direct and significant association was observed between higher adherence to a Western dietary pattern and risk of bladder cancer (Hazard Ratio (HR) comparing highest with lowest tertile scores: 1.54, 95% confidence interval (CI): 1.37, 1.72; p-trend=0.001). This association was observed for men (HR comparing highest with lowest tertile scores: 1.72; 95% CI: 1.51, 1.96; p-trend=0.001), but not women (p-het=0.001). Results were consistent with HR above 1.00 after stratification on cancer sub-types (non-muscle invasive and muscle invasive bladder cancer).

Conclusion: We found evidence that adherence to a Western dietary pattern is associated with an increased risk of bladder cancer for men but not women.

Key words: Bladder cancer; Epidemiology; Risk factor; Western diet

Introduction

Recent estimates from the International Agency for Research on Cancer (IARC) rank bladder cancer globally as the seventh and seventeenth most common malignancy for men and women, respectively [1, 2]. Most (75%) cancers are non-muscle-invasive bladder cancer (NMIBC) that frequently recur but require intensive treatment and follow-up measures posing a large burden on national health care budgets and patient quality of life [2, 3].

Epidemiological studies have identified several factors which potentially influence bladder cancer risk, including; sex, smoking, age and occupation [3-5]. In addition, evidence suggests that other factors related to environmental and lifestyle (e.g. body mass index (BMI), physical activity and diet) also might affect the bladder cancer risk [6, 7]. Since the bladder is an excretory organ, diet might especially play an essential role in the development of bladder cancer [8]. Previous research reported that high fluid, fruit, vegetable and yogurt intakes are associated with a reduced risk [9], while barbecued meat, pork, and total fat intakes are associated with an increased risk [10-12].

Nutritional observational studies have long focused on associations between single food items and disease risk. However, given that individuals do not consume foods (or nutrients) in isolation, but in a complex combination of multiple foods (or nutrients), this single food item approach might be unable to measure the impact of the interaction among different foods on disease risk. Therefore, an increasing number of researchers are taking a more holistic dietary approach, by defining food consumption patterns to characterize a population's dietary intake and to examine potential relationships of these patterns with diseases risk. However, although this approach has received much attention during the past few years, evidence on the relation between dietary patterns (DPs) and bladder cancer risk is still scarce. As a consequence of the Neolithic- and Industrial revolutions, which introduced staple foods and new methods of food processing, the Western diet was introduced [13]. The Western dietary pattern is characterized by high intakes of red and processed meat, fast foods, convenience products, sugary soft-drinks, snacks, eggs, refined cereals, high fat dairy products and hydrogenated fat [14-17]. Particularly meats, eggs and dairy products are considered as prominent features of the Western diet [18-20]. This dietary pattern has been linked to a range of health outcomes, including several types of cancer. Evidence for any association between a Western dietary pattern and bladder cancer risk is limited. To our knowledge, only one study has investigated this association. In a multi-centric, hospital-based, case-control study in Montevideo, Uruguay, it was found that people who adhered to a Westernized diet had a 2.35 times higher risk of bladder cancer [21].

Given the biases to which case-control studies are prone, we aimed to investigate prospectively the potential association between adherence to a Western dietary pattern

and the risk of bladder cancer, by pooling data from 13 prospective cohort studies in the BLEND consortium.

Methods

Study sample

The study was conducted within the of the BLEND consortium. BLEND is a large international nutritional consortium, which includes 16 prospective cohort studies from several populations [22]. For the current study, data from 13 cohorts with sufficient collected information on the intake of food items of interest (i.e. those required for scoring the chosen Western dietary pattern) were included in the analyses. Studies originated from centers in Australia [23, 24], Denmark [25], France [26], Germany [27], Greece [28], Italy [29], Norway [30], Spain [28], Sweden [31, 32], the Netherlands [33, 34], the United Kingdom [35, 36], and the United States [37].

Data collection and coding

Details of BLEND consortium protocols and methodology have been described elsewhere [22]. Briefly, the primary data from all included studies were gathered into an integrated database. Data were checked and the food consumption was converted to grams per day by the use of country specific food tables and the frequency responses. Each study ascertained incident bladder cancer, defined to include all urinary bladder neoplasms according to the International Classification of Diseases for Oncology (ICD-O-3 code C67) using population-based cancer registries, health insurance records, or medical records [38].

Dietary data were obtained using a valid food frequency questionnaire (FFQ), and were recoded using the Eurocode 2 food coding system [39]. In addition to the information on dietary intake, other baseline data included study characteristics e.g. design, method of dietary assessment, recall period of dietary intake and geographical region, demographic information (age, sex and ethnicity), pathology of bladder cancer (disease subtype) (non-muscle-invasive bladder cancer [NMIBC] and muscle-invasive bladder cancer [MIBC]), and smoking status (current/former/never) and quantity (packs/year), all measured at baseline.

Western diet score (WDS)

In the present study eight food groups were selected to define the Western dietary pattern. This selection was based on prior knowledge [14-20] and data availability, and included: eggs, butter, margarine, animal fat, sugar and sugar added products, red and processed meats, dressings, and dips. For each food item, a score from 1–5 was assigned based on quintiles of overall intake. A score of "1" was assigned to those in the lowest

quintiles and "5" was assigned to those in the highest quintiles. Each participant's overall score was calculated by summing the scores received for each individual food item. Accordingly, the score ranged from 8 (minimal adherence) to 40 (highest adherence). Participants were then classified into tertiles (low, medium and high adherence to a Western dietary pattern) according to their score.

Statistical analysis

Baseline characteristics of study participants were compared between the tertiles of adherence to the Western dietary pattern using analysis of variance or independent sample t-test, for continuous variables, or ANCOVA for categorical variables. We used the Cox proportional hazard modelling approach with recruitment as the starting point on the time scale to assess that association between adherence to the Western dietary pattern and bladder cancer risk. Hazard ratios and 95% confidence intervals (CIs) for developing bladder cancer were calculated with the first tertile assigned as reference group. The proportional hazards assumption was examined graphically and we found no apparent violation to the assumption. Survival time was estimated by subtracting age at exit by age at entry in the cohort as T0, thereby correcting for age in the analysis. Study was included as a random effect. The Cox regression models were performed as crude, and adjusted model-1 for: total energy intake in kilocalories, sex, smoking status (never, former or current smoker) and smoking intensity ((pack/day)*years), and additionally for: fluid, vegetables and fruits intake (model-2). Analyses were stratified on smoking status, sex and disease sub-type (non-muscle-invasive or muscle-invasive disease). All statistical analyses were performed using Stata/SE version 14.2. P-values less than 0.05 were considered as statistically significant.

Results

Baseline characteristics

Dietary data from 580,768 study participants, including 3,401 incident cases and 577,367 non-cases were analyzed, with a total of 6,451,306 person-years of follow-up (median follow-up: 11.4 years). Disease type was known for 2,570 cases, of which 945 (36.7%) were MIBC and 1,625 (63.3%) were NMIBC. Baseline characteristics of the study sample are presented in **Table 3.1**.

In total, 192,691 (33%) men and 388,077 (67%) women were included. As shown in **Table 3.1**, compared with non-cases, bladder cancer cases were more likely to be men (76%) and to be current (36%) or former smokers (43%). Mean (±SD) age was 52.7 years (±10.2) for cases and 60.5 (±7.3) 52.6 (±10.1) for controls. The median (interquartile) time from exposure collection to diagnosis with bladder cancer was 8.5 year (4.9–12.0).

Table 3.1. General characteristics of participants by cohort study

	NLCS	VITAL	CVV&MCCS	EPIC-Denmark	EPIC-France	EPIC-Germany	EPIC-Greece
Characteristics	N=5,238	N=66,518	N=37,218	N=55,670	N=64,204	N=48,754	N=25,005
Subjects (number)							
Case/non-case	876/4,362	337/66,181	503/36,715	386/55,284	31/64,173	205/48,549	50/24,955
Person-year	73,688.8	448,995.4	715,158.9	608,813	667,809.9	482,453.3	238,122
Baseline age (mean ±SD)							
Case	62.73 (4.09)	66.16 (7.01)	59.90 (7.37)	58.50 (4.37)	58.04 (6.00)	56.41 (7.13)	60.89 (10.31)
Non-case	61.85 (4.21)	61.18 (7.37)	54.96 (8.67)	56.67 (4.37)	52.74 (6.63)	50.55 (8.56)	53.30 (12.59)
Sex n (%)							
Men	2,867 (54.73)	33,394 (50.20)	15,267 (41.02)	26,532 (47.66)	0 (0.00)	21,168 (43.42)	10,327 (41.30)
Women	2,371 (45.27)	33,124 (49.80)	21,951 (58.98)	29,138 (52.34)	64,204 (100.00)	27,586 (56.58)	14,678 (58.70)
Smoking status n (%)							
Current smoker	1,613 (30.79)	5,366 (8.07)	4,164 (11.19)	19,140 (34.38)	5,862 (9.13)	10,165 (20.85)	6,899 (27.59)
Former smoker	1,930 (36.85)	29,644 (44.57)	11,576 (31.10)	16,998 (30.53)	13,013 (20.27)	16,194 (33.22)	4,195 (16.78)
Never smoker	1,695 (32.36)	31,508 (47.37)	21,478 (57.71)	19,532 (35.09)	45,329 (70.60)	22,395 (45.93)	13,911 (55.63)
⁎ Smoking intensity pack- year (mean ±SD)	32.89 (12.28)	26.25 (23.49)	25.01 (13.03)	19.73 (17.74)	22.52 (16.66)	11.32 (13.47)	10.96 (14.85)

Table 3.1. *Continued*

Characteristics	EPIC-Italy N=44,663	EPIC-Spain N=40,389	EPIC-Sweden N=48,625	EPIC-the Netherlands N=36,801	EPIC- the UK N= 74,379	EPIC-Norway N=33,304	Total N=580,768
Subjects (number)							
Case/non-case	186/44,477	149/40,240	301/48,324	107/36,694	247/74,132	23/33,281	3,401/ 577,367
Person-year	502,020.3	487,491.1	638,482.8	434,974.5	828,991.7	6,437,305.7	6,451,306
Baseline age (mean ±SD)							
Case	55.24 (6.75)	54.49 (7.19)	60.27 (7.07)	56.20 (8.03)	63.62 (9.98)	49.30 (4.38)	60.50 (7.35)
Non-case	50.50 (7.92)	49.19 (8.03)	51.93 (10.89)	48.94 (11.93)	49.05 (14.34)	48.07 (4.30)	52.66 (10.14)
Sex n (%)							
Men	13,774 (30.84)	15,259 (37.78)	22,214 (45.68)	9,629 (26.17)	22,260 (29.93)	0 (0.00)	192,691 (33.18)
Women	30,889 (69.16)	25,130 (62.22)	26,411 (54.32)	27,172 (73.83)	52,119 (70.07)	33,304 (100.00)	388,077 (66.82)
Smoking status n (%)							
Current smoker	12,385 (27.73)	10,847 (26.86)	11,474 (23.60)	11,233 (30.52)	9,040 (12.15)	11,101 (33.33)	119,289 (20.54)
Former smoker	11,945 (26.74)	7,147 (17.70)	13,269 (27.29)	11,501 (31.25)	23,724 (31.90)	10,292 (30.90)	171,428 (29.52)
Never smoker	20,333 (45.53)	22,395 (55.45)	23,882 (49.11)	14,067 (38.22)	41,615 (55.95)	11,911 (35.76)	290,051 (49.94)
⁎ Smoking intensity pack- year (mean ±SD)	12.83 (14.02)	10.57 (13.70)	12.26 (15.09)	14.28 (14.81)	8.51 (13.30)	14.01 (13.47)	17.01 (15.07)

⁎ Among past and current smokers; pack-years = number of packs of cigarettes smoked per day multiplied by the number of years of smoking.

Table 3.2. Baseline characteristics and dietary items based on participants' status and Western diet score tertile

	Participants [1]			WDS[¥] tertile [2]			
Characteristics	Cases	Non-cases	P-value	Tertile 1	Tertile 2	Tertile 3	P-value
Participants (number (%))	-	-	-				<0.001*
Case/non-case				822 (24.16)/ 198,253 (34.34)	1,315 (38.67)/ 194,823 (33.74)	1,264 (37.17)/ 184,291 (31.92)	
Person-year	28,455.67	6,422,851	<0.001ǂ	2,086,731	2,243,150	2,121,425	<0.001ǂ
Baseline age (mean ±SD)	60.50 (7.35)	52.66 (10.14)	<0.001ǂ	53.88 (10.39)	52.28 (10.44)	51.92 (9.42)	<0.001ǂ
WD score (mean ±SD)	23.05 (4.21)	22.30 (4.51)	0.001	17.44 (2.27)	22.37 (1.13)	27.46 (2.19)	0.001ǂ
Cancer subtype (number (%))			-				0.184*
NMIBC**	1,365	-		334 (24.47)	547 (40.07)	484 (35.46)	
MIBC+	874	-		189 (21.62)	380 (43.48)	305 (34.90)	
Sex, n (%)			<0.001*				<0.001*
Men	2,579 (75.83)	190,112 (32.93)		58,159 (30.18)	63,315 (32.86)	71,217 (36.96)	
Women	822 (24.17)	387,255 (67.07)		140,916 (36.31)	132,823 (34.23)	114,338 (29.46)	
Smoking status, n (%)			<0.001*				<0.001*
Current smoker	1,235 (36.31)	118,054 (20.45)		33,360 (27.97)	39,344 (32.98)	46,585 (39.05)	
Former smoker	1,462 (42.99)	169,966 (29.44)		60,750 (35.44)	57,471 (33.52)	53,207 (31.04)	
Never smoker	704 (20.70)	289,347 (50.11)		104,965 (36.19)	99,323 (34.24)	85,763 (29.57)	
Smoking intensity, pack-year (mean ±SD)	33.33 (12.71)	23.61 (12.47)	<0.001ǂ	22.20 (12.52)	23.49 (12.48)	25.00 (12.39)	<0.0001ǂ
Cream, gram per day (mean ±SD)	2.13 (7.32)	2.33 (4.72)	0.01ǂ	1.55 (3.87)	2.36 (4.69)	3.14 (5.47)	<0.0001ǂ
Egg, gram per day (mean ±SD)	17.84 (15.19)	16.96 (16.09)	0.001ǂ	10.25 (11.21)	16.29 (14.58)	24.90 (18.40)	<0.0001ǂ

Table 3.2. *Continued*

Characteristics	Participants [1]			WDS[¥] tertile [2]			
	Cases	Non-cases	P-value	Tertile 1	Tertile 2	Tertile 3	P-value
Red and processed meet, gram per day (mean ±SD)	92.75 (58.72)	78.85 (60.78)	<0.001‡	48.21 (42.30)	73.05 (54.61)	118.11 (62.51)	<0.0001ǂ
Butter, gram per day (mean ±SD)	5.08 (10.97)	3.84 (8.18)	<0.001‡	1.80 (5.51)	3.74 (8.01)	6.18 (9.99)	<0.0001ǂ
Margarine, gram per day (mean ±SD)	18.26 (20.20)	11.28 (15.46)	<0.001‡	7.84 (12.93)	11.51 (15.41)	14.85 (17.20)	0.001ǂ
Animal fat, gram per day (mean ±SD)	0.22 (1.54)	0.21 (1.16)	0.35‡	0.02 (0.29)	0.11 (0.91)	0.51 (1.78)	<0.0001ǂ
Pasta, gram per day (mean ±SD)	32.04 (48.63)	35.31 (50.49)	0.001‡	32.43 (39.75)	32.22 (42.10)	41.62 (65.94)	<0.0001ǂ
Sugar, gram per day (mean ±SD)	16.70 (21.01)	18.02 (47.57)	0.10‡	10.94 (26.97)	15.81 (43.24)	27.92 (64.32)	<0.0001ǂ
Dressing, gram per day (mean ±SD)	4.79 (7.44)	6.30 (9.83)	<0.001‡	2.80 (6.61)	6.24 (9.66)	10.08 (11.36)	<0.0001ǂ
Dips, gram per day (mean ±SD)	4.41 (9.47)	5.57 (9.57)	<0.001‡	2.99 (6.26)	5.85 (9.06)	8.01 (12.03)	<0.0001ǂ
Vegetables, gram per day (mean ±SD)	206.92 (138.40)	198.94 (141.96)	<0.001‡	184.04 (150.51)	204.76 (141.26)	208.91 (131.48)	<0.0001ǂ
Fruits, gram per day (mean ±SD)	122.53 (111.26)	120.33 (110.10)	0.24‡	109.94 (111.78)	122.03 (106.63)	129.71 (110.95)	<0.0001ǂ
Fluid, milliliters per day (mean ±SD)	1,563.81 (861.36)	1,429.51 (878.16)	0.001‡	1,244.57 (786.36)	1,427.15 (817.62)	1,632.87 (982.52)	<0.001ǂ

‡: based on independent sample t-test. ǂ: based on one-way analysis of variance. *: based on ANCOVA. ¥ WD = Western diet ** NMIBC = non-muscle-invasive bladder cancer, +MIBC = muscle-invasive bladder cancer.

[1] 100 % is computed across column (participants' status). [2] 100 % is computed across rows (study variables).

Baseline characteristics and dietary information based on tertiles of adherence to the Western dietary pattern are reported in **Table 3.2**. Roughly 1,264 (37%) of the cases were in the highest tertile of adherence to the Western dietary pattern compared to 184,291 (32%) for non-cases. Current smokers with a high smoking intensity were more common among those in the highest tertile of adherence to the Western dietary pattern (39%) compared to those in lower tertiles of adherence (28%). The mean (±SD) of the WDS was 23.1 (4.2) and 22.3 (4.5) for cases and non-cases respectively.

Associations between the Western dietary pattern and bladder cancer risk

The HR estimates for bladder cancer associated with adherence to the Western dietary pattern are presented in **Table 3.3**. Overall, greater adherence to the Western dietary pattern was associated with an increased risk of bladder cancer (model 2: HR comparing highest with lowest tertile: 1.54, 95% CI: 1.37, 1.72). Test for linear trend across the tertiles of Western dietary pattern adherence was significant (p-trend=0.001). Results

Table 3.3. Hazard ration (HR) and 95% confidence intervals (CIs) based on tertile of Western diet score

	Tertile 1 HR (95% CI) * 18 (16, 19) §	Tertile 2 HR (95% CI) 22 (21, 23) §	Tertile 3 HR (95% CI) 27 (26, 29) §	P-trend
All participants				-
Participants (number)				-
Case/non-case	822/198,253	1,315/194,823	1,264/184,291	
Pearson-year	2,086,731	2,243,150	2,121,425	-
Crude	1 (reference)	1.51 (1.38, 1.65)	1.76 (1.61, 1.92)	<0.001
Model 1 [1]	1 (reference)	1.30 (1.18, 1.43)	1.33 (1.20, 1.48)	<0.001
Model 2 [2]	1 (reference)	1.44 (1.29, 1.59)	1.54 (1.37, 1.72)	0.001
Women				-
Participants (number)				-
Case/non-case	258/140,658	342/132,481	222/114,116	
Pearson-year	1,508,860	1,519,577	1,298,213	-
Crude	1 (reference)	1.30 (1.11, 1.53)	1.10 (0.91, 1.31)	0.213
Model 1 [1]	1 (reference)	1.24 (1.01, 1.52)	1.06 (0.85, 1.34)	0.584
Model 2 [2]	1 (reference)	1.25 (1.02, 1.54)	1.09 (0.86, 1.38)	0.466
Men				
Participants (number)				-
Case/non-case	564/57,595	973 /62,342	1,042/70,175	
Pearson-year	577,871.8	723,572.9	823,212.2	-
Crude	1 (reference)	1.50 (1.35, 1.67)	1.68 (1.51, 1.86)	0.001
Model 1 [1]	1 (reference)	1.33 (1.19, 1.48)	1.42 (1.26, 1.59)	0.001
Model 2 [2]	1 (reference)	1.53 (1.35, 1.73)	1.72 (1.51, 1.96)	0.001

* HR = hazard ratio, CI = confidence interval. §: Median WD score (range).

[1] Adjusted for energy intake, smoking status, smoking intensity, age and sex.

[2] Adjusted for model 1+ fluid intake, fruit and vegetables intakes.

for men (model 2: HR highest compared with lowest tertile: 1.72, 95% CI: 1.51, 1.96 (p-trend=0.001) were comparable and in line with the overall estimates. For women no evidence of association (model 2: HR highest compared with lowest tertile: 1.09, 95% CI: 0.86, 1.38) was observed (p-trend=0.46; p-het=0.001).

After stratification by sex and smoking the findings were in line with the overall results suggesting that apart from smoking status, higher adherence to the Western diet is a risk factor for men but not women (**Supplementary Table S3.1**). Additionally, after stratification by disease sub-type, results remained consistently above 1.00 for both NMIBC (HR: 1.28, 95% CI: 1.02, 1.63) and MIBC (HR: 1.28, 95% CI: 1.01, 1.64) patients (**Supplementary Table S3.2**).

In the present study, it was also assessed whether any association with the Western dietary pattern would change by excluding each single component of the Western diet. Results, however, remained stable and therefore are not reported.

Discussion

Using prospective cohort studies data from the BLEND consortium, we investigated associations between adherence to a Western dietary pattern and bladder cancer risk and observed an overall direct association between a high adherence to Western dietary pattern and bladder cancer risk for men, but not women. Analyses stratified by disease sub-type showed similar results to the overall findings, indicating that the association is unlikely to be confounded by factors that might differ between the different bladder cancer subtypes.

Although we are the first to examine an a priori defined Western dietary pattern in association with bladder cancer risk, a previous study, identified a factor analysis derived Western dietary pattern to be associated with bladder cancer risk [21]. De-Stephani et al. suggested that adherence to a Western dietary pattern is associated with a 2.3-fold risk of bladder cancer. Similar results were reported for bladder cancer recurrence, with individuals who highly adhere to the Western dietary pattern experiencing a 1.48 times higher risk of recurrence compared with those with low adherence to the Western dietary pattern.

Although evidence of association for the whole Western dietary pattern with bladder cancer risk is limited, several studies have focused on some key elements of this dietary pattern and reported positive associations. Red and processed meat is such an element positively associated with bladder cancer risk. A recent meta-analysis showed, by combining results from five cohort studies and eight case-control studies, an increment of 50g of processed meat per day was associated with 20% increased risk

of bladder cancer [40]. In addition, the authors showed that red meat consumption was associated with bladder cancer, with a 51% increased risk per increment of 100 grams per day. However, this association with red meat consumption could only be observed among case-control studies. More recently this association was confirmed by a cohort study [41]. The effect of meat consumption may be explained by the carcinogenic compounds that are produced during the cooking and processing of meat, which include nitrate, nitrite, heterocyclic amines and polycyclic aromatic hydrocarbons. Since these compounds are excreted in the urine, they come in close contact with the inner lining of the bladder wall which may exert a carcinogenic effect on urothelial cells.

