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Association of Intake of Whole Grains and Dietary Fiber With Risk of Hepatocellular Carcinoma in US Adults

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IMPORTANCE Increased intake of whole grain and dietary fiber has been associated with lower risk of insulin resistance, hyperinsulinemia, and inflammation, which are known predisposing factors for hepatocellular carcinoma (HCC). Therefore, we hypothesized that long-term intake of whole grains and dietary fiber may be associated with lower risk of HCC.

OBJECTIVE To assess the associations of whole grain and dietary fiber intake with the risk of HCC.

DESIGN, SETTING, AND PARTICIPANTS Cohort study of the intake of whole grains, their subcomponents (bran and germ), and dietary fiber (cereal, fruit, and vegetable) in 125 455 participants from 2 cohorts from the Nurses' Health Study and the Health Professionals Follow-up Study.

EXPOSURES Intake of whole grains, their subcomponents (bran and germ), and dietary fiber (cereal, fruit, and vegetable) were collected and updated almost every 4 years using validated food frequency questionnaires.

MAIN OUTCOMES AND MEASURES Multivariable hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards regression model after adjusting for most known HCC risk factors.

RESULTS After an average follow-up of 24.2 years, we identified 141 patients with HCC among 125 455 participants (77 241 women and 48 214 men (mean [SD] age, 63.4 [10.7] years). Increased whole grain intake was significantly associated with lower risk of HCC (the highest vs lowest tertile intake: HR, 0.63; 95% CI, 0.41-0.96; $P = .04$ for trend). A nonsignificant inverse HCC association was observed for total bran (HR, 0.70; 95% CI, 0.46-1.07; $P = .11$ for trend), but not for germ. Increased intake of cereal fiber (HR, 0.68; 95% CI, 0.45-1.03; $P = .07$ for trend), but not fruit or vegetable fiber, was associated with a nonsignificant reduced risk of HCC.

CONCLUSIONS AND RELEVANCE Increased intake of whole grains and possibly cereal fiber and bran could be associated with reduced risk of HCC among adults in the United States. Future studies that carefully consider hepatitis B and C virus infections are needed to replicate our findings, to examine these associations in other racial/ethnic or high-risk populations, and to elucidate the underlying mechanisms.

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Supplemental content

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Primary liver cancer is the sixth most commonly occurring cancer and the second leading cause of death from cancer worldwide.[1-3] The predominant histological form of primary liver cancer is hepatocellular carcinoma (HCC). In the United States, the incidence of HCC has been increasing since the 1980s,[4] and HCC is projected to be among the top 3 causes of cancer-related mortality by 2030.[5] A large proportion of HCC cases in the United States cannot be explained by current known risk factors, including hepatitis B and C virus (HBV and HCV) infections, metabolic disorders, and smoking.[6] Although chronic HBV and HCV infections are the most important risk factors for HCC, their prevalence rates (approximately 0.11% for HBV[7] and 1.0% for HCV[8]) in the general US population are relatively low. Dietary factors have been suspected as important, but only excessive alcohol use and aflatoxin-contaminated foods are considered to be established dietary risk factors for HCC.[9]

Whole grains are a major source of dietary fiber and consist of bran, germ, and endosperm, compared with refined grains that contain only the endosperm. The whole grains are good sources of dietary fiber, vitamins, minerals, phytonutrients, and other numerous nutrients, which are removed during the refining process. Consumption of whole grains and dietary fiber, especially cereal fiber, has been associated with lower risk of obesity,[10,11] type 2 diabetes,[11-13] and nonalcoholic fatty liver disease,[14,15] which are known predisposing factors for HCC.[6] In addition to improving insulin sensitivity and metabolic regulation and decreasing systemic inflammation,[10,14,16-18] intake of whole grains and dietary fiber may improve gut integrity[19] and alter gut microbiota composition, thereby leading to increased production of microbiota-related metabolites, including short-chain fatty acids, particularly butyrate.[20-22] Gut integrity, the composition of gut microbiota, and metabolites may play an important role in the development of liver diseases, including HCC.[14,23,24] We thus hypothesized that long-term intake of whole grains and dietary fiber may lower the risk of HCC.

