

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

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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 have 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.