Grain and dietary fiber intake and bladder cancer risk: a pooled analysis of prospective cohort studies

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ABSTRACT

Background: Higher intakes of whole grains and dietary fiber have been associated with lower risk of insulin resistance, hyperinsulinemia, and inflammation, which are known predisposing factors for cancer.

Objectives: Because the evidence of association with bladder cancer (BC) is limited, we aimed to assess associations with BC risk for intakes of whole grains, refined grains, and dietary fiber.

Methods: We pooled individual data from 574,726 participants in 13 cohort studies, 3214 of whom developed incident BC. HRs, with corresponding 95% CIs, were estimated using Cox regression models stratified on cohort. Dose–response relations were examined using fractional polynomial regression models.

Results: We found that higher intake of total whole grain was associated with lower risk of BC (comparing highest with lowest intake tertile: HR: 0.87; 95% CI: 0.77, 0.98; HR per 1-SD increment: 0.95; 95% CI: 0.91, 0.99; *P* for trend: 0.023). No association was observed for intake of total refined grain. Intake of total dietary fiber was also inversely associated with BC risk (comparing highest with lowest intake tertile: HR: 0.86; 95% CI: 0.76, 0.98; HR per 1-SD increment: 0.91; 95% CI: 0.82, 0.98; *P* for trend: 0.021). In addition, dose–response analyses gave estimated HRs of 0.97 (95% CI: 0.95, 0.99) for intake of total whole grain and 0.96 (95% CI: 0.94, 0.98) for intake of total dietary fiber per 5-g daily increment. When considered jointly, highest intake of whole grains with the highest intake of dietary fiber showed 28% reduced risk (95% CI: 0.54, 0.93; *P* for trend: 0.031) of BC compared with the lowest intakes, suggesting potential synergism.

Conclusions: Higher intakes of total whole grain and total dietary fiber are associated with reduced risk of BC individually and jointly. Further studies are needed to clarify the underlying mechanisms for these findings. *Am J Clin Nutr* 2020;112:1252–1266.

Keywords: bladder cancer, grain, dietary fiber, dose-response analysis, cohort study

Introduction

Bladder cancer (BC) is the 10th most common malignancy worldwide, with an estimated 550,000 new cases and 200,000 deaths annually (1, 2). Incidence rates of BC are highest in Europe and North America, with a strong predominance in males and the elderly (3–8). BC is reported to be the most expensive of all cancers in terms of lifetime treatment owing to its high rate of recurrence (9). Diet has been suspected to be important, in addition to smoking and occupational exposure, but only arsenic-contaminated food is considered to be an established dietary risk factor for BC (10–14). Because grain intake is an important component of numerous dietary guidelines globally, interest in the health effects of grain intake is increasing (15, 16).

Whole grains contain all components of the kernel, i.e., the bran, germ, and endosperm. Both the bran outer coating and the inner germ are major sources of dietary fiber, vitamins, minerals, phytonutrients, and numerous other nutrients which may be beneficial to health (17). However, during the refining process, the outer bran and inner germ are removed and only the endosperm is retained. This results in a substantial reduction in dietary fiber, vitamins, minerals, and other components. Although many vitamins and minerals are often added back to refined grains by subsequent processing, the fiber content remains greatly diminished (18, 19).

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Supplemental Figures 1–3 and Supplemental Tables 1–12 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

The data that support the findings of this study are available on reasonable request pending approval from the corresponding author, AW. The data are not publicly available owing to their containing information that could compromise the privacy of research participants.

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Abbreviations used: BC, bladder cancer; BLEND, BLadder cancer Epidemiology and Nutritional Determinants; MIBC, muscle invasive bladder cancer; NLCS, NetherLands Cohort Study; NMIBC, nonmuscle invasive bladder cancer.

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An accumulation of evidence shows that intake of dietary fiber is associated with lower risk of insulin resistance, hyperinsulinemia (20), and inflammation (21), which are known predisposing factors for cancer (22); however, evidence of association with BC risk is sparse, with only 2 case-control studies reporting insufficient evidence of an inverse association for intake of whole grains (23, 24). In contrast to the beneficial health associations of whole grains containing rich fiber, studies of refined grains mainly show no association with health (25–29), or harmful associations (30, 31), and there is no strong evidence of association with BC risk.

We therefore assessed associations with BC risk for intakes of whole grains and refined grains, using data from 13 prospective cohort studies pooled in the BLEND (BLadder cancer Epidemiology and Nutritional Determinants) international study. In addition, we also investigated the potential association of dietary fiber intake with BC risk by evaluating total and individual food sources (i.e., cereal, fruit, and vegetable fiber).

Methods

Study sample

Data were obtained from BLEND, an international nutritional consortium currently consisting of 19 case-control studies and 16 cohort studies. Thirteen cohort studies with a total of 574,726 participants, 3214 of whom developed incident BC, had sufficient information on grain intake to be eligible for inclusion in the present study (**Supplementary Figure 1**). These studies originated from 12 countries in 3 continents {i.e., Europe: EPIC [European Prospective Investigation into Cancer and Nutrition cohort study] (32) [Denmark (33), France (34), Germany (35), Greece (36), Italy (37), Spain (36), Sweden (38, 39), the Netherlands (40), the United Kingdom (41, 42), and Norway (43)] and NLCS (NetherLands Cohort Study) (44); North America: VITAL (VITamins And Lifestyle cohort study) in the United States (45); and Oceania: MCCS (Melbourne Collaborative Cohort Study) in Australia (46, 47)}. Person-years of follow-up for each participant were calculated from the date of study enrolment until the date of BC diagnosis or the date of last follow-up (e.g., date of death, lost to follow-up, or study exit), whichever came first. For the NLCS study, a nested case-cohort design was applied in order to increase the follow-up coverage and efficiency, in which the number of person-years at risk was estimated based on a subcohort that was randomly sampled (44). Each study was approved by their local ethical research committee (32, 44, 45, 47) (**Supplemental Table 1**). Informed consent was obtained from all individual participants included in each study.

Data collection and coding

Details on the methodology of the BLEND consortium have been described elsewhere (48). In brief, all included studies used a self-administered or trained interviewer–administered FFQ that was validated on either food groups (45, 49–52) and/or energy intake (49, 52, 53). For each study, participants were asked to report on their usual intake during the year before study enrolment of individual types of whole grains [i.e., brown rice, wheat or oat, and basic products of other cereals (e.g., buckwheat, millet, sorghum, or spelt)] and of refined grains [i.e., white rice, pasta or noodles, leavened bread, unleavened bread, other bakery wares, savory cereal dishes (e.g., dumplings, couscous, risotto, pizza, pancake, or pie), and breakfast cereals]. These data were harmonized using the hierarchal Eurocode 2 food coding system developed by the European Union (54), with weekly, monthly, or yearly intake converted to grams per day. This resulted in an aggregated data set with unified dietary intakes across the different studies included. In order to extract dry weight (e.g., uncooked pasta or noodles, uncooked rice, uncooked wheat or oat) across all grains, the water content of grains was determined according to the composition database from the USDA and subtracted from the grain intake (55). Total intakes of dietary fiber and dietary fiber from cereal, fruit, and vegetables were calculated by multiplying the amount of each food consumed by the dietary fiber content per gram according to the USDA.

Each study ascertained incident BC, defined to include all urinary bladder neoplasms according to the International Classification of Diseases for Oncology, third edition (code C67), using population-based cancer registries, health insurance records, or medical records. BCs were classified as nonmuscle invasive bladder cancer (NMIBC) or muscle invasive bladder cancer (MIBC). For the present study, the primary outcome was defined as BC cases or non-BC cases, and the secondary outcome was defined as NMIBC, MIBC, or non-BC cases. NMIBC included noninvasive papillary carcinomas confined to the urothelium (stage Ta) and carcinomas that invaded the lamina propria of the bladder wall (stage T1). High-grade flat noninvasive carcinomas confined to the urothelium (carcinoma in situ) without other concomitant tumor stages [i.e., T1/Ta (classified to nonmuscle invasive prior) or muscle invasive] were also classified as NMIBC. MIBC included carcinomas that invaded into the detrusor muscle (stage T2), carcinomas that invaded into the peri-vesical tissue (stage T3), and carcinomas that invaded adjacent tissues and organs (most often the prostate or uterus, stage T4).

In addition to information on grain and other dietary intakes, the BLEND data set also included data on study characteristics (design, method of dietary assessment, geographical region), participant demographics (age, sex, and ethnicity), smoking status, and smoking pack-years (i.e., the number of cigarettes smoked per day multiplied by the years of smoking), which were measured at baseline.