Another element of the Western dietary pattern that might explain the adverse effect of this diet on bladder cancer risk is fat intake [42-44]. A meta-analysis conducted in 2000 by Steinmaus et al. [45], found that high fat intake significantly elevated the risk of bladder cancer (relative risk (RR) = 1.37, 95% CI: 1.16, 1.62). This was confirmed by the Netherlands Cohort Study on diet and cancer that reported that a high intake of butter increased bladder cancer risk by 61% [46]. In contrast, a Japanese cohort study could not find an association between butter intake and bladder cancer risk [47]. In line with these findings, a Belgian case-control study could not detect any association between high intake of animal products, which are also high in their fat content, and bladder cancer risk [48]. More research on fat consumption, and on the different sources of fat, is needed to elucidate any role of fat intake and different sources of fat on bladder cancer risk.

Eggs contain a lot of cholesterol, which has been shown to increase the formation of secondary bile acids in both humans and animals. Bile acids are linked to several mechanisms causing cancer [49]. In addition, eggs can also be a source of heterocyclic amines when cooked in high temperature [50]. A meta-analysis, including four cohort studies and nine case-control studies, however, did not observe an association between egg consumption and bladder cancer risk, except for a possible positive relationship with the intake of fried eggs [51]. It therefore remains inconclusive whether egg intake contributes to the positive association of the Western dietary pattern with bladder cancer risk identified in our study.

Sugar is another important element of the Western dietary pattern that has been investigated but its influence on risk of bladder cancer remains inconclusive. While the NIH-AARP Diet and Health Study showed that sugar is not significantly associated with the risk of bladder cancer [52], Stefani et al. [21], showed that, sugar intake may increases the risk of bladder cancer by 124%. When studying sweetened beverages, which are considered the main sugar source, results are more in line, in that regular consumption is positively associated with bladder cancer risk [53, 54]. Unfortunately, due to lack of data, we were unable to included sugar sweetened beverages in our Western dietary pattern analysis, which might have led to underestimation of our result.

In the present study, the sex stratified results showed a diversity (p-het=0.001) in the association between high adherence to the Western dietary pattern and the risk of bladder cancer for men and women. An explanation for this observation might be genetic variability by sex, which might cause a different effect of similar environmental exposures to the bladder carcinogenesis [55, 56]. It has been suggested that gender disparity in bladder cancer risk could be explained by sex-specific differences in the metabolism of bladder cancer carcinogens that are influenced by sex hormone [57]. However, the mechanisms by which Western diet could modulate bladder cancer risk differently in men and women remains to be explored. Furthermore, the limited number of women cases (n=822) could also affect the outcome of the analyses. Research on the epigenetics of diet and bladder cancer is still in its infancy and need to be explored in detail in future research. Results of the sex and smoking stratified analyses showed no difference between smokers and non-smokers. Therefore, the effect of residual confounding of smoking on the relation between the Western diet and bladder cancer is suggested to be minor. Finally, in order to determine the single study effect, sensitivity analyses were performed by removing each individual study in turn from the main analysis. Results showed that the main finding remained robust.

Strengths and limitations

Although BLEND is so far the largest pooled cohort study investigating the associations between adherence to a Western dietary pattern and risk of developing bladder cancer, and designed with enough statistical power to permit detailed analyses and to detect smaller effects, it has several limitations which should be considered. Not all studies had information on some food items that are consumed in the Western diet, including: refined grains, and potatoes. Including these items might help to better examine the association between the Western dietary pattern diet and bladder cancer. However, these factors were not fully considered as main components of the Western dietary pattern by previous studies [21, 58]. It worth noting that as the definition of a Western diet may vary between different studies [44, 58, 59], by conducting a comprehensive review on the literature we used a more common definition of Western diet in order to create a Western diet adherence score [14-17]. Also, limited information was available for some possible risk factors of bladder cancer, such as body mass index, physical inactivity, socioeconomic status, and occupational exposures to carcinogenic chemicals. The possibility to adjust for these factors would have allow more accurate risk estimates. Though, the current literature suggests only a small proportion of bladder cancer cases can be attributed to these factors [5, 60, 61]. We were also not able to take into account any possible changes to dietary and lifestyle habits over time, which would better reflect the effect of long-term diet. Likewise, information bias, which as a consequence of self-reported information on food consumption is a common bias in nutritional epidemiology studies [62], should be taken into account when intenerating

results. However, it is expected that the distribution of this bias was not significantly different between cases and non-cases, suggesting that the impact of information bias on our findings might be minimal.

Conclusions

In conclusion, our analysis revealed that higher adherence to a Western dietary pattern is associated with increased risk of bladder cancer, particularly for men. This finding supports the hypothesis that Western dietary pattern may play a role in the etiology of bladder cancer. Further research is necessary to investigate the possible mechanisms for the Western dietary pattern effects on carcinogenesis of bladder cancer and to identify the components of Western dietary pattern that may be predominantly responsible for the observed association with bladder cancer risk.

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Supplementary Materials to Chapter 3

Supplementary Table S3.1. Hazard ration (HR) and 95% confidence intervals (CIs) based on tertile of Western diet score stratified by gender and smoking status

Subgroup	Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
Women				
Current smoker				-
Participants (number)				-
Case/non-case	56/ 23,263	94/ 23,912	88/ 23,674	
Pearson year	248,664.7	265,448.4	266,072.3	-
Crude	1 (reference)	1.38 (0.99, 1.91)	1.25 (0.90, 1.75)	0.217
Model 1 [1]	1 (reference)	1.45 (1.03, 0.03)	1.40 (0.97, 2.02)	0.080
Model 2 [2]	1 (reference)	1.45 (1.03, 2.03)	1.36 (0.96, 2.00)	0.999
Former smoker				-
Participants (number)				-
Case/non-case	86/ 35,031	94/ 32,064	47/ 26,387	
Pearson year	357,183.6	363,339.4	299,911.1	-
Crude	1 (reference)	1.02 (0.76, 1.37)	0.70 (0.49, 1.00)	0.079
Model 1 [1]	1 (reference)	1.10 (0.81, 1.49)	0.80 (0.54, 1.19)	0.377
Model 2 [2]	1 (reference)	1.11 (0.81, 1.51)	0.81 (0.55, 1.21)	0.425
Never smoker				
Participants (number)				-
Case/non-case	114/ 82,364	154/ 76,505	87/ 64, 055	
Pearson year	903,011.4	890,789.3	732,229.1	-
Crude	1 (reference)	1.38 (1.09, 1.77)	1.09 (0.82, 1.45)	0.358
Model 1 [1]	1 (reference)	1.49 (1.16, 1.91)	1.28 (0.95, 1.47)	0.055
Model 2 [2]	1 (reference)	1.47 (1.14, 1.89)	1.27 (0.93, 1.72)	0.073
Men				
Current smoker				
Participants (number)				-
Case/non-case	166/ 9,873	364/ 14,974	465/ 22,358	
Pearson year	106,860.5	170,458	252,179	-
Crude	1 (reference)	1.49 (1.24, 1.80)	1.47 (1.23, 1.76)	<0.001
Model 1 [1]	1 (reference)	1.56 (1.29, 1.88)	1.61 (1.34, 1.95)	0.001
Model 2 [2]	1 (reference)	1.63 (1.35, 1.96)	1.78 (1.46, 2.16)	<0.001
Former smoker				
Participants (number)				-
Case/non-case	305/ 25,328	469/ 24,844	461/ 26,312	
Pearson year	243,256	282,458.2	308,673.5	-
Crude	1 (reference)	1.40 (1.21, 1.62)	1.55 (1.34, 1.80)	<0.001
Model 1 [1]	1 (reference)	1.47 (1.26, 1.70)	1.71 (1.46, 2.00)	0.001
Model 2 [2]	1 (reference)	1.44 (1.24, 1.68)	1.67 (1.42, 1.96)	<0.001
Never smoker				
Participants (number)				-
Case/non-case	93/ 22,394	140/ 22,524	116/ 21,505	
Pearson year	227,755.3	270,656.7	262,359.7	-
Crude	1 (reference)	1.38 (1.06, 1.79)	1.35 (1.02, 1.78)	0.032
Model 1 [1]	1 (reference)	1.40 (1.07, 1.84)	1.39 (1.04, 1.87)	0.029
Model 2 [2]	1 (reference)	1.39 (1.06, 1.83)	1.37 (1.01, 1.85)	0.045

* HR = hazard ratio, CI = confidence interval.

[1] Adjusted for energy intake, smoking status, smoking intensity, age and sex.

[2] Adjusted for model 1+ fluid intake, fruit and vegetables intakes.

Supplementary Table S3.2. Hazard ration (HR) and 95% confidence intervals (CIs) based on tertile of Western diet score by cancer sub-types

	Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
NMIBC*				-
Participants (number)				-
Cases	334	547	484	
Pearson year	2,469.457	5,147.161	4,333.148	-
Crude	1 (reference)	0.83 (0.72, 0.95)	0.94 (0.82, 1.09)	0.701
Model 1 [1]	1 (reference)	1.10 (0.91, 1.31)	1.40 (1.16, 1.69)	<0.001
Model 2 [2]	1 (reference)	1.09 (0.86, 1.37)	1.28 (1.02, 1.63)	<0.001
MIBC+				-
Participants (number)				-
Cases	189	380	305	
Pearson year	1,616.891	3,944.66	3,117.87	-
Crude	1 (reference)	0.87 (0.73, 1.04)	0.93 (0.78, 1.12)	0.672
Model 1 [1]	1 (reference)	1.20 (0.95, 1.50)	1.33 (1.05, 1.69)	0.019
Model 2 [2]	1 (reference)	1.09 (0.86, 1.37)	1.28 (1.01, 1.64)	0.028

* HR = hazard ratio, CI = confidence interval. ** NMIBC = non-muscle-invasive bladder cancer, +MIBC = muscle-invasive bladder cancer.

[1] Adjusted for energy intake, smoking status, smoking intensity, age and sex.

[2] Adjusted for model 1+ fluid intake, fruit and vegetables intakes.

Chapter 4

The association between meat and fish consumption and bladder cancer risk: a pooled analysis of 11 cohort studies

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Abstract

Background: Evidence on the effects of meat consumption from different sources on the risk of bladder cancer (BC) is limited and controversial. Therefore, this study aimed to evaluate the associations between meat consumption and BC risk using a pooled data approach.

Methods: Individual data from 11 prospective cohorts comprising 2,848 BC cases and 515,697 non-cases with a total of 5,498,025 person-years of follow-up was pooled and analysed to investigate the potential associations between total red meat and products, red meat, processed meat, poultry and total fish and BC risk. Hazard ratios (HRs), with corresponding 95% confidence intervals (CIs), were estimated using Cox regression models stratified on cohort.

Results: Overall, an increased BC risk was found for high intake of organ meat (HR comparing highest with lowest tertile: 1.18, 95% CI: 1.03, 1.36, p-trend=0.03). On the contrary, a marginally inverse association was observed for total fish intake and BC risk among men (HR comparing highest with lowest tertile: 0.79, 95% CI: 0.65, 0.97, p-trend=0.04). No associations were observed for other meat sources.

Conclusion: Results of this prospective study suggest that organ meat consumption may be associated with BC development. Replication in large-scale prospective studies and investigation of possible causal mechanisms is needed.

Key words: Bladder cancer; Meat; Fish; Risk factor; Epidemiology

Introduction

Cancer of the bladder (BC) is among the top ten most common cancer types in the world, with approximately 573,000 new cases and 213,000 deaths [1]. Incidence rates of BC are the highest in Southern and Eastern Europe Africa and the Middle East, and in North America [2]. BC occurs mainly in men and elderly [1] and approximately 75% of the bladder cancers are non-muscle-invasive (NMIBC) which require intensive treatment and follow-up measures, thereby posing a large burden on national health care budgets [3]. Epidemiological studies have identified several factors which potentially influence BC risk, including; sex, smoking, age and certain occupations [3, 4]. Well-established BC carcinogens include aromatic amines like heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs) and arsenic and repetitive urinary tract infections have also been reported to increase BC risk [5]. In addition, a wider range of evidence is becoming available on the plausible role of dietary factors in BC occurrence [5]. However, the latest World Cancer Research Fund International (WCRF) report stated that evidence from epidemiologic studies on the association between diet and BC is still scarce and largely inconsistent [6].

Meat is a rich source of multiple potentially carcinogenic compounds, including nitrate, nitrite, HCAs and PAHs, with a known effect on tumor growth induction [7-10]. Since these compounds are excreted in the urine and therefore come in close contact with the inner lining of the bladder wall, these components might play an important role in BC development [11].

There is however limited and inconsistent epidemiological evidence on the association between meat consumption and BC. While a Swedish cohort study found no association between the consumption of red meat, processed meat, poultry, or fried meats/fish and BC risk [12], other prospective cohort studies suggested an increased BC risk with cumulative consumption of processed red meat [13, 14]. A positive association between meat consumption and BC risk was also confirmed by a meta-analysis, including five cohort and eight case-control studies from all over the world. It was shown that an increment of 50 g of processed meat per day was associated with 20% increased risk of BC [15]. In addition, the authors showed that red meat consumption was associated with BC, with a 51% increased risk per increment of 100 g per day. However, this association with red meat consumption could only be observed among the included case-control studies. A more recent meta-analysis only identified a positive association between red and processed meat among Americans, while an absence of an association was observed for individuals from other continents [16].

These controversial findings might be due to the small sample sizes of previously conducted studies, which consequently would lack statistical power to detect significant associations. Although meta-analysis might overcome this power issue, they

solely rely on previously published data, thereby potentially introducing reporting bias. The present study, therefore, aims to provide a more comprehensive estimate for the associations between meat consumption and BC risk, by pooling individual data from 11 cohort studies, thereby not only increasing the power to detect small effect sizes, but also allowing for data homogenization and common adjustment for potential confounding factors.

Methods

Study sample

Data were derived from the BLadder cancer Epidemiology and Nutritional Determinants consortium (BLEND) [17]. BLEND is a large international epidemiology consortium, aimed to pool available data from epidemiological studies on diet and BC [17]. BLEND consists of 19 case-control studies and 16 cohort studies. Eleven cohort studies, with a total of 518,545 participants, 2,848 of whom developed incident BC, had sufficient information on both meat and fish consumption, and on the most important covariates gender and smoking, to be eligible for inclusion in the present study. These studies originated from 11 countries [i.e. Europe: European Prospective Investigation into Cancer and Nutrition cohort studies (EPIC) [18] (Denmark [19], France [20], Germany [21], Italy [22], The Netherlands [23], Norway [24], Spain [25], Sweden [26, 27], United Kingdom [28, 29]), Netherlands cohort study (NLCS) [30]; and North America: VITamins and Lifestyle cohort study (VITAL) [31]].

Data collection and pre-processing

Details on the protocol of the BLEND consortium have been described in the BLEND methodology paper [17]. Briefly, the primary data from all the included studies were assembled into an integrated database. Data were checked and the food consumption was converted to grams per day (g/day) by the use of country specific food tables and the frequency responses. National specific standard portions sizes for each food item were used to calculate consumption in g/day. Each study ascertained incident bladder cancer cases, defined to include all subjects with urinary bladder neoplasms according to the International Classification of Diseases for Oncology (ICD-O-3 code C67) using population-based cancer registries, health insurance records, or medical records [32, 33]. Dietary data were obtained using self-administered or trained interviewer administered food frequency questionnaire (FFQ) that was validated on either food groups [31, 34, 35], and/or energy intake [35, 36]. For each study, participants were asked to report on their usual intake during the year before study enrolment of meat and fish. These data were harmonized using the hierarchal Eurocode 2 food coding system developed by the European Union [37], with weekly, monthly or yearly intake converted to grams

(g) per day. This resulted in an aggregated dataset with unified dietary intakes across the different studies included.

Dietary meat consumption

By conducting a comprehensive review of the literature, we were able to use a more common definition of different meat categories [12, 13, 15, 38]. Dietary meat consumptions were categorized in the following groups including total meat and meat products (all meat groups except fish), total red meats and products (total meat and meat products minus poultry), red meat (beef, veal, mutton/lamb and pork), processed meats (preserved meat and meat products), organ meat (liver and other offal), poultry, and fish (fish and fish products). As a result of data availability, red meat, processed meat, organ meat, poultry, and fish consumption were calculated in grams per 1000 kilocalories per day (g/1000 kcal/day, nutrient density method), to account for total energy intake and reduce extraneous variation in dietary intakes [39, 40], and were categorized into tertiles for individual meat types [40]. Then, dietary meat consumptions were divided into 3 groups based on a tertile ordered distribution: low consumption (tertile 1), medium consumption (tertile 2) and high consumption (tertile 3).

Other variables

In addition to dietary consumption information, other baseline data included study characteristics including study design, method of dietary assessment, recall period of dietary consumption and geographical region, demographic information (age, sex and ethnicity), pathology of BC (non-muscle-invasive bladder cancer [NMIBC] and muscle-invasive bladder cancer [MIBC]), and smoking status (current/former/never) and quantity (packs/year).

Statistical analyses

Baseline characteristics of the study participants, meat sources and other potential confounders were compared between case and non-case groups using independent samples t-test, for continuous variables, or chi-square for categorical variables. Cox proportional hazard modelling approach was used with age at recruitment as the starting point on the time scale to assess the association between consumptions of meat and BC risk. Hazard ratios (HRs) and 95% confidence intervals (CIs) for developing BC were calculated with the first tertile assigned as reference group. The proportional hazards assumption was examined graphically, and we found no apparent violation to the assumption. Survival time was estimated by subtracting age at exit by age at entry in the cohort as T0, thereby correcting for age in the analysis. Also, study was included as a random effect. The Cox regression models were performed as crude, and based on literature review adjusted model-1 for: age, sex, smoking status (never, former or

current smoker), total energy intake in kilocalories, and additionally for: vegetables and fruits consumption (model-2). In addition, when testing for white meat and fish consumption analyses were corrected for red meat intake and vice versa (model 3).

To understand the relevance of plausible effect modification, interaction terms for sex, age and smoking status, and meat- and fish consumption were alternately added to the fully adjusted regression models. This was done by adding the multiplication of meat- and fish consumption in tertiles and: (a) the categorized age (<40, 40–50, 50–60, >60), (b) gender, (c) smoking status (current, former and smokers). The Wald-test was used to test for the presence of interaction, and p-interaction < 0.05 was considered statistically significant. Based on the knowledge that BC subtype (i.e. NMIBC and MIBC) have a different etiology, additional subgroup analyses were performed on BC subtypes.

We further assessed the potential dose–response relations of meat consumptions with BC risk by fractional polynomial regression using the ln (natural logarithm) of the HRs (model 3) across categories of consumption, in which the best-fitting second-order fractional polynomial regression model was defined as the model with the lowest deviance [40, 41]. A likelihood ratio test was used to assess the difference between the nonlinear (i.e., the absolute dose and dose squared) and linear (i.e., the absolute dose) models to test for linearity or nonlinearity [41]. For this, we categorized each source meat to six groups including (a) total meat and meat products, (b) red meats, (c) processed meats, (d) organ meats, (e) poultry and (f) fish and fish products into 10 doses (g/1000 kcal/day) according to the range of consumption of meat sources, by which the intervals of each consumption were different. P-values for trend were estimated by assigning medians to each category of consumption as a continuous variable.

Finally, in order to determine the single study effect, sensitivity analyses were performed by removing each individual study in turn from the main analysis. All statistical analyses were performed using Stata/SE version 14.2. P-values less than 0.05 were considered as statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study population are shown in **Table 4.1**. Baseline characteristics for the 11 included cohort studies individually are shown in **Supplementary Table S4.1**. Dietary data from 518,545 study participants, including 2,848 incident cases and 515,697 non-cases with a total of 5,498,025 person-years of follow-up (median follow-up: 11.3 years) were analyzed. The study population consisted of 1,088 NMIBC cases (63%) and 648 MIBC cases (37%).

Table 4.1. Baseline characteristics meat sources among non-cases and bladder cancer cases in the BLEND international study

	Cases	Non-cases	
Categories of data	n=2,848	n=515,697	P-value
Baseline age year (mean (SD))	60.6 (7.28)	52.5 (10.09)	<0.001^
Person-year	Total: 21,210.08	Total: 5,476,815	<0.001^
	Median: 7.45	Median: 10.62	
Sex n (%)			<0.001^
Men	2,144 (75.3)	164,953 (32.0)	
Women	704 (24.7)	350,744 (68.0)	
Smoking status n (%)			<0.001*
Current	1,118 (39.3)	107,108 (20.8)	
Former	1,183 (41.5)	154,474 (30.0)	
Never	547 (19.2)	254,115 (49.2)	
Dietary meat sources, g/1000 kcal/day (mean (SD))			
Total meat and meat products	49.06 (28.4)	49.38 (30.65)	0.571^
Total red meats and products	39.98 (26.37)	39.21 (27.40)	0.135^
Red meats	17.38 (17.96)	15.62 (17.15)	<0.001^
Processed meats	16.34 (13.93)	15.42 (13.08)	<0.001^
Organ meats	3.11 (4.43)	2.54 (4.53)	<0.001^
Poultry	8.87 (9.95)	9.99 (11.56)	0.731^
Fish and fish products	3.58 (5.42)	5.76 (6.83)	<0.001^
Potential confounders			
Energy intake, kcal/day (mean (SD)	2,179.13 (630.32)	2,051.59 (642.12)	<0.001^
Fruits, g/1000 kcal/day (mean (SD))	77.39 (77.63)	91.74 (222.40)	0.776^
Vegetables, g/1000 kcal/day (mean (SD))	135.88 (103.18)	151.51 (380.96)	<0.001^
Ethnicity (%)			
Caucasian	2,834 (99.6)	511,934 (99.3)	0.094*
Non-Caucasian	12 (0.4)	3,507 (0.7)	

Abbreviations: SD: standard deviation, g: gram, mg: milligram, ml: milliliters, kcal: kilocalorie.
^: based on independent sample t-test. *: based on Chi-2 test.

