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Research Article

Cancer Prevention Research

A Prospective Study of Nut Consumption and Risk of Primary Hepatocellular Carcinoma in the U.S. Women and Men

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Abstract

Although increasing evidence suggests a potential beneficial effect of nut consumption on various diseases, no epidemiologic study has yet examined the association between nut consumption and risk of hepatocellular carcinoma (HCC). We prospectively examined this association in 88,783 women from the Nurses' Health Study and 51,492 men from the Health Professionals Follow-up Study. Nut consumption was assessed every 4 years using validated food frequency questionnaires. Multivariable HRs and 95% confidence intervals (95% CI) were estimated using Cox proportional hazards regression models after adjusting for HCC risk factors. After an average of 27.9 years of follow-up, we identified a total of 162 incident HCC cases. Higher total nut consumption was not significantly associated with HCC risk (the highest vs. lowest tertile intake, HR, 0.84; 95% CI, 0.56–1.26). For the same comparison, higher tree nut consumption was associated with a lower HCC risk (HR, 0.64; 95% CI, 0.43–0.95). We found nonsignificant inverse associations with consumption of walnuts, peanuts, and peanut butter. Overall, nut consumption was not strongly associated with HCC risk. There was a suggestive inverse association with tree nut consumption. Future studies should carefully consider hepatitis B or C virus infections and examine these associations in other racial/ethnic groups.

Introduction

Worldwide, liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death (1). The predominant histologic form of primary liver cancer is hepatocellular carcinoma (HCC) (2). In the United States, HCC has one of the most rapidly increasing incidence rates among both women and men (3). In addition, the median survival time after HCC diagnosis remains less than 1 year (4). Currently, the major known risk factors for HCC are hepatitis B or hepatitis C virus (HBV/HCV) infections, aflatoxin contamination, smoking, obesity, type II diabetes, nonalcoholic fatty liver diseases (NAFLD), and heavy alcohol drinking (5). Other dietary factors might play an important role in HCC development (6), but the current epidemiologic studies on diet and HCC risk are very limited.

Nuts are good sources of unsaturated fatty acids, vitamins, folate, fiber, minerals, and other bioactive compounds (7, 8). Nut consumption might influence risk of HCC through mechanisms related to insulin sensitivity and inflammation. For example, higher nut consumption may cause sustained weight loss and improved insulin sensitivity (9), and was inversely associated with circulating levels of IL6 and C-reactive protein (10), higher levels of which were associated with higher HCC risk (11, 12). Furthermore, higher nut consumption was associated with a lower risk of type II diabetes (13), a risk factor for HCC (14, 15). Despite this evidence, no epidemiologic study to our knowledge has

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yet examined the association between nut consumption and HCC risk.

We hypothesized that higher nut consumption may decrease risk of developing HCC. We tested this hypothesis by utilizing two large U.S.–based prospective cohort studies of women (the Nurses' Health Study, NHS) and men (the Health Professionals Follow-up Study, HPFS).

Materials and Methods

Study population

For this study, we included two ongoing prospective cohort studies: the NHS, which consists of 121,700 female nurses 30–55 years of age in 1976; and the HPFS, which consists of 51,529 male health professionals 40–75 years of age in 1986 (16, 17). In each cohort, the follow-up questionnaires were sent biennially to collect information on demographics, medical history, lifestyles, as well as health conditions. The follow-up rate has been over 90% in each cohort. This study was approved by the Institutional Review Boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health (Boston, MA).