Statistical analyses

To assess the influence of intake of grains and fiber on BC risk, Cox regression analyses with a stratification approach to adjust for cross-cohort heterogeneity (56) were used to estimate the pooled HRs and 95% CIs. The proportional hazard assumption was examined for each analysis and no evidence of violation was found. In addition, the appropriateness of the use of the log-normal distribution was tested using a Wald test, and again no evidence of violation was found. Grain intake (i.e., total grain, total whole grain, total refined grain, brown rice, wheat or oat, basic products of other cereals, white rice, pasta or noodles, leavened bread, unleavened bread, bakery wares, savory cereals, and breakfast cereals) and dietary fiber intake (i.e., total dietary fiber from all food sources, cereal fiber, fruit fiber, and vegetable fiber) were divided into 3 groups defined by tertile based on the pooled data: low intake (tertile 1), medium intake (tertile 2), and high intake (tertile 3). Low intake was used as the reference group and associations were assessed applying 2 models: model 1 adjusted for age (y), sex (male/female), smoking, and total energy intake [kcal/d; continuous; using a residual model to remove extraneous variation (57)] and included cohort as a stratification variable (**Supplemental Tables 2–5** provide results) and model 2 in addition adjusted for ethnicity (Caucasian/non-Caucasian) and for potential dietary factors that affect the development of BC (10), including alcohol intake (mL/d; continuous), sugar intake (g/d; continuous), meat intake (g/d; continuous), vegetable intake (g/d; continuous), fruit intake (g/d; continuous), fat intake (g/d; continuous), and total fluid intake (mL/d; continuous). Smoking was defined as a dummy variable as follows: 0 (never smokers); 1 [current light smokers (i.e., smoking $<$20 pack-years)]; 2 [current heavy smokers (i.e., smoking $>$20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e., smokers who ceased smoking $>$1 y prior and smoked $<$20 pack-years)]; 5 [former heavy smokers (i.e., smokers who ceased smoking $>$1 y prior and smoked $>$20 pack-years)]; and 6 [former smokers (smokers who ceased smoking $>$1 y prior and no information on pack-years)]. The main interaction terms (between grain/dietary fiber and age, sex, and smoking; between total whole grain and total dietary fiber) were added to model 1 (P-interaction < 0.05 was considered statistically significant). Stratified analyses were performed by BC subtype (i.e., NMIBC and MIBC), sex, and smoking status. In addition, the HRs and 95% CIs of BC per 1-SD increase in grain and dietary fiber intakes were also estimated using the same models. Furthermore, a potential joint association of total whole grain and total dietary fiber intakes with BC risk was assessed using the lowest intakes of both total whole grain and total dietary fiber as the reference. To test for linearity or nonlinearity, we included both linear and quadratic terms (i.e., the absolute intake and intake squared) in the models, then a likelihood ratio test was used to assess the difference between the nonlinear and linear models (58). Because results showed no evidence of a nonlinear association, linear models were applied in the present study. A P for trend test was conducted by assigning medians to per 1 SD as a continuous variable in the models. The variables of BC status (i.e., cases or noncases), follow-up time, age, sex, smoking, ethnicity, and total energy intake were complete without missing values. Missing variables (e.g., alcohol intake, sugar intake, meat intake, vegetable intake, fruit intake, fat intake, and total fluid intake; missing proportions were all $<$5%) were imputed separately in each participating cohort by the multiple imputation method. Only participants with complete information on BC status, age, sex, smoking, ethnicity, and total energy intake were included when building the imputation models. Linear regression models were then fitted for those variables with missing data separately.

In our secondary analyses, potential dose–response relations of grain/dietary fiber with BC risk were assessed by using fractional polynomial regression from the ln of the HRs across categories of intake, in which the best-fitting second-order fractional polynomial regression model was defined as the model with the lowest deviance (59, 60). For this, we categorized each source of grain (e.g., total whole grain or total refined grain) and dietary fiber (e.g., total dietary fiber, cereal fiber, fruit fiber, and vegetable fiber) into 10 doses according to the range of intake of each grain or dietary fiber, by which the intervals of each intake were different. *P* values for trend were estimated by assigning medians to each category of intake as a continuous variable. 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 (58). Model 2 was applied in dose–response analyses.

Sensitivity analyses were performed by *1*) removing cases diagnosed within the first 2 y after recruitment to each study and *2*) only including the complete data set, thereby excluding the participants with missing data on variables included in model 2. An extra sensitivity analysis for total refined grain was assessed by excluding pasta source in order to test whether the possible misclassification of pasta would influence the result. Furthermore, the role of smoking was tested by replacing the smoking dummy variable by both smoking status (never, former, and current) and smoking pack-years (continuous). In addition, a quintile-based analysis was performed in order to test whether the differently categorized intakes would affect the results. As a last step, the associations between intake of grains/dietary fiber and BC risk were assessed in each participating cohort separately and combined in a meta-analysis using a random-effect model; subsequently, we conducted a sensitivity analysis by excluding the study that mostly likely dominated the analysis for each dietary factor examined in the present study.

All statistical analyses were performed using STATA version 14 SE (Stata Corporation). A 2-tailed *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the study sample. In total, 574,726 study participants contributed 6,335,667 person-years of follow-up over a median of 11 y, with 3214 incident BC cases (2416 males, 798 females) diagnosed. Of these, 2041 (63%) cases had available diagnosis records of NMIBC (39%) or MIBC (24%). The median age at baseline was 53 y. The majority (99.3%) of participants were Caucasian. No statistical interaction with age, sex, and smoking was found for total whole grain and total dietary fiber. Total refined grain intake showed a significant interaction with sex (*P*-interaction = 0.048).

Associations of grain and dietary fiber intakes with BC risk

Total grain intake and BC risk.

For the different categories of intake of "total grains," no evidence of association for tertile of intake was observed overall, by cancer subtype, by sex, or by smoking status (**Table 2**). However, the HR per 1-SD increment showed a decreased risk (model 2: 0.91; 95% CI: 0.85, 0.98; *P* for trend = 0.011) of BC among males.

Whole grain intake and BC risk.

Table 2 shows the results of the Cox regression analyses for the associations between total whole grains and BC risk. In multivariable-adjusted analyses (model 2), higher total whole grain intake was significantly associated with lower BC risk (comparing the highest with the lowest tertile of intake: HR: 0.87; 95% CI: 0.77, 0.98; HR per 1-SD increment: 0.95; 95% CI: 0.91, 0.99; *P* for trend = 0.023). No evidence of association for tertile of intake was observed in the stratified analyses by cancer subtype, whereas the HR per 1-SD increment showed a borderline decreased risk (HR_{model2}: 0.92; 95% CI: 0.85, 1.00; *P* for trend = 0.038) of MIBC. Results were consistent for both males (comparing the highest with the lowest intake tertile: HR_{model2}: 0.85; 95% CI: 0.74, 0.98; HR per 1-SD increment: 0.93; 95% CI: 0.83, 1.02; *P* for trend = 0.059) and females (comparing the highest with the lowest intake tertile: HR_{model2}: 0.83; 95% CI: 0.71, 0.96; HR per 1-SD increment: 0.93; 95% CI: 0.85, 1.01; *P* for trend = 0.053). No evidence of association was observed in the smoking-stratified analyses.

Of the individual whole grains assessed, only higher intake of brown rice was significantly associated with a decreased BC risk (comparing the highest with the lowest intake tertile: HR_{model2}: 0.78; 95% CI: 0.67, 0.92; HR per 1-SD increment: 0.89; 95% CI: 0.82, 0.95; *P* for trend = 0.001) (**Table 3**). All other whole grains showed a null-association.

Refined grain intake and BC risk.

Overall, no evidence of association between different categories of total refined grain intake and BC risk was observed. However, males showed a borderline decreased BC risk per 1-SD increment ($HR_{model\ 2}$: 0.92; 95% CI: 0.86, 1.00; *P* for trend = 0.040) (Table 2). Looking at the individual refined grain sources, similar null-associations were found, except for the intake of "pasta or noodles," which was inversely associated with BC risk when comparing medium intake with low intake (HR_{model2}: 0.90; 95% CI: 0.81, 0.99; HR per 1-SD increment: 0.99; 95% CI: 0.94, 1.04; *P* for trend = 0.697) (Table 3).

Dietary fiber intake and BC risk.

Table 4 shows the associations of the intakes of total dietary fiber and dietary fiber from different food sources with BC risk. The intake of total dietary fiber was inversely associated with BC risk (comparing the highest with the lowest intake tertile: HR_{model2}: 0.86; 95% CI: 0.76, 0.98; HR per 1-SD increment: 0.91; 95% CI: 0.82, 0.98; *P* for trend = 0.021). Consistent results were observed for both males (comparing the highest with the lowest intake tertile: HR_{model2}: 0.89; 95% CI: 0.79, 0.98; HR per 1-SD increment: 0.90; 95% CI: 0.83, 0.97; *P* for trend = 0.007) and females (comparing the highest with the lowest intake tertile: HR_{model2}: 0.79; 95% CI: 0.66, 0.97; HR per 1-SD increment: 0.89; 95% CI: 0.79, 1.00; *P* for trend = 0.049); however, no association was observed in the smoking-stratified analyses. For the individual dietary fiber food sources, only vegetable fiber showed a borderline decreased BC risk per 1-SD increment (HR_{model2}: 0.93; 95% CI: 0.86, 1.00; *P* for trend = 0.046).