In total, 167,095 (32%) men and 351,444 (68%) women were included. As shown in **Table 4.1**, compared to non-cases, BC cases were more likely to be men (75%) and to be current (39%) or former smokers (41%). Mean (± SD) age for was 60.6 (± 7.3) for cases and 52.5 (± 10.1) for non-cases. The median (interquartile) time from exposure collection to BC diagnosis was 8.5 years (4.9, 12.0). Almost all participants were Caucasian [i.e., 99.6% of the cases and 99.3% of the non-case (p=0.09)].

Regarding dietary factors, compared to non-cases, cases had a higher mean (±SD) consumption of all assessed food items (i.e. total red meat and products 39.9 (26.4) vs. 39.2 (27.4), red meats 17.4 (17.9) vs. 15.6 (17.1), processed meats 16.3 (13.9) vs. 15.4 (13.1), organ meats 3.1 (4.4) vs. 2.5 (4.5), energy intake 2,179.1 (630.3) vs. 2,051.6 (642.1), except for poultry (8.9 (9.9) vs. 10.0 (11.6)), fish and fish products (3.58 (5.4) vs. 5.7 (6.8)),

vegetables (135.9 (103.2) vs. 151.5 (380.9)), and fruits (77.4 (77.6) vs. 91.7 (222.4)), which showed to be consumed in a lower amount among cases (**Table 4.1**).

Associations between meat consumption and BC risk comparing high to low consumption

The results of the Cox regression for subsequent categories of meat consumption are shown in **Table 4.2**. We found that greater consumption of organ meats was associated with an increased risk of BC (model 2: HR comparing highest to lowest tertile: 1.18, 95% CI: 1.03, 1.36, p-trend=0.03). This association remained stable after additional adjustment for poultry meat and fish intake (model 3: HR comparing highest to lowest tertile: 1.21, 95% CI: 1.05, 1.38, p-trend=0.014). An inverse association between higher consumption of poultry meat and risk of BC was observed (model 2: HR comparing highest to lowest tertile: 0.71, 95% CI: 0.65, 0.78, p-trend<0.001). However, after adjustment for red meat intake this association disappeared (model 3: HR comparing highest to lowest tertile: 0.98, 95% CI: 0.84, 1.12, p-trend 0.54) (Table 4.2). Furthermore, a marginally non-significant association between total fish and fish products (model 2: HR comparing highest with lowest tertile: 0.84, 95% CI: 0.72, 1.00, p-trend=0.08; model 3: HR comparing highest with lowest tertile: 0.89, 95% CI: 0.63, 1.25, p-trend=0.369) and the risk of BC was observed. No associations were found for any other meat sources.

Subgroup analysis

A significant interaction was observed between fish consumption and gender and smoking (p-interaction=0.03, 0.01, respectively). No other interaction terms showed to be relevant.

An inverse association between total fish and fish products consumption and BC risk in men (model 2: HR comparing highest with lowest tertile: 0.81, 95% CI: 0.67, 0.98, p-trend=0.03; model 3: HR comparing highest with lowest tertile: 0.79, 95% CI: 0.65, 0.97, p-trend=0.04) was observed, but no association was found in women (model 2: HR comparing highest with lowest tertile: 0.96, 95% CI: 0.63, 1.45, p-trend=0.69; and model 3: HR comparing highest with lowest tertile: 1.07, 95% CI: 0.76, 1.51, p-trend=0.658, p-heterogeneity=0.02) (**Table 4.3**). No significant association for fish intake and BC risk was observed in the different smoking categories (**Table 4.3**).

Stratified results for BC subtypes (i.e., NMIBC and MIBC) showed no different effect of any of the meat- and fish intake on the different BC subtype risks (p-heterogeneity for all > 0.05) (**Supplementary Table S4.2**).

Table 4.2. Hazard ratio (HR) and 95% confidence interval (CI) of the association of meat and meat types, and risk of BC based on tertiles of meat and meat types

Meat and meat types		Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
Total Red Meats and Products	Participants (cases/non-cases)	(856/171,991)	(1,103/171,741)	(889/171,959)	-
	Person-years	1,790,142	1,845,531	1,862,353	-
	Crude	1 (reference)	1.25 (1.15, 1.36)	1.13 (1.04, 1.23)	0.007
	Model 1 [1]	1 (reference)	1.13 (1.04, 1.24)	0.96 (0.87, 1.05)	0.222
	Model 2 [2]	1 (reference)	1.12 (1.02, 1.23)	0.94 (0.85, 1.03)	0.085
	Model 3 [3†]	1 (reference)	1.08 (0.94, 1.23)	1.01 (0.84, 1.21)	0.248
Red Meats	Participants (cases/non-cases)	(445/148,483)	(577/148,350)	(613/148,316)	-
	Person-year	1,671,793	1,636,671	1,666,877	-
	Crude	1 (reference)	1.18 (1.04, 1.38)	1.13 (0.99, 1.29)	0.079
	Model 1 [1]	1 (reference)	1.08 (0.95, 1.23)	0.99 (0.86, 1.13)	0.750
	Model 2 [2]	1 (reference)	1.09 (0.96, 1.24)	1.02 (0.89, 1.17)	0.868
	Model 3 [3†]	1 (reference)	1.06 (0.93, 1.20)	1.03 (0.88, 1.21)	0.721
Processed Meats	Participants (cases/non-cases)	(505/148,425)	(561/148,365)	(569/148,359)	-
	Person-year	1,665,703	1,658,865	1,650,773	-
	Crude	1 (reference)	1.16 (1.04, 1.30)	1.30 (1.16, 1.45)	<0.001
	Model 1 [1]	1 (reference)	0.95 (0.84, 1.07)	0.99 (0.88, 1.11)	0.895
	Model 2 [2]	1 (reference)	0.94 (0.84, 1.06)	0.98 (0.88, 1.11)	0.822
	Model 3 [3†]	1 (reference)	0.89 (0.72, 1.10)	0.95 (0.73, 1.24)	0.304

Table 4.2 continues on next page.

Table 4.2. *Continued*

Meat and meat types		Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
Organ Meats	Participants (cases/non-cases)	(389/149,366)	(541/147,560)	(705/148,223)	-
	Person-year	1,658,709	1,676,021	1,640,611	-
	Crude	1 (reference)	1.31 (1.15, 1.49)	1.48 (1.29, 1.69)	<0.001
	Model 1 [1]	1 (reference)	1.25 (1.09, 1.43)	1.20 (1.05, 1.39)	0.015
	Model 2 [2]	1 (reference)	1.21 (1.06, 1.39)	1.18 (1.03, 1.36)	0.032
	Model 3 [3†]	1 (reference)	1.22 (1.06, 1.40)	1.21 (1.05, 1.38)	0.014
Poultry	Participants (cases/non-cases)	(1,022/171,827)	(977/171,867)	(849/171,997)	-
	Person-year	1,891,568	1,858,982	1,747,476	-
	Crude	1 (reference)	0.77 (0.71, 0.84)	0.62 (0.57, 0.68)	<0.001
	Model 1 [1]	1 (reference)	0.82 (0.75, 0.89)	0.73 (0.67, 0.81)	<0.001
	Model 2 [2]	1 (reference)	0.81 (0.74, 0.89)	0.71 (0.65, 0.78)	<0.001
	Model 3 [3‡]	1 (reference)	0.91 (0.81, 1.04)	0.98 (0.84, 1.12)	0.54
Total Fish and Fish products	Participants (cases/non-cases)	(252/61,489)	(473/61,269)	(812/60,929)	-
	Person-year	666,381.6	603,304.3	497,419.5	-
	Crude	1 (reference)	0.73 (0.61, 0.85)	0.54 (0.47, 0.63)	<0.001
	Model 1 [1]	1 (reference)	0.85 (0.73, 0.96)	0.88 (0.75, 1.03)	0.257
	Model 2 [2]	1 (reference)	0.85 (0.73, 1.00)	0.84 (0.72, 1.00)	0.080
	Model 3 [3‡]	1 (reference)	0.92 (0.76, 1.11)	0.89 (0.63, 1.25)	0.369

*HR = Hazard Ratio, CI = confidence interval.

[1] adjusted for age, sex, smoking status and total energy intake.

[2] adjusted for model 1 + vegetables and fruits intakes.

[3] adjusted for † model 2+ poultry and fish intake ‡ model 2 + red meat intake.

Table 4.3. Hazard ratio (HR) and 95% confidence interval (CI) of the association of fish consumption, and risk of BC based on tertiles of intakes by gender and smoking status

	Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend		Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
Women					Men				
Total fish and fish products					Total fish and fish products				
Case/non-case	80/44,180	94/37,374	161/34,470		Case/non-case	172/17,309	379/23,895	651/26,459	
Person-year	479,226.23	377,769.02	281,772.08		Person-year	186,702.27	225,122.36	215,306.94	
Crude	1 (reference)	0.80 (0.58, 1.10)	0.60 (0.43, 0.83)	0.001	Crude	1 (reference)	0.75 (0.64, 0.90)	0.68 (0.58, 0.81)	<0.001
Model 1 [1]	1 (reference)	0.77 (0.55, 1.08)	0.91 (0.61, 1.36)	0.575	Model 1 [1]	1 (reference)	0.86 (0.72, 1.02)	0.85 (0.71, 1.02)	0.134
Model 2 [2]	1 (reference)	0.78 (0.55, 1.09)	0.96 (0.63, 1.45)	0.698	Model 2 [2]	1 (reference)	0.86 (0.72, 1.03)	0.81 (0.67, 0.98)	0.036
Model 3 [3‡]	1 (reference)	1.07 (0.76, 1.51)	0.77 (0.39, 1.50)	0.658	Model 3 [3‡]	1 (reference)	0.85 (0.71, 1.02)	0.79 (0.65, 0.97)	0.047

Table 4.3 continues on next page.

Table 4.3. *Continued*

	HR (95% CI) *	HR (95% CI)	HR (95% CI)	P-trend		HR (95% CI) *	HR (95% CI)	HR (95% CI)	P-trend
Never Smoker					Former smoker				
Total fish and fish products					Total fish and fish products				
Cases/Non-cases	52/29,617	65/23,628	141/27,235		Cases/Non-cases	100/19,101	211/21,765	384/24,616	
Person-year	323,773.01	231,752.69	213,767.02		Person-year	204,627.5	206,186.25	194,456.23	
Crude	1 (reference)	0.72 (0.49, 1.05)	0.55 (0.38, 0.80)	0.001	Crude	1 (reference)	0.83 (0.66, 1.04)	0.73 (0.58, 0.91)	0.005
Model 1 [1]	1 (reference)	0.93 (0.60, 1.43)	1.24 (0.74, 2.08)	0.434	Model 1 [1]	1 (reference)	0.84 (0.66, 1.08)	0.79 (0.62, 1.01)	0.072
Model 2 [2]	1 (reference)	0.93 (0.60, 1.44)	1.24 (0.74, 2.10)	0.416	Model 2 [2]	1 (reference)	0.85 (0.67, 1.09)	0.77 (0.60, 0.99)	0.042
Model 3 [3‡]	1 (reference)	0.93 (0.60, 1.43)	1.24 (0.74, 2.08)	0.592	Model 3 [3‡]	1 (reference)	0.84 (0.66, 1.08)	1.17 (0.72, 1.95)	0.823

	HR (95% CI) *	HR (95% CI)	HR (95% CI)	P-trend
Current smoker				
Total fish and fish products				
Cases/Non-cases	100/12,771	197/15,876	287/9,078	
Person-year	137,527.99	164,952.43	88,855.77	
Crude	1 (reference)	0.79 (0.63, 0.99)	0.78 (0.62, 0.99)	0.089
Model 1 [1]	1 (reference)	0.87 (0.69, 1.10)	0.90 (0.71, 1.16)	0.535
Model 2 [2]	1 (reference)	0.87 (0.69, 1.10)	0.88 (0.68, 1.13)	0.364
Model 3 [3‡]	1 (reference)	0.87 (0.65, 1.15)	0.75 (0.44, 1.28)	0.210

*HR = Hazard Ratio, CI = confidence interval.
[1] adjusted for age, sex, and total energy intake.
[2] adjusted for model 1 + vegetables and fruits intakes.
[3‡] adjusted for model 2 + red meat intake.

Dose–response and sensitivity analyses

Dose–response relationships between different sources of meat consumptions and the risk of BC are displayed in **Figure 4.1**. Although cox-regression showed a significantly increased BC risk for organ meat consumption of over 15 g/1000 kcal/day, no significant dose–response relationship was observed for any meat-type and neither for fish (**Figure 4.1**).

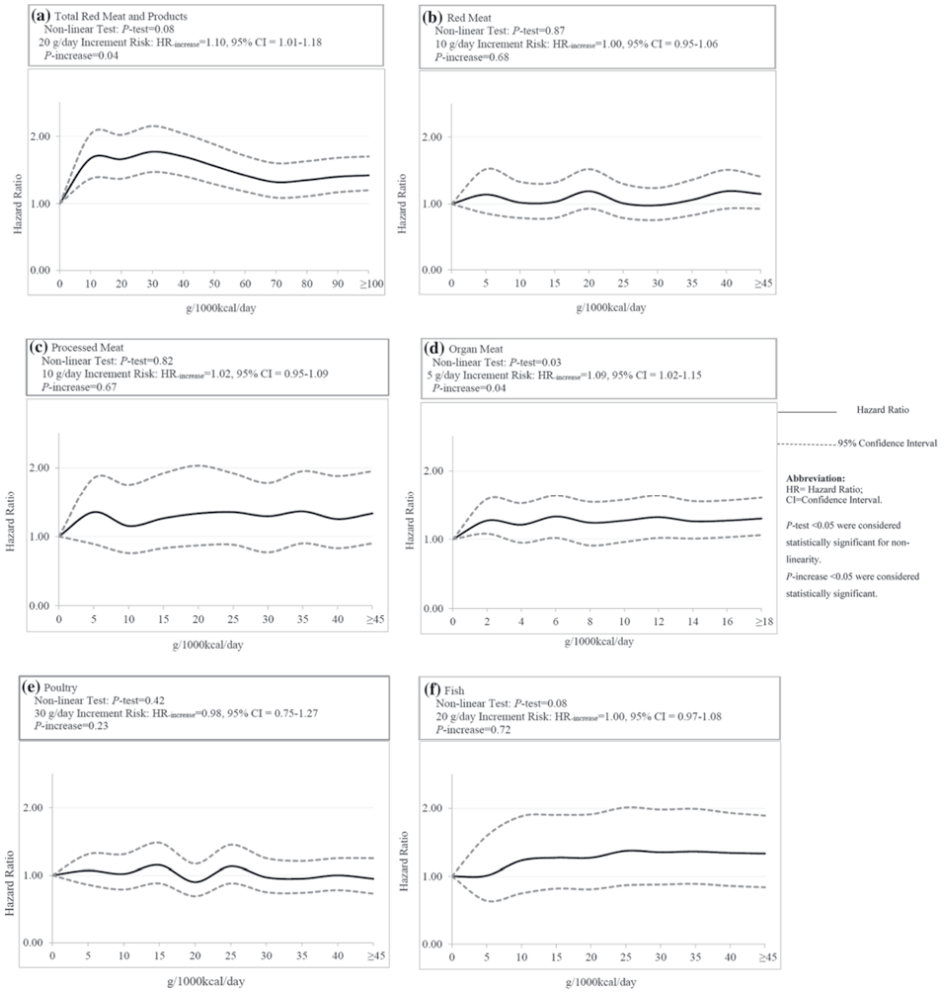

Figure 4.1. Dose–response relationships between meat intakes and the risk of bladder cancer among **a** total red meats and products; **b** red meats; **c** processed meats; **d** organ meats; **e** poultry and **f** total fish and fish products. The solid lines represent the hazard ratios (HRs); the dashed lines represent the 95% confidence intervals (CIs) for the trend. The HRs were adjusted for age (years, continuous), sex (men or women), smoking (never smokers, former smokers or current smokers), energy intake (kcal/day, continuous), vegetable intake (g/1000 kcal/day, continuous), fruit intake (g/1000 kcal/day, continuous) poultry (g/1000 kcal/day, continuous) and fish (g/1000 kcal/day, continuous) intake or red meat intake (g/1000 kcal/day, continuous) (model 3). g gram; kcal kilocalorie. Referent group was non-intake.

In order to determine the single study effect, sensitivity analyses were performed by removing each individual study in turn from the main analysis. Results showed that the main finding remained robust.

Discussion

By bringing together the world's data on meat and fish consumption and BC risk, this large prospective study demonstrates an overall significant association between high consumption of organ meat and BC risk and a slightly inverse association for high consumption of fish among men.

Epidemiological evidence on the association between organ meats and BC risk is mainly lacking. To our knowledge, only one previously conducted case-control study assessed this association [42]. In line with results from the present study, the authors found an increased BC risk among South and East Chinese individuals [42]. A possible explanation for the observed association between organ meat and BC risk, is the high fat content (especially saturated fats) of organ meat, which has been reported to increase the BC risk [43, 44]. In addition, it has been suggested that the cooking procedure of fat-rich meat forms mutagens and consequently affect BC risk [45-47]. As such, it is reported that different procedures of cooking meat i.e.; at higher temperatures (roasting) or for prolonged times (e.g. stewing), were associated with an increased BC risk [48]. Another possible explanation could be the fact that most organ meats are high in toxins [49], which might cause dysbiosis of the urinary tract, thereby indirectly causing an increased BC risk [50-52].

Bioassays and epidemiological studies indicated that tobacco smoking might modify the effect of dietary fat and cancer risk by enhancing the carcinogenic potency of meat and exerted a synergistic effect on cancer risk [53-55]. Moreover, the N-nitroso components of meat, the nitrosation of nicotine during tobacco processing, and the tobacco-specific nitrosamines resulted from cigarette smoking might lead to an increased total N-nitroso compound consumption, thereby increasing the BC risk of meat in current smokers [56]. However, in the present study no interaction between meat consumption and smoking status could be observed. This might be due residual confounding, which could not be assess in the present study.

In the present study we found no significant association between poultry intake and BC risk. This is in line with the results of a meta-analysis of eight studies, also revealing a non-significant association between poultry and BC risk (RR: 0.77, 95% CI: 0.48, 1.06) [57]. However, the NIH-AARP Diet and Health study reported a statistically significant decreased BC risk associated with a 10 g/per in white meat consumption [38]. It is suggested that, compared to red meat, white meat (including poultry) contains less

saturated fat and heme iron, potential inducers of oxidative stress and DNA damage [58], and release less mutagenic substitutes during the cooking procedure. It could, therefore, be possible that the previously observed inverse association between poultry and BC risk was not due to a protective effect of poultry itself, but rather due to a reduced intake of red meat, for which only limited adjustment was performed.

In the present study we found an inverse association between fish consumption and BC risk in men, but not in women. Although the evidence of the association of fish consumption and BC is scarce, a previously conducted Spanish case-control study also reported an inverse association between fish intake and BC risk [59]. This protective effect of fish on BC risk might possibly be due to the concentrated doses of anti-inflammatory, long-chain n-3 fatty acids in fish, shown to inhibit cancer development and progression [60]. On the contrary, however, several observation studies on fish intake and BC risk observed a null-association [12, 61, 62]. It is suggested that the way fish is served may be quite different between cultures and also preparation, conservation, and processing methods may have deleterious health effects (e.g. Cantonese-style salted fish or heavily battered and deep fried) [63]. So, future research is needed to elucidate the exact role of fish on the development of BC, considering also differences in fish processing.

Overall, a null-association between red- and processed meat consumption and BC risk was observed. Although this is in line with several previously conducted studies, including three cohort studies and a meta-analysis [12, 13, 14, 57], other studies, including two meta-analyses and a cohort study, reported a direct negative association between both red- and processed meat consumption and the BC risk [15, 16, 64]. Potential mechanisms underlying the association of meat consumption and BC risk are still unclear. Therefore, future research is warranted to clarify the underlying mechanisms.

Strengths and limitations

So far, the BLEND database is the largest pooled prospective cohort study investigating the associations between consumption of different sources of meat and the risk of developing BC and allows enough statistical power to conduct detailed analyses in detecting small effects. The use of individual participant data enables adjustments to be made for the same confounders across all studies. Additionally, eliminating possible sources of heterogeneity with the use of prospective cohort studies only, precludes recall bias which commonly occur in case-control and retrospective cohort studies.

Alternatively, several limitations to our study should be considered. Some information in the BLEND database was only in portions per week. This was converted to grams per day using the BLEND Nutrient 100-g database. However, the conversions were not

country specific. Also, limited information was available for some potential risk factors of BC, such as BMI, physical inactivity, socioeconomic status, and occupational exposures to carcinogenic chemicals. The possibility to adjust for these factors will provide more accurate risk estimates. Moreover, it is a possibility that people with a high intake of fish and poultry might have generally healthier lifestyles and diets than those with a low intake, thus we could not rule out the possibility that some of the associations could be or partially due to unmeasured factors related to a healthy lifestyle than to purely white meat intakes [65]. However, the current literature suggests only a small proportion of BC cases can be attributed to lifestyle and environmental factors [66]. In addition, we were unable to take into account possible changes in dietary and lifestyle habits over time, which would better reflect the effect of long-term diet. Furthermore, it is suggested that meat might be involved in the bladder carcinogenesis via multiple potentially carcinogenic fish/meat-related compounds related to cooking and processing, including nitrate, nitrite, HCAs, and PAHs. However, in this study there was no information on meat preparation or cooking methods. Besides, for most cohorts, the exposure variable was assessed by FFQs, therefore, measurement error and misclassification of study participants in terms of the exposure and outcome are unavoidable. Likewise, information bias, as a consequence of self-reported information on food consumption is a common bias in nutritional studies [67]. However, the strength and direction of this bias should not be significantly different between cases and non-cases, suggesting that the impact of information bias on our findings might be minimal. Finally, the present study sample consisted mostly of Caucasians, and this may limit the generalizability of our results to other racial/ethnic populations or geographic regions.

Conclusion

In summary, this large prospective study added new insights into the role of meat consumptions toward BC carcinogenesis. It was found that organ meats may be a risk factor for the development of BC, and fish might play a protective role against BC risk among men.