Dietary assessments

We used food frequency questionnaires (FFQ) to assess nut consumption and other dietary factors such as alcohol and coffee consumption (18). Briefly, the FFQs were administered to NHS participants in 1980, 1984, 1986, and every 4 years thereafter. A similar FFQ was administered to HPFS participants in 1986 and every 4 years thereafter. In the FFQ, participants were asked how often on average they have had consumed a serving of nuts [serving size, 28 g (1 oz)] during the preceding year with nine responses ranging from never or less than once a month to more than six times a day. In 1986 and subsequent FFQs in each cohort, the question about nuts was split into peanuts and other nuts. Starting in 1998 in each cohort, walnut consumption was collected. Consistent with previous studies from the same cohorts (19, 20), we defined total nut consumption as the intake of peanuts, walnuts (if available), and other nuts. "Other nuts" was defined as all types of tree nuts, including walnuts, hazelnuts, almonds, macadamias, pecans, cashews, and pistachios (not including peanuts, which are legumes, but with a similar fatty acid and nutrient profile as tree nuts). Nut intake was measured with reasonable validity, with the corrected correlation coefficient of 0.75 comparing the intake from the FFQ and those from the four 1-week dietary records (21).

Assessments of covariates

We also inquired information on factors such as age, race, height, body weight, physical activity, total calorie intake, type II diabetes, Alternative Healthy Eating Index-2010 (AHEI-2010), aspirin use, and smoking status. Participants reported the average amount of time spent per week during the previous year participating in each of the following specific activities: walking; jogging; running; bicycling; lap swimming; racquet sports (tennis, squash, and racquetball); and calisthenics/rowing, and other aerobics. Each specific activity was assigned a metabolic equivalent task (MET) score (22), and participants were assigned a weekly physical activity score expressed in MET hours per week. Total physical activity was calculated by summing the MET-hours per week across all activities reported by the participant. The AHEI-2010 was based on foods and nutrients predictive of chronic disease risk and was used to clarify the role of additional dietary factors in the development of chronic disease (23). The AHEI-2010 consists of 11 components [vegetables, fruit, whole grains, nuts and legumes, sugar-sweetened beverages and fruit juice, red and processed meat, trans fat, long-chain omega-3 fats, polyunsaturated fatty acids (PUFA), sodium, and alcohol; ref. 24]. Each component ranges from 0 to 10 points with a total score ranging from 0 to 110 points.

Ascertainment of incident HCC

In each cohort, participants who reported a diagnosis of HCC on the biennial questionnaire were asked for written permission to obtain their medical records. Considering potential unreported cancer cases, we further searched State Cancer Registries and the National Death Index (25). For all deaths attributable to HCC, we contacted next of kin for the deceased participants to obtain permission to review the medical records. Physicians who were blinded to exposure status (i.e., nut consumption) reviewed medical records to confirm the incident of HCC. For all HCC cases, physicians also extracted information on the histologic subtypes of the cancer (e.g., HCC vs. intrahepatic cholangiocarcinoma), underlying cirrhosis diagnosed by histopathology or by appropriate cross-sectional imaging, and HBV/HCV infection status. Additional data on HBV/HCV infection status were also available from a nested case–control study of HCC in the NHS/HPFS, which were derived from laboratory blood tests (26).

Statistical analyses

In this study, we defined baseline as 1980 for women (NHS) and 1986 for men (HPFS), when nut consumption data was first available. We excluded the participants with a history of cancer (except for nonmelanoma skin cancer) at baseline, or with implausibly energy intake, or missing data on nut consumption. After exclusions, we included 88,783 women in the NHS and 51,492 men in the HPFS for this analysis. We calculated each individual's person-time from the date of the return of baseline 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 the NHS and January 31, 2012 for the HPFS), whichever came first.

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To better represent long-term diet and minimize within-person variations, we calculated cumulative average of nut consumption and other dietary factors from each FFQ (20). Nut consumption was energy adjusted using the residual method (27). Multivariable HRs and 95% confidence intervals (CI) of HCC by the gender-specific tertiles of energy-adjusted total nut intake were estimated using time-varying Cox proportional hazard regression models after adjusting for most known HCC risk factors. We also performed separate analyses for peanuts, tree nuts, walnuts, and peanut butter. Cox regression models were stratified by age in months and year of questionnaire return, enabling fine control of confounding for age and secular trends. In multivariable analyses, we adjusted for race, physical activity, body mass index (BMI), smoking status, type II diabetes, aspirin use, alcohol intake, and total energy intake, because these are risk factors for HCC and correlated with nut consumption (see below). Furthermore, alcohol intake often links to coffee consumption, which is a probable protective factor for HCC (28), we also adjusted for total coffee intake.