TABLE 1 Characteristics of the study population (3214 cases and 571,512 noncases) according to tertiles of grain and dietary fiber intakes[1]

	Total whole grain					Total refined grain					Total dietary fiber				
	Low (tertile 1)	Medium (tertile 2)	High (tertile 3)	Mean ± SD, g/d	*P* -interaction	Low (tertile 1)	Medium (tertile 2)	High (tertile 3)	Mean ± SD, g/d	*P* -interaction	Low (tertile 1)	Medium (tertile 2)	High (tertile 3)	Mean ± SD, g/d	*P* -interaction
Overall population, *n* (%)	72,821 (33.5)	74,285 (34.1)	70,450 (32.4)	9.82 ± 12.69		191,576 (33.4)	191,575 (33.3)	191,575 (33.3)	156.37 ± 102.19		191,576 (33.4)	191,575 (33.3)	191,575 (33.3)	23.37 ± 12.38	
Noncases, *n* (%)	71,830 (33.3)	73,932 (34.3)	70,061 (32.4)	10.79 ± 14.19		190,572 (33.4)	190,337 (33.3)	190,603 (33.4)	156.39 ± 102.24		190,402 (33.3)	190,371 (33.3)	190,739 (33.4)	23.38 ± 12.40	
Cases, *n* (%)	991 (57.2)	353 (20.4)	389 (22.4)	9.81 ± 12.68		1004 (31.3)	1238 (38.5)	972 (30.2)	153.34 ± 93.32		1174 (36.5)	1204 (37.5)	836 (26.0)	21.04 ± 9.07	
TNM stage															
MIBC, *n* (%)	360 (63.7)	92 (16.3)	113 (20.0)	5.73 ± 11.50		267 (34.5)	356 (46.1)	150 (19.4)	135.49 ± 75.98		273 (35.3)	323 (41.8)	177 (22.9)	20.68 ± 8.56	
NMIBC, *n* (%)	424 (59.5)	133 (18.7)	156 (21.8)	6.78 ± 13.65		422 (33.3)	491 (38.7)	355 (28.0)	149.82 ± 97.02		472 (37.2)	467 (36.8)	329 (26.0)	20.84 ± 9.13	
Person-years	1,016,724	870,317	855,859	9.82 ± 12.69		1,929,466	2,262,417	2,143,784	156.38 ± 102.23		2,001,790	2,187,860	2,146,058	23.37 ± 12.38	
Sex					0.906					0.048					0.336
Male, *n* (%)	22,476 (36.1)	18,167 (29.2)	21,659 (34.7)	10.98 ± 14.52		57,331 (30.4)	51,474 (27.3)	80,057 (42.4)	177.41 ± 118.64		67,336 (35.7)	59,435 (31.5)	62,091 (32.8)	22.02 ± 10.68	
Female, *n* (%)	50,345 (32.4)	56,118 (36.2)	48,791 (31.4)	9.40 ± 11.93		134,245 (34.8)	140,101 (36.3)	111,518 (28.9)	146.08 ± 91.34		124,240 (32.2)	132,140 (34.3)	129,484 (33.6)	24.03 ± 13.09	
Age,[2] y	52.98	49.75	48.51	9.82 ± 12.69	0.724	54.96	52.07	50.90	156.37 ± 102.19	0.406	54.93	51.86	51.14	23.37 ± 12.38	0.431
≤55, *n* (%)	40,336 (28.4)	50,475 (35.6)	50,994 (36.0)	10.22 ± 12.66		97,204 (28.6)	117,384 (34.5)	125,269 (36.9)	166.82 ± 104.19		97,474 (28.7)	117,242 (34.5)	125,141 (36.8)	24.52 ± 12.49	
55–60, *n* (%)	12,111 (37.8)	10,592 (33.1)	9300 (29.1)	9.04 ± 11.61		33,855 (34.5)	31,659 (32.3)	32,527 (33.2)	154.42 ± 102.14		33,998 (34.7)	32,299 (32.9)	31,744 (32.4)	23.03 ± 12.43	
60–65, *n* (%)	10,241 (41.8)	7687 (31.4)	6557 (26.8)	9.13 ± 12.47		28,094 (35.4)	26,446 (33.3)	24,846 (31.3)	149.48 ± 96.97		29,037 (36.6)	26,494 (33.4)	23,855 (30.0)	22.34 ± 11.85	
65–70, *n* (%)	6919 (52.1)	3653 (27.5)	2709 (20.4)	8.92 ± 13.95		18,125 (50.6)	11,241 (31.4)	6464 (18.0)	116.61 ± 83.20		17,708 (49.4)	10,284 (28.7)	7838 (21.9)	19.74 ± 11.78	
70–75, *n* (%)	2311 (54.7)	1305 (30.9)	610 (14.4)	8.08 ± 12.60		12,691 (68.5)	3917 (22.2)	1909 (10.3)	88.89 ± 68.98		12,691 (68.5)	3917 (22.2)	1909 (10.3)	15.85 ± 8.61	
>75, *n* (%)	903 (51.4)	573 (32.6)	280 (16.0)	8.15 ± 13.10		1607 (51.9)	928 (30.0)	560 (18.1)	111.71 ± 76.90		1331 (43.0)	897 (29.0)	867 (28.0)	21.23 ± 11.68	
Smoking status															
Never, *n* (%)	38,321 (32.0)	42,404 (35.4)	39,024 (32.6)	9.91 ± 12.91		97,586 (34.1)	98,375 (34.4)	90,409 (31.6)	152.51 ± 98.36		89,338 (31.2)	94,872 (33.1)	102,160 (35.7)	24.37 ± 13.21	
Former, *n* (%)	21,503 (36.3)	19,219 (32.4)	18,553 (31.3)	9.43 ± 12.97		62,296 (36.8)	52,397 (31.0)	54,517 (32.2)	151.42 ± 103.60		62,807 (37.1)	54,623 (32.3)	51,780 (30.6)	22.25 ± 11.83	
Current, *n* (%)	12,997 (33.7)	12,662 (32.9)	12,873 (33.4)	9.36 ± 11.52		31,694 (26.6)	40,803 (34.3)	46,649 (39.2)	172.70 ± 107.43		39,431 (33.1)	42,080 (35.3)	37,635 (31.6)	22.56 ± 10.79	
Smoking pack-years[3]	22.99	19.22	19.72	9.65 ± 12.30		24.50	22.66	23.08	150.29 ± 102.03		24.84	22.72	22.36	23.03 ± 12.67	
Smoking[4]					0.878					0.984					0.970
0, *n* (%)	38,321 (32.0)	42,404 (35.4)	39,024 (32.6)	9.91 ± 12.91		97,586 (34.1)	98,375 (34.4)	90,409 (31.6)	152.51 ± 98.36		89,338 (31.2)	94,872 (33.1)	102,160 (35.7)	24.37 ± 13.21	
1, *n* (%)	5526 (29.8)	6513 (35.2)	6489 (35.0)	9.55 ± 11.85		16,366 (28.9)	19,438 (34.3)	20,834 (36.8)	166.01 ± 104.24		18,745 (33.1)	20,112 (35.5)	17,781 (31.4)	22.49 ± 10.71	
2, *n* (%)	5930 (39.7)	4418 (29.6)	4594 (30.8)	8.95 ± 11.10		12,788 (24.8)	18,134 (35.1)	20,703 (40.1)	176.88 ± 109.31		17,486 (33.9)	18,410 (35.7)	15,729 (30.4)	22.31 ± 10.46	
3, *n* (%)	3555 (66.6)	693 (13.0)	1087 (20.4)	11.99 ± 16.22		22,466 (81.6)	4201 (15.3)	869 (3.2)	67.58 ± 46.92		19,501 (70.8)	5459 (19.8)	2576 (9.4)	14.31 ± 8.10	
4, *n* (%)	2505 (72.0)	368 (10.6)	606 (17.4)	12.53 ± 16.88		8996 (74.8)	2450 (20.4)	582 (4.8)	76.84 ± 52.01		8111 (67.4)	2612 (21.7)	1305 (10.9)	14.93 ± 8.31	
5, *n* (%)	1541 (30.4)	1731 (34.2)	1790 (35.4)	9.82 ± 11.33		2540 (23.3)	3231 (29.7)	5112 (47.0)	187.69 ± 112.19		3200 (29.4)	3558 (32.7)	4125 (37.9)	24.15 ± 12.48	
6, *n* (%)	15,443 (30.6)	18,158 (36.0)	16,860 (33.4)	9.73 ± 12.58		30,834 (23.8)	45,746 (35.3)	53,066 (40.9)	176.15 ± 103.30		35,195 (27.1)	46,552 (35.9)	47,899 (37.0)	24.61 ± 11.77	
Ethnicity															
Non-Caucasian, *n* (%)						3772 (94.0)	228 (5.7)	15 (0.3)	49.05 (31.28)		3302 (82.2)	514 (12.8)	199 (5.0)	11.88 (7.26)	
Caucasian,[5] *n* (%)	72,821 (33.5)	74,285 (34.1)	70,450 (32.4)	9.82 ± 12.69		187,804 (32.9)	191,347 (33.5)	191,560 (33.6)	157.13 ± 102.12		188,274 (33.0)	191,061 (33.5)	191,376 (33.5)	23.45 ± 12.37	
Energy intake, kcal/d	2055.90	2074.74	2251.09	9.82 ± 12.69		1731.56	2002.27	2455.98	156.37 ± 102.19		1726.74	2016.21	2446.86	23.37 ± 12.38	
Alcohol intake, mL/d	9.17	9.79	11.09	9.69 ± 12.43		7.20	9.57	12.44	157.61 ± 103.54		8.17	9.77	11.26	23.61 ± 12.39	
Fat intake, g/d	24.21	22.77	24.55	9.80 ± 12.69		16.88	25.30	31.74	156.57 ± 101.98		18.55	25.78	29.59	23.44 ± 12.52	
Fruit intake, g/d	154.49	147.67	160.53	9.83 ± 12.87		101.98	132.83	134.84	156.71 ± 101.48		72.61	118.01	179.02	23.37 ± 12.39	
Meat intake, g/d	85.93	82.24	88.92	9.80 ± 12.63		54.48	75.45	91.59	160.86 ± 101.79		54.50	73.94	93.09	23.75 ± 12.38	
Sugar intake, g/d	22.10	23.97	23.52	9.96 ± 13.06		20.73	23.32	27.37	155.95 ± 102.80		18.69	20.77	31.96	22.99 ± 11.97	
Vegetable intake, g/d	222.97	239.05	263.39	9.82 ± 12.69		181.77	212.32	204.19	156.68 ± 102.06		130.47	189.46	278.35	23.38 ± 12.38	
Total fluid intake, mL/d	1189.35	1264.41	1153.81	9.82 ± 12.69		1368.74	1337.53	1444.93	156.64 ± 102.07		1420.23	1397.25	1333.72	23.37 ± 12.38	