To our knowledge, no epidemiological study has yet examined the association between whole grain intake and HCC risk, and only 1 cohort study[25] has investigated dietary fiber in relation to HCC risk. We thus conducted this study to assess these associations by using data from 2 large prospective cohort studies, the Nurses' Health Study (NHS)[26] and the Health Professionals Follow-up Study (HPFS).[27] For whole grains, we also investigated each individual grain food group and the grain subcomponents bran and germ for their potential association with reduced HCC risk. For dietary fiber, we also investigated the associations of fiber by food source (ie, cereal, fruit, and vegetable fiber) with HCC risk.

Key Points

Question Is high intake of whole grains and dietary fiber associated with lower risk of developing hepatocellular carcinoma (HCC)?

Findings In this cohort study of 125 455 participants in the United States, including 141 patients with HCC, with an average follow-up of 24.2 years, increased intake of whole grains was associated with a reduced risk of HCC. A nonsignificant inverse HCC association was observed for total bran but not for germ; increased intake of cereal fiber but not fruit or vegetable fiber was associated with a nonsignificant lower risk of HCC.

Meaning Increased intake of whole grains and possibly cereal fiber and bran could be associated with reduced risk of HCC among US adults.

Methods

Sampling and Data Collection

The NHS cohort was established in 1976 with enrollment of 121 700 female registered nurses aged 30 to 55 years. The HPFS cohort was established in 1986 with enrollment of 51 529 male health professionals aged 32 to 87 years. Every 2 years, participants have updated their information on medical history, lifestyle, and incidence of chronic diseases using validated questionnaires, with a response rate of more than 90% in each cohort. The study protocol was approved by the Human Research Committee of Brigham and Women's Hospital and the Harvard T. H. Chan School of Public Health. The completion of the self-administered questionnaire was considered to imply written informed consent.

Assessments of Diet

In the NHS and HPFS cohorts, a validated food frequency questionnaire (FFQ)[26,27] was administered in 1980 and 1986, respectively, and almost every 4 years thereafter. The FFQs inquired about average consumption of foods (with a prespecified standard portion size) during the previous year using 9 categories of intake frequency ranging from "never or less than once per month" to "6 or more times per day." Nutrient intake, including dietary fiber and dietary fiber from fruits, vegetables, and cereals, was calculated by multiplying the frequency of each food consumed by the nutrient content per serving of that food and summing across all foods and beverages. The nutrient content was primarily obtained from the composition database from the US Department of Agriculture (USDA).[28] Details on assessments of dietary intake of whole grains and fiber as well as their validity and reproducibility are described in the eMethods in the Supplement.

Ascertainment of HCC

In each cohort, participants were asked for written permission to obtain their medical records and pathological reports if they reported liver cancer on biennial questionnaires. For all deaths attributable to liver cancer, we requested permission from next of kin to review medical and pathological records. All possible cancer cases were further confirmed by 1 study physician who was blinded to exposure data and who extracted information from the medical or pathological reports regarding the presence of underlying cirrhosis diagnosed by histopathologic analysis; appropriate cross-sectional imaging; the presence of HBV or HCV infections; and the histological subtypes of the cancer (ie, HCC vs intrahepatic cholangiocarcinoma). We further searched state vital statistics records using the National Death Index for potential unreported cancer

deaths; this approach can capture more than 98% of overall deaths.[29] Additional data on HBV/HCV infection status, which were derived from laboratory blood tests, were also available from a nested case-control study of HCC in the NHS/HPFS cohort (26 participants with HCC and 78 control participants).[30]

Assessments of Other Covariates

We collected information on age, weight, smoking status, physical activity (metabolic equivalent task-hours per week), aspirin use, and type 2 diabetes status at baseline and during follow-up. Detailed descriptions on the validity and reproducibility of these self-reported data, such as body weight and physical activity, have been published elsewhere.[31,32]