To maximize the statistical power, we combined two cohorts because we did not detect any statistically significant heterogeneity in the association between total or tree nut consumption and HCC risk by gender. Consistent with the previous study from the same cohorts (20), the trend tests were conducted using the median values of each category of nut consumption as a continuous variable. There was no violation of proportional hazard assumption after testing an interaction term of nut consumption and follow-up time.

Although viral hepatitis is one of the most important risk factors for HCC, we do not have such data in the full cohorts. However, we have conducted three analyses: (i) we evaluated the associations of nut consumption with the risk of HCC according to HBV/HCV infection status (i.e., viral vs. nonviral HCC), and test the potential heterogeneity by these two subtypes; (ii) we excluded HCC cases with known HBV/HCV infections; and (iii) we calculated Spearman correlation coefficients between nut consumption and HBV/HCV infection status among participants with such data to evaluate to what extent the associations might be confounded by HBV/HCV infection status.

Furthermore, we have conducted other sensitivity analyses: (i) we additionally adjusted for tooth loss and periodontal diseases because tooth loss and periodontal diseases might affect nut consumption and might also be associated with liver cancer risk (29); (ii) we adjusted for intake of PUFAs because nuts might improve liver health via being a good food source of PUFAs (30); (iii) we adjusted for one of the most commonly used dietary pattern (i.e., AHEI-2010); (iv) we evaluated each nut consumption in relation to HCC by a history of cirrhosis status (i.e., cirrhosis vs. non-cirrhosis HCC); and (v) we did not adjust for total energy intake in the multivariable analysis as nut consumption is not a major source of total energy intake.

We also conducted exploratory subgroup analyses by age (<70 vs. $\geq$70 years), BMI (<30 vs. $\geq$30 kg/m^2), smoking status (never vs. ever), type II diabetes (no vs. yes), alcohol consumption (<15 vs. $\geq$15 g/day), physical activity (<9 vs. $\geq$9 METS-hours/week), and aspirin use (no vs. yes). All analyses were two-sided and conducted using the SAS Statistical Package (version 9.4, SAS Institute).

Results

After an average of 27.9 years of follow-up, we documented a total of 162 HCC cases (85 in women and 77 in men). Participants with higher total nut consumption were generally leaner, more likely to be physically active and use aspirin, drink alcohol, and less likely to be current smokers (Table 1). Similar patterns were observed for peanuts, tree nuts and walnuts (Supplementary Table S1).

After adjusting for most known HCC risk factors, we observed a nonsignificant inverse association between total nut consumption and HCC risk (the highest vs. lowest tertiles, HR, 0.84; 95% CI, 0.56–1.26; Table 2). For the same comparison, we observed a significant inverse association between tree nut intake and HCC risk (HR, 0.64; 95% CI, 0.43–0.95). We also observed nonsignificant inverse associations with peanuts, walnuts, peanut butter, and peanut with peanut butter (Table 2). Similar inverse associations were observed for both women (Supplementary Table S2) and men (Supplementary Table S3), as well as in the pooled analysis not adjusting for total energy intake (Supplementary Table S4), although most associations were not statistically significant.