[1] The intervals of tertiles were defined as follows: total whole grain: 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; total refined grain: 0 ≤ tertile 1 ≤ 102 g/d, 102 < tertile 2 ≤ 181 g/d, tertile 3 > 181 g/d; total dietary fiber: 0 ≤ tertile 1 ≤ 17 g/d, 17 < tertile 2 ≤ 25 g/d, tertile 3 > 25 g/d. *P*-interaction < 0.05 was considered statistically significant. MIBC, muscle invasive bladder cancer; NMIBC, nonmuscle invasive bladder cancer; TNM, tumor, nodes, and metastasis classification.

[2] Age at the time of recruitment.

[3] Pack-years was defined as the number of cigarettes smoked per day multiplied by the years of smoking.

[4] Smoking was defined as a dummy variable: 0 (never smokers); 1 [current light smokers (i.e., smoking <20 pack-years)]; 2 [current heavy smokers (i.e., smoking >20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e., smokers who ceased smoking >1 y prior and smoked <20 pack-years)]; 5 [former heavy smokers (i.e., smokers who ceased smoking >1 y prior and smoked >20 pack-years)]; or 6 [former smokers (smokers who ceased smoking >1 y prior and no information on pack-years)].

[5] All of the included participants for whole grain intake were Caucasian.

TABLE 2 Risk of bladder cancer according to intakes of total grains, total whole grains, and total refined grains[1]

Grain source, subgroup, intake tertiles	Cases/participants, *n*	Model 2[2]		
		HR (95% CI)	HR per 1-SD increase (95% CI)	*P*-trend
Total grains, g/d				
Overall				
Tertile 1	1005/191,576	Ref.	0.97 (0.92, 1.02)	0.240
Tertile 2	1227/191,575	0.93 (0.84, 1.02)		
Tertile 3	982/191,575	0.94 (0.83, 1.05)		
MIBC				
Tertile 1	263/190,834	Ref.	0.90 (0.78, 1.02)	0.119
Tertile 2	350/190,698	0.89 (0.74, 1.08)		
Tertile 3	160/190,753	0.79 (0.61, 1.02)		
NMIBC				
Tertile 1	425/190,996	Ref.	0.99 (0.91, 1.07)	0.750
Tertile 2	481/190,829	0.96 (0.82, 1.13)		
Tertile 3	352/190,955	0.93 (0.77, 1.14)		
Male				
Tertile 1	793/62,954	Ref.	0.91 (0.85, 0.98)	0.011
Tertile 2	1049/62,954	0.89 (0.80, 1.00)		
Tertile 3	574/62,954	0.88 (0.77, 1.02)		
Female				
Tertile 1	287/128,622	Ref.	1.07 (0.97, 1.19)	0.174
Tertile 2	291/128,621	0.97 (0.81, 1.17)		
Tertile 3	220/128,621	1.10 (0.88, 1.37)		
Never smoker				
Tertile 1	212/95,457	Ref.	1.00 (0.90, 1.13)	0.801
Tertile 2	244/95,457	1.02 (0.79, 1.32)		
Tertile 3	201/95,456	0.94 (0.75, 1.17)		
Current smoker				
Tertile 1	403/39,716	Ref.	0.97 (0.89, 1.06)	0.488
Tertile 2	456/39,715	1.04 (0.90, 1.20)		
Tertile 3	339/39,715	0.99 (0.82, 1.19)		
Former smoker				
Tertile 1	416/56,404	Ref.	0.90 (0.82, 1.01)	0.517
Tertile 2	543/56,403	0.85 (0.72, 1.00)		
Tertile 3	400/56,403	0.85 (0.69, 1.02)		
Total whole grains, g/d				
Overall				
Tertile 1	991/72,821	Ref.	0.95 (0.91, 0.99)	0.023
Tertile 2	353/74,285	1.01 (0.89, 1.15)		
Tertile 3	389/70,450	0.87 (0.77, 0.98)		
MIBC				
Tertile 1	360/72,190	Ref.	0.92 (0.85, 1.00)	0.038
Tertile 2	92/74,024	1.21 (0.95, 1.53)		
Tertile 3	113/70,174	0.86 (0.70, 1.07)		
NMIBC				
Tertile 1	424/72,254	Ref.	0.96 (0.90, 1.03)	0.281
Tertile 2	133/72,065	1.07 (0.87, 1.32)		
Tertile 3	156/70,217	0.85 (0.70, 1.03)		
Male				
Tertile 1	787/22,476	Ref.	0.93 (0.83, 1.02)	0.059
Tertile 2	259/19,149	0.98 (0.84, 1.14)		
Tertile 3	295/20,677	0.85 (0.74, 0.98)		
Female				
Tertile 1	204/51,754	Ref.	0.93 (0.85, 1.01)	0.053
Tertile 2	104/51,830	0.98 (0.83, 1.15)		
Tertile 3	84/51,670	0.83 (0.71, 0.96)		
Never smoker				
Tertile 1	188/39,917	Ref.	0.96 (0.87, 1.06)	0.434
Tertile 2	93/40,808	1.04 (0.86, 1.45)		
Tertile 3	77/39,024	0.83 (0.63, 1.10)		

(*Continued*)

TABLE 2 (*Continued*)

Grain source, subgroup, intake tertiles	Cases/participants, *n*	Model 2[2]		
		HR (95% CI)	HR per 1-SD increase (95% CI)	*P*-trend
Current smoker				
Tertile 1	362/12,997	Ref.	0.96 (0.90, 1.02)	0.167
Tertile 2	117/12,699	1.00 (0.80, 1.25)		
Tertile 3	151/12,836	0.87 (0.71, 1.08)		
Former smoker				
Tertile 1	425/19,760	Ref.	0.94 (0.87, 1.02)	0.125
Tertile 2	152/19,970	0.98 (0.80, 1.19)		
Tertile 3	168/19,545	0.90 (0.75, 1.09)		
Total refined grains, g/d				
Overall				
Tertile 1	1004/191,576	Ref.	0.97 (0.92, 1.02)	0.242
Tertile 2	1238/191,575	0.93 (0.85, 1.03)		
Tertile 3	972/191,575	0.95 (0.84, 1.07)		
MIBC				
Tertile 1	267/190,839	Ref.	0.93 (0.81, 1.07)	0.327
Tertile 2	356/190,693	0.90 (0.74, 1.08)		
Tertile 3	150/190,753	0.80 (0.61, 1.04)		
NMIBC				
Tertile 1	422/190,994	Ref.	0.99 (0.91, 1.08)	0.906
Tertile 2	491/190,828	1.00 (0.85, 1.18)		
Tertile 3	355/190,958	0.98 (0.80, 1.20)		
Male				
Tertile 1	808/62,954	Ref.	0.92 (0.86, 1.00)	0.040
Tertile 2	1048/62,954	0.89 (0.80, 1.00)		
Tertile 3	560/62,954	0.87 (0.75, 1.01)		
Female				
Tertile 1	283/128,623	Ref.	1.08 (0.98, 1.20)	0.135
Tertile 2	295/128,620	1.00 (0.83, 1.20)		
Tertile 3	220/128,621	1.11 (0.89, 1.40)		
Never smoker				
Tertile 1	217/95,457	Ref.	0.99 (0.91, 1.10)	0.720
Tertile 2	232/95,457	0.92 (0.70, 1.08)		
Tertile 3	208/95,456	0.99 (0.81, 1.24)		
Current smoker				
Tertile 1	404/39,716	Ref.	0.98 (0.90, 1.07)	0.679
Tertile 2	464/39,715	1.07 (0.92, 1.24)		
Tertile 3	330/39,715	1.00 (0.83, 1.21)		
Former smoker				
Tertile 1	414/56,404	Ref.	0.91 (0.84, 1.00)	0.054
Tertile 2	552/56,403	0.89 (0.73, 1.07)		
Tertile 3	393/56,403	0.88 (0.75, 1.02)		