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Supplementary Table S4.1. Additional baseline characteristic for included studies in BLEND study

	NLCS	VITAL	EPIC-Denmark	EPIC-France	EPIC-Germany	EPIC-Italy	EPIC-Spain	EPIC-Sweden	EPIC-the Netherlands	EPIC- the UK	EPIC-Norway
Characteristics	N=5,238	N=66,518	N=55,670	N=64,204	N=48,754	N=44,663	N=40,389	N=48,625	N=36,801	N=74,379	N=33,304
Initiate year of baseline assessment	1986	2000	1993	1990	1994	1992	1992	1991	1993	1993	1991
Length of follow up (years)	14	7	11	10	10	11	12	13	12	11	10
Subjects (number)											
Case/	876/	337/	386/	31/	205/	186/	149/	301/	107/	247/	23/
non-case	4.362	66.181	55.284	64.173	48.549	44.477	40.24	48.324	36.694	74.132	33.281
Person-year	73,688.8	448,995.4	608.813	667,809.9	482,453.3	502,020.3	487,491.1	638,482.8	434,974.5	828,991.7	6,437,305.7
Baseline age (years) (mean ±SD)											
Case	62.73 (4.09)	66.16 (7.01)	58.50 (4.37)	58.04 (6.00)	56.41 (7.13)	55.24 (6.75)	54.49 (7.19)	60.27 (7.07)	56.20 (8.03)	63.62 (9.98)	49.30 (4.38)
Non-case	61.85 (4.21)	61.18 (7.37)	56.67 (4.37)	52.74 (6.63)	50.55 (8.56)	50.50 (7.92)	49.19 (8.03)	51.93 (10.89)	48.94 (11.93)	49.05 (14.34)	48.07 (4.30)
Sex n (%)											
Men	2,867 (54.73)	33,394 (50.20)	26,532 (47.66)	0 (0.00)	21,168 (43.42)	13,774 (30.84)	15,259 (37.78)	22,214 (45.68)	9,629 (26.17)	22,260 (29.93)	0 (0.00)
Women	2,371 (45.27)	33,124 (49.80)	29,138 (52.34)	64,204 (100.00)	27,586 (56.58)	30,889 (69.16)	25,130 (62.22)	26,411 (54.32)	27,172 (73.83)	52,119 (70.07)	33,304 (100.00)

Abbreviations:
EPIC: European Prospective Investigation into Cancer
NLCS: The Netherlands Cohort Study
VITAL: VITamins and Lifestyle study

Supplementary Table S4.2. Hazard ratio (HR) and 95% confidence interval (CI) of the association of meat and meat types, and risk of BC based on tertiles of meat and meat types for stratification of bladder cancer subtype

	Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend		Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
NMIBC					MIBC				
Total red meat and products					Total red meat and products				
Person-year	2,581.20	3,185.39	2,392.94		Person-year	1,628.40	2,632.94	1,242.26	
Crude	1 (reference)	1.20 (1.05, 1.38)	1.13 (0.99, 1.30)	0.092	Crude	1 (reference)	1.23 (1.04, 1.45)	1.23 (1.04, 1.45)	0.018
Model 1 [1]	1 (reference)	1.17 (1.01, 1.36)	1.17 (1.01, 1.36)	0.045	Model 1 [1]	1 (reference)	1.04 (0.86, 1.25)	1.03 (0.85, 1.24)	0.760
Model 2 [2]	1 (reference)	1.27 (1.09, 1.48)	1.26 (1.09, 1.47)	0.004	Model 2 [2]	1 (reference)	1.18 (0.98, 1.43)	1.22 (1.00, 1.49)	0.049
Model 3 [3†]	1 (reference)	0.94 (0.75, 1.17)	1.23 (0.92, 1.64)	0.302	Model 3 [3†]	1 (reference)	0.98 (0.77, 1.25)	1.18 (0.82, 1.68)	0.522
Red Meats					Red Meats				
Person-year	3,035.28	3,028.05	2,078.18		Person-year	2,006.56	2,550.43	917.253	
Crude	1 (reference)	0.81 (0.62, 1.07)	0.75 (0.57, 0.98)	0.047	Crude	1 (reference)	0.79 (0.40, 1.54)	0.77 (0.39, 1.53)	0.611
Model 1 [1]	1 (reference)	0.59 (0.45, 0.79)	0.47 (0.35, 0.62)	<0.001	Model 1 [1]	1 (reference)	0.40 (0.20, 0.82)	0.40 (0.19, 0.82)	0.155
Model 2 [2]	1 (reference)	0.61 (0.46, 0.81)	0.52 (0.39, 0.69)	<0.001	Model 2 [2]	1 (reference)	0.39 (0.19, 0.81)	0.43 (0.21, 1.02)	0.299
Model 3 [3†]	1 (reference)	1.00 (0.81, 1.25)	1.16 (0.89, 1.49)	0.457	Model 3 [3†]	1 (reference)	0.94 (0.74, 1.20)	1.06 (0.79, 1.41)	0.381
Processed Meats					Processed Meats				
Person-year	1,364.27	1,235.78	1,110.98		Person-year	352.62	387.88	229.48	
Crude	1 (reference)	1.23 (1.02, 1.49)	1.25 (1.03, 1.52)	0.021	Crude	1 (reference)	1.14 (0.85, 1.54)	1.63 (1.18, 2.26)	0.005
Model 1 [1]	1 (reference)	1.34 (1.09, 1.65)	1.35 (1.09, 1.66)	0.005	Model 1 [1]	1 (reference)	1.46 (1.04, 2.06)	1.65 (1.16, 2.34)	0.004
Model 2 [2]	1 (reference)	1.36 (1.10, 1.68)	1.40 (1.13, 1.73)	0.002	Model 2 [2]	1 (reference)	1.47 (1.04, 2.08)	1.82 (1.28, 2.60)	0.001
Model 3 [3†]	1 (reference)	2.11 (1.18, 3.77)	1.09 (0.48, 2.45)	0.972	Model 3 [3†]	1 (reference)	1.48 (1.05, 2.11)	1.91 (1.32, 2.72)	0.001

Supplementary Table S4.2 continues on next page.

Supplementary Table S4.2. *Continued*

	Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend		Tertile 1 HR (95% CI) *	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
NMIBC					MIBC				
Organ Meats					Organ Meats				
Person-year	543.42	1,641.58	1,526.03		Person-year	109.86	432.60	427.52	
Crude	1 (reference)	1.04 (0.78, 1.37)	0.97 (0.72, 1.29)	0.688	Crude	1 (reference)	1.46 (0.75, 2.83)	1.19 (0.59, 2.39)	0.917
Model 1 [1]	1 (reference)	1.43 (1.07, 1.90)	1.22 (0.91, 1.64)	0.417	Model 1 [1]	1 (reference)	1.21 (062, 2.36)	1.08 (0.52, 2.26)	0.951
Model 2 [2]	1 (reference)	1.45 (1.07, 1.95)	1.27 (0.93, 1.72)	0.351	Model 2 [2]	1 (reference)	1.03 (0.47, 2.25)	0.94 (0.43, 2.08)	0.758
Model 3 [3†]	1 (reference)	1.46 (1.08, 1.96)	1.26 (0.92, 1.70)	0.280	Model 3 [3†]	1 (reference)	1.07 (0.51, 2.31)	0.96 (0.47, 2.12)	0.321
Poultry					Poultry				
Person-year	3383.46	2,907.79	1,868.28		Person-year	2,477.57	2,062.90	963.12	
Crude	1 (reference)	1.08 (0.94, 1.25)	0.98 (0.85,1.12)	0.700	Crude	1 (reference)	0.89 (0.74, 1.06)	0.81 (0.68, 0.97)	0.019
Model 1 [1]	1 (reference)	1.03 (0.89, 1.20)	0.83 (0.71, 0.97)	0.023	Model 1 [1]	1 (reference)	0.72 (0.60, 0.88)	0.75 (0.62, 0.91)	0.004
Model 2 [2]	1 (reference)	1.00 (0.86, 1.16)	0.85 (0.73, 0.99)	0.046	Model 2 [2]	1 (reference)	0.80 (0.66, 0.97)	0.80 (0.66, 0.98)	0.028
Model 3 [3‡]	1 (reference)	1.35 (1.06, 1.70)	1.27 (0.97, 1.67)	0.047	Model 3 [3‡]	1 (reference)	1.20 (0.74, 1.94)	1.03 (0.57, 1.84)	0.447
Total fish and fish products					Total fish and fish products				
Person-year	556.97	1,407.47	2,717.96		Person-year	168.77	1,136.48	2,539.23	
Crude	1 (reference)	0.92 (0.69, 1.23)	0.65 (0.49, 0.85)	<0.001	Crude	1 (reference)	0.59 (0.39, 0.89)	0.48 (0.33, 0.71)	<0.001
Model 1 [1]	1 (reference)	0.89 (0.66, 1.21)	0.61 (0.45, 0.82)	<0.001	Model 1 [1]	1 (reference)	0.56 (0.36, 0.87)	0.42 (0.28, 0.63)	<0.001
Model 2 [2]	1 (reference)	0.93 (0.68, 1.25)	0.70 (0.51, 0.94)	0.001	Model 2 [2]	1 (reference)	0.58 (0.37, 0.90)	0.47 (0.31, 0.72)	0.001
Model 3 [3‡]	1 (reference)	1.04 (0.57, 1.14)	0.81 (0.42, 0.85)	0.001	Model 3 [3‡]	1 (reference)	0.54 (0.34, 0.93)	0.46 (0.29, 0.73)	0.001

*HR = Hazard Ratio, CI = confidence interval.

[1] adjusted for age, sex, smoking status and total energy intake.

[2] adjusted for model 1 + vegetables and fruits intakes.

[3] adjusted for † model 2+ poultry and fish intake ‡ model 2 + red meat intake.

Chapter 5

Dietary fats and their sources in association with the risk of bladder cancer: A pooled analysis of 11 prospective cohort studies

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Abstract

Background: The effects of fat intake from different dietary sources on bladder cancer (BC) risk is still unidentified. Therefore, the present study aimed to investigate the association between fat intake, derived from different sources, and BC risk by merging world data on this topic.

Methods: Data from 11 cohort studies in the BLadder cancer Epidemiology and Nutritional Determinants (BLEND) study, provided sufficient information on fat intake for a total of 2,731 BC cases and 544,452 non-cases, which yielded 5,400,168 person-years of follow-up. Hazard ratios (HRs), with corresponding 95% confidence intervals (CIs), were estimated using Cox-regression models stratified on cohort. Analysis were adjusted for total energy intake in kilocalories, gender, smoking status (model-1) and additionally for sugar and sugar products, beers, wine, dressing, and plant-based and fruits intakes (model-2).

Results: Among women, an inverse significant association was observed between mono-unsaturated fatty acids (MUFAs) and BC risk (HR comparing the highest with the lowest tertile: 0.73, 95% CI: 0.58, 0.93, p-trend=0.01). Overall, this preventative effect of MUFAs on BC risk was only observed for the non-muscle invasive bladder cancer (NMIBC) (HR: 0.69, 95% CI: 0.53, 0.91, p-trend=0.004). Among men, a high intake of total cholesterol showed to be significantly associated with an increased BC risk for men (HR: 1.37, 95% CI: 1.16, 1.61, p-trend=0.01). Regarding fat sources, high consumption of animal fats showed to be associated with an increased BC risk (HR: 3.76, 95% CI: 3.43, 4.12; p-trend=0.001), while an inverse association was observed between BC risk and high intake of both plant-based fats and oils and sunflower oil (HR: 0.94, 95% CI: 0.82, 0.99; p-trend=0.09 and HR: 0.72, 95% CI: 0.58, 0.90; p-trend=0.004, respectively). No other significant associations were observed.

Conclusion: This large prospective study added new insights into the role of fat and oils in BC carcinogenesis, showing an inverse association between consumption of MUFAs and the development of NMIBC in women and a direct association between high intakes of dietary cholesterol and BC risk in men.

Key words: Bladder cancer; Diet; Fat; Oil; Risk factor; Epidemiology

Introduction

According to the GLOBOCAN cancer statistics in 2020, bladder cancer is the 10th most commonly diagnosed cancer worldwide, with approximately 573,000 new cases and 213,000 deaths [1]. Approximately 75% of BC cases are non-muscle invasive bladder cancer (NMIBC) characterized by frequent recurrences, which requires intensive treatments and follow-up measures, posing a large burden on the national health care budgets and patient's quality of life [2].

Several epidemiological studies have identified factors that potentially influence BC risk. These factors include gender, smoking, age, and occupation [2-4]. In addition, evidence suggests that factors related to lifestyle, physical activity and diet, might also affect the risk of BC [5, 6]. Previous research on diet and BC reported that higher intakes of fluid, fruit, vegetables and yogurt are associated with a reduced risk of BC [7].

In addition, several dietary patterns have been associated with BC risk [8-10], including a Western diet, which was shown to be associated with a higher BC risk [11], and the Mediterranean diet, which was shown to be inversely associated with BC risk [12]. One of the major differences between the Western and the Mediterranean diet is the source of dietary fat [13]. Accordingly, while the Mediterranean dietary fat intake mainly derives from plants such as olives (high in monounsaturated fats), the dietary fat intake from the Western diet mainly derives from animal products (high in saturated fats) [14]. This important difference may suggest that the sources of dietary fat might have different effects on BC risk. Previous in vitro [15] and animal [16] studies confirmed this hypothesis by showing that the effect of dietary fat intake on BC may range from anti-carcinogenic to carcinogenic, depending on the type of fat/fatty acids involved.

Epidemiological evidence on the relation between dietary fat and BC and the various effects of different dietary fat sources, however, is scarce and inconclusive. While a Spanish case-control study found that the observed increased BC risk with high intake of monounsaturated fatty acids (MUFAs) disappeared following adjustment for saturated fat [17], a Japanese case–control study reported an inverse association between both saturated and monounsaturated fat intakes and BC risk [18]. In addition, an observational study from Serbia highlighted the importance of the fat sources when establishing the effect of dietary fat intake on BC [19]. The authors reported an inverse association of sunflower oil and BC risk, while a positive association was observed for animal fat intake.

Due to this current lack of knowledge and contradictory evidence, the present study aims to investigate the association between dietary fat intake from major sources and BC risk by pooling data from 11 prospective cohort studies.

Methods

Study sample

The study was conducted within the Bladder Cancer Epidemiology and Nutritional Determinants (BLEND) consortium [20]. BLEND is one of the largest international nutritional consortium, which includes 16 prospective cohort studies from 13 countries. For the present study, 11 cohort studies originated from 11 different countries [i.e. Europe: European Prospective Investigation into Cancer and Nutrition cohort studies (EPIC) [21] (Denmark [22], France [23], Germany [24], Italy [25], The Netherlands [26], Norway [27], Spain [28], Sweden [29, 30], United Kingdom [31, 32]), Netherlands cohort study (NLCS) [33]; and North America: VITamins and Lifestyle cohort study (VITAL) [34]], with sufficient information on fat and oils consumption were eligible for inclusion in the present study.

Data collection and coding

Details of the BLEND consortium protocol and methodology have been provided elsewhere [20]. All included studies used a self-administered or interview administered food frequency questionnaire (FFQ) that was validated on either food groups [34-38], and/or energy intake [35, 38, 39]. The collected dietary fat intake was harmonized and categorized by using the hierarchal Eurocode 2 food coding system developed by the European Union [40]. National specific standard portions sizes for each food item were used to calculate intake in gr/day. As a result of data availability, groups of fat and oils intakes were calculated in grams per day per 1000 kcal (g/1000 kcal/day, nutrient density method) to account for total energy intake and reduce extraneous variation in dietary intakes [41, 42]. All fat and oils intakes were energy-adjusted using the nutrient density method (in g/1000 kcal/day) and were categorized into tertiles for individual fat types [42]. Dietary fats were classified as total lipids, total fatty acids, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), and cholesterol. Also, dietary fat sources included: total fats and oils, plant-based fats and oils, animal fat, cream, butter, margarine, corn oil, soya bean oil, rapeseed oil, grape seed oil, peanut oil, sunflower oil, and olive oil in g/1000 kcal/day.

Person-years of follow-up for each participant was calculated from date of study enrolment until the date of BC diagnosis, or date of ending follow up (e.g., date of death, lost to follow-up, or study exit), whichever came first.

Each study ascertained incident bladder cancer, defined to include all urinary bladder neoplasms according to the International Classification of Diseases for Oncology (ICD-O-3 code C67) using population-based cancer registries, health insurance records, or medical records [43]. In addition, to the information on dietary intake, the BLEND dataset also includes data on study characteristics (e.g., design, method of dietary assessment, recall period of dietary intake), geographical region, demographic infor-

mation (age, gender and ethnicity), pathology of BC (disease category) (non-muscle-invasive [NMIBC] and muscle-invasive bladder cancer [MIBC]), and smoking (current/former/never) and its quantity (packs/year), which were measured at the baseline.

Statistical analyses

Baseline characteristics of the study participants, types of fat and oils and their dietary sources, and other potential confounders were compared between case and non-case groups using analysis of variance or independent samples t-test for continuous variables, or chi-square or ANCOVA for categorical variables.

To assess the influence of the different sources of dietary fat and BC risk, Cox proportional hazard regression was used to obtain hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Based on the adjusted model 2, the p for heterogeneity was calculated using the Wald test. The proportional hazards assumptions were examined graphically [44] and no violation was observed.

Dietary fat intake was divided into 3 groups based on a tertile ordered distribution: low intake (tertile 1), medium intake (tertile 2) and high intake (tertile 3). The intake of some plant-based fat sources was not variable enough to be categorized into tertiles (i.e., corn oil, soya bean oil, rapeseed oil, grapeseed oil, peanut oil, and sunflower oil). For these sources we used the median intake as a cut-off to categorize the participants into low and high intake groups.

In the Cox regression model age was used as a time scale, thereby correcting for age in the analysis. Also, the effect of each study was analyzed as a random effect. The Cox regression models were fitted as crude, and adjusted models (adjusted for total energy intake in kilocalories (continuous), gender (women, men), smoking status (never, former or current smoker) (model 1), and additionally for: sugar and sugar products (continuous), beers (continuous), wine (continuous), dressing (continuous), and plant-based and fruits intakes (continuous) (model-2)). The analyses were stratified on gender and disease category (NMIBC and MIBC). To understand the relevance of interaction, the main interaction terms between fat and oils consumption and gender and smoking were added to the model 1. P-values for trend were estimated by assigning medians to each category of consumption as a continuous variable.

Finally, in order to determine the study effect, sensitivity analysis was performed by removing each individual study from the main model. All statistical analyses were performed using Stata/SE version 14.2 [45]. P-values less than 0.05 were considered as statistically significant.

Table 5.1. Baseline characteristics and fat sources among non-cases and bladder cancer cases in the BLEND international study

Categories of data	Cases n=2,731	Non-cases n=544,452	P-value
Baseline age year (mean (SD))	60.36 (7.81)	51.16 (10.56)	<0.001 ǂ
Person-year	Total: 20,784.46 Median: 7.32	Total: 5,379,384 Median: 11.32	<0.001 ǂ
Gender, n (%)			<0.001*
Men	2,006 (73.45)	152,620 (28.03)	
Women	725 (26.55)	391,832 (71.97)	
Smoking status, n (%)			<0.001*
Current	1,057 (38.70)	111,967 (20.57)	
Former	1,142 (41.82)	164,637 (30.24)	
Never	532 (19.48)	267,848 (49.20)	
Fat and oil types, g/1000 kcal/day (mean (SD))			
Total lipid	34.41 (12.42)	32.76 (11.33)	<0.001 ǂ
Total Fatty acids	30.98 (1404)	29.47 (13.21)	0.001
Saturated fatty acids	9.78 (4.04)	9.15 (3.87)	<0.001
Mono-unsaturated fatty acids	12.56 (5.77)	12.27 (5.44)	0.04
Poly-unsaturated fatty acids	8.64 (4.22)	8.05 (3.87)	<0.001
Total Cholesterol	128.75 (67.46)	123.42 (69.38)	0.003
Dietary fat sources, g/1000 kcal/day (mean (SD))			
Total fats and oils	22.24 (14.01)	19.40 (12.90)	0.001 ǂ
Plant-based fats and oils	5.72 (10.90)	5.53 (5.50)	0.416
Animal fat	0.22 (0.93)	0.16 (0.68)	0.003
Cream	2.44 (5.39)	2.29 (4.70)	0.230
Butter	5.41 (11.27)	3.94 (8.26)	0.001
Margarine	12.67 (14.89)	9.65 (12.60)	0.001
Corn oil	0.15 (0.89)	0.15 (1.38)	0.897
Soya bean oil	0.18 (1.14)	0.18 (1.07)	0.938
Rapeseed oil	0.04 (0.49)	0.02 (0.28)	0.001
Grape seed oil	0.04 (0. 54)	0.02 (0.39)	0.084
Peanut oil	0.05 (0.57)	0.17 (1.09)	0.001
Sunflower oil	0.62 (3.95)	0.71 (3.25)	0.291
Olive oil	4.49 (9.74)	4.18 (9.21)	0.203
Potential confounders			
Energy intake, kcal/day (mean (SD)	2,161.03 (673.04)	2,061.10 (633.82)	0.001 ǂ
Fruits, g/1000 kcal/day (mean (SD))	115.47 (105.42)	115.55 (104.19)	0.482
Vegetables, g/1000 kcal/day (mean (SD))	203.70 (140.18)	182.97 (124.82)	<0.001
Red & processed meat, g/1000 kcal/day (mean (SD))	37.23 (36.12)	35.67 (34.83)	<0.001
Eggs, g/1000 kcal/day (mean (SD))	17.36 (15.21)	16.50 (15.68)	0.004
Sugar and sugar products, g/1000 kcal/day (mean (SD))	17.54 (22.37)	17.91 (44.41)	0.668
Beer, ml/day (mean (SD))	4.08 (9.53)	2.55 (7.32)	<0.001
Wine, ml/day (mean (SD))	6.01 (13.50)	6.28 (12.03)	0.235
Dressing, g/1000 kcal/day (mean (SD))	4.78 (7.33)	6.18 (9.79)	<0.001

Abbreviations: SD: standard deviation, gr: gram, mg: milligram, ml: milliliters, kcal: kilocalorie. ǂ: based on independent sample t-test. *: based on Chi-2 test.