Statistical Analyses

In the present study, we used the year 1984 as the baseline for the NHS cohort and 1986 for the HPFS cohort. We excluded participants with a history of cancer (except for nonmelanoma skin cancer) or those with no reports of dietary intake at baseline. After exclusions, 125 455 participants (77 241 women and 48 214 men) were included in this analysis. We calculated person-years of follow-up from the return date of the first dietary questionnaire to the date of diagnosis of HCC, date of death, loss to follow-up, or the end of follow-up (June 1, 2012, for NHS or January 31, 2012, for HPFS), whichever came first. To better represent long-term dietary habits and lifestyle and to minimize within-person variation, we created and used the cumulative average of whole grain and dietary fiber intake, as well as other covariates, including physical activity, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), smoking habits, regular aspirin use, alcohol intake, and type 2 diabetes.[33] Intakes of whole grains and dietary fiber were energy adjusted using the residual method.[34]

Time-varying Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% CIs and were stratified by age (months) and calendar time (2-year intervals). For whole grains, we assessed the association of grain subcomponents, bran and germ, with HCC risk. For dietary fiber, we assessed major food sources of fiber according to intake of the food and by the amount of fiber contained within the food. In multivariable analyses, we controlled for race, physical activity, BMI, smoking habits, regular aspirin use, alcohol intake, and type 2 diabetes. Adjustment for total coffee intake yielded essentially the same results and thus was not included in the final multivariable models. To maximize statistical power, we combined results from the 2 cohorts because we did not detect any significant heterogeneity by sex for all heterogeneity tests of whole grain and dietary fiber. We presented HRs by tertiles and per 1 SD increase of total and specific whole grain and dietary fiber intake (grams per day). To assess departure from linearity, we included both linear and quadratic terms (ie, the absolute value and the value squared) in the model and found no evidence of a nonlinear association. Linear trend test was conducted by assigning medians to each tertile as a continuous variable in the models. We found no violation of proportional hazard assumption after testing an interaction term between whole grain or dietary fiber intake and follow-up time. We performed several sensitivity analyses (eMethods in the Supplement). All statistical tests were 2-sided and performed using SAS (version 9.4, SAS Institute Inc).

Results

After an average follow-up of 24.2 years, we identified 70 women and 71 men with incident HCC. Among 125 455 participants (77 241 women and 48 214 men (mean [SD] age, 63.4 [10.7] years), those in the highest tertiles of whole grain intake and dietary fiber intake were slightly older, had lower BMI, engaged in more physical activity, consumed less alcohol, were less likely to be smokers, were more likely to use aspirin and postmenopausal hormone (women only), and tended to have higher intake of fruits, vegetables, total folate, multivitamin, and dietary vitamin D, but less fat, compared with participants in the lowest tertiles (**Table 1**). Similar patterns were observed in women and men (eTable 1 in the Supplement).

In multivariable-adjusted analyses, higher whole grain intake was significantly associated with lower HCC risk (comparing the highest to the lowest tertile intake: HR, 0.63; 95% CI, 0.41-0.96; P = .04 for trend) (**Table 2**). We found a suggestive but not significant inverse association between total bran intake and HCC (HR, 0.70; 95% CI, 0.46-1.07) and a weaker association for total germ (HR, 0.89; 95% CI, 0.58-1.36). These associations changed only slightly after mutual adjustment for bran and germ (bran: HR, 0.66; 95% CI, 0.41-1.07; germ: HR, 1.10; 95% CI, 0.67-1.82). Additionally, added bran showed an inverse association (HR, 0.69; 95% CI, 0.45-1.06), whereas added germ showed a positive association (HR, 1.22; 95% CI, 0.82-1.82) with HCC risk. When we separately assessed the associations of specific whole grain and grain subcomponents with HCC risk in each cohort, the results were similar to the pooled analyses (eTable 2 in the Supplement).

We did not find any significant associations of total fiber intake, fruit, or vegetable fiber intake with the risk of HCC (**Table 3**). A suggestive but not significant inverse association was observed for cereal fiber intake (HR, 0.68; 95% CI, 0.45-1.03; P = .06 for trend). The associations of dietary fiber and fiber by food source with HCC risk in each cohort were consistent with the results from the pooled analyses (eTable 3 in the Supplement). We further analyzed the associations with HCC risk according to whole-grain food groups and found a suggestive but not significant inverse association with whole grain cold breakfast cereal (HR, 0.82; 95% CI, 0.54-1.23) (eTable 4 in the Supplement).