[1]The intervals of tertiles were defined as follows: total grains: *1*) overall, 0 ≤ tertile 1 ≤ 105 g/d, 105 < tertile 2 ≤ 186 g/d, tertile 3 > 186 g/d; *2*) MIBC, 0 ≤ tertile 1 ≤ 105 g/d, 105 < tertile 2 ≤ 186 g/d, tertile 3 > 186 g/d; *3*) NMIBC, 0 ≤ tertile 1 ≤ 105 g/d, 105 < tertile 2 ≤ 186 g/d, tertile 3 > 186 g/d; *4*) male, 0 ≤ tertile 1 ≤ 113 g/d, 113 < tertile 2 ≤ 215 g/d, tertile 3 > 215 g/d; *5*) female, 0 ≤ tertile 1 ≤ 102 g/d, 102 < tertile 2 ≤ 173 g/d, tertile 3 > 173 g/d; *6*) never smoker, 0 ≤ tertile 1 ≤ 104 g/d, 104 < tertile 2 ≤ 181 g/d, tertile 3 > 181 g/d; *7*) current smoker, 0 ≤ tertile 1 ≤ 121 g/d, 121 < tertile 2 ≤ 204 g/d, tertile 3 > 204 g/d; *8*) former smoker, 0 ≤ tertile 1 ≤ 96 g/d, 96 < tertile 2 ≤ 182 g/d, tertile 3 > 182 g/d; total whole grains: *1*) overall, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; *2*) MIBC, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; *3*) NMIBC, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; *4*) male, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 9 g/d, tertile 3 > 9 g/d; *5*) female, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; *6*) never smoker, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; *7*) current smoker, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; *8*) former smoker, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; total refined grains: *1*) overall, 0 ≤ tertile 1 ≤ 102 g/d, 102 < tertile 2 ≤ 181 g/d, tertile 3 > 181 g/d; *2*) MIBC, 0 ≤ tertile 1 ≤ 102 g/d, 102 < tertile 2 ≤ 181 g/d, tertile 3 > 181 g/d; *3*) NMIBC, 0 ≤ tertile 1 ≤ 102 g/d, 102 < tertile 2 ≤ 181 g/d, tertile 3 > 181 g/d; *4*) male, 0 ≤ tertile 1 ≤ 111 g/d, 111 < tertile 2 ≤ 211 g/d, tertile 3 > 211 g/d; *5*) female, 0 ≤ tertile 1 ≤ 99 g/d, 99 < tertile 2 ≤ 169 g/d, tertile 3 > 169 g/d; *6*) never smoker, 0 ≤ tertile 1 ≤ 100 g/d, 100 < tertile 2 ≤ 176 g/d, tertile 3 > 176 g/d; *7*) current smoker, 0 ≤ tertile 1 ≤ 119 g/d, 119 < tertile 2 ≤ 201 g/d, tertile 3 > 201 g/d; *8*) former smoker, 0 ≤ tertile 1 ≤ 93 g/d, 93 < tertile 2 ≤ 178 g/d, tertile 3 > 178 g/d. Reference group was lowest intake (tertile 1). *P*-trend < 0.05 was considered statistically significant. MIBC, muscle invasive bladder cancer; NMIBC, nonmuscle invasive bladder cancer.

[2]Model 2 of Cox regression: adjusted for age (y; continuous), sex (male or female, if applicable), smoking {smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e., smoking <20 pack-years)]; 2 [current heavy smokers (i.e., smoking >20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e., smokers who ceased smoking >1 y prior and smoked <20 pack-years)]; 5 [former heavy smokers (i.e., smokers who ceased smoking >1 y prior and smoked >20 pack-years)]; or 6 [former smokers (smokers who ceased smoking >1 y prior and no information on pack-years)]}, total energy intake (kcal/d; continuous), ethnicity (Caucasian or non-Caucasian, if applicable), alcohol intake (mL/d; continuous), fruit intake (g/d; continuous), fat intake (g/d; continuous), meat intake (g/d; continuous), sugar intake (g/d; continuous), vegetable intake (g/d; continuous), and total fluid intake (mL/d; continuous).

TABLE 3 Risk of bladder cancer according to individual intakes of whole grains and refined grains[1]

Grain source, subgroup, intake tertiles	Cases/participants, *n*	Model 2[2] HR (95% CI)	HR per 1-SD increase (95% CI)	*P*-trend
Whole grains, g/d				
Brown rice				
Tertile 1	910/64,959	Ref.	0.89 (0.82, 0.95)	0.001
Tertile 2	262/64,685	0.97 (0.83, 1.13)		
Tertile 3	270/64,822	0.78 (0.67, 0.92)		
Wheat or oat				
Tertile 1	877/15,715	Ref.	0.99 (0.92, 1.06)	0.747
Tertile 2	81/3590	1.20 (0.95, 1.52)		
Tertile 3	210/9032	0.93 (0.80, 1.09)		
Basic products of other cereals[3]				
Tertile 1	820/4802	Ref.	0.98 (0.91, 1.06)	0.637
Tertile 2	25/233	0.78 (0.52, 1.16)		
Tertile 3	32/212	1.03 (0.72, 1.47)		
Refined grains, g/d				
White rice				
Tertile 1	976/44,980	Ref.	0.96 (0.88, 1.04)	0.344
Tertile 2	288/44,951	1.09 (0.93, 1.28)		
Tertile 3	221/44,954	1.05 (0.92, 1.21)		
Pasta or noodles				
Tertile 1	806/193,351	Ref.	0.99 (0.94, 1.04)	0.697
Tertile 2	787/188,377	0.90 (0.81, 0.99)		
Tertile 3	744/187,751	0.90 (0.80, 1.01)		
Leavened bread				
Tertile 1	1057/191,576	Ref.	0.99 (0.94, 1.05)	0.746
Tertile 2	1260/191,594	1.01 (0.91, 1.11)		
Tertile 3	897/191,556	1.01 (0.89, 1.15)		
Unleavened bread				
Tertile 1	775/119,122	Ref.	0.95 (0.89, 1.00)	0.070
Tertile 2	939/181,124	0.95 (0.85, 1.06)		
Tertile 3	863/181,124	0.97 (0.87, 1.09)		
Bakery wares				
Tertile 1	1732/477,213	Ref.	0.99 (0.96, 1.01)	0.307
Tertile 2	688/14,011	1.08 (0.76, 1.54)		
Tertile 3	448/14,011	1.00 (0.70, 1.44)		
Savory cereals dishes[4]				
Tertile 1	161/28,872	Ref.	0.95 (0.83, 1.08)	0.423
Tertile 2	96/18,996	0.96 (0.74, 1.24)		
Tertile 3	89/21,623	0.89 (0.67, 1.17)		
Breakfast cereals				
Tertile 1	1013/33,151	Ref.	0.97 (0.90, 1.04)	0.422
Tertile 2	251/32,949	1.01 (0.86, 1.20)		
Tertile 3	250/31,728	0.97 (0.81, 1.16)		

[1]The intervals of tertiles were defined as follows: total whole grains: *1*) brown rice, 0 ≤ tertile 1 ≤ 4 g/d, 4 < tertile 2 ≤ 9 g/d, tertile 3 > 9 g/d; *2*) wheat or oat, tertile 1 = 0 g/d, 0 < tertile 2 ≤ 2 g/d, tertile 3 > 2 g/d; *3*) basic products of other cereals: tertile 1 = 0 g/d, 0 < tertile 2 ≤ 3 g/d, tertile 3 > 3 g/d; total refined grains: *1*) white rice, 0 ≤ tertile 1 ≤ 4 g/d, 4 < tertile 2 ≤ 11 g/d, tertile 3 > 11 g/d; *2*) pasta or noodles, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 9 g/d, tertile 3 > 9 g/d; *3*) leavened bread, 0 ≤ tertile 1 ≤ 73 g/d, 73 < tertile 2 ≤ 160 g/d, tertile 3 > 160 g/d; *4*) unleavened bread, tertile 1 = 0 g/d, 0 < tertile 2 ≤ 4 g/d, tertile 3 > 4 g/d; *5*) bakery wares, tertile 1 = 0 g/d, 0 < tertile 2 ≤ 27 g/d, tertile 3 > 27 g/d; *6*) savory cereals dishes, 0 ≤ tertile 1 ≤ 3 g/d, 3 < tertile 2 ≤ 7 g/d, tertile 3 > 7 g/d; *7*) breakfast cereals, 0 ≤ tertile 1 ≤ 6 g/d, 6 < tertile 2 ≤ 27 g/d, tertile 3 > 27 g/d. Reference group was lowest intake (tertile 1). *P*-trend < 0.05 was considered statistically significant.

[2]Model 2 of Cox regression: adjusted for age (y; continuous), sex (male/female), smoking {smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e., smoking <20 pack-years)]; 2 [current heavy smokers (i.e., smoking >20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e., smokers who ceased smoking >1 y prior and smoked <20 pack-years)]; 5 [former heavy smokers (i.e., smokers who ceased smoking >1 y prior and smoked >20 pack-years)]; or 6 [former smokers (smokers who ceased smoking >1 y prior and no information on pack-years)]}, total energy intake (kcal/d; continuous), ethnicity (Caucasian or non-Caucasian, if applicable), alcohol intake (mL/d; continuous), fruit intake (g/d; continuous), fat intake (g/d; continuous), meat intake (g/d; continuous), sugar intake (g/d; continuous), vegetable intake (g/d; continuous), and total fluid intake (mL/d; continuous).

[3]"Basic products of other cereals": buckwheat, millet, sorghum, or spelt.

[4]"Savory cereals dishes": dumplings, couscous, risotto, pizza, pancake, or pie.