Results

Baseline characteristics

Baseline characteristics of the study population are presented in **Table 5.1**. Altogether, 2,731 (2,006 men and 725 women) cases and 544,452 (152,620 men and 391,832 women) non-cases with a total of 5,400,168 person-years of follow-up (median follow-up=11.4 years) were included in our analysis. Compared to non-cases, BC cases were older at baseline (mean=60.4 years [SD: ±7.8] vs mean=51.2 years [SD: ±10.6])) and were more likely to be male (73% versus 28%). Cases were mainly current- (39%) or former smokers (42%), while non-cases were more likely to be never smokers (50%). The mean intake of all fat types, including total lipid (34.4 vs.32.8 (g/1000 kcal/day)), total fatty acids (30.9 vs. 29.5), SFAs (9.8 vs. 9.1), MUFAs (12.5 vs. 12.3), PUFAs (8.6 vs. 8.0), and total cholesterol (128.7 vs. 123.4) was statistically significantly higher among BC cases compared to non-cases. The intakes of total fats and oils ((g/1000 kcal/day) 22.24 (14.01) vs 19.40 (12.90)), animal fat (0.22 (0.93) vs 0.16 (0.68)), butter (5.41 (11.27) vs 3.94 (8.26)), margarine (12.67 (14.89) vs 9.65 (12.60)) and rapeseed oil (0.04 (0.49) vs 0.02 (0.28)) were significantly higher among BC cases compared to non-cases, while the intake of peanut oil was significantly higher among non-cases (0.17 (1.09) vs 0.05 (0.57)). Additional baseline characteristics are provided in **Supplementary Table S5.1**.

Overall analysis

Fat types and BC risk

The estimated HRs for the association between fat and oil intakes with BC are presented in **Table 5.2**. Overall, we found that higher consumption of MUFAs decreases the BC risk (HRhigh vs low: 0.84, 95% CI: 0.73, 0.96, p-trend=0.01), while higher intake of total cholesterol was associated with an increased BC risk (HRhigh vs low: 1.27, 95% CI: 1.05, 1.37, p-trend=0.01). No other fat types showed to be associated with BC risk.

Fat sources and BC risk

High consumption of animal fats showed to be associated with an increased BC risk (HRhigh vs low: 3.76, 95% CI: 3.43, 4.12; p-trend=0.001), while an inverse association was observed between BC risk and high intake of both plant-based oils and oils and sunflower oil (HRhigh vs low: 0.94, 95% CI: 0.82, 0.99; p-trend=0.09 and HRhigh vs median: 0.72, 95% CI: 0.58, 0.90; p-trend=0.004, respectively). No other fat sources showed to be associated with BC risk (**Tables 5.3** and **5.4**).

Table 5.2. Hazard ratio (HR) and 95% confidence interval (CI) of the association of fat and oils types, and risk of BC based on tertile of fat and oils

Fat and oil types		Tertile 1 HR (95% CI) ◊	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
Total lipid	*Participants (number)*				
	Case/non-case	430/ 139,575	454/ 139,551	541/ 139,464	-
	Pearson-year	1,523,368	1,543,497	1,611,960	-
	Crude	1 (reference)	1.08 (0.96, 1.23)	1.04 (0.91, 1. 91)	0.512
	Model 1 [1]	1 (reference)	1.14 (1.00, 1.30)	0.97 (0.85, 1.11)	0.653
	Model 2 [2]	1 (reference)	1.13 (0.99, 1.29)	0.95 (0.83, 1.09)	0.451
Total Fatty acids	*Participants (number)*				
	Case/non-case	411/ 139,594	414/ 139,591	600/ 139,405	-
	Pearson-year	1,539,499	1,527,401	1,611,925	-
	Crude	1 (reference)	0.96 (0.84, 1.11)	1.16 (1.02, 1.31)	0.015
	Model 1 [1]	1 (reference)	0.97 (0.84, 1.12)	0.94 (0.82, 1.06)	0.342
	Model 2 [2]	1 (reference)	0.96 (0.84, 1.11)	0.90 (0.79, 1.03)	0.161
Saturated fatty acids	*Participants (number)*				
	Case/non-case	376/ 139,629	463/ 139,542	586/ 139,419	-
	Pearson-year	1,523,593	1,565,893	1,589,340	-
	Crude	1 (reference)	1.18 (1.03, 1.35)	1.23 (1.08, 1.41)	0.002
	Model 1 [1]	1 (reference)	1.14 (0.99, 1.31)	1.09 (0.95, 1.25)	0.235
	Model 2 [2]	1 (reference)	1.12 (0.97, 1.28)	1.04 (0.91, 1.20)	0.583
Mono-unsaturated fatty acids	*Participants (number)*				
	Case/non-case	485/ 139,520	448/ 139,557	492/ 139,513	-
	Pearson-year	1,526,609	1,546,260	1,605,956	-
	Crude	1 (reference)	0.91 (0.80, 1.04)	0.82 (0.72, 0.94)	0.004
	Model 1 [1]	1 (reference)	0.96 (0.84, 1.09)	0.83 (0.73, 0.95)	0.008
	Model 2 [2]	1 (reference)	0.98 (0.86, 1.11)	0.84 (0.73, 0.96)	0.013
Poly-unsaturated fatty acids	*Participants (number)*				
	Case/non-case	426/ 139,579	434/ 139,571	565/ 139,440	-
	Pearson-year	1,516,905	1,535,911	1,626,010	-
	Crude	1 (reference)	1.08 (0.94, 1.23)	1.23 (1.08, 1.40)	0.001
	Model 1 [1]	1 (reference)	1.00 (0.88, 1.15)	0.97 (0.85, 1.10)	0.611
	Model 2 [2]	1 (reference)	1.01 (0.88, 1.15)	0.96 (0.84, 1.10)	0.604
Total Cholesterol	*Participants (number)*				
	Case/non-case	409/ 139,596	482/ 139,523	534/ 139,471	-
	Pearson-year	1,582,561	1,545,622	1,550,642	-
	Crude	1 (reference)	1.11 (0.97, 1.26)	1.17 (1.03, 1.33)	0.006
	Model 1 [1]	1 (reference)	1.09 (0.96, 1.25)	1.17 (1.03, 1.34)	0.031
	Model 2 [2]	1 (reference)	1.11 (0.97, 1.26)	1.27 (1.05, 1.37)	0.017

◊ HR = Hazard Ratio, CI = confidence interval.
[1] Adjusted for smoking status, age, gender and total energy intake in kilocalories.
[2] Adjusted for model 1+ sugar and sugar products, beers, wine, dressing, vegetables and fruits.

Table 5.3. Hazard ratio (HR) and 95% confidence interval (CI) of the association of fat and oils intake, and risk of BC based on tertile of fat and oils

Fat and oil source		Tertile 1 HR (95% CI) ◊	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P-trend
Total fats and oils	*Participants (number)*				
	Case/non-case	367/ 139,638	478/ 139,527	580/ 139,425	-
	Pearson-year	1,515,977	1,536,487	1,626,361	-
	Crude	1 (reference)	1.28 (1.12, 1.47)	1.39 (1.12, 1.58)	0.001
	Model 1 [1]	1 (reference)	1.08 (0.93, 1.24)	1.05 (0.92, 1.21)	0.476
	Model 2 [2]	1 (reference)	1.07 (0.93, 1.23)	1.04 (0.91, 1.19)	0.574
Plant-based fats and oils	*Participants (number)*				
	Case/non-case	617/ 139,388	374/ 139,631	434/ 139,571	-
	Pearson-year	1,594,911	1,510,110	1,573,804	-
	Crude	1 (reference)	0.79 (0.69, 0.90)	0.89 (0.78, 1.01)	0.056
	Model 1 [1]	1 (reference)	0.95 (0.83, 1.08)	1.01 (0.97, 1.27)	0.140
	Model 2 [2]	1 (reference)	0.94 (0.82, 1.07)	0.94 (0.82, 0.99)	0.097
Animal fat	*Participants (number)*				
	Case/non-case	1,330/ 395,682	95 / 22,680	208/ 125,853	-
	Pearson-year	4,422,730	253,572.4	2,522.467	-
	Crude	1 (reference)	1.42 (1.15, 1.75)	3.17 (2.93, 3.44)	0.001
	Model 1 [1]	1 (reference)	1.31 (1.06, 1.62)	4.82 (4.18, 5.52)	<0.001
	Model 2 [2]	1 (reference)	1.35 (1.09, 1.67)	3.76 (3.43, 4.12)	0.001
Butter	*Participants (number)*				
	Case/non-case	654/139,351	355/ 139,650	416/ 139,589	
	Pearson-year	1,613,190	1,542,855	1,522,779	-
	Crude	1 (reference)	0.78 (0.68, 0.89)	0.78 (0.69, 0.88)	0.001
	Model 1 [1]	1 (reference)	0.98 (0.86, 1.12)	1.01 (0.89, 1.15)	0.840
	Model 2 [2]	1 (reference)	0.92 (0.81, 1.05)	0.93 (0.82, 1.06)	0.283
Cream	*Participants (number)*				
	Case/non-case	553/139,452	424/ 139,581	448/ 139,557	-
	Pearson-year	1,581,301	1,516,669	1,580,854	-
	Crude	1 (reference)	0.82 (0.72, 0.93)	0.81 (0.71, 0.92)	0.001
	Model 1 [1]	1 (reference)	0.91 (0.79, 1.03)	0.96 (0.82, 1.10)	0.584
	Model 2 [2]	1 (reference)	0.89 (0.80, 1.04)	0.91 (0.80, 1.04)	0.172
Margarine	*Participants (number)*				
	Case/non-case	414/139,591	410/ 139,595	601/ 139,404	-
	Pearson-year	1,545,415	1,521,002	1,612,407	-
	Crude	1 (reference)	0.95 (0.83, 1.10)	1.15 (1.02, 1.31)	0.015
	Model 1 [1]	1 (reference)	0.92 (0.80, 1.06)	0.92 (0.81, 1.05)	0.275
	Model 2 [2]	1 (reference)	0.95 (0.82, 1.09)	0.90 (0.78, 1.03)	0.136
Olive oil	*Participants (number)*				
	Case/non-case	781/139,683	211/ 86,335	433/ 139,572	-
	Pearson-year	2,201,173	932,829	1,544,823	-
	Crude	1 (reference)	0.89 (0.77, 1.04)	1.06 (0.94, 1.20)	0.23
	Model 1 [1]	1 (reference)	1.02 (0.91, 1.14)	0.94 (0.84, 1.06)	0.15
	Model 2 [2]	1 (reference)	1.10 (0.10, 1.24)	1.05 (0.90, 1.22)	0.27

◊ HR = Hazard Ratio, CI = confidence interval.

[1] Adjusted for smoking status, age, gender and total energy intake in kilocalories.

[2] Adjusted for model 1+ sugar and sugar products, beers, wine, dressing, vegetables and fruits.

Table 5.4. Hazard ratio (HR) and 95% confidence interval (CI) of the association of different vegetable oils intake according to median of intakes, and risk of BC

Fat and oil source			Under median	Above median	P-value
Corn oil	*Participants (number)*				
	Case/non-case		1,334/ 400,459	81/ 18,131	-
	Pearson-year		4,462,137	216,687.9	-
		Crude	1 (reference)	1.05 (0.84, 1.31)	0.661
		Model 1 [1]	1 (reference)	1.10 (0.88, 1.39)	0.374
		Model 2 [2]	1 (reference)	1.03 (0.82, 1.29)	0.760
Soya bean oil	*Participants (number)*				
	Case/non-case		1,294/ 362,613	131/ 55,977	-
	Pearson-year		4,057,981	620,844	-
		Crude	1 (reference)	0.85 (0.71, 1.02)	0.089
		Model 1 [1]	1 (reference)	1.02 (0.85, 1.23)	0.784
		Model 2 [2]	1 (reference)	1.05 (0.87, 1.27)	0.574
Rapeseed oil	*Participants (number)*				
	Case/non-case		1,405/ 415,701	20/ 2,889	-
	Pearson-year		4,646,888	31,937.39	-
		Crude	1 (reference)	1.42 (0.91, 2.22)	0.134
		Model 1 [1]	1 (reference)	0.98 (0.61, 1.56)	0.940
		Model 2 [2]	1 (reference)	1.18 (0.76, 1.85)	0.444
Grape seed oil	*Participants (number)*				
	Case/non-case		1,408/ 415,777	19/ 2,813	-
	Pearson-year		4,647,315	31,509.75	-
		Crude	1 (reference)	1.28 (0.79, 2.06)	0.309
		Model 1 [1]	1 (reference)	1.01 (0.94, 1.64)	0.948
		Model 2 [2]	1 (reference)	1.13 (0.70, 1.83)	0.602
Peanut oil	*Participants (number)*				
	Case/non-case		1,403/ 396,221	22/ 22,369	-
	Pearson-year		4,440,423	238,402.4	-
		Crude	1 (reference)	0.30 (0.20, 0.47)	<0.001
		Model 1 [1]	1 (reference)	0.84 (0.52, 1.36)	0.490
		Model 2 [2]	1 (reference)	0.66 (0.43, 1.02)	0.063
Sunflower oil	*Participants (number)*				
	Case/non-case		1,335/ 360,389	90/ 58,201	-
	Pearson-year		4,032,881	645,943.9	-
		Crude	1 (reference)	0.45 (0.36, 0.56)	<0.001
		Model 1 [1]	1 (reference)	0.80 (0.64, 1.01)	0.064
		Model 2 [2]	1 (reference)	0.72 (0.58, 0.90)	0.004

◊ HR = Hazard Ratio, CI = confidence interval.
[1] Adjusted for smoking status, age, gender and total energy intake in kilocalories.
[2] Adjusted for model 1+ sugar and sugar products, beers, wine, dressing, vegetables and fruits.

Stratified analysis

Fat types and BC risk by gender and BC category stratification

Significant heterogeneity between men and women was observed in the associations of MUFAs, and total cholesterol intake with BC (p-het=0.001 and <0.001, respectively). Interestingly, higher intakes of MUFAs significantly decreased the risk of BC for women (HRhigh vs low: 0.73, 95% CI: 0.58, 0.93, p-trend=0.01), but not for men (HRhigh vs low: 0.94, 95% CI: 0.80, 1.11; p-het=0.001). In contrast, higher intakes of total cholesterol significantly increased the risk of BC for men (HRhigh vs low: 1.37, 95% CI: 1.16, 1.61; p-trend=0.001), but not for women (HRhigh vs low: 0.90, 95% CI: 0.71, 1.13, p-het<0.001). No other associations were found in neither men and women (**Supplementary Table S5.2**).

Higher intakes of total lipids significantly decreased the NMIBC risk (HRhigh vs low: 0.73, 95% CI: 0.55, 0.96; p-trend=0.01), but not the MIBC risk (HRhigh vs low: 1.19, 95% CI: 0.65, 1.17, p-het=0.001). Also, higher intakes of MUFAs significantly decreased the NMIBC risk (HRhigh vs low: 0.69, 95% CI: 0.53, 0.91, p-trend=0.004), but not the MIBC risk (HRhigh vs low: 0.86, 95% CI: 0.44, 1.64; p-het=0.002) (**Supplementary Table S5.3**).

Fat sources and BC risk by gender and BC subtypes stratification

Higher intakes of total fat and oils, butter and margarine were found to significantly increase the risk of BC for men (HRhigh vs low; fats and oils: 1.34, 95% CI: 1.17, 1.53; HRhigh vs low; butter: 1.42, 95% CI: 1.27, 1.58; HRhigh vs low; margarine: 1.70, 95% CI: 1.50, 1.92), but not for women. No other sources showed to be associated with BC risk either for men nor women (data are not shown). Stratification by NMIBC and MIBC and fat sources shows relatively similar results to the overall findings.

No single study effect could be observed. After removing each individual study from the main model results remained the same.

Discussion

To our best knowledge, this is the first pooled longitudinal cohort study on the associations between different types and sources of fat and oils and BC risk. Here we found that a high intake of MUFAs was significantly associated with a decreased risk in BC, particularly in women. In contrast, higher intake of cholesterol was associated with an increased BC risk, particularly in men. In addition, we found that higher consumption of animal fat was associated with an increased BC risk, while plant-based fats and oils and sunflower oil decrease BC risk.

During the last decade the role of MUFA, primarily oleic acid (OA) (18:1n-9), has attracted much attention. Especially since the Mediterranean diet, which is rich in olive oil (and

thereby rich in MUFAs), has been traditionally linked to a protective effect on cancer [46], however, epidemiological evidence on the effect of MUFAs on BC risk, however, is scarce and inconclusive [47-50]. The present study shows that high intake of MUFAs is associated with an overall decreased BC risk. When stratifying for BC subtype, results show that this association, only remained significant for the NMIBC subtype. However, the low statistical power, especially among the MIBC subtype (n=715), might have hampered the statistical power to find a significant result. These findings are in agreement with a recent meta-analysis of observational studies and a Japanese case–control study, also suggesting an inverse association between high intake of MUFAs and BC risk [18, 51]. In contrast, two previously conducted cohort studies on MUFAs intake and BC risk reported a null association [50, 52]. Moreover, a Spanish multi-center case-control study found a slightly increased BC risk for high MUFA intake [17]. Interestingly, however, this initially found positive association disappeared after adjustment for saturated fat intake. A possible explanation for these controversial findings might be the source of the MUFAs. Monounsaturated fat can be obtained from either olive oil [46] or from animal sources, e.g. beef [53], which showed to have an opposite effect on BC risk [54].

In this study we observed an inverse association between plant-based fats and oils intakes and BC risk. This is in line with findings of the New Hampshire case-control study, also suggesting a decreased BC risk with high vegetable oil intake [50]. In addition, Brinkman et.al., reported a clear reduced BC risk for high intakes of α-linolenic acid and vegetable fat. Furthermore, the same study showed a reduced BC risk was observed for polyunsaturated fat and linoleic acid [50]. The protective effects of plant-based oils, could be explained by its provision of various amounts of MUFAs, PUFAs and energy, which are potential antioxidants and chemo preventive factors that might affect the initiation, promotion and progression of cancers through several potential biologic mechanisms, including reduced cellular oxidative stress and probably decreased DNA damage [55, 56].

In the last two decades, there have been puzzling results regarding the possible role of dietary olive oil in cancer prevention and treatment [57]. Oleic acid, which is a MUFA that is highly available in olive oil, canola oil, sunflower oil, soybeans oil, rapeseed oil and peanuts oil has been traditionally linked to a protective effect on cancer [46]. It is, therefore, surprising that the present study shows no effect of olive oil (MUFA: 73% vs. PUFAs: 11%) and nor rapeseed oils (MUFA: 62% vs. PUFAs: 32%) intakes on BC risk. This null-effect however has been observed in a previous study in which oils rich in MUFAs, derived from the seeds of soybean or grapeseed oil, did not exert health benefits and may not be associated with BC risk [58]. This may be extrapolated to olive oils. Our results further indicate that the protective effect of MUFA on BC risk is explained by dietary intake of multiple sources.

Interestingly, stratification for gender showed that a high intake of MUFAs may significantly decrease the risk of BC for women but not for men. Wakai et al. also reported gender discrepancy in the association of MUFAs intake and BC risk [18]. This discrepancy might be related to overall gender differences in reporting diet [59, 60], and genetics, causing a different effect of similar environmental exposures to the bladder carcinogenesis [61, 62]. Furthermore, the sex hormone profile in itself (especially androgens) might play a role in the development and progression of BC [63]. It should be taken into account, however, that the present study contains a limited number of female cases (n=642), which could have led to a power issue, thereby enabling the detection of small size effects. However, it cannot be ruled out that residual confounding by other factors might explain the gender difference. Therefore, future research is needed to clarify this gender difference in the role of MUFA's on BC risk.

To our knowledge, this is the first epidemiological study reporting the association between MUFAs and BC subtypes, showing that the NMIBC risk was significantly reduced with increased MUFA intake, while a null-association was observed for the MIBC subtype. Surprisingly, results showed that a higher intake of total lipid may significantly decrease the NMIBC risk but not the MIBC risk. Mechanisms underlying the different associations between MUFAs and total lipid with NMIBC and MIBC risk are not yet clear. However, a limited number of MIBC cases (n=715) could have influenced the discrepant findings for the two disease categories. Future research on the influence of MUFAs on the different BC subtypes is therefore warranted. Total lipid intake was shown to significantly decrease the NMIBC risk but not the MIBC risk. However, as mentioned before, the low power in the MIBC group might have prohibited to detect small effects. In this study it was shown that the total lipid intake was mainly derived from MUFA. Since MUFAs are suggested to have a protective role against BC, the association found between total lipid intakes and NMIBC might be related to higher intakes of MUFAs.

ω-3 PUFAs have been reported as one potential modifiable protective factor against cancers [64]. Although not fully understood, it is suggested that n-3 PUFAs may possibly inhibit carcinogenesis through its anti-inflammatory activity [52, 65]. Epidemiological studies on the intake of PUFAs and BC risk, however, showed inconsistent results. While some studies showed a null association between PUFA intake and BC risk [66, 67], others reported an inverse association [68]. In the present study a null association was observed. For fat and oil sources, which contain more PUFAs than MUFAs, a similar non-effect was shown for soybean (MUFA: 24% vs. PUFAs: 61%), and corn oil (MUFA: 24% vs. UFA: 59%) and BC risk. However, when assessing sunflower oil (MUFA: 20%, vs. PUFAs: 69%) independently, an inverse association with BC risk was observed. The controversial results obtained in different studies might again be due to the different sources (i.e. animal and different plants) from which the PUFAs derive [69]. Besides, also the cooking method of the PUFA sources might explain the variability in the results of the different studies [52].

Limited evidence and contradictory findings are available on the association between a high trans fatty acids (TFAs) intake and BC risk [50, 70, 71]. While several studies reported a direct association between higher TFAs intakes and BC risk [70, 71], others reported no significant association [50, 72]. The present study also showed no evidence for an association between TFAs and BC risk, nor for high intake of saturated fatty acids (SFAs), and PUFAs.

In recent years, cholesterol has received increasing attention due its role in carcinogenesis [73, 74]. Clinical and experimental evidence suggest that an increased cholesterol level in blood is associated with a higher cancer risk and that cholesterol-lowering drugs (e.g., statins) exhibit beneficial effects on bladder cancer development [75, 76]. So far, some mechanisms have been suggested to explain the possible role of cholesterol in the development of cancer, including; a) changes in lipid and apolipoprotein levels that may result in cellular inflammation, by increasing the levels of pro-inflammatory cytokines, including tumor necrosis factor-α and interleukin-6 [77] and b) the deregulation of cholesterol homeostasis through the disruption of the cholesterol pathway and the induction of elevated mitochondrial cholesterol levels leading to resistance to apoptotic signals [75]. In the present study we found that cholesterol was associated with an increased BC risk among men but not among women. The null-association observed among women is in line with results from a Belgian case–control study and the New Hampshire case–control, showing an overall null-association between cholesterol intake and BC risk [50, 52]. Since, evidence on the gender specific relations between cholesterol and BC risk are scarce, it remains unclear why in the present study a discrepancy between men and women was observed. However, the involvement of certain steroids, such as estrogen, in reducing the adverse effects of cholesterol, might explain the observed difference. Estrogen is proposed to protect against chronic diseases (i.e., breast cancer and cardiovascular diseases or atherosclerosis) via its role in reverse cholesterol transport [78]. Furthermore, increased use of statins among men compared to women need to be taken into account in future research on the gender specific relation between cholesterol and BC.