Among 105 patients with HCC who had information on HBV/HCV infection status, 23 patients were infected with HBV or HCV. We did not detect any differential associations of whole grain, bran and germ, or dietary fiber with the risk of viral and nonviral HCC, although the statistical power was limited owing to the small number of participants with cancer. In addition, the overall results did not materially change after excluding patients with HCC and HBV or HCV infection (n = 23) (data available from the authors). Likewise, there was no evidence of differential associations of whole grain or dietary fiber with the risk of cirrhotic and noncirrhotic HCC. In exploratory

Table 1. Age-Standardized Characteristics of Participants From the Nurses' Health Study and Health Professionals Follow-up Study[a]

	Whole Grain			Dietary Fiber		
Characteristic	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Whole grain, g/d	8.1 (4.5)	18.4 (5.8)	35.8 (14.7)	12.6 (8.7)	20.1 (11.5)	30.0 (17.6)
Dietary fiber, g/d	16.0 (4.3)	18.8 (4.5)	22.7 (6.0)	14.2 (2.5)	18.7 (2.4)	24.8 (5.2)
Cereal fiber, g/d	3.5 (1.2)	5.1 (1.6)	7.7 (3.2)	4.1 (1.5)	5.3 (2.0)	7.1 (3.6)
Fruit fiber, g/d	3.5 (2.4)	4.2 (2.3)	5.0 (2.6)	2.5 (1.3)	4.0 (1.6)	6.1 (2.8)
Vegetable fiber, g/d	6.1 (2.6)	6.6 (2.5)	7.2 (3.0)	4.9 (1.5)	6.4 (1.8)	8.7 (3.2)
Age, y[b]	62.2 (10.6)	63.2 (10.7)	64.8 (10.7)	61.5 (10.5)	63.3 (10.7)	65.5 (10.6)
White, %	96.1	97.5	97.5	96.9	97.3	96.9
Body mass index[c]	26.1 (4.6)	26.0 (4.3)	25.2 (4.0)	26.0 (4.5)	26.0 (4.3)	25.4 (4.2)
Physical activity, MET-h/wk	18.0 (21.9)	21.0 (22.6)	23.3 (24.1)	16.7 (20.0)	20.5 (21.8)	25.1 (26.1)
Type 2 diabetes, %	5.6	5.6	5.1	5.3	5.7	5.3
Regular aspirin use, %[d]	34.8	39.6	40.6	35.3	39.4	40.4
Past smoking, %	42.9	44.0	42.6	43.1	43.9	42.8
Current smoking, %	17	9.6	6.0	17.3	9.1	6.0
Multivitamin use, %	37.9	48.3	53.3	41.3	47.6	51.0
Postmenopausal status, %	87.3	87.9	88.5	87.5	87.7	88.7
Menopausal hormone therapy use, %	48.2	55.7	58.3	51.2	55.2	56.1
Fruit, servings/d	2.0 (1.3)	2.4 (1.3)	2.6 (1.3)	1.6 (0.9)	2.3 (1.0)	3.1 (1.5)
Vegetables, servings/d	2.8 (1.4)	3.1 (1.4)	3.2 (1.5)	2.2 (0.9)	3.0 (1.1)	3.9 (1.7)
Alcohol, g/d	9.9 (14.2)	7.8 (11.1)	5.9 (8.9)	11.0 (15.0)	7.4 (10.3)	5.4 (7.9)
Total folate intake, µg/d	417 (203)	483 (210)	547 (235)	409 (199)	478 (203)	564 (235)
Total vitamin D intake, IU/d	332 (219)	387 (221)	446 (247)	350 (219)	383 (222)	434 (252)
Total fat, g/d	65.7 (12.3)	62.5 (11.1)	57.4 (11.0)	66.6 (12.2)	62.6 (10.6)	56.2 (10.5)

Abbreviation: MET, metabolic equivalent of task.

[a] Unless otherwise indicated, values are mean (SD) and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding. Updated information over the entire study follow-up was used.