TABLE 4 Risk of bladder cancer according to intakes of total dietary fiber and individual sources of dietary fiber[1]

Grain source, subgroup, intake tertiles	Cases/participants, *n*	Model 2[2]		
		HR (95% CI)	HR per 1-SD increase (95% CI)	*P*-trend
Total dietary fiber, g/d				
Overall				
Tertile 1	1015/191,576	Ref.	0.91 (0.82, 0.98)	0.021
Tertile 2	1097/191,575	0.92 (0.83, 1.02)		
Tertile 3	1102/191,575	0.86 (0.76, 0.98)		
Male				
Tertile 1	775/62,954	Ref.	0.90 (0.83, 0.97)	0.007
Tertile 2	971/62,954	0.94 (0.85, 1.03)		
Tertile 3	670/62,954	0.89 (0.79, 0.98)		
Female				
Tertile 1	322/128,622	Ref.	0.89 (0.79, 1.00)	0.049
Tertile 2	272/128,621	0.81 (0.68, 0.96)		
Tertile 3	204/128,621	0.79 (0.66, 0.97)		
Never smoker				
Tertile 1	242/95,457	Ref.	0.95 (0.80, 1.12)	0.523
Tertile 2	272/95,457	0.91 (0.69, 1.20)		
Tertile 3	170/95,456	0.84 (0.67, 1.04)		
Current smoker				
Tertile 1	436/39,716	Ref.	0.94 (0.85, 1.03)	0.287
Tertile 2	438/39,715	0.92 (0.78, 1.09)		
Tertile 3	324/39,715	0.82 (0.67, 1.00)		
Former smoker				
Tertile 1	473/56,404	Ref.	0.89 (0.80, 1.00)	0.059
Tertile 2	492/56,403	0.97 (0.82, 1.14)		
Tertile 3	394/56,403	0.85 (0.70, 1.05)		
Cereal fiber, g/d				
Overall				
Tertile 1	1111/191,576	Ref.	0.96 (0.91, 1.01)	0.124
Tertile 2	1203/191,576	0.95 (0.86, 1.04)		
Tertile 3	900/191,574	0.95 (0.85, 1.07)		
Male				
Tertile 1	869/62,954	Ref.	0.91 (0.86, 1.01)	0.058
Tertile 2	1017/62,954	0.95 (0.85, 1.05)		
Tertile 3	530/62,954	0.89 (0.77, 1.03)		
Female				
Tertile 1	300/128,622	Ref.	0.97 (0.91, 1.07)	0.329
Tertile 2	293/128,621	1.07 (0.85, 1.34)		
Tertile 3	205/128,621	1.03 (0.86, 1.23)		
Never smoker				
Tertile 1	227/95,457	Ref.	0.98 (0.91, 1.04)	0.435
Tertile 2	245/95,457	1.01 (0.80, 1.34)		
Tertile 3	185/95,456	0.99 (0.81, 1.23)		
Current smoker				
Tertile 1	462/39,723	Ref.	0.97 (0.89, 1.06)	0.525
Tertile 2	416/39,718	1.00 (0.87, 1.16)		
Tertile 3	320/39,705	0.96 (0.79, 1.15)		
Former smoker				
Tertile 1	450/56,404	Ref.	0.90 (0.86, 1.01)	0.275
Tertile 2	557/56,403	0.88 (0.76, 1.02)		
Tertile 3	352/56,403	0.82 (0.69, 1.00)		
Fruit fiber, g/d				
Overall				
Tertile 1	1059/191,576	Ref.	0.98 (0.90, 1.06)	0.573
Tertile 2	950/191,613	0.98 (0.87, 1.11)		
Tertile 3	1205/191,537	0.97 (0.89, 1.07)		
Male				
Tertile 1	688/62,954	Ref.	1.01 (0.92, 1.11)	0.792
Tertile 2	689/62,954	0.98 (0.88, 1.10)		
Tertile 3	1039/62,954	1.02 (0.89, 1.17)		

(*Continued*)

TABLE 4 (*Continued*)

Grain source, subgroup, intake tertiles	Cases/participants, *n*	Model 2[2]		
		HR (95% CI)	HR per 1-SD increase (95% CI)	*P*-trend
Female				
Tertile 1	250/128,628	Ref.	0.87 (0.73, 1.03)	0.119
Tertile 2	264/128,615	0.94 (0.78, 1.13)		
Tertile 3	284/128,337	0.76 (0.58, 1.02)		
Never smoker				
Tertile 1	170/95,459	Ref.	0.94 (0.78, 1.13)	0.517
Tertile 2	231/95,455	1.02 (0.88, 1.19)		
Tertile 3	256/95,456	0.89 (0.73, 1.09)		
Current smoker				
Tertile 1	380/39,716	Ref.	0.99 (0.88, 1.18)	0.574
Tertile 2	376/39,715	1.17 (0.95, 1.43)		
Tertile 3	442/39,715	1.11 (0.83, 1.49)		
Former smoker				
Tertile 1	396/56,413	Ref.	0.97 (0.86, 1.10)	0.639
Tertile 2	384/56,394	0.93 (0.81, 1.08)		
Tertile 3	579/56,403	1.03 (0.86, 1.24)		
Vegetable fiber, g/d				
Overall				
Tertile 1	1185/191,576	Ref.	0.93 (0.86, 1.00)	0.046
Tertile 2	1223/191,575	0.98 (0.89, 1.08)		
Tertile 3	806/191,575	0.91 (0.79, 1.05)		
Male				
Tertile 1	718/62,954	Ref.	0.95 (0.88, 1.02)	0.176
Tertile 2	810/62,954	1.02 (0.91, 1.15)		
Tertile 3	888/62,954	0.90 (0.78, 1.05)		
Female				
Tertile 1	359/128,622	Ref.	0.88 (0.74, 1.05)	0.151
Tertile 2	295/128,621	0.90 (0.75, 1.08)		
Tertile 3	144/128,621	0.77 (0.59, 1.01)		
Never smoker				
Tertile 1	282/95,457	Ref.	0.92 (0.76, 1.12)	0.400
Tertile 2	237/95,457	0.93 (0.76, 1.13)		
Tertile 3	138/95,457	0.93 (0.70, 1.24)		
Current smoker				
Tertile 1	403/39,716	Ref.	0.87 (0.76, 1.01)	0.171
Tertile 2	453/39,715	0.95 (0.81, 1.12)		
Tertile 3	342/39,715	0.84 (0.67, 1.04)		
Former smoker				
Tertile 1	488/56,404	Ref.	0.94 (0.82, 1.07)	0.328
Tertile 2	497/56,403	1.01 (0.87, 1.17)		
Tertile 3	374/56,403	0.89 (0.72, 1.09)		

[1]The intervals of tertiles were defined as follows: total dietary fiber: *1*) overall, 0 ≤ tertile 1 ≤ 17 g/d, 17 < tertile 2 ≤ 25 g/d, tertile 3 > 25 g/d; *2*) male, 0 ≤ tertile 1 ≤ 17 g/d, 17 < tertile 2 ≤ 26 g/d, tertile 3 > 26 g/d; *3*) female, 0 ≤ tertile 1 ≤ 18 g/d, 18 < tertile 2 ≤ 26 g/d, tertile 3 > 26 g/d; *4*) never smoker, 0 ≤ tertile 1 ≤ 18 g/d, 18 < tertile 2 ≤ 26 g/d, tertile 3 > 26 g/d; *5*) current smoker, 0 ≤ tertile 1 ≤ 17 g/d, 17 < tertile 2 ≤ 25 g/d, tertile 3 > 25 g/d; *6*) former smoker, 0 ≤ tertile 1 ≤ 17 g/d, 17 < tertile 2 ≤ 25 g/d, tertile 3 > 25 g/d; cereal fiber: *1*) overall, 0 ≤ tertile 1 ≤ 7 g/d, 7 < tertile 2 ≤ 12 g/d, tertile 3 > 12 g/d; *2*) male, 0 ≤ tertile 1 ≤ 7 g/d, 7 < tertile 2 ≤ 13 g/d, tertile 3 > 13 g/d; *3*) female, 0 ≤ tertile 1 ≤ 6 g/d, 6 < tertile 2 ≤ 11 g/d, tertile 3 > 11 g/d; *4*) never smoker, 0 ≤ tertile 1 ≤ 6 g/d, 6 < tertile 2 ≤ 11 g/d, tertile 3 > 11 g/d; *5*) current smoker, 0 ≤ tertile 1 ≤ 8 g/d, 8 < tertile 2 ≤ 13 g/d, tertile 3 > 13 g/d; *6*) former smoker, 0 ≤ tertile 1 ≤ 6 g/d, 6 < tertile 2 ≤ 11 g/d, tertile 3 > 11 g/d; fruit fiber: *1*) overall, 0 ≤ tertile 1 ≤ 2 g/d, 2 < tertile 2 ≤ 4 g/d, tertile 3 > 4 g/d; *2*) male, 0 ≤ tertile 1 ≤ 1 g/d, 1 < tertile 2 ≤ 3 g/d, tertile 3 > 3 g/d; *3*) female, 0 ≤ tertile 1 ≤ 2 g/d, 2 < tertile 2 ≤ 4 g/d, tertile 3 > 4 g/d; *4*) never smoker, 0 ≤ tertile 1 ≤ 2 g/d, 2 < tertile 2 ≤ 4 g/d, tertile 3 > 4 g/d; *5*) current smoker, 0 ≤ tertile 1 ≤ 1 g/d, 1 < tertile 2 ≤ 3 g/d, tertile 3 > 3 g/d; *6*) former smoker, 0 ≤ tertile 1 ≤ 1 g/d, 1 < tertile 2 ≤ 3 g/d, tertile 3 > 3 g/d; vegetable fiber: *1*) overall, 0 ≤ tertile 1 ≤ 5 g/d, 5 < tertile 2 ≤ 9 g/d, tertile 3 > 9 g/d; *2*) male, 0 ≤ tertile 1 ≤ 4 g/d, 4 < tertile 2 ≤ 7 g/d, tertile 3 > 7 g/d; *3*) female, 0 ≤ tertile 1 ≤ 5 g/d, 5 < tertile 2 ≤ 9 g/d, tertile 3 > 9 g/d; *4*) never smoker, 0 ≤ tertile 1 ≤ 5 g/d, 5 < tertile 2 ≤ 9 g/d, tertile 3 > 9 g/d; *5*) current smoker, 0 ≤ tertile 1 ≤ 5 g/d, 5 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; *6*) former smoker, 0 ≤ tertile 1 ≤ 4 g/d, 4 < tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d. Reference group was lowest intake (tertile 1). *P*-trend < 0.05 was considered statistically significant.