It is suggested that animal fat increases oxidative stress and levels of reactive oxygen species (ROS) that interfere with cellular processes. Healthy cells are attacked by free radicals, which cause peroxidation and eventually DNA damage. Thereby, ROS can lead to tumor initiation and progression of cancer cells [79]. The present study strengthens this hypothesis by showing an increased BC risk associated with an animal fat intake, which is in line with a previously conducted case-control study [19]. However, Brinkman et al. showed a null association between intakes of animal fat and BC risk [50]. Again, this observed difference between the different studies might be due to the different type, composition, and cooking method of the consumed animal fats included in the analysis. No association was observed for higher intakes of total fats and oils and BC risk. Contrary to our finding, a meta-analysis revealed that the total dietary fat intake

increases the BC risk [80]. However, this could only be observed among the European populations, while no association was reported for the North American populations [80].

Strengths and limitations

In our knowledge, BLEND is one of the largest pooled cohort studies investigating the associations between the intake of different sources of fat and oils and risk of developing BC, thereby allowing to performed detailed analysis to find small effect sizes. Nevertheless, the present study has some limitations; a) some of the dietary information was only available in portions per week. Though this data was converted to grams per day using the United States Department of Agriculture (USDA) food composition database, the conversions were not country specific. Previous studies, however, suggested that the application of a common food composition database has advantages over the use of country specific food composition databases in that errors are consistent between the countries, hence making data more comparable [81, 82]; b) unfortunately, data potential known BC risk factors, such as BMI, physical inactivity, socioeconomic status, and occupational exposures to carcinogenic chemicals was missing. Moreover, it might be possibility that some lifestyle and/or environmental factor are associated with an individual's diet. Generally, people with a healthier diet have an overall healthier lifestyle. However, the current literature suggests only a small proportion of BC cases can be attributed to lifestyle and environmental factors [4, 83, 84; c) although people are less likely to change their dietary habits at an older age, most of the included studies only measured their participants at baseline and we were, therefore, unable to take possible changes of dietary habits over time into account. This could have led to misclassification of long-term exposure; d) the effect of fat and oil on bladder carcinogenesis might be induced by compounds related to the cooking and processing of fat and oils. However, in the present study no information on fat and oils preparation or cooking methods was available, thereby lacking the ability to adjust or stratify on these factors; e) for most cohorts the exposure and outcome variable was assessed by FFQs, therefore, measurement error and misclassification of study participants in terms of the exposure and outcome are unavoidable. Likewise, information bias, as a consequence of self-reported information on food consumption, might have occurred. However, the strength and direction of this type of bias is not expected to be significantly different between cases and non-cases, and therefore the impact of information bias is expected to be minimal; f) although we found similar results after adjusting for potential dietary risk factors, it is still possible that the observed associations were confounded by other dietary constituents or additives associated with fat intake; g) the present study sample consists mostly of Caucasians, and this may limit the generalizability of our results to other racial/ethnic populations or geographic regions; h) although status as well as duration and intensity of smoking were taken into account in our analysis, the adjustment for smoking might still be imperfect due

to differences in smoking practices (e.g., depth of inhalation or amount of inhalation), differences in types of smoke exposure, or lack of information on passive smoking [85]; i) some tumor subtype information was missing, which hampered the statistical power required for stratified subgroup analyses.

Conclusions

In conclusion, this large prospective study adds new insights into the role of fat and oils in BC development. Results revealed that higher dietary cholesterol and animal fat intake might increase the BC risk in men, while higher intake of MUFAs and plant-based oils decrease the BC risk in women. These findings suggest that BC prevention strategies should include a nutritional scheme that controls for the quality of fat consumed. However, further experimental, prospective and interventional studies are needed to clarify the exact effects and mechanisms of fat and oils in the etiology of BC.

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Supplementary Materials to Chapter 5

Supplementary Table 5.1. Additional baseline characteristic for included studies in BLEND study

Characteristics	NLCS [1]	VITAL [2]	EPIC-Denmark [3]	EPIC-France [4]	EPIC-Germany [5]	EPIC-Italy [6]
	N=5,238	N=66,518	N=55,670	N=64,204	N=48,754	N=44,663
Initiate year of baseline assessment	1986	2000	1993	1990	1994	1992
Length of follow up (years)	14	7	11	10	10	11
Subjects (number)						
Case/	876	337	386	31	205	186
Non-case	4,362	66,181	55,284	64,173	48,549	44,477
Person-year	73,688.8	448,995.4	608,813	667,809.9	482,453.3	502,020.3
Baseline age (years) (mean ±SD)						
Case	62.73 (4.09)	66.16 (7.01)	58.50 (4.37)	58.04 (6.00)	56.41 (7.13)	55.24 (6.75)
Non-case	61.85 (4.21)	61.18 (7.37)	56.67 (4.37)	52.74 (6.63)	50.55 (8.56)	50.50 (7.92)
Gender n (%)						
Men	2,867 (54.73)	33,394 (50.20)	26,532 (47.66)	0 (0.00)	21,168 (43.42)	13,774 (30.84)
Women	2,371 (45.27)	33,124 (49.80)	29,138 (52.34)	64,204 (100.00)	27,586 (56.58)	30,889 (69.16)

Characteristics	EPIC-Spain	EPIC-Sweden	EPIC-the Netherlands [7]	EPIC- the UK	EPIC-Norway
	N=40,389	N=48,625	N=36,801	N=74,379	N=33,304
Initiate year of baseline assessment	1992	1991	1993	1993	1991
Length of follow up (years)	12	13	12	11	10
Subjects (number)					
Case/	149	301	107	247	23
Non-case	40,240	48,324	36,694	74,132	33,281
Person-year	487,491.1	638,482.8	434,974.5	828,991.7	6,437,305.7
Baseline age (years) (mean ±SD)					
Case	54.49 (7.19)	60.27 (7.07)	56.20 (8.03)	63.62 (9.98)	49.30 (4.38)
Non-case	49.19 (8.03)	51.93 (10.89)	48.94 (11.93)	49.05 (14.34)	48.07 (4.30)
Gender n (%)					
Men	15,259 (37.78)	22,214 (45.68)	9,629 (26.17)	22,260 (29.93)	0 (0.00)
Women	25,130 (62.22)	26,411 (54.32)	27,172 (73.83)	52,119 (70.07)	33,304 (100.00)

Abbreviations:
EPIC: European Prospective Investigation into Cancer
NLCS: The Netherlands Cohort Study
VITAL: VITamins and Lifestyle study.

Supplementary Table S5.2. Hazard ratio (HR) and 95% confidence interval (CI) of the association of oil and fat types, and risk of BC based on tertiles of intakes for stratification of gender

	Tertile 1	Tertile 2	Tertile 3	
	HR (95% CI) *	HR (95% CI)	HR (95% CI)	P-trend
Women				
Total lipid				
Case/non-case	144/ 102,374	159/ 103,923	154/ 97,467	
Pearson-year	1,111,433	1,140,187	1,105,761	
Crude	1 (reference)	1.10 (0.88, 1.38)	0.98 (0.78, 1.24)	0.911
Model 1 [1]	1 (reference)	1.11 (0.89, 1.40)	0.98 (0.77, 1.23)	0.863
Model 2 [2]	1 (reference)	1.13 (0.90, 1.42)	0.97 (0.77, 1.23)	0.833
Total Fatty acids				
Case/non-case	133/ 105,134	154/ 106,809	170/ 91,821	
Pearson-year	1,147,538	1,164,204	1,045,638	
Crude	1 (reference)	1.10 (0.87, 1.39)	1.23 (0.87, 1.39)	0.069
Model 1 [1]	1 (reference)	1.04 (0.82, 1.31)	1.06 (0.84, 1.34)	0.589
Model 2 [2]	1 (reference)	1.03 (0.81, 1.31)	0.97 (0.76, 1.24)	0.819
Saturated fatty acids				
Case/non-case	143/ 106,587	126/ 101,948	188/ 95,229	
Pearson-year	1,154,378	1,134,166	1,068,837	
Crude	1 (reference)	0.88 (0.69, 1.12)	1.21 (0.97, 1.51)	0.067
Model 1 [1]	1 (reference)	0.89 (0.70, 1.13)	1.22 (0.98, 1.52)	0.060
Model 2 [2]	1 (reference)	0.87 (0.68, 1.11)	1.13 (0.90, 1.42)	0.221
Mono-unsaturated fatty acids				
Case/non-case	166/ 98,563	147/ 102,840	144/ 102,361	
Pearson-year	1,073,998	1,130,764	1,152,618	
Crude	1 (reference)	0.84 (0.67, 1.05)	0.71 (0.56, 0.89)	0.003
Model 1 [1]	1 (reference)	0.80 (0.64, 1.00)	0.68 (0.54, 0.85)	0.001
Model 2 [2]	1 (reference)	0.86 (0.69, 1.08)	0.73 (0.58, 0.93)	0.010
Poly-unsaturated fatty acids				
Case/non-case	166/ 108,103	132/ 104,099	159/ 91,562	
Pearson-year	1,169,728	1,134,201	1,053,452	
Crude	1 (reference)	0.88 (0.70, 1.10)	1.12 (0.89, 1.40)	0.341
Model 1 [1]	1 (reference)	0.85 (0.67, 1.07)	1.03 (0.82, 1.29)	0.820
Model 2 [2]	1 (reference)	0.86 (0.68, 1.08)	1.02 (0.81, 1.29)	0.851
Total Cholesterol				
Case/non-case	152/ 98,433	156/ 101,110	149/ 104,221	
Pearson-year	1,100,883	1,110,559	1,145,938	
Crude	1 (reference)	0.94 (0.75, 1.17)	0.84 (0.67, 1.06)	0.150
Model 1 [1]	1 (reference)	0.94 (0.75, 1.18)	0.86 (0.68, 1.08)	0.196
Model 2 [2]	1 (reference)	0.96 (0.71, 1.13)	0.90 (0.71, 1.13)	0.376

Supplementary Table S5.2 continues on next page.

Supplementary Table S5.2. *Continued*

	Tertile 1	Tertile 2	Tertile 3	
	HR (95% CI) *	HR (95% CI)	HR (95% CI)	P-trend
Men				
Total lipid				
Case/non-case	286/ 37,201	295/ 35,628	387/ 41,997	
Pearson-year	411,935.7	403,310.4	506,198.4	
Crude	1 (reference)	1.12 (0.95, 1.33)	0.93 (0.80, 1.09)	0.347
Model 1 [1]	1 (reference)	1.15 (0.98, 1.36)	0.98 (0.83, 1.14)	0.703
Model 2 [2]	1 (reference)	1.15 (0.97, 1.36)	0.98 (0.83, 1.15)	0.773
Total Fatty acids				
Case/non-case	278/ 34,460	260/ 32,782	430/ 47,584	
Pearson-year	391,961.2	363,196.5	566,286.7	
Crude	1 (reference)	0.93 (0.78, 1.10)	0.86 (0.73, 1.00)	0.053
Model 1 [1]	1 (reference)	0.93 (0.79, 1.11)	0.88 (0.76, 1.03)	0.130
Model 2 [2]	1 (reference)	0.96 (0.81, 1.15)	0.90 (0.76, 1.07)	0.256
Saturated fatty acids				
Case/non-case	233/ 33,042	337/ 37,594	398/ 44,190	
Pearson-year	369,214.8	431,727.2	520,502.5	
Crude	1 (reference)	1.26 (1.07, 1.49)	1.00 (0.85, 1.19)	0.739
Model 1 [1]	1 (reference)	1.29 (1.09, 1.52)	1.05 (0.89, 1.24)	0.846
Model 2 [2]	1 (reference)	1.28 (1.08, 1.51)	1.04 (0.88, 1.24)	0.867
Mono-unsaturated fatty acids				
Case/non-case	319/ 40,957	301/ 36,717	348/ 37,152	
Pearson-year	452,611.2	415,495.3	453,337.9	
Crude	1 (reference)	1.04 (0.89, 1.22)	0.91 (0.78, 1.06)	0.243
Model 1 [1]	1 (reference)	1.05 (0.89, 1.23)	0.93 (0.79, 1.10)	0.413
Model 2 [2]	1 (reference)	1.06 (0.91, 1.25)	0.94 (0.80, 1.11)	0.535
Poly-unsaturated fatty acids				
Case/non-case	260/ 31,476	302/ 35,472	406/ 47,878	
Pearson-year	347,176.5	401,709.9	572,558	
Crude	1 (reference)	1.09 (0.92, 1.29)	0.91 (0.78, 1.07)	0.208
Model 1 [1]	1 (reference)	1.10 (0.93, 1.30)	0.95 (0.81, 1.12)	0.488
Model 2 [2]	1 (reference)	1.09 (0.93, 1.29)	0.96 (0.82, 1.13)	0.592
Total Cholesterol				
Case/non-case	257/ 41,163	326/ 38,413	385/ 35,250	
Pearson-year	481678.3	435,062.5	404,703.6	
Crude	1 (reference)	1.25 (1.06, 1.47)	1.46 (1.25, 1.71)	<0.001
Model 1 [1]	1 (reference)	1.18 (1.01, 1.40)	1.36 (1.16, 1.60)	0.001
Model 2 [2]	1 (reference)	1.19 (1.01, 1.41)	1.37 (1.16, 1.61)	0.001

◊ HR = Hazard Ratio, CI = confidence interval.

[1] Adjusted for smoking status, age, and total energy intake in kilocalories.

[2] Adjusted for model 1+ sugar and sugar products, beers, wine, dressing, vegetables and fruits.

Supplementary Table S5.3. Hazard ration (HR) and 95% confidence interval (CI) of the association of oil and fat types, and risk of BC based on tertiles of intakes for stratification of bladder cancer subtype

	Tertile 1	Tertile 2	Tertile 3	
	HR (95% CI) *	HR (95% CI)	HR (95% CI)	P-trend
NMIBC				
Total lipid				
Pearson-year	1,148.70	1,209.08	654.63	
Crude	1 (reference)	0.90 (0.72, 1.12)	0.96 (0.73, 1.25)	0.652
Model 1 [1]	1 (reference)	0.76 (0.60, 0.95)	0.75 (0.57, 0.98)	0.020
Model 2 [2]	1 (reference)	0.74 (0.60, 0.94)	0.73 (0.55, 0.96)	0.014
Total Fatty acids				
Pearson-year	1,237.80	1,066.81	707.81	
Crude	1 (reference)	0.96 (0.77, 1.21)	0.97 (0.75, 1.25)	0.807
Model 1 [1]	1 (reference)	1.14 (0.89, 1.44)	1.11 (0.89, 1.44)	0.379
Model 2 [2]	1 (reference)	1.10 (0.85, 1.40)	1.01 (0.77, 1.32)	0.864
Saturated fatty acids				
Pearson-year	946.77	1,168.43	897.22	
Crude	1 (reference)	1.00 (0.79, 1.27)	1.04 (0.81, 1.33)	0.745
Model 1 [1]	1 (reference)	0.83 (0.65, 1.05)	0.87 (0.67, 1.12)	0.290
Model 2 [2]	1 (reference)	0.84 (0.65, 1.07)	0.88 (0.68, 1.15)	0.408
Mono-unsaturated fatty acids				
Pearson-year	1,290.45	1,045.06	676.91	
Crude	1 (reference)	0.87 (0.70, 1.09)	0.88 (0.68, 1.14)	0.273
Model 1 [1]	1 (reference)	0.71 (0.57, 0.90)	0.68 (0.52, 0.89)	0.002
Model 2 [2]	1 (reference)	0.74 (0.59, 0.94)	0.69 (0.53, 0.91)	0.004
Poly-unsaturated fatty acids				
Pearson-year	1,188.09	1,328.95	495.38	
Crude	1 (reference)	1.02 (0.82, 1.27)	1.04 (0.78, 1.38)	0.745
Model 1 [1]	1 (reference)	0.85 (0.68, 1.06)	0.89 (0.67, 1.19)	0.304
Model 2 [2]	1 (reference)	0.86 (0.69, 1.08)	0.85 (0.63, 1.15)	0.211
Total Cholesterol				
Pearson-year	776.76	1,027.05	1,208.617	
Crude	1 (reference)	1.24 (0.96, 1.61)	1.12 (0.87, 1.44)	0.447
Model 1 [1]	1 (reference)	1.28 (0.98, 1.66)	0.90 (0.70, 1.16)	0.251
Model 2 [2]	1 (reference)	1.29 (0.99, 1.69)	1.01 (0.77, 1.31)	0.825

Supplementary Table S5.3 continues on next page.

Supplementary Table S5.3. *Continued*

	Tertile 1	Tertile 2	Tertile 3	
	HR (95% CI) *	HR (95% CI)	HR (95% CI)	P-trend
MIBC				
Total lipid				
Pearson-year	281.15	366.05	158.14	
Crude	1 (reference)	1.01 (0.66, 1.55)	0.78 (0.45, 1.34)	0.437
Model 1 [1]	1 (reference)	0.99 (0.63, 1.54)	1.14 (0.64, 2.00)	0.701
Model 2 [2]	1 (reference)	1.06 (0.67, 1.68)	1.19 (0.65, 2.17)	0.569
Total Fatty acids				
Pearson-year	230.76	296.60	277.98	
Crude	1 (reference)	0.93 (0.58, 1.47)	0.61 (0.37, 1.00)	0.047
Model 1 [1]	1 (reference)	0.93 (0.58, 1.50)	0.66 (0.40, 1.10)	0.111
Model 2 [2]	1 (reference)	0.87 (0.52, 1.46)	0.58 (0.32, 1.05)	0.065
Saturated fatty acids				
Pearson-year	211.14	393.06	201.14	
Crude	1 (reference)	0.96 (0.60, 1.51)	0.95 (0.57, 1.59)	0.860
Model 1 [1]	1 (reference)	0.95 (0.59, 1.55)	1.23 (0.71, 2.12)	0.464
Model 2 [2]	1 (reference)	0.88 (0.53, 1.45)	1.35 (0.76, 2.38)	0.366
Mono-unsaturated fatty acids				
Pearson-year	306.39	368.55	130.39	
Crude	1 (reference)	0.82 (0.54, 1.25)	0.63 (0.36, 1.11)	0.107
Model 1 [1]	1 (reference)	0.87 (0.70, 1.09)	0.88 (0.68, 1.14)	0.050
Model 2 [2]	1 (reference)	0.75 (0.47, 1.18)	0.86 (0.44, 1.64)	0.436
Poly-unsaturated fatty acids				
Pearson-year	295.86	318.87	190.61	
Crude	1 (reference)	1.10 (0.71, 1.70)	0.90 (0.54, 1.50)	0.795
Model 1 [1]	1 (reference)	1.12 (0.71, 1.76)	1.18 (0.70, 1.98)	0.497
Model 2 [2]	1 (reference)	1.09 (0.69, 1.74)	1.16 (0.67, 1.98)	0.574
Total Cholesterol				
Pearson-year	173.96	354.93	276.44	
Crude	1 (reference)	1.16 (0.69, 1.95)	1.22 (0.72, 2.08)	0.431
Model 1 [1]	1 (reference)	1.33 (0.77, 2.28)	1.19 (0.69, 2.06)	0.611
Model 2 [2]	1 (reference)	1.27 (0.73, 2.21)	1.14 (0.63, 2.07)	0.736

◊ HR = Hazard Ratio, CI = confidence interval.

[1] Adjusted for smoking status, age, gender and total energy intake in kilocalories.

[2] Adjusted for model 1+ sugar and sugar products, beers, wine, dressing, vegetables and fruits.

Chapter 6

Summary and General discussion

The aim of this thesis was to provide detailed evidence on the association between the Western diet and its main components with bladder cancer risk, using data from the Bladder cancer Epidemiology and Nutritional Determinants (*BLEND*) consortium. Using a meta-analysis approach, I first summarized the current body of evidence on the association between the major dietary patterns and bladder cancer (**chapter 2**). Then, in **chapters 3**, **4**, and **5** I explored the possible influence of the Western diet as a whole (chapter 3) and its main components on the development of bladder cancer (chapter 4 and 5). In **chapter 4** I described the association between different meat sources and bladder cancer risk. In **chapter 5** I described the relationship between dietary fat and oil and their sources with bladder cancer risk.

The current chapter (**chapter 6**) gives a summary and a broad review on the main findings of our study. At the end of this chapter, I discussed several methodological concerns, future research directions, and possible implications for bladder cancer prevention.

6.1 Summary of the main findings

6.1.a Meta-analysis of dietary patterns and bladder cancer risk

In **chapter 2**, a meta-analysis was conducted to investigate the current knowledge on the association between the Western diet, the Mediterranean diet, and the dietary-inflammatory-index (DII) with the risk of bladder cancer. Here, I showed that there is a direct and positive association between the Western diet and bladder cancer risk, while the Mediterranean diet seems to have an inverse association with bladder cancer risk. However, no significant association between DII and the risk of bladder cancer was observed. The association between the Western diet (or a proxy of this diet) and bladder cancer risk, however, was reported only from studies with a cohort design, rather than a case-control design (see **chapter 2** for more details). The observed positive association between adherence to the Western diet and bladder cancer in cohort studies alone is in line with our findings which are reported in **chapter 3**. The lack of finding an association in case-control studies might be due to recall bias in case-control studies and/or small sample size of the included case control studies.

6.1.b Western dietary pattern and risk of bladder cancer

Chapter 3 aimed to examine the association between adherence to the Western diet and risk of bladder cancer, by pooling data from 13 cohorts included in the BLEND study. Overall, I reported a significant association between higher adherence to the Western dietary pattern and risk of bladder cancer (HR=1.54, 95% CI: 1.37, 1.72). Stratified analysis, however, showed that this association is significant among men (HR=1.72; 95% CI: 1.51, 1.96), but not women (HR=1.09, 95% CI: 0.86, 1.38).

The results that suggesting a Western diet accelerates tumor onset and its progression (presented in **chapter 3**) are also supported by experimental studies [1]. As a result, nutritional guidelines that recommend the main components of this diet are to be restricted may help in reducing the risk of bladder cancer.