[b] Values were not age adjusted.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Regular aspirin use was defined as the consumption of aspirin at least 2 times per week.

Table 2. Energy-Adjusted Intake of Whole Grain and Risk of Hepatocellular Carcinoma in the Nurses' Health Study and Health Professionals Follow-up Study

	Tertiles, HR (95% CI)				
Whole Grain/Component	Tertile 1	Tertile 2	Tertile 3	HR per 1 SD Increase (95% CI)	*P* Value for Trend
Whole grain, No. of cases	54	49	38	NA	NA
Age-adjusted model	1 [Reference]	0.78 (0.53-1.15)	0.54 (0.36-0.83)	0.79 (0.65-0.96)	.01
Multivariable-adjusted model[a]	1 [Reference]	0.86 (0.58-1.27)	0.63 (0.41-0.96)	0.84 (0.69-1.02)	.04
Total bran, No. of cases	53	46	42	NA	NA
Age-adjusted model	1 [Reference]	0.73 (0.49-1.09)	0.60 (0.40-0.90)	0.76 (0.61-0.93)	.02
Multivariable-adjusted model[a]	1 [Reference]	0.80 (0.54-1.19)	0.70 (0.46-1.07)	0.81 (0.66-1.00)	.11
Total germ, No. of cases	47	53	41	NA	NA
Age-adjusted model	1 [Reference]	1.00 (0.67-1.48)	0.80 (0.52-1.21)	0.90 (0.72-1.12)	.34
Multivariable-adjusted model[a]	1 [Reference]	1.08 (0.72-1.61)	0.89 (0.58-1.36)	0.94 (0.76-1.16)	.68
Added bran, No. of cases	52	51	38	NA	NA
Age-adjusted model	1 [Reference]	0.86 (0.58-1.27)	0.58 (0.38-0.89)	0.74 (0.59-0.92)	.01
Multivariable-adjusted model[a]	1 [Reference]	0.96 (0.65-1.43)	0.69 (0.45-1.06)	0.79 (0.63-0.99)	.05
Added germ, No. of cases	48	39	54	NA	NA
Age-adjusted model	1 [Reference]	0.91 (0.58-1.41)	1.11 (0.75-1.64)	0.99 (0.83-1.18)	.52
Multivariable-adjusted model[a]	1 [Reference]	0.97 (0.62-1.51)	1.22 (0.82-1.82)	1.02 (0.88-1.20)	.29

Abbreviations: HR, hazard ratio; NA, not applicable.

[a] Adjusted for age (in months); race (white vs nonwhite); physical activity level (metabolic equivalent of task-hours per week; continuous variable); body mass index (calculated as weight in kilograms divided by height in meters squared, continuous variable); smoking (0, 1 to <10, ≥10 pack-years); regular aspirin use (yes or no); alcohol intake (<5, 5 to <15, ≥15 g/d); and type 2 diabetes (yes or no). The median values (g/d) for each tertile category were 7.35, 17.86, 33.28 for whole grain; 1.30, 4.33, 9.97 for total bran; 0.30, 0.72, 1.48 for total germ; 0.09, 1.75, 6.11 for added bran; and 0, 0.04, 0.33 for added germ.

Table 3. Energy-Adjusted Intake of Dietary Fiber and Risk of Hepatocellular Carcinoma in the Nurses' Health Study and Health Professionals Follow-up Study

