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 (BLEND) International Study

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

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Novelty and Impact

The association between adherence to a Western diet and risk of bladder cancer is not well-established. By pooling data from 13 prospective cohort studies in the BLEND consortium on 580,768 study participants, we aimed to investigate prospectively this association. We found a direct and significant association between higher adherence to a Western dietary pattern and risk of bladder cancer. Interestingly, we found evidence that adherence to a Western dietary pattern is associated with an increased risk of bladder cancer for men but not women. Also, results were consistent after stratification on cancer sub-types.

ABSTRACT

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

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, 11,12]

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 questionnaires (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 1**.

In total, 192,691 (33%) men and 388,077 (67%) women were included. As shown in **Table 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).

Baseline characteristics and dietary information based on tertiles of adherence to the Western dietary pattern are reported in **Table 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**. 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 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 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 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.

Ethics approval and consent to participate

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

Authorship agreement and conflict of interest disclosure

The authors declare that they have no conflict of interest.

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Data Accessibility

Datasets that are minimally required to replicate the outcomes of the study will be made available upon reasonable request.

Disclaimer

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.

Contributors

A.W., M.D., MZ and M.B, were involved in the study conceptualization, methodology, writing and editing the manuscript. A.S., E.Y. and M.F. helped in data analysis and manuscript review. P.B., E.W., E.W., F.C., M.G., I. H., F.L., G.S., A.T., E.R., G.G. and R.M. were involved in writing and editing the manuscript and providing critical feedback. All authors have read and agreed to the published version of the manuscript.

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Table 1. General characteristics of participants by cohort study