6.1.c Meat and fish consumption and the risk of bladder cancer

Nowadays meat plays an important role in almost all diets around the world. It is, therefore, not surprising that research interests are raised in the health effects of meat intake. However, evidence on the effect of different meat sources on bladder cancer was mainly lacking. Therefore, in **chapter 4**, individual data from 11 prospective cohorts was analyzed to explore this association.

In chapter 4 I demonstrated an overall significant association between high consumption of organ meat and higher bladder cancer risk and a significant inverse association between higher consumption of fish meat with the risk of bladder cancer among men. In addition, a dose–response relationship between organ meat consumption and bladder cancer risk was reported. No association was observed between the intake of poultry and red and processed meat with bladder cancer risk. In line with our findings, the results of a well-known systematic review found no evidence on the association between lower intakes of red and processed meat with a decreased risk of bladder cancer, making a causal inference questionable [2].

6.1.d Different sources of dietary fat and the risk of bladder cancer

In **chapter 5**, using data from 11 cohort studies, the association between dietary fats and oils and bladder cancer risk was examined. As the second aim, I assessed the possible effects of different dietary fat and oils sources and bladder cancer. Overall, I found that higher consumption of Monounsaturated fatty acids (MUFAs) decreases the risk of bladder cancer for about 0.84-times, while higher intake of total cholesterol was significantly associated with a 1.27-fold increase in the risk of bladder cancer. After stratifying by sex, the higher intakes of MUFAs significantly decreased bladder cancer risk among women. In contrast, higher intake of total cholesterol significantly increased the risk of bladder cancer among men only. Stratification by cancer subtype showed that a higher intake of total lipids decreased the NMIBC risk by 0.73-times, but not the MIBC risk. In addition, higher intakes of MUFAs decreased the NMIBC risk by 0.69-times, but again, no significant association was observed for the risk of MIBC. The protective role of MUFAs is confirmed by few other epidemiological studies on the effect of the Mediterranean diet and bladder cancer risk. Since the results on the association of MUFAs and bladder cancer showing that MUFAs decelerate tumor onset and progression are supported by experimental studies [3, 4], nutritional guidelines should stimulate the intake of MUFAs in order to prevent bladder cancer.

Looking at the different fat and oil sources, high consumption of animal fats showed to be associated with an increased bladder cancer risk, while an inverse association was observed between bladder cancer risk and high intake of both plant-based oils and sunflower oil. Again, the results showed a diversity in the associations when stratified by sex as our results suggested that higher intakes of total fat, oils, butter, and margarine significantly increase the risk of bladder cancer for men, but not for women.

6.1.e Gender differences

As suggested in **chapter 3**, **chapter 4**, and **chapter 5**, gender differences were found in the association of adherence to the Western dietary pattern, meat and oil and fat intakes and bladder cancer risk. The observed gender differences might be explained by sex-based genetic heterogeneity, which could result in different effects of comparable hormone exposures on bladder carcinogenesis among different genders [5-8]. For example, it has been established that the male hormone *androgen* promotes bladder carcinogenesis in the progression phase while the female hormone *estrogen* inhibits this process [9]. In animal studies, however, *N*-butyl-*N*-(*4-hydroxybutyl*) nitrosamine [*BBN*] which is a widely used experimental bladder carcinogen, causes higher incidence of bladder cancer in male animals than in their female counterparts, this is because androgen may actually promote the initiation of BBN-induced bladder carcinogenesis [10]. In addition, as mentioned in **chapter 5**, this diversity might also be related to overall gender discrepancies in reporting diet, as it is suggested that women report significantly healthier diet compared to men [5-8]. Although women may report their diet biased toward healthier habits; hence, we might expect differential misclassification in reporting diet between the two genders, evidence suggested that this diversity could mainly be explained by sex-based genetic and hormone heterogeneity [9, 11] and misclassification in reporting diet might has minimal effects on the observed gender difference in the association of diet and bladder cancer in the previous study and our findings [5-8]. However, the exact mechanisms through which a Western diet can affect bladder cancer risk differently in men and women, have yet to be discovered by further studies.

6.2 Methodological considerations

In this thesis I examined the associations between the Western diet and its main components and bladder cancer risk. The nature of several studies included in this thesis (i.e. observational studies) and the quality of data collection used in these studies, might raise some concerns and might influence the implication of the results into practice.

6.2.a Misclassification

6.2.a.a Study design

Generally, to examine the effect of dietary items on health and disease, a variety of study designs can be applied. Conducting a correlation or ecologic studies is considered as the early step in nutritional epidemiological studies investigating the relation between diet/nutrients and disease occurrence. These types of studies are usually cheap and easily conducted, since they make use of data on a population level and do not need data on an individual level. Within these studies the diseases rates are compared between populations with the populations per capita consumption of specific dietary factors and rates of diseases or health conditions. Although these types of studies have been very useful in the rapidly generation of hypotheses about relationship between dietary factors and disease occurrence, they are considered as providing the weakest type of evidence for any sort of causality. In contrast, randomized clinical trials (RCTs) are often considered as the ultimate approach to provide evidence for causality in nutritional epidemiology. However, RCTs have methodological and practical constraints in assessing the influence of food and nutrient on late-life conditions, such as bladder cancer. As a result, the outcomes of RCTs may not be applicable to different doses of a dietary factor, different population, in different periods. Furthermore, late-life dietary interventions, which is required to assure a sufficient number of bladder cancer cases, may not be beneficial, because cumulative exposures throughout time are likely to be relevant, and dietary intake may have the largest influence early in life. Therefore, observational studies (i.e. cohort studies and case-control studies) are mainly used to track food consumption in large groups of people to answer nutritional research questions [12-14]. However, two major issues remain using an observational design to identify causality. First, only a limited range of diet variation can be examined in observational studies, and second, most cohort studies are unable to accumulate a significant number of cases in an adequate length of time. Therefore, the integration of original data from 27 separate cohort studies conducted in over 16 different nations with genetic background throughout the world, as done within the BLEND study, to answer the research questions presented in this thesis, offers a unique opportunity to investigate the associations between dietary intake and risk of developing bladder cancer. This allows the conduction of detailed analyses in order to detect small effects by pooling the results of different studies with relatively high sample size.

6.2.a.b Data collection

i. Exposure variables:

The aim of data collection in nutritional research is to identify the type and quantity of foods consumed. For this, there are several methods available including; diet/food records, diet-history, 24-hour recalls, and measuring food frequency. Diet/food records rely on food diaries, in which participants are asked to carefully describe their daily

food intake over a period of 3–4 days [15, 16]. All other assessment methods rely on the respondent's ability to remember and properly define foods consumption. Diet/food records and 24-hour recalls are the most reliable methods of this type of dietary data collection. However, they are only appropriate for evaluating short-term food consumption, this is because these methods ask for a limited number of habitual food intakes during a limited period of time [17, 18]. However, when examining the impact of diet on chronic diseases, such as bladder cancer, it is important to gather information on food consumption over a longer period of time. Therefore, the most widely used assessment methods (i.e., FFQ) identify the typical (i.e., average) daily intakes of foods and nutrients over a period of several months or a year [19]. However, a drawback of the use of FFQ is that people may find it challenging to remember their exact food intake and average their intakes over a longer period of time. So, FFQs may lead to an inevitably deviation from real intake levels, defined as "measurement error" [20]. Furthermore, the workload of filling out an FFQ often affects the accuracy of the data collection. It is suggested that short FFQs may underestimate food intake, while relatively long FFQs may overestimate the actual food intake [21].

Another challenge in the collection of dietary data is the conversion of the quantity of food items consumed to its actual weight and its nutritional content. This process tends to be time-consuming, laborious, and highly expensive to implement [22]. As a consequence of these limitations in dietary data collection, estimates calculated in observational research may be incorrect and over- or under-estimate the real strength of the associations between dietary exposures and the diseases of interest.

All studies in the BLEND used FFQs to collect dietary data. The diversity in the included regions and the wide variety in the design of the FFQs (i.e. in the number of questions examined and the time required to complete it) and the cohort design of the included studies in this thesis could minimize the impact of biases (i.e., recall bias) related to exposure assessment, interview bias [23], and measurement errors related to the design of the study [24].

In addition, to investigate the association between bladder cancer and the consumption of the food items of interest in **chapter 3-5**, the intake was categorized into tertiles, to compare high vs. medium or low intakes. Here, another issue is that differential misclassification is sometimes assumed to be very minor in prospective studies, in which dietary data is obtained before to the onset of the disease under investigation. Even if measurement error is random and the research is prospective, differential misclassification is likely to occur in reporting dietary intake especially when it is divided into tertiles or quantiles and hence misclassification might occur due to knowing exposure status. However, since the results of all the included studies were separately examined using sensitivity and dose-response analyses, minor differential misclassification is expected in the included studies [17].

ii. Outcome variable:

In this thesis, prospective cohort studies were included in the analysis. In epidemiological studies, however, the use of imperfect diagnostic procedures or laboratory techniques may lead to misclassification or error in measuring the primary outcome. Here, any misclassification or measurement error at baseline or at follow-up may lead to biases including diagnosis or misclassification bias [25]. Regarding misclassification of the outcome, a negligible systematic error in the BLEND studies is expected. This is because, the accuracy in the criteria to diagnose and differentiate the stage of bladder cancer used by the studies were well defined. Although applying the International Classification of Diseases for Oncology (ICD-O-3 code C67), all included studies used population-based cancer registries, health insurance records, or medical records to find new cases of bladder cancer misclassification may still have occurred, especially among small tumors and carcinoma in situ (CIS), this is because the gold standard for bladder cancer diagnosis (i.e., cystoscopy) has a poor sensitivity [26]. Also, misclassification in the sub-types of bladder cancer is another concern. However, we believe that this outcome-related misclassification is minimal due to using ICD-O criteria, prospective design and he large number of cases of the included studies.

6.2.b Confounding

A confounder is a factor associated with both the exposure and outcome being studied, resulting in a change in the interested relationship. As a result, appropriately defining and controlling for confounding effects is critical to assure the validity of the results [27]. Controlling for confounding can be done in either the design phase or in the analytic phase of the study. Since BLEND makes use of previously conducted studies, and thereby no influence could be made on the design, here only controlling techniques for the analytic phase will be discussed.

For observational data in epidemiology several analytic techniques to adjust for confounders are available; including; stratification, standardization, the use of a propensity score and multivariable adjustment [28]. Each of these approaches has its own set of advantages and pitfalls, and none of them is universally superior to the others. The choice of the method used is, therefore, depending on researcher and their data.

Stratification is often referred to as the easiest method of controlling for confounding. Although, stratification is an attractive method because of its simplicity, there are limitations to the number of factors that can be stratified, so that information can be extracted from the analysis. In epidemiological studies, we are expected to build on the current knowledge base and select a large number of potential confounders. Hence, when we attempt to control for confounding in the analysis, we will soon face the limitations of the stratification method regarding the number of potential confounders that are practically controllable. As such, although it is hampered by

some of the same limitations as in stratification, standardization (direct and indirect standardization) is referred to as the simple method of controlling for confounding [28, 29]. Even in large registry-based studies, disease rates are often standardized to age, and sometimes to sex and race. Therefore, if more factors are taken into account, then separate analyses must be conducted for specific subgroups. Stratification and Standardization are consequently rarely used exclusively to control for confounding in studies on chronic diseases with multiple risk factors (i.e., bladder cancer) that a large number of confounders is considered. Also, both stratification and standardization represent ways of learning about the data, and these methods might be used as preliminary analysis, before we use other approaches such as multivariable analysis or propensity score methods to adjust for confounding [28]. Therefore, when multiple confounders are taken into account, it is suggested to use other alternatives including propensity score or multivariable adjustment.

Propensity score is another approach for controlling confounders in the analysis phase and the use of this method is to modify the study so that exposure groups that we want to compare become comparable without influence from confounding factors, and exposure must be a categorical variable. Also, propensity score approach is a robust method when exposure is common. Although the use of the propensity score has received much attention in the recent years and has increased in popularity, it cannot handle exposure defined as a continuous variable (e.g., diet dosage), unless dosage is categorized, typically dichotomized into the presence or absence of exposure, associated with the risk of losing important information on the association between an exposure and baseline characteristics [28]. Also, when balancing the propensity score of comparison groups, a subset of data is extracted according to certain rules, and therefore, the sample size is reduced, which in case a rare disease is considered (i.e., bladder cancer), may hamper the feasibility and interpretability of the results obtained by the propensity score method [30, 31].

Given the limitations toward the propensity score method, the most frequently used method to correct for confounding in epidemiological studies is multivariable adjustment. In contrast with propensity score method, the multivariable adjustment is easy to include a large number of potential confounders, hence, models can handle large numbers of covariates and also confounders (both categorical and continues variables) simultaneously [29].

In this thesis, the most common method used for adjustment of confounding in epidemiology, multivariable adjustment, was applied. In this thesis, the most important general risk factors for bladder cancer development (i.e., age, sex, and smoking) were included in all analyses; in addition, the effect of other available factors were examined for their association with bladder cancer risk using multiple cox-regression analysis. Nevertheless, some important confounders might be missing in our analysis due to a

lack of information in the BLEND. For example, the lack of data on cooking methods used (**chapter 4** and **5**), as well as BMI and physical activity (**chapter 3**, **4** and **5**), different types of fish (**chapter 4**) consumed by the participants, might have affected the findings. It is known that many nutrients are preserved when foods are eaten raw, or undercooked while many water-soluble nutrients might be destroyed when foods are overcooked. This is because, many nutrients, including vitamin C, thiamin, and folic acid are temperature sensitive [32]. In addition, there are numerous alternatives for the same sort of ingredients or foods, thereby differing in their nutrient content. Another potential source of confounding that could have influenced the results of this thesis, is the confounding effect of factors related to the dietary intake under investigation. For example, people with a healthy diet, are more likely to have a healthier behavior in terms of physical activity, smoking and other positive lifestyles [2]. Limited information on these factors in the BLEND data set might have affected the results. However, the current literature suggests that only a small proportion of bladder cancer cases can be attributed to these factors [33]. Because all of the thesis' main risk estimates were stable after adjusting for all potential and available confounders, it's unlikely that inappropriate adjustments had a significant impact on our findings. Nevertheless, residual confounding by unknown variables, as well as residual confounding of smoking, might have influenced our findings.

6.2.c Causal inference

All of the associations between dietary items (in **chapter 4** and **5**) and bladder cancer risk found in the present study are based on observational data, which is considered to be inferior to experimental data in determining causality.

In epidemiology, if adequate knowledge with regard to the relevant underlying causal relationships is available it would be practical to judge about the causality of associations. Therefore, in order to establish epidemiologic evidence of a causal relationship between a presumed cause and an observed effect, the Causal Pie Model (or sufficient-component cause model) by Rothman [34] and the 9 Bradford Hill's criterion can be used [35]. In this section, I discuss these two famous causality models in epidemiological studies.

6.2.c.a Causal Pie Model (or sufficient-component cause model)

The Causal Pie model was first introduced by Rothman in 1976 and is a conceptualization of causality. In this model, *sufficient cause* for an outcome is determined by a set of minimal conditions and events that unavoidably produce the outcome of interest [36]. This means that for the outcome to occur, all minimal conditions or events must be present [36, 37]. Therefore, each *component cause* is an essential element of the causal mechanism to which it contributes; in other words, no one factor is stronger than any of the others. Thus, this concept recognizes that disease outcomes have multiple con-

tributing determinants that may act together to produce a given instance of disease. For example, exposure to cigarette smoking, as a main risk factor for bladder cancer, does not necessarily result in the occurrence of bladder cancer. Moreover, the set of risk factors that produce bladder cancer in one individual may not be the same set of risk factors that were responsible for the occurrence of bladder cancer in another individual. Therefore, in this thesis, the factors shown to be associated with bladder cancer (**chapter 3**, **4** and **5**) meet the criteria for causality based on the causal pie model.

6.2.c.b The 9 Bradford Hill's criterion

The *strength of associations* is the first criteria for causality introduced by Hill. The stronger the association between exposure and the outcome, the more likely the association is causal. However, the associations observed in this thesis (**chapter 4** and **5**), were mainly moderate or weak, thereby failing to fulfill the first Bradford Hill criteria. Nevertheless, failing this first criterion does not necessarily imply a lack of causality, especially when the outcome of interest is a multi-factorial disease (i.e., a disease caused by a number of risk factors with minor individual effects), such as bladder cancer. Therefore, the moderate-to-weak associations found in this thesis likely have significant public implications, especially given that the investigated dietary factors are used widely in the communities and bladder cancer is a serious public health concern. However, the results reported in **chapter 4** should be interpreted cautiously, due to the possibility of residual confounding of the cooking methods used by the different participants.

The second criterion acknowledged by Bradford Hill is the *consistency of the association*, that reduces the possibility that a discovered relationship is due to differences in the selected methods or population resulting of error, bias, or residual confounding. Therefore, extreme caution is recommended when hypothesis testing is affected by different study designs, methodologies, and populations. BLEND consists of data collected from different studies, all with their own design and different populations included. Therefore, by performing study specific sensitivity analysis the consistency of the association could be easily assessed. In chapter 4 and 5 it is shown that the study specific sensitivity analyses show similar results among all included studies, thereby, strengthening the plausibility of a causal relationship. However, there are discrepancies in associations found in **chapter 4** and **5** with previous literature and thereby reducing the plausibility of causality.

The fourth criterion is *temporality*, meaning, in order to establish a causal relationship, the exposure should always occur before the outcome. In a well-designed cohort study, this criterion it is expected to be fulfilled. However, regarding the outcome of interest in this thesis (bladder cancer) it might have happened that bladder cancer patients had symptoms from their disease long before the diagnosis. Since several dietary factors involve low levels of exposure over extended time frames with low incidence diseases

(e.g. bladder cancer) [38], this criterion should be carefully taken into account when determining the weight of the evidence on the association of diet and bladder cancer.

Biological gradient and *coherence* are the other Bradford Hill criteria for causality. *Biological gradient* means "*if a dose response is seen, it is more likely that the association is causal*". According to the traditional interpretation of this criterion, the presence of a linear association supports the causal inference of the relationship between the exposure and outcome [39]. In this thesis (**chapter 4**) a dose–response association is found only for consumption of organ meat and risk of bladder cancer. In reality, on nutritional effects, most dose–response curves are non-linear, and their form varies from one study to the next, depending on the specific features of the population, exposure routes, and even molecular endpoints examined [40]. Individual susceptibility and the synergistic or antagonistic effects of cumulative exposures (e.g., diet) might make it even more difficult to describe some biological gradients. Traditionally, plausibility has been determined by the availability of established biological or social models that explain the association of interest. Previously, causal inference was done under the assumption of a one-factor direct relationship (i.e. A causes B). Many disease outcomes, however, are now recognized to be the consequence of the interaction and synergy of numerous contributory and intermediary factors [38]. As a result, establishing the biological plausibility of a causal relationship can be complex.

Coherence has been viewed as being similar to biological plausibility. It means that a causal inference should not substantially contradict current substantive knowledge. The lack of such knowledge, however, would not rule out a non-causal explanation. Hence, due to insufficient knowledge in the biological aspects of the association of diet and bladder cancer, the application of these two criteria might not be feasible in many epidemiological studies including our study [41].

The next criterion acknowledged by Bradford Hill is *Experiment*. Hill highlighted that experimental evidence, particularly in epidemiological studies following an intervention or cessation of exposure, may provide the strongest support for causal inference. However, experimentation must take into account the fact that many diseases are the consequences or the interaction of many exposures, which follow complex progression pathways. In addition, eliminating the exposure, as indicated by Hill, may not reverse or appreciably slow the progression of the disease. Similarly, in some diseases including bladder cancer, multiple risk factors (i.e., food, exercise, smoking, chemical exposures, and genetic factors) can contribute to the cancer onset and its progression [38, 39].

The final criterion acknowledged by Bradford Hill is *analogy*. When there is compelling evidence of a causal association between a specific agent and a definite disease, it is indicated that researchers should be more accepting of weaker evidence that a similar agent may cause a similar disease. This criterion has been understood to indicate that

when one causal agent is established, the evidence is lowered for a second causal agent that is similar in some way [42]. Nowadays, the current value of *analogy* is gained through developing and testing mechanical hypotheses rather than establishing a causal conclusion [38]. So, I believe that our results will be useful for the future research and developing hypotheses on the mechanism of the effect of diet on bladder cancer.

6.2.d Bias

In nutritional epidemiologic studies that utilize self-report instruments, the measured exposure (i.e., estimated dietary intake) has an error that is frequently considerable and likely larger than the error for most other common epidemiological important exposures (i.e. smoking) [43, 44]. It is suggested that, dietary measurement bias creates substantial challenges to reliably and accuracy of new diet–disease relationships in nutritional cohort studies [44]. In nutritional epidemiologic studies it is suggested that, as a result of this error, effect sizes (i.e., relative/ hazard risks) are significantly underestimated, and statistical power for identifying true associations is significantly reduced. Given often relatively limited variation in dietary intake within study populations, the results of case-control and cohort studies are significantly depended on accurate assessment of the dietary exposure and other covariates, especially in the view of a moderate effect size seen in several nutrition studies [44]. In cancer-nutrition studies, this measurement error in dietary factors leads to seriously biased relative risk of cancer for dietary intakes and substantially decreases the statistical power to identify existing associations [43]. Hence, error in measuring exposure leads to a biased and imprecise estimate of the association of the exposure with the disease [45].

The assessed associations of the single food items in **chapter 3**, **4** and **5** of this thesis are adjusted for nutrients other than those of interest. Therefore, this type of bias might have occurred and should be taken in to account when interpreting the results. However, the impact of this bias on our results is expected to be minimal, because all the included cohort studies used similar and valid methods (FFQs) to measure diet. Interestingly, it is supposed that, the international consortium of cohort studies or the pooling projects (i.e. BLEND) gain precision in relative risk estimates and overcome loss of statistical power by combining analyses of individual data from multiple studies that examine associations between diet and cancer and, hence, it decreases information biases related to a single study and measurement bias [46, 47].

In most cohort studies, selection bias from recruitment processes is uncommon since the outcomes have not yet happened at the time participants are enrolled, thus the ultimate outcome status of a potential participant is not affecting the above bias [48]. However, in a prospective cohort research, selection bias might emerge as a result of variations in retention over the follow-up period following recruitment [49]. If there are disparities in the chance of loss to follow-up that are related to exposure status

and outcome, lost to follow-up might introduce bias. Hence, in the BLEND study, it is not expected that the exposures under study (dietary factors) are significantly associated with loss to follow up or death, as a result, this bias is pointedly less effective in our results.