Fiber	Tertiles, HR (95% CI)			HR per 1 SD Increase (95% CI)	*P* Value for Trend
	Tertile 1	Tertile 2	Tertile 3		
Dietary fiber, No. of cases	47	45	49	NA	NA
Age-adjusted model	1 [Reference]	0.79 (0.52-1.19)	0.76 (0.50-1.14)	0.85 (0.71-1.02)	.23
Multivariable-adjusted model[a]	1 [Reference]	0.85 (0.56-1.29)	0.88 (0.57-1.35)	0.90 (0.75-1.09)	.67
Cereal fiber, No. of cases	55	45	41	NA	NA
Age-adjusted model	1 [Reference]	0.72 (0.49-1.07)	0.58 (0.39-0.88)	0.76 (0.62-0.94)	.01
Multivariable-adjusted model[a]	1 [Reference]	0.79 (0.53-1.17)	0.68 (0.45-1.03)	0.82 (0.67-1.01)	.07
Fruit fiber, No. of cases	32	55	54	NA	NA
Age-adjusted model	1 [Reference]	1.36 (0.88-2.11)	1.21 (0.78-1.90)	1.04 (0.88-1.22)	.49
Multivariable-adjusted model[a]	1 [Reference]	1.48 (0.95-2.32)	1.39 (0.88-2.21)	1.09 (0.92-1.29)	.20
Vegetable fiber, No. of cases	52	43	46	NA	NA
Age-adjusted model	1 [Reference]	0.76 (0.51-1.14)	0.79 (0.53-1.18)	0.87 (0.72-1.05)	.34
Multivariable-adjusted model[a]	1 [Reference]	0.78 (0.52-1.17)	0.81 (0.54-1.21)	0.88 (0.73-1.06)	.42

Abbreviations: HR, hazard ratio; NA, not applicable.

[a] Adjusted for age (in months); race (white vs nonwhite); physical activity level (metabolic equivalent of task–hours per week, continuous variable); body mass index (calculated as weight in kilograms divided by height in meters squared, continuous variable); smoking (0, 1 to <10, ≥10 pack-years); regular aspirin use (yes or no); alcohol intake (<5, 5 to <15, ≥15 g/d); and type 2 diabetes (yes or no). The median values (g/d) for each tertile category were 14.15, 18.23, 24.02 for dietary fiber; 3.15, 4.90, 7.59 for cereal fiber; 1.99, 3.80, 6.30 for fruit fiber; and 4.30, 6.20, 8.85 for vegetable fiber.

subgroup analyses, we found no significant interactions with age, BMI, physical activity, smoking, alcohol drinking, type 2 diabetes, and aspirin use (eTable 5 in the Supplement).

Discussion

Our findings indicate a potential benefit from whole grain, bran, and cereal fiber intake in HCC primary prevention. After controlling for alcohol intake, BMI, type 2 diabetes, and other well-known HCC risk factors, we found that participants with increased intake of whole grain had a significantly lower risk of HCC. A stronger association was observed for bran than for germ. Cereal fiber was also suggestively but not significantly associated with reduced risk of HCC, whereas intake of fiber from fruits and from vegetables had no association with HCC risk.

Increased intake of whole grain and its component bran as well as cereal fiber has been associated with improved insulin sensitivity, metabolic regulation, and reduced inflammation.[10,14,16-18] Insulin resistance, hyperinsulinemia, and inflammation are known hallmarks of cancer.[35] Therefore, increasing intake of whole grain, bran, and cereal fiber may protect against HCC by mitigating the carcinogenic effect of hyperinsulinemia and inflammation. Also, experimental studies showed that whole grain may exert its potential antitumor (including cancers of colorectum and liver) activity through improvement of gut integrity and alteration of gut microbiota composition.[19-22]

We observed a stronger beneficial association for the whole grain subcomponent of bran than for germ in relation to HCC risk. Similar patterns were also observed for added bran and germ. Results from previous studies of the NHS and HPFS cohorts have suggested that bran, but not germ, was significantly associated with lower risk of total and cardiovascular disease–specific mortality,[36] type 2 diabetes,[37] hypertension,[38] coronary heart disease,[39] and cardiovascular disease–specific mortality among individuals with diabetes.[40] A potential explanation is that the intake level of germ in our study population is rather low (median intake, 4.2 g/d for total bran vs 0.74 g/d for total germ). Alternatively, bioactive compounds, such as cereal fiber, vitamins, minerals, and phytonutrients, which may potentially explain whole grains' favorable associations,[41] mainly exist in the bran component.[39]