[2]Model 2 of Cox regression: adjusted for age (y; continuous), sex (male/female), smoking {smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e., smoking <20 pack-years)]; 2 [current heavy smokers (i.e., smoking >20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e., smokers who ceased smoking >1 y prior and smoked <20 pack-years)]; 5 [former heavy smokers (i.e., smokers who ceased smoking >1 y prior and smoked >20 pack-years)]; or 6 [former smokers (smokers who ceased smoking >1 y prior and no information on pack-years)]}, total energy intake (kcal/d; continuous), ethnicity (Caucasian or non-Caucasian, if applicable), alcohol intake (mL/d; continuous), fruit intake (g/d; continuous), fat intake (g/d; continuous), meat intake (g/d; continuous), sugar intake (g/d; continuous), vegetable intake (g/d; continuous), and total fluid intake (mL/d; continuous).

TABLE 5 Joint association of intake of total whole grain and total dietary fiber with bladder cancer risk[1]

	Total whole grain and total dietary fiber, g/d				
	Model 2[2]				
Total dietary fiber, g/d	Tertile 1	Tertile 2	Tertile 3	*P*-trend	*P*-interaction
Tertile 1					
Cases, *n*	348	421	222	0.031	0.027
HR (95% CI)	Ref.	0.91 (0.79, 1.06)	0.89 (0.70, 1.14)		
Tertile 2					
Cases, *n*	93	157	103		
HR (95% CI)	0.94 (0.74, 1.21)	0.86 (0.69, 1.08)	0.82 (0.63, 1.09)		
Tertile 3					
Cases, *n*	84	152	153		
HR (95% CI)	0.79 (0.60, 1.03)	0.71 (0.57, 0.88)	0.72 (0.54, 0.93)		

[1]The intervals of tertiles were defined as follows: total whole grain: $0 \leq$ tertile 1 ≤ 3 g/d, $3 <$ tertile 2 ≤ 8 g/d, tertile 3 > 8 g/d; total dietary fiber: $0 \leq$ tertile 1 ≤ 17 g/d, $17 <$ tertile 2 ≤ 25 g/d, tertile 3 > 25 g/d. *P*-trend < 0.05 was considered statistically significant. Reference group was lowest intake of both total whole grain and total dietary fiber.

[2]Model 2 of Cox regression: adjusted for age (y; continuous), sex (male/female), smoking {smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e., smoking <20 pack-years)]; 2 [current heavy smokers (i.e., smoking >20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e., smokers who ceased smoking >1 y prior and smoked <20 pack-years)]; 5 [former heavy smokers (i.e., smokers who ceased smoking >1 y prior and smoked >20 pack-years)]; or 6 [former smokers (smokers who ceased smoking >1 y prior and no information on pack-years)]}, total energy intake (kcal/d; continuous), ethnicity (Caucasian or non-Caucasian, if applicable), alcohol intake (mL/d; continuous), fruit intake (g/d; continuous), fat intake (g/d; continuous), meat intake (g/d; continuous), sugar intake (g/d; continuous), vegetable intake (g/d; continuous), and total fluid intake (mL/d; continuous).

Joint association of total whole grain and total dietary fiber with BC risk.

Table 5 shows the results of the Cox regression analyses for the potential joint effect of total whole grain and total dietary fiber on BC. Individuals with the highest intake of both total whole grain and total dietary fiber showed a 28% reduced BC risk (95% CI: 0.54, 0.93; *P* for trend = 0.031) compared with individuals with the lowest intakes of both total whole grain and total dietary fiber.

Dose-response analyses

Figure 1, **Supplemental Table 6**, and **Supplemental Figure 2** show dose–response relations between grain/dietary fiber intake and the risk of BC. There were inverse associations of intakes of total whole grain and total dietary fiber with BC risk, but no association was observed of intakes of total refined grain, cereal fiber, fruit fiber, and vegetable fiber with BC risk. A significant reduction of risk was shown at >15 g/d intake of total whole grain and >25 g/d intake of total dietary fiber; the estimated HRs were 0.97 (0.95, 0.99) and 0.96 (0.94, 0.98) per 5-g daily increment, respectively.

Sensitivity analyses

Removing BC cases diagnosed within the first 2 y after enrolling into each individual study gave similar results, in which a decreased BC risk was observed for total whole grain (comparing the highest with the lowest intake tertile: HR_{model2}: 0.81; 95% CI: 0.67, 0.97; HR per 1-SD increment: 0.95; 95% CI: 0.91, 1.00; *P* for trend = 0.040) and for total dietary fiber (comparing the highest with the lowest intake tertile: HR_{model2}: 0.85; 95% CI: 0.76, 0.96; HR per 1-SD increment: 0.86; 95% CI: 0.78, 0.94; *P* for trend = 0.002) (**Supplemental Table 7**). The analysis excluding missing data (model 2) showed similar results to the analysis with multiple imputation (**Supplemental Table 8**). Results of the quintile-based analyses showed inverse associations between total whole grain and total dietary fiber intakes and BC risk (comparing the highest with the lowest intake quintile: HR_{model2}: 0.86; 95% CI: 0.75, 0.98; *P* for trend = 0.032; and HR_{model2}: 0.84; 95% CI: 0.72, 0.98; *P* for trend = 0.022, respectively) (**Supplemental Table 9**). In addition, excluding pasta as a source of total refined grain showed the same results as when pasta intake was included (**Supplemental Table 10**). The analysis adjusting for both smoking status and smoking pack-years showed similar results with the adjustment of the smoking dummy variable (**Supplemental Table 11**). The meta-analysis approach showed similar results, that is, a significantly reduced BC risk with total whole grain intake (HR: 0.89; 95% CI: 0.81, 0.98) and total dietary fiber intake (HR: 0.89; 95% CI: 0.80, 0.98), whereas there was no evidence of association for intakes of total refined grain and individual sources of dietary fiber with BC risk (**Supplementary Figure 3**); in addition, after removing the study that most likely dominated the analysis for each dietary factor, results remained the same (**Supplemental Table 12**).

Discussion

This large, multicenter, prospective cohort study indicates a potential beneficial effect of total whole grain (particularly brown rice) and total dietary fiber intake for the prevention of BC, whereas intakes of total refined grain and individual fiber sources (i.e., cereal, fruit, and vegetable) did not show any significant association with BC risk.

To our knowledge, this is the first prospective study to investigate the association between whole grain intake and BC risk; in line with this result a previously conducted case-control study reported a nonsignificant protective effect of higher