In sensitivity analyses, although the statistical power was limited because of the number of HCC cases, we did not detect any statistically significant heterogeneity (all P> 0.30) according to HBV/HCV infection status. The results did not appreciably change after excluding HCC cases with HBV/HCV infections with multivariable HRs of 0.92 (95% CI, 0.59–1.43) for total nut and 0.59 (95% CI, 0.38–0.90) for tree nut consumption. In addition, we found nonsignificant associations for total nut consumption after separately adjusting for tooth loss (HR, 0.91; 95% CI, 0.60–1.37), periodontal disease (HR, 0.92; 95% CI, 0.61–1.38), PUFAs (HR, 0.86; 95% CI, 0.57–1.28), and AHEI-2010 (HR, 0.89; 95% CI, 0.59–1.34). Furthermore, we found inverse associations for tree nut consumption, after separately adjusting for tooth loss (HR, 0.67; 95% CI, 0.45–0.99), periodontal disease (HR, 0.68; 95% CI, 0.46–1.01), intake of PUFAs (HR, 0.63; 95% CI, 0.42–0.93), and AHEI-2010 (HR, 0.65; 95% CI, 0.44–0.97). There was no statistically significant heterogeneity in the association between total nut or tree nut consumption and HCC risk according to cirrhosis status (all P > 0.60).

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Table 1. Characteristics of participants according to intake of total nut consumption in the NHS and HPFS

	Total nut consumption		
	Tertile 1	**Tertile 2**	**Tertile 3**
Women (NHS)			
Age (year)[a]	59.7 (11.9)	60.5 (11.2)	61.7 (11.1)
White, %	97.9	97.4	97.3
BMI, kg/m^2	25.4 (4.7)	25.2 (4.5)	24.6 (4.2)
Physical activity, MET-hours/week	13.6 (13.5)	14.9 (14.7)	16.7 (16.2)
Type II diabetes, %	6.4	5.9	5.0
Regular aspirin use, %	40.1	40.8	40.2
Past smoking, %	37.2	39.4	41.3
Current smoking, %	18.2	14.7	13.2
Food and nutrient intakes			
Alcohol, g/day	4.5 (7.3)	5.1 (8.1)	6.4 (9.2)
Total coffee intake, cups/day	2.3 (1.7)	2.3 (1.6)	2.3 (1.6)
Peanuts, serving/week	0.06 (0.41)	0.19 (0.44)	0.91 (1.37)
Tree nuts, serving/week	0.04 (0.26)	0.15 (0.32)	0.75 (1.16)
Walnuts, serving/week	0.05 (0.27)	0.13 (0.37)	0.35 (0.77)
Peanut butter, serving/week	0.8 (1.6)	1.1 (1.6)	1.5 (1.9)
Polyunsaturated fat, (% of energy)	5.6 (1.1)	5.7 (1.0)	5.9 (1.1)
Men (HPFS)			
Age (year)[a]	67.8 (12.6)	65.2 (12.2)	66.7 (12.0)
White, %	95.2	95.8	96.1
BMI, kg/m^2	25.9 (3.6)	25.9 (3.5)	25.6 (3.4)
Physical activity, MET-hours/week	25.6 (26.7)	28.4 (28.2)	31.4 (29.3)
Type II diabetes, %	3.6	4.0	4.0
Regular aspirin use, %	26.4	32.2	33.8
Past smoking, %	30.8	34.8	36.6
Current smoking, %	4.5	4.8	4.9
Food and nutrient intakes			
Alcohol, g/day	5.7 (1.2)	5.8 (1.1)	6.2 (1.2)
Total coffee intake, cups/day	9.2 (13.1)	10.9 (13.6)	12.6 (14.8)
Peanuts, serving/week	0.10 (0.14)	0.52 (0.29)	2.38 (2.41)
Tree nuts, serving/week	0.07 (0.12)	0.41 (0.29)	1.60 (1.83)
Walnuts, serving/week	0.06 (0.39)	0.18 (0.51)	0.50 (1.23)
Peanut butter, serving/week	1.2 (2.2)	1.4 (2.1)	1.9 (2.6)
Polyunsaturated fat, (% of energy)	5.7 (1.2)	5.8 (1.1)	6.2 (1.2)
Pooled NHS and HPFS cohorts			
Age (year)[a]	63.1 (12.9)	62.0 (11.7)	63.2 (11.6)
White, %	96.8	96.9	97.0
BMI, kg/m^2	25.6 (4.3)	25.4 (4.2)	24.9 (4.0)
Physical activity, MET-hours/week	18.6 (20.9)	19.3 (21.1)	21.1 (22.0)
Type II diabetes, %	5.1	5.3	4.8
Regular aspirin use, %	34.4	38.1	38.4
Past smoking, %	34.4	38.0	40.0
Current smoking, %	12.9	11.4	10.6
Food and nutrient intakes			
Alcohol, g/day	6.5 (10.4)	7.0 (10.6)	8.2 (11.5)
Total coffee intake, cups/day	2.1 (1.7)	2.1 (1.6)	2.1 (1.6)
Peanuts, serving/week	0.08 (0.34)	0.29 (0.42)	1.35 (1.86)
Tree nuts, serving/week	0.05 (0.22)	0.23 (0.33)	1.00 (1.44)
Walnuts, serving/week	0.06 (0.32)	0.14 (0.41)	0.39 (0.91)
Peanut butter, serving/week	1.0 (1.9)	1.2 (1.8)	1.6 (2.2)
Polyunsaturated fat, (% of energy)	5.6 (1.1)	5.7 (1.0)	6.0 (1.1)