Finally, missing outcome information due to death or emigration can potentially cause selection bias in cohort studies. For example, it is possible that bladder cancer is not detected at the time that a participant drops out of the study due to any reason or due to death caused by any reason other than bladder cancer, resulting in an underestimate of bladder cancer incidence and a risk set that no longer reflects the sample. Unfortunately, no particular information on the loss of follow-up or the reason of death among participants is available in BLEND to determine the degree of this type of bias. However, because bladder cancer is typically diagnosed at an early stage in the source populations, bladder cancer case is unlikely to alter the chance of lost to follow-up or death before diagnosis when compared to non-cases. As a result, this missing outcome information is only expected to have a minimal impact in BLEND-derived analyses.

6.3 Application of the results

Nutritional epidemiology research of chronic diseases, including cancer, has now been putting more emphasis on food groups and the overall dietary patterns instead of a single food item [50]. Since people consume a combination of nutrients as a meal, nutritional research findings on dietary patterns are more easily translated into public health practice [50]. Accordingly, even before the mechanism behind the observed associations are completely understood, the observed associations between dietary patterns and health outcomes can be translated into diet recommendations and nutritional policies.

As it is reported in chapter 3, adherence to the Western diet is associated with an increased risk of bladder cancer. In addition, when examining the main elements of the Western dietary pattern and bladder cancer risk in **chapter 4** and **5**, some elements showed to have a direct association with the risk of bladder cancer.

Therefore, in order to prevent bladder cancer, dietary guidelines should support more non-Western diet food item consumption, such as vegetables, fruits, seafood (fish) and plant-based oils, rather than red, organ and processed meat, animal-based oils and sugary soft drinks [51, 52]. Since the Western diet is also suggested to be associated with other cancer types and common chronic diseases, adherence to such non-Western diet guidelines would not only reduce the number of bladder cancer, it would also reduce the number of many other diseases [53-58].

6.4 Future perspectives

Due to advances in the nutritional research, a paradigm change in how nutritional epidemiology research is conducted is predicted to occur in the future. Not only in terms of dietary data collection, but also in terms of dietary data analysis. Therefore, in this last part of the thesis I will discuss the most recent and promising advances in nutritional epidemiology.

6.4.a Dietary assessment

Two food assessment methods that prevail in the vast majority of nutritional epidemiological field are the FFQs, which are mainly used in studies evaluating associations of diets and diseases, and the 24-hour dietary recalls, which are largely used in nutrition surveillance studies monitoring population's nutritional status and helping to identify groups in need of dietary interventions. Although both methods have led to promising results, they both still face a lot of criticism and validation studies revealed that the measurement error within these methods are significant. Therefore, there is high need for improvement of the quality of the dietary data and design new methods in order the increase the accuracy of the dietary intake. This paragraph will focus on future/ new methods/ techniques to measure dietary intake and on possible research options to increase the accuracy of currently existing and highly used methods.

6.4.a.a New methods/ techniques

Recent advancements in digital technology and computational sciences have laid the foundation for emerging dietary assessment solutions. These advancements have catalyzed the development of new methods aimed at automating the assessment of dietary intake, thereby limiting or eliminating the need for self-report, resulting in minimization of recall bias and social desirability errors. So far, the most well-developed new methods are the image-based and the biochemical sensors.

Image-based method:

The image-based method makes use of smart phones, which gained a lot of popularity since the introduction of smart phone by Steve Jobs and is now the most commonly used mobile device worldwide. This broad usage of the smartphone facilitated the introduction of smart phone applications (apps) specially designed to collect individual consumption data about a series of foods/drinks. By using these apps, individuals can make photos of their daily consumed food and beverages, which will either be reviewed and coded into nutrition software by trained research staff (image-assisted assessment) or analyzed by software designed to identify the type and volume of foods in the image (image-based assessment). Although underestimation of some major nutrients (i.e., fat and oils, and protein) by these applications (i.e., MyFitnessPal and LifeSum) is a drawback for using this method, these image-based dietary assessment apps have several advantages: a)

the elimination of the need for self-report will lead to minimization of recall bias and social desirability errors, b) the rapid and easy collection of the food and beverages intake data will significantly reduce the respondents burden [59], thereby likely increasing the number of participant and decreasing the number of loss-to-follow up, c) portion sizes are estimated by a trained assessor or algorithm, resulting in more accurate measures and less errors, and over or underestimation of the daily intake [59-61]. Hence, it is suggested that image-based dietary assessment will play a significant role in nutritional studies and chronic diseases (i.e., bladder cancer) in the near future [18, 62].

Biochemical sensors:
Nowadays, biochemical sensors are gaining a lot of attention for their importance in continuous monitoring of the human's health and personalized medicine. Biomarkers in sweat, saliva, blood, urine, as well as tears can be precisely measured by wearable biochemical sensors to monitor the health condition of the body and diseases progression [63, 64]. For instance, recently wearable sensors have been used for monitoring drug abuse, alcohol intake, medication compliance, and vitamins [64, 65]. Also, the newly developed wearable health monitoring devices have been proved to be beneficial for tracking biochemical indicators such as metabolites and electrolytes in various bodily fluids with a continuous and noninvasive method. On the other hand, although the use of wearable biochemical sensors for precision nutritional measurements has been rarely explored, various physical sensors have been recently proposed for monitoring quantity food intake via measuring the action of swallowing and chewing [64]. Nevertheless, to date there is no wearable chemical sensors for monitoring eating habits and dietary intakes. The ability to continuously and non-invasively monitor the intake of food will greatly support studies on dietary and changes in nutritional behaviors, dietary intakes and their effects on the human health [63, 64, 66, 67]. In the future, the use of wearable sensors is expected to be extremely useful for personalized monitoring and altering nutritional habits in preventing chronic diseases (i.e., bladder cancer).

6.4.a.b Research options to increase accuracy
Besides the development of new techniques/ methods to assess dietary data, several researchers are working on large epidemiological studies for dietary questionnaire validation and calibration. While A "validation study" aims to understand the structural equation of the measurement error model, a "calibration study", is designed to calculate the correction factors (the attenuation factor) for the estimated effect sizes [68]. Both studies make use of reference method of which the measurement error should be independent of the error of the method under research. Examples of such methods are: using multiple weighed dietary records by using 24-hour recalls as a reference to provide the best possible proxy for the individuals' true intakes or using food record, 24-h dietary recall, or biomarkers as a part of validation studies to increase accuracy of the measurements [69, 70].

6.4.a.c Biomarkers of dietary intake

A biomarker is a biological sample (i.e. blood, plasma, serum, urine, nails, saliva, feces, and tissue samples) that has the potential to reflect the nutrient intake or metabolism [71]. The advantages of these markers are that biomarkers are highly correlated with dietary intake levels, are independent of individual's recall, and are not based on the subject's ability to define the type and quantity of food consumed. This can be either acute (reflecting intake over hours/days and are usually measured in urine, plasma, or serum), medium-term (reflecting intake over weeks/months and are usually measured in red blood cells or adipose tissue), or long-term (reflecting intake over months/years, and are usually measured in hair, nails, or teeth) exposure or outcomes [71, 72]. Therefore, measuring nutritional biomarkers will be crucial for future studies into the relationships between food and health, without the bias related to self-reporting errors, and will overcome the problem of interaction effect between food items/nutrients.

However, although biomarkers are considered promising in terms of accuracy of dietary intake, they also have some drawbacks. At first, from a variety of biomarkers it is known that they provide integrated measurements of absorption and metabolism. This could be correlated with both dietary intake and metabolic disorders. Secondly, it is shown that metabolites are influenced by disease, homeostatic regulation, gender, age, tobacco smoking, medication, physical activity and genes [9]. Furthermore, the invasiveness and costs of measuring biomarkers might lead to reduced numbers of individuals willing to participate [22, 73].

6.4.a.d Combination of different dietary assessment methods

It has been proposed that a combination of current available methods, such as the FFQs with 24-hour dietary recalls, or the FFQ with biomarker levels, would achieve more accurate dietary intake estimates than using just a single method [22, 74]. Research showed an increased correlation between true dietary intake, measured by a FFQ With 24-Hour recalls, and the use of combination of instruments [74].

Taking the advantage of different traditional methods, biomarkers and new approaches by the application of state-of-the-art technology (i.e., internet and smartphones), substantial efforts to improve the accuracy and feasibility of nutritional epidemiology studies are still ongoing.

6.4.a.e Omics and nutritional research

Investigating the molecular and nutrient metabolism helps us understand the key pathways underlying the relationship between dietary patterns and health. Likewise, dietary patterns may cause different health effects in different individuals. Therefore, a key purpose of nutritional research is to determine the role of diet in metabolic regulation and to identify factors that influences an individual's response to diet. Recent

breakthroughs in "Omics" technologies, such as genomics, lipidomics, microbiomics, metabolomics, and proteomics, have opened up plenty of new opportunities towards this purpose. These new "Omics" technologies have the great potential to learn more about the complex associations between food/nutrients, metabolism and complex diseases [75].

6.4.a.e.1 Genomics

Genomics refers to genome modifications that result in gene expression variations, allowing for diverse expression of similar genetic information [76]. Nutrigenomics, therefore, explains the interaction between individual's genome and nutrition [77]. To date, investigating the interactions between diet and genetic factors is a unique and a relatively novel research field. Genomics approaches are increasingly being used in population-based observational and interventional studies, resulting in a great interest in potentially relevant diet-gene interactions.

Multiple genetic polymorphisms in nutrition-metabolizing enzyme systems have been shown to modify the impacts of dietary exposures on cancer risk. In addition, several diet-related biomarkers have been identified that causes gene mutations and play an essential role in gene activation [78]. For example, it has been shown that dietary fat may affect Glutathione S-Transferases (GSTs) activity. GSTs catalyze the conjugation of reduced glutathione to a large number of electrophilic compounds, which in turn can bind to DNA, forming adducts and potentially DNA mutations, thereby playing a critical role in protecting cell against cytotoxic and mutagenic effects. The GSTs are divided into four major isozymes-alpha (GSTA), pi (GSTP), mu (GSTM), and theta (GSTT). Research showed that deletions in the GSTM1 and GSTT1 gene result in deficiencies of the GSTM1 and GSTT1 isozymes, thereby increasing the risk for several cancer types, including bladder cancer [78, 79]. This might explain the results found in **chapter 5**, showing that dietary fats and oils directly effects the bladder cancer risk. However, although, advances in genomics may shed light on complex gene environment interactions and might explain some important underlying mechanisms, thereby increasing tailored preventive measures for bladder cancer, the magnitude of the importance of the application this omic, is still unknown [80, 81].

6.4.a.e.2 Metabolomics

Metabolomics can be defined as the screening of small-molecule metabolites present in samples of biological origins. The characterization of all metabolites can yield a metabolic picture and a molecular fingerprint [82]. By monitoring and comparing metabolic markers, metabolomics may be utilized to assess the associations between nutrition and health [83]. Therefore, "nutritional metabolomics", as a new field of metabolomics, is the study of endogenous and gut microbiota metabolic response to dietary consumption, and the identification of metabolites that derive from food and might be used as biomarkers or indicators of exposure to certain foods [84]. In

addition, metabolomics can identify a wide range of environmental substances in foods and beverages, including toxins and other poisons, which might be associated with the risk of bladder cancer. Detecting metabolites in urine indicates whether a person consumes fatty acids. For example, when compared to the urine of healthy individuals, it is shown that in bladder cancer patients the number of urinary metabolites involved in the fatty acid metabolism are increased in the urine (especially NMIBC patients) [85]. Also, this method can clarify whether individuals actually consumed what they stated. For example, by using urine and serum samples, investigators are able to detect markers associated with meat (1-methylhistidine, O-acetylcarnitine) and fish (1-methylhistidine) consumption [86-88].

This clearly shows that this metabolic field has a great potential to improve bladder cancer diagnostics. Especially, since the bladder is a temporary storage of urine, urinary metabolic analyses might greatly enhance the diagnostic accuracy to this specific cancer type [89]. However, despites these promising results, current evidence is only based on small cohorts with little validation. Hence, bladder cancer metabolomic analysis is still in its early phases.

6.4.a.e.3 Proteomics

Proteomics defines the way our genome is expressed as a response to dietary proteins [90]. This approach is the systematic evaluation of changes in cell protein composition to identify pathway of protein-diseases processes [91]. The proteome is the entire set of proteins expressed by a genome, cell, tissue, or organism at any particular time. The gathering of data on proteins and peptides, their cellular locations and functions, as well as their expression patterns in various tissues and cells, provide valuable information for developing hypotheses about important biomarkers in serum/plasma, which may then be tested.

An animal model revealed new insights in the mechanisms by which dietary interventions with different sources of fatty acids (fish oil, conjugated linoleic acid, and elaidic acid) regulates the lipid metabolism and other related pathways, and determined the changes in lipemia and insulin concentration [92]. The field of proteomics already showed its potential role in both the diagnosis and prognosis of bladder cancer [93]. It has been shown that urine proteomic was able to contribution in the detection of bladder cancer and its grading [94]. In addition, it has been suggested that M2 and TP53 may predict the outcomes of radiotherapy and/or chemotherapy in patients with bladder cancer [93-95]. Also, the use of proteomic in the diagnosis of bladder cancer enables us to identify alterations in gene expression that occur as a result of dietary changes.

6.4.a.e.4 Lipidomics

Lipidomics is acknowledged as the metabolomic analysis of lipids. Lipidomics is mainly known for its detection and diagnostic ability of inborn lipid metabolism defects [96].

However, more recently it has also proven to be valuable in understanding metabolic pathways via which dietary intake may have health consequences [97]. It is used to track dietary exposure and to connect food consumption and health [98, 99]. For example, previous lipidomics research indicated that coffee consumption significantly decreases arachidonic acid (AA, 20:4n6) and has a potential impact on the regulation of glycerophospholipid metabolism [97]. AA is an "essential" fatty acid and helps protect the cells from oxidative stress [100] and the metabolites of glycerophospholipid pathway probably maintained the stability of cell membranes against hypoxic stress to relieve the cell injury [101]. In addition is has been shown that dietary fat intake significantly increases four lipid biomarkers (PCae36:4, PCae36:5, PCae36:3, and PCae38:5). Since this thesis shows that dietary fat influences BC risk (chapter 5), these findings might explain a possible pathway through which dietary fat consumption and lipid metabolism might predict alterations in the bladder cancer cells, and shows that the field of lipidomics may assist in unravelling the complex interplay between diet and bladder cancer risk.

6.4.a.e.5 Microbiomics

Microbiomics is the study of the quality, quantity, and activity of over 100 trillion microorganisms in the human gut [102]. Microbiota, which is defined as the assemblage of microorganisms in human body, can metabolize nutritional ingredients into new bioactive compounds that can influence disease risk.

Research in the field of microbiomics showed that adherence to a Western diet might alter the composition of the gut microbiota, by altering the short-chain fatty acids production [103], which are suggested to have a crucial role in cancer occurrence and progression [104]. This shows the great potential of microbiomics in cancer development [103]. Results showing an increase cancers risk initiated by hydrogen sulfide, or secondary bile acids, such as the daidzein metabolite equol or the ellagic acid metabolites urolithins, due to its negative impact on cancer processes, are examples of the success of microbiomics so far [105, 106].

However, although, the urinary microbiome is now an emerging field of research [107], at present, data linking microbiome to the diagnosis and prognosis of bladder cancer is lacking. Future microbiomics research is needed to show the potential of this field in unravelling the link between dietary intake and bladder cancer diagnosis and prognosis and showing possible new treatment options for bladder cancer patients [108].

In summary, the above-mentioned prospective options and innovative approaches for diet and nutrition research in cancer prevention, require advanced infrastructure and solid proof of their value in nutritional studies. Nevertheless, they have the potential to significantly improve the understanding of the diet-cancer associations. However, traditional epidemiological approaches will not be eliminated since they are critical in understanding how our health behaviors (i.e., dietary habits) affect cancer risk.

To finish, although the results of "Omics" are still preliminary and applying these methods is expensive for large epidemiological studies, they are inevitably important technologies for the future discoveries in the nutritional-health sciences.

6.5 Conclusion

In this thesis I examined the association between the Western diet and its main components, and bladder cancer risk. Results indicate that higher adherence to the Western diet could increase bladder cancer risk, which might derive from high consumption of organ meat. Little evidence of an inverse association was found between fish consumption and bladder cancer risk. This thesis also highlighted the role of fats and oils in association with the bladder cancer risk, showing the protective effects of MUFAs and adverse effects of higher intake of cholesterol on bladder cancer risk. Higher consumption of animal fat might be detrimental, while plant-based fats and oils and sunflower oil could be beneficial for bladder cancer prevention. I believe that the results of the present thesis could be applicable for the prevention of bladder cancer by providing guidelines in order to minimize the adherence to the Western diet and encourage people to follow a healthier diet (i.e., the Mediterranean diet).

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Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Ethics approval

The Bladder Cancer Prognoses Programme (BCPP) study involved humans and ethical approval was obtained, ethics reference: 06/MRE04/65. The protocol had been registered in clinicaltrials.gov, registration number: NCT00553215. All participants provided written informed consent before they were included in the study.

Each participating study in the BLEND consortium has been approved by the local ethic committee. Informed consent was obtained from all individual participants included in each participating study.

Conflict of interest

The authors have no conflict of interest to declare.

The impact

Bladder cancer (BC), one of the ten most prevalent cancer types worldwide and will continue to have a significant economic effect on both individual lives and public health in general. It is suggested that nearly half (49%) of bladder cancer cases could be prevented by lifestyle change [1, 2].

Since the bladder is an excretion organ, it is constantly exposed to both toxic and healthy elements of a person's diet. It is, therefore, suggested that diet plays a significant role in the development of bladder cancer and should be considered in bladder cancer prevention programs. Indeed, according to the USA National Cancer Institute, changes in diet might prevent one-third of all bladder cancer mortality [3]. This could lead to a reduction in the annual medical treatment cost of 1.2 billion US dollars. It is, therefore, crucial to identify which specific dietary factors contribute to the development of this disease.

This thesis focused on the effects of the Western diet, and its components, on the risk of bladder cancer as it was suspected that adherence to the Western diet might negatively influence several health outcomes, including cancers. This thesis confirms this hypothesis for bladder cancer.

The association between adherence to the Western diet and increased bladder cancer risk, might be due to the high content of organ meat and / or low fish intake in a Western diet. In addition, this thesis highlights the importance of fats and oils in relation to the risk of bladder cancer risk, in that MUFAs, sunflower oil and other plant-based fats and oils showed to be beneficial, while higher cholesterol consumption and animal fat intake detrimental.

It remains a major challenge to translate the findings from this thesis into daily practice. Although in recent years, dietary guidance became increasingly science-based, there seems to be an ever-widening gap between the scientific evidence and an individual's behavior. Our society is exposed to a vast variety of dietary and nutritional non-evidence-based suggestions and recommendations, deriving from book authors and television personalities, the popular press, or by browsing the internet. This can overwhelm people, making it hard for individuals to make accurate nutritional decisions. I believe that it is the task for scientific experts and governments to fill this gap and provide accurate evidence-based nutritional recommendations. For this, not only close collaboration and knowledge exchange between scientists, health professionals like dietitians and nutritionists and health care organization are needed, but it is also important to increase the society and policymakers' nutrition knowledge based on the latest scientific evidence.

To this end, results of this thesis have been published in internationally prestigious journals and will be shared with the Union for International Cancer Control (UICC) and

IARC. These organizations could advice to reduce the amount organ meat, dietary cholesterol, and animal fat and to consume more fish and poultry meat and MUFAs and plant-based oils.

The results of this thesis might provide recommendations for the government to take positive action to improve the nutritional plan of society. Given the high burden of bladder cancer and the contributory role of dietary fat and meat, inducing even small dietary adjustments might result in significant reductions in bladder cancer incidence at the population level. For example, governments could carefully targeted fat tax on animal fat and cholesterol enriched foods to reduce the sale of these products, thereby decreasing the consumption of un-healthy fats (i.e., animal fats) containing products [4].

Recently, the World Health Organization's (WHO) ambitious started a project to eliminate industrially produced harmful substances, including non-healthy fats and oils, from the global food supply and replace them with healthy fats and oils [5, 6]. The WHO reports that 58 countries have so far introduced laws that will protect 3.2 billion people from the harmful substance by the end of 2021. From 4 May-1 June 2018, WHO is also running an online public consultation to review updated draft guidelines on the intake of fats for individuals. The findings from this thesis could be useful as input for these consultations.

Lastly, to increase the public awareness directly, a lay version of our results will be published on Wikipedia (https://en.wikipedia.org/wiki/Bladder_cancer), e-how/health, and the project's own website.

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About the author

Mostafa Dianati was born in Dehdasht, Iran, on September 21, 1989. In 2006, after graduating from secondary school and receiving a high school diploma in Applied Sciences, he went on to study public health and received his BSc from Yasuj Medical University (Yasuj, Iran) in 2012. Afterward, Mostafa continued his studies with a Master in Epidemiology at the Shiraz University of Medical Sciences (a highly ranked university in Shiraz, Iran), where he completed his master in cancer epidemiology in November 2015. During his studies, Mostafa has received some outstanding honors, including the 1st prize for the researcher of the year amongst B.Sc. (2013) and M.Sc. (2015) students and the top lecturer among the faculty members (2018 and 2019).

Then, after graduation with a master's certificate in Epidemiology, he had this great opportunity to work at HIV/AIDS and cancer research centers in Shiraz, Iran, and subsequently to work from 2017 to 2019 as a faculty member in Iran. Mostafa now has over 60 scientific publications to his name and serves on the editorial board of the BMC Public Health journal and Frontiers in Public Health journal.

To do his PhD at Maastricht University, since October 2019, he has worked under the supervision of Prof. Dr. M. Zeegers and Dr. A. Wesselius at the department of Epidemiology and Complex Genetics, Maastricht University, on the development of a consortium initiative on the association between Western diet and the risk of bladder cancer by working on 13 international cohort studies. Mostafa had the chance to work directly on the development of an international scientific project, which made him even more determined to work in academia. Mostafa is looking forward to making a significant impact on cancer patients' health by contributing to applicable projects in practice.

List of publications

[1] Foroozani E, Akbari A, Amanat S, Rashidi N, Bastam D, Ataee S, **Dianatinasab M**. Adherence to a western dietary pattern and risk of invasive ductal and lobular breast carcinomas: a case–control study. Scientific Reports. 2022;12(1).

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