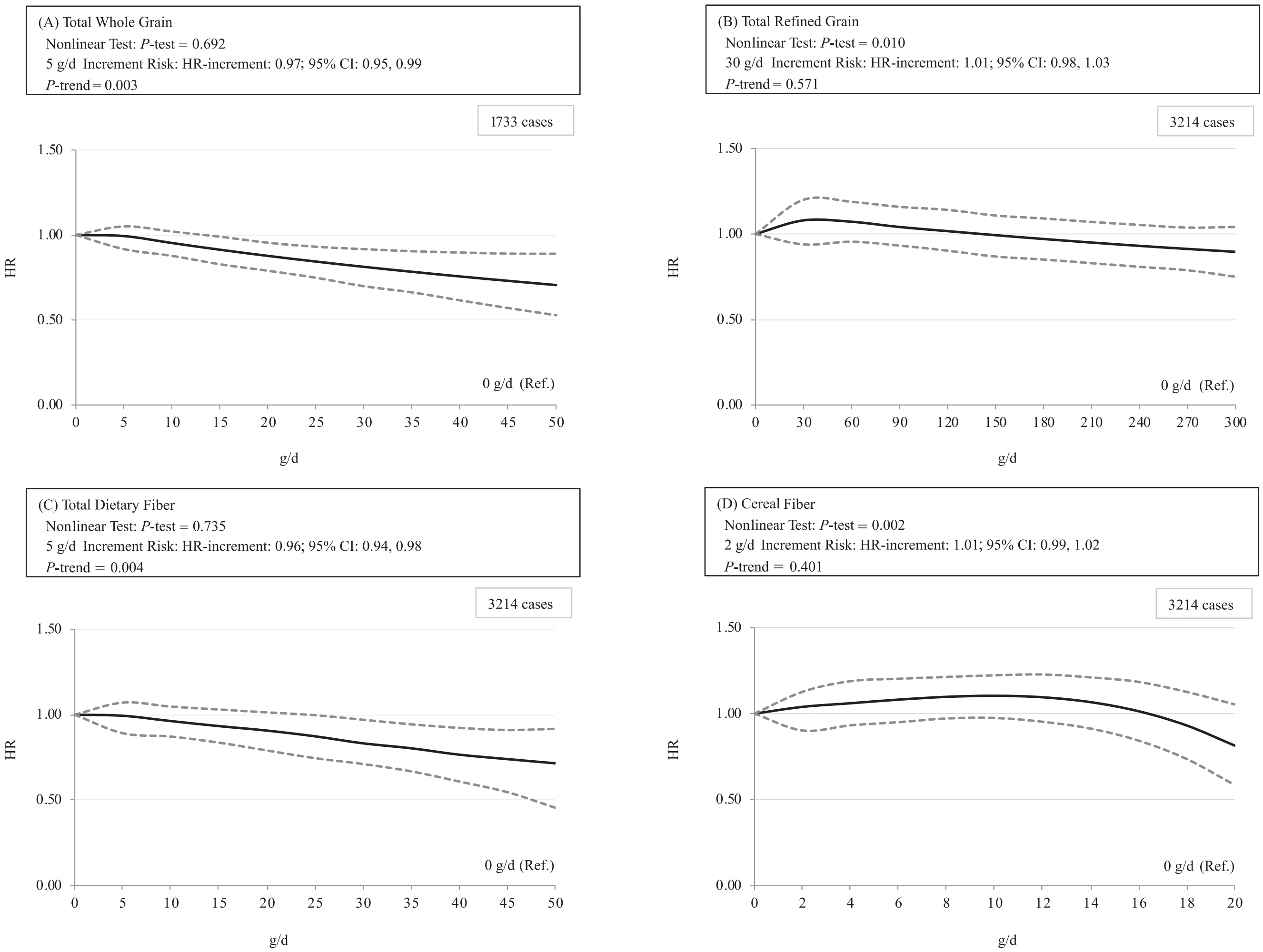

FIGURE 1 Dose–response relations between grain/dietary fiber intake and the risk of bladder cancer among total whole grain (A), total refined grain (B), total dietary fiber (C), and cereal fiber (D). The solid lines represent the HRs; the dashed lines represent the 95% CIs for the trend. The HRs were adjusted for age (y; continuous), sex (male/female), smoking {smoking was defined as: 0 (never smokers); 1 [current light smokers (i.e., smoking <20 pack-years)]; 2 [current heavy smokers (i.e., smoking >20 pack-years)]; 3 [current smokers (no information on pack-years)]; 4 [former light smokers (i.e., smokers who ceased smoking >1 y prior and smoked <20 pack-years)]; 5 [former heavy smokers (i.e., smokers who ceased smoking >1 y prior and smoked >20 pack-years)]; or 6 [former smokers (smokers who ceased smoking >1 y prior, and no information on pack-years)]}, ethnicity (Caucasian or non-Caucasian, if applicable), alcohol intake (mL/d; continuous), fruit intake (g/d; continuous), fat intake (g/d; continuous), meat intake (g/d; continuous), sugar intake (g/d; continuous), vegetable intake (g/d; continuous), and total fluid intake (mL/d; continuous) (model 2). Reference group was nonintake. *P* values < 0.05 were considered statistically significant for nonlinearity. *P*-increments < 0.05 were considered statistically significant.

intake of total whole grains on BC risk (23), and another case-control study conducted in the 1980s reported a modest inverse association (24). Because it was reported that an increased BC risk was associated with a high dietary glycemic load (23), which has been reported to be reduced by the postprandial glucose and insulin responses to whole grain intake (61), the authors suggested that any potential benefit of whole grain intake to BC risk may act by mitigating the carcinogenic effects of hyperglycemia and hyperinsulinemia (62–64). In addition, our findings are strengthened by experimental studies which show that whole grains may exert their potential antitumor activity through the reduction of inflammation (65), which is thought to be related to a decreased BC risk (66).

One plausible reason total refined grain was not found to be protective for BC is that refined grains lack a high amount of dietary fiber and other bioactive compounds which are rich in whole grains (67, 68). The lack of dietary fiber could especially be emphasized because the present study shows that high intake both of total whole grain and of total dietary fiber was associated with a decreased BC risk. Epidemiological studies have shown that the intakes of whole grains and of dietary fiber were associated with a lower risk of chronic diseases (69–73), including various cancer types (74–76). In addition, experimental studies have reported that dietary fiber may protect cancer by improving insulin sensitivity and metabolic regulation, reducing inflammation, modulating the gut microbiota, removal of damaged cells, diluting carcinogens, and decreasing transit time (65, 77–81).

Although most standard pastas are made with refined wheat flour, several whole-wheat pastas are available and worldwide consumed in nontrivial amounts (68, 82). Considering that several cohorts have been conducted after the 2000s, the pasta intake could be a mixture of pasta made of refined and whole grains. Unfortunately, we were unable to distinguish between these types of pasta intake. Nevertheless, we only found a borderline-decreased BC risk for medium intake of "pasta or noodles." In addition, the results of total refined grains were unchanged after excluding pasta intake. Because the lack of information on pasta types might have led to inaccurate estimates, results from the present study on the influence of pasta could be due to chance, therefore, they must be interpreted with caution. Further investigation of the influence of specific pasta types on BC risk may be warranted.

Half of the world's population relies on rice as a daily staple food and it is considered one of the most important crops globally. The association of this specific grain with BC risk might differ from any other grains, because rice has been reported to contain considerable amounts of inorganic arsenic (83), which has been acknowledged to be a human carcinogen for bladder (84). A previous prospective study in the United States found no association for BC risk with either brown rice or white rice (85). In our study we showed that both brown and white rice do not cause an increased BC risk; in addition, it has been reported that the washing and cooking procedure reduces the arsenic content of rice (83, 86), therefore, the potential influence of arsenic on the findings of the present study is minimal.

In the present study we found that high intake of total dietary fiber was significantly associated with a lower BC risk. However, none of the dietary fiber sources were associated with BC risk individually. One possible explanation is that individual dietary fiber intakes failed to reach the threshold at which a protective effect is manifested. In addition, some residual confounding such as "cooking methods" might mask the potential beneficial effect of cereal-, fruit-, or vegetable-fiber intake.

The joint effect of both whole grains and dietary fiber showed a stronger inverse association with BC risk than did the intakes individually. This finding confirmed the assumption that potential benefits of fiber may be derived from its combination with nutrients of whole grains working together, which suggests the simultaneous intake of both as part of a healthy, nutritious diet. Although current dietary guidelines recommend that individuals derive at least half of their grain intake from whole grains, no quantifications are given for the amount of total whole grains to be consumed (87). The present study shows that a daily intake of $\geq$15 g (uncooked) should be consumed in order to reduce the BC risk. For dietary fiber, the European Commission's strategy recommends a daily dietary fiber intake of 25–38 g in order to prevent noncommunicable diseases (88). This is in accordance with our observation of 25 g/d total dietary intake for reducing BC.

The present study pooled data from 13 prospective cohorts, enabling detailed analyses with good precision and statistical power. However, this study also includes some limitations: *1*) other than the included adjustments, limited information was available on other possible risk factors [e.g., BMI (89) and diabetes (90)] or dietary additives (e.g., dip or sauce); *2*) some tumor subtype information was missing, which hampered the statistical power required for stratified subgroup analyses; *3*) although status as well as duration and intensity of smoking were taken into account, residual confounding by smoking is difficult to rule out completely—however, because never smokers showed similar results to the overall analysis adjusted for smoking, the effect of residual confounding is likely to be minimal; *4*) people with a high intake of whole grains might have generally healthier lifestyles and diets than those with a low intake (91, 92), thus we could not rule out the possibility that some of the associations could be more likely due to a healthy lifestyle than to whole grain intake per se; *5*) the sample size for whole grains was significantly smaller than for refined grains and dietary fiber, which may have led to less statistical power; *6*) data were not available on dietary fiber types (e.g., soluble compared with insoluble), thus we were unable to investigate the association by dietary fiber subtypes; *7*) 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; and *8*) 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.

In summary, our study, of >3200 cases of incident BC occurring in almost 0.6 million participants, indicates a decreased BC risk with higher intakes of total whole grain (>8 g/d) and total dietary fiber (>23 g/d) individually and jointly. This, in turn, supports recommendations to increase the intakes of whole grains and dietary fiber to improve public health.

The authors' responsibilities were as follows—AW and MPZ: conceived and designed the study; EYWY: conducted data analyses and interpretation and drafted the manuscript; MB, PvdB, E White, E Weiderpass, FLC-K, MG, IH, FL, GS, AT, ER, GGG, and RLM: provided the data; MB, PvdB, E White, E Weiderpass, FLC-K, MG, IH, FL, GS, AT, ER, GGG, RLM, AW, SM, and MPZ: revised the manuscript; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

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