NOTE: Values were means (SD) or percentages and were standardized to the age distribution of the study population.
[a]Value was not age adjusted.

In exploratory subgroup analyses, there were no significant interactions with age, physical activity, smoking, alcohol drinking, type II diabetes, coffee intake, and aspirin use (all $P \geq 0.10$). Furthermore, among participants who have information on HBV/HCV infection status (including 105 HCC cases and 78 noncases), we found no correlation between nut consumption and HBV/HCV infection status. The Spearman correlation coefficients between HBV/HCV infection and total nut and tree nut consumption were −0.05, and 0.01, respectively. Similar results were observed when we calculated the correlations separately among HCC cases and non-HCC cases.

Discussion

In these two cohort studies with an average of 27.9 years of follow-up, we observed that higher total nut consumption appeared not strongly associated with HCC risk, although there was a suggestive inverse association with tree nut consumption. These findings represent one of the

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Table 2. Nut consumption and risk of HCC in the pooled NHS and HPFS

	Nut consumption, HR (95% CI)			
	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Nuts				
Number of cases	45	52	65	
Age-adjusted model[a]	1 (Reference)	0.83 (0.55–1.24)	0.94 (0.64–1.38)	0.98
Multivariable-adjusted model[b]	1 (Reference)	0.79 (0.53–1.19)	0.84 (0.56–1.26)	0.63
Peanuts[c]				
Number of cases	54	41	62	
Age-adjusted model[a]	1 (Reference)	0.79 (0.52–1.19)	0.96 (0.66–1.38)	0.90
Multivariable-adjusted model[b]	1 (Reference)	0.74 (0.49–1.12)	0.84 (0.57–1.23)	0.62
Tree nuts[c]				
Number of cases	63	44	50	
Age-adjusted model[a]	1 (Reference)	0.70 (0.47–1.04)	0.72 (0.49–1.04)	0.17
Multivariable-adjusted model[b]	1 (Reference)	0.68 (0.45–1.01)	0.64 (0.43–0.95)	0.07
Walnuts[d]				
Number of cases	55	10	33	
Age-adjusted model[a]	1 (Reference)	0.58 (0.26–1.32)	0.69 (0.44–1.07)	0.19
Multivariable-adjusted model[b]	1 (Reference)	0.63 (0.28–1.43)	0.71 (0.45–1.12)	0.23
Peanut butter				
Number of cases	44	61	57	
Age-adjusted model[a]	1 (Reference)	1.10 (0.74–1.63)	0.88 (0.59–1.32)	0.34
Multivariable-adjusted model[b]	1 (Reference)	1.07 (0.72–1.60)	0.83 (0.55–1.25)	0.22
Peanuts and peanut butter				
Number of cases	44	58	60	
Age-adjusted model[a]	1 (Reference)	1.01 (0.68–1.51)	0.90 (0.61–1.34)	0.52
Multivariable-adjusted model[b]	1 (Reference)	0.95 (0.63–1.42)	0.81 (0.53–1.22)	0.27