We found that the potential inverse association between dietary fiber intake and HCC risk appeared to differ by food sources, with cereal fiber associated with lower risk of HCC, whereas fruit or vegetable fiber showed no association. To our knowledge, only 1 published prospective study to date has assessed the risk of incident HCC associated with intake of dietary fiber and its source. This study included 477 206 participants, of which 191 had HCC, from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and reported a significant inverse association for cereal fiber, but not for fruit or vegetable fiber.[25] These observations are generally consistent with our findings that increasing intake of cereal fiber and whole grain, a primary source of cereal fiber, was associated with reduced risk of HCC. Interestingly, compared with fruit or vegetable fiber, cereal fiber has been shown in our study and other cohort studies to be more consistently associated with lower risk of total mortality,[13,42] cardiovascular disease,[13,43] type 2 diabetes,[12,13] and colorectal cancer.[44-48] However, our results on the association of cereal fiber with HCC risk could have been due to chance. Alternatively, a potential explanation is that fruits and vegetables, particularly fruit juice, contain sugar or added sugar such as fructose and sucrose, which may lead to hepatic damage and nonalcoholic fatty liver disease,[49] thereby masking the potential benefit of fruit- or vegetable-fiber intake. Overall, the exact reasons for such a difference remain unknown and require further investigation.

Limitations

Our study has several limitations. First, despite an average follow-up of 24.2 years in these 2 cohorts, the number of par-

ticipants with incident HCC is relatively small. This may reduce the precision of the risk estimates in the analysis. However, the reported significant associations of whole grain, and possibly bran and cereal fiber, with decreased HCC risk are biologically plausible. Nonetheless, future studies with a large number of participants with HCC are warranted to confirm our findings.

Second, potential misclassifications in dietary data are present in any observational study. The misclassification of exposure variables in a cohort study could be nondifferential in most situations and is likely to lead to the underestimation of the observed association if exposure data are binary.[50] In the present study, misclassification can lead to bias in either direction even if the misclassification is nondifferential, given the continuous or polytomous exposure data in the analysis. However, FFQs used in these cohorts have showed reasonable reproducibility and validity for assessing intake of grains and fiber as well as other dietary factors.[26,27,51]

Third, we did not have data on chronic HBV/HCV infection status in all participants, and we were unable to conduct analyses adjusting for or stratifying by HBV/HCV infection status. However, among a subset of participants in which such data were available (183 participants, including 105 with HCC and 78 control participants), HBV/HCV infection status was not correlated with intake of whole grains or dietary fiber. Additionally, previous studies also reported no correlations between obesity,[52] smoking habits,[30] alcohol use,[30] or coffee intake[53] and HBV/HCV virus infection. Moreover, results were similar when we excluded the patients with HCC and known chronic HBV/HCV infections. Taken together, our results were less likely to be substantially confounded by HBV/HCV infection status.

Fourth, although our results showed no evidence of the differential association of whole grain and dietary fiber with the risk of viral and nonviral HCC or with the risk of cirrhotic and noncirrhotic HCC, the small number of patients with HCC in the cohort may limit the statistical power of the study and restrict further interaction analyses in these high risk-populations. Thus, future cohort studies are warranted to further investigate this association among high-risk populations (eg, patients with chronic HBV/HCV infection or with chronic liver diseases).

Fifth, the potential selection bias owing to loss to follow-up cannot be totally ruled out, although there is a high follow-up rate in each cohort (>90%). In particular, if there are differences in likelihood of loss to follow-up that are related to exposure status and/or outcome, the observed associations might have been biased. However, our follow-up using the National Death Index,[29] which was 1 approach we used to identify unreported HCC in our study, may help capture data from almost all participants with HCC given the high fatality rate of the disease. Finally, our cohorts consist mostly of white patients of European origin living in the United States, and this may limit the generalizability of our results to other racial/ethnic populations or geographic regions.

Conclusions

The present study demonstrated that increased intake of whole grain and possibly bran and cereal fiber was associated with lower risk of HCC. These findings should be interpreted with caution, given the lack of data on HBV/HCV infection in the full cohort and the limited number of participants with HCC in the analysis. Future studies that carefully consider HBV and HCV infections are needed to further examine these associations in other racial/ethnic or high-risk populations and to elucidate the underlying mechanisms. Pooled analyses across cohorts with a large number of participants with HCC would also be helpful, given the low incidence of the disease in the United States. If our findings are confirmed, increasing whole grain consumption may serve as a possible strategy for prevention of primary HCC.

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