Characteristics	NLCS [33]	VITAL [37]	CVV&MCCS	EPIC-Denmark [25]	EPIC-France [26]	EPIC-Germany [27]	EPIC-Greece	EPIC-Italy [29]	EPIC-Spain	EPIC-Sweden	EPIC-the Netherlands [34]	EPIC- the UK	EPIC-Norway	Total
	N=5,238	N=66,518	N=37,218	N=55,670	N=64,204	N=48,754	N=25,005	N= 44,663	N=40,389	N=48,625	N=36,801	N= 74,379	N=33,304	N=580,768
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	186/44,477	149/40,240	301/48,324	107/36,694	247/74,132	23/33,281	3,401/ 577,367
Person-year	73688.8	448995.4	715158.9	608813	667809.9	482453.3	238122	502020.3	487491.1	638482.8	434974.5	828991.7	6437305.7	6451306
Baseline age (mean ±SD) Case Non-case	62.73 (4.09) 61.85 (4.21)	66.16 (7.01) 61.18 (7.37)	59.90 (7.37) 54.96 (8.67)	58.50 (4.37) 56.67 (4.37)	58.04 (6.00) 52.74 (6.63)	56.41 (7.13) 50.55 (8.56)	60.89 (10.31) 53.30 (12.59)	55.24 (6.75) 50.50 (7.92)	54.49 (7.19) 49.19 (8.03)	60.27 (7.07) 51.93 (10.89)	56.20 (8.03) 48.94 (11.93)	63.62 (9.98) 49.05 (14.34)	49.30 (4.38) 48.07 (4.30)	60.50 (7.35) 52.66 (10.14)
Sex n (%) *Men* *Women*	2,867 (54.73) 2,371 (45.27)	33,394 (50.20) 33,124 (49.80)	15,267 (41.02) 21,951 (58.98)	26,532 (47.66) 29,138 (52.34)	0 (0.00) 64,204 (100.00)	21,168 (43.42) 27,586 (56.58)	10,327 (41.30) 14,678 (58.70)	13,774 (30.84) 30,889 (69.16)	15,259 (37.78) 25,130 (62.22)	22,214 (45.68) 26,411 (54.32)	9,629 (26.17) 27,172 (73.83)	22,260 (29.93) 52,119 (70.07)	0 (0.00) 33,304 (100.00)	192,691 (33.18) 388,077 (66.82)
Smoking status n (%) *Current smoker* *Former smoker* *Never smoker*	1,613 (30.79) 1,930 (36.85) 1,695 (32.36)	5,366 (8.07) 29,644 (44.57) 31,508 (47.37)	4,164 (11.19) 11,576 (31.10) 21,478 (57.71)	19,140 (34.38) 16,998 (30.53) 19,532 (35.09)	5,862 (9.13) 13,013 (20.27) 45,329 (70.60)	10,165 (20.85) 16,194 (33.22) 22,395 (45.93)	6,899 (27.59) 4,195 (16.78) 13,911 (55.63)	12,385 (27.73) 11,945 (26.74) 20,333 (45.53)	10,847 (26.86) 7,147 (17.70) 22,395 (55.45)	11,474 (23.60) 13,269 (27.29) 23,882 (49.11)	11,233 (30.52) 11,501 (31.25) 14,067 (38.22)	9,040 (12.15) 23,724 (31.90) 41,615 (55.95)	11,101 (33.33) 10,292 (30.90) 11,911 (35.76)	119,289 (20.54) 171,428 (29.52) 290,051 (49.94)
⁎ **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)	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 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 (%))* *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)	<0.001*
Person-year	28455.67	6422851	<0.001 ǂ	2086731	2243150	2121425	<0.001$
Baseline age (mean ±SD)	60.50 (7.35)	52.66 (10.14)	<0.001ǂ	53.87869 (10.39)	52.28 (10.44)	51.91639 (9.42)	<0.001 $
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)	0.001$
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)	<0.001 ǂ	22.20 (12.52)	23.49 (12.48)	25.00 (12.39)	<0.0001 $
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)	<0.0001 $
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)	<0.0001 $
Red and processed meet *gram per day (mean ±SD)*	92.75 (58.72)	78.85 (60.78)	<0.001ǂ	48.21 (42.30)	73.05 (54.61)	118.11 (62.51)	<0.0001 $
Butter *gram per day (mean ±SD)*	5.08 (10.97)	3.84 (8.18)	<0.001ǂ	1.80 (5.51)	3.74 (8.01)	6.18 (9.99)	<0.0001 $
Margarine *gram per day (mean ±SD)*	18.26 (20.20)	11.28 (15.46)	<0.001ǂ	7.84 (12.93)	11.51 (15.41)	14.85 (17.20)	0.001 $
Animal fat *gram per day (mean ±SD)*	0.22 (1.54)	0.21 (1.16)	0.35ǂ	0.02 (0.29)	0.11 (0.91)	0.51 (1.78)	<0.0001 $
Pasta *gram per day (mean ±SD)*	32.04 (48.63)	35.31 (50.49)	0.001ǂ	32.43 (39.75)	32.22 (42.10)	41.62 (65.94)	<0.0001 $
Sugar *gram per day (mean ±SD)*	16.70 (21.01)	18.02 (47.57)	0.10ǂ	10.94 (26.97)	15.81 (43.24)	27.92 (64.32)	<0.0001 $
Dressing *gram per day (mean ±SD)*	4.79 (7.44)	6.30 (9.83)	<0.001ǂ	2.80 (6.61)	6.24 (9.66)	10.08 (11.36)	<0.0001 $
Dips *gram per day (mean ±SD)*	4.41 (9.47)	5.57 (9.57)	<0.001ǂ	2.99 (6.26)	5.85 (9.06)	8.01 (12.03)	<0.0001 $
Vegetables *gram per day (mean ±SD)*	206.92 (138.40)	198.94 (141.96)	<0.001ǂ	184.04 (150.51)	204.76 (141.26)	208.91 (131.48)	<0.0001 $
Fruits *gram per day (mean ±SD)*	122.53 (111.26)	120.33 (110.10)	0.24ǂ	109.94 (111.78)	122.03 (106.63)	129.71 (110.95)	<0.0001 $
Fluid *milliliters per day (mean ±SD)*	1563.81 (861.36)	1429.51 (878.16)	0.001ǂ	1244.57 (786.36)	1427.15 (817.62)	1632.87 (982.52)	<0.001$

ǂ: based on independent sample t-test. ⸭: 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).

Table 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	2086731	2243150	2121425	-
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	1508860	1519577	1298213	-
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	577871.8	723572.9	823212.2	-
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.