NOTE: The mean values (serving/week) for each tertile category were 0.08, 0.52, and 2.45 for total nuts; 0.03, 0.26, and 1.53 for peanuts; 0.01, 0.23, and 1.25 for tree nuts; 0, 0.03, and 0.62 for walnuts; 0.03, 0.50, and 2.86 for peanut butter; and 0.17, 0.87, and 3.66 for peanuts and peanut butter.

[a]Adjusted for age (in months).

[b]Adjusted for age (in months), gender (women, men), race (white, non-white), physical activity (MET-hours/week, continuous), BMI (kg/m^2, continuous), smoking status (never, past, current), aspirin use (no, yes), type II diabetes (no, yes), total alcohol intake (g/day, continuous), total coffee intake ($\leq$1, 2–3, $\geq$4 cups/day), and total calorie intake (kcal/day, continuous).

[c]First reported in 1986.

[d]First reported in 1998.

first prospective epidemiologic studies on the topic and add to the existing data on nut consumption on certain disease risk.

Previous epidemiologic studies, although very limited, have examined associations between nut consumption and certain gastrointestinal cancers with mixed results. The Netherlands Cohort Study showed that increased total nut consumption ($\geq$10 g/day vs. nonconsumers) was significantly associated with lower risk of gastric noncardia adenocarcinoma (HR, 0.73; 95% CI, 0.55–0.97; ref. 31), esophageal squamous cell carcinoma (HR, 0.54; 95% CI, 0.30–0.96; ref. 31), and pancreatic cancer (HR, 0.54; 95% CI, 0.30–0.96; ref. 32), but not with risk of gastric cardia adenocarcinoma (HR, 0.91; 95% CI, 0.56–1.49; ref. 31), or esophageal adenocarcinoma (HR, 1.19; 95% CI, 0.74–1.91; ref. 31). The NIH-AARP Diet and Health Study reported inverse association between nut consumption (over a half cup vs. nonconsumers) and gastric noncardia adenocarcinoma (HR, 0.73; 95% CI, 0.57–0.94), but null association for esophageal squamous cell carcinoma (HR, 1.01; 95% CI, 0.66–1.55; ref. 33). In contrast, the Golestan Cohort Study showed inverse association between nut consumption (top vs. bottom tertiles) and risk of esophageal squamous cell carcinoma (HR, 0.60; 95% CI, 0.39–0.93; ref. 34). Moreover, in the NHS and HPFS cohorts, we reported inverse associations between nut consumption ($\geq$2 times/week vs. never) and risk of colorectal cancer (HR, 0.87; 95% CI, 0.72–1.05; ref. 35), and pancreatic cancer (HR, 0.73; 95% CI, 0.54–0.99; ref. 36). Beyond cohort studies, one case–control study reported inverse association between nut consumption ($\geq$3 servings per week vs. nonconsumers) and risk of colorectal cancer in women (OR, 0.30; 95% CI, 0.15–0.60) and men (OR, 0.28; 95% CI, 0.17–0.47; ref. 37). The other one found null association with gastric cancer (top vs. bottom tertiles, HR, 0.9; 95% CI, 0.3–3.3; ref. 38). Differences in nut intake levels, confounding control, and number of cases may partially explain some of the observed differential associations.

Although our study did not support a strong association between total nut consumption and HCC risk, most associations were inverse and there was suggestive possible benefit of tree nuts. These results may be due to chance. Alternatively, it is plausible that higher nut consumption might influence HCC risk through mechanisms related to insulin resistance, hyperinsulinemia, and inflammation. Higher consumption of total nuts (39), tree nuts (40), and walnuts (41), was associated with lower risk of type II diabetes, a risk factor for HCC, as well as inversely associated with insulin levels (42). Moreover, nut consumption was associated with weight loss (43) and reduced risk of NAFLD (44). Obesity and NAFLD,

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established risk factors for HCC (45, 46), are strongly associated with insulin resistance (47, 48).

Nut consumption might also influence HCC risk via its possible role in improving inflammation and lipid profiles. Persistent inflammation could increase the risk and accelerate the development of HCC (49). In the NHS and HFPS cohorts, intakes of tree nuts and peanuts were both inversely associated with circulating inflammatory markers (CRP, tumor necrosis factor receptor 2, and IL6; ref. 50). Similarly, inverse associations between higher nut consumption and circulating levels of CRP, IL6 were also reported from other prospective cohort studies (10). In addition, cholesterol overload in the liver induces profound cellular redox imbalances and may exert an oxidative stress–mediated effect, and promote the development of HCC (51). Higher nut consumption was linked to lower levels of total cholesterol (52), thereby possibly influencing HCC risk via its influence on lipid profiles. Furthermore, other bioactive compounds contained in nuts, such as vitamins, polyphenols, phytosterols, and selenium may also play a role, which requires further investigation. The reason why most associations were nonsignificant in this study may partly be because of the limited number of HCC cases. Interestingly, because nuts can be a source of aflatoxin exposure, the overall inverse associations between nut consumption and HCC risk suggest that participants in this study are less likely to be exposed to high levels of aflatoxins (53, 54), one of the most known potent hepatocarcinogens.

The strengths of this study include its prospective design, repeated measurements of detailed dietary and lifestyles, validated HCC outcome, and high rates of follow-up. Our study has some limitations. Our study populations were primarily white health professionals and the results may not be generalizable to other racial/ethnical groups. Although FFQs used in these cohorts have shown reasonable reproducibility and validity (21), self-reported diet and lifestyle data have potential measurement errors, as with any observational study. Although we examined peanuts, tree nuts, and walnuts separately, we were unable to examine other tree nuts such as hazelnuts, almonds, macadamias, pecans, cashews, and pistachios. Information on chronic HBV/HCV infection status was not available in the entire cohorts. So, we were unable to conduct analyses adjusting for or stratifying by HBV/HCV infection status in the full cohort analysis. However, among a subset of participants in which HBV/HCV data are available, there was no correlation with nut consumption. Previous studies also suggested no correlations between smoking status, alcohol and coffee intake, obesity, and HBV/HCV infections (26, 55, 56). In addition, we observed similar results when HCC cases with these infections were excluded. Thus, our results were less likely to be substantially confounded by HBV/HCV infections.

In conclusion, we did not observe a strong association between nut consumption and HCC risk, although most associations were inverse and there was suggestive benefit for tree nuts. Our findings should be interpreted with caution, given the limited number of HCC cases and lack of data on HBV/HCV infections in the full cohorts. Future studies should carefully consider HBV/HCV infections and examine the associations in other racial/ethnic groups.

Disclosure of Potential Conflicts of Interest

J.A. Meyerhardt is a consultant/advisory board member for Taiho, Ignyta, and COTA. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J. Sui, E.L. Giovannucci, X. Zhang
Development of methodology: J. Sui, X. Zhang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.L. Giovannucci, A.T. Chan, X. Zhang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Sui, W. Yang, Y. Ma, T.Y. Li, J.A. Meyerhardt, G. Liang, E.L. Giovannucci, X. Zhang
Writing, review, and/or revision of the manuscript: J. Sui, W. Yang, T.G. Simon, J.A. Meyerhardt, G. Liang, E.L. Giovannucci, A.T. Chan, X. Zhang
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Cancer Prevention Research

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