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ABSTRACT

Background/Objectives: Increasing nut consumption has been associated with reduced risk of obesity and type II diabetes, which are risk factors for colorectal cancer. However, the association between nut consumption and colorectal cancer risk is unclear. We aimed to examine the association of long-term nut consumption with risk of colorectal cancer.

Subjects/Methods: We prospectively followed 75,680 women who were free of cancer at baseline in the Nurses' Health Study, and examined the association between nut consumption and colorectal cancer risk. Nut consumption was assessed at baseline and updated every 2 to 4 years. Relative risks (RRs) and 95% confidence intervals (95% CIs) were estimated using Cox proportional hazards models.

Results: During 2,103,037 person-years of follow-up, we identified 1,503 colorectal cancer cases. After adjustment for other known or suspected risk factors, women who consumed nuts 2 or more times per week (i.e., ≥56 grams per week) had a 13% lower risk of colorectal cancer compared to those who rarely consumed nuts, but the association was not statistically significant (RR: 0.87; 95% CI: 0.72, 1.05; *P* trend: 0.06). No association was observed for peanut butter.

Conclusions: In this large prospective cohort of women, frequent nut consumption was not significantly associated with colorectal cancer risk after adjusting for other risk factors.

INTRODUCTION

Colorectal cancer is the second most common cancer in women and the third most common cancer in men worldwide[1]. Beyond well-known risk factors such as older age, family history, and inherited genetic conditions, the risk of colorectal cancer is also higher among individuals with excess body weight[2] or type 2 diabetes[3]. Since nuts have been associated with improved insulin resistance[4, 5], less weight gain[6, 7], and a decreased risk of type 2 diabetes[8-10], increasing nut consumption may result in reduced risk of developing colorectal cancer. In addition, *in vitro* fermented nuts exhibit chemopreventive effects in colon cancer cells[11], and nut intake inhibited colorectal cancer growth in mice[12].

Nonetheless, few epidemiologic studies have investigated the association between nut consumption and colorectal cancer risk. Earlier case-control studies reported inconsistent results[13-15]. More recent data from prospective cohort studies suggested an inverse association[16-18], especially among women[17, 18]. However, the previous studies grouped nuts with seeds or legumes[13-15, 17], had only one measure of nut intake[13-18], had a relatively short follow-up (if cohort studies)[16, 17], or had a limited number of colorectal cancer cases[13, 16, 18]. We therefore examined the association between long-term nut consumption and risk of colorectal cancer in a large cohort of women with a follow-up of 30 years.

SUBJECTS AND METHODS

Study Population

The Nurses' Health Study (NHS) was initiated in 1976 and enrolled 121,700 U.S. female nurses aged 30-55 years. Participants completed a baseline questionnaire and biennial follow-up questionnaires to update information on new disease diagnoses and potential risk factors for

chronic diseases. In 1980, a validated semi-quantitative food frequency questionnaire was sent to collect dietary information[19]. The follow-up rate exceeded 90% in each 2-year cycle.

For the present analysis, study baseline was defined as the year of the first food frequency questionnaire (i.e., 1980). At baseline, 92,468 women completed the dietary questionnaire. We excluded 3,670 women who had a history of cancer, 1,141 women who did not provide information on nut intake, and 11,977 women who did not provide information on anthropometric measures or physical activity, or reported implausible nutritional information (>9 missing food items or estimated daily energy intake <500 kcal or >3500 kcal). This left 75,680 women eligible for the analyses. This study was approved by the Human Research Committee at the Brigham and Women's Hospital.

Assessment of Dietary and Non-dietary Factors

Validated semi-quantitative food frequency questionnaires were used to assess dietary intake in 1980, 1984, 1986, and every 4 years thereafter. We asked participants to report their average frequency of intake over the preceding year for a specified serving size of each food. In the 1980 and 1984 dietary questionnaires, the participants were asked how often they had consumed nuts (serving size, 28 g [1 oz]) over the preceding year: never/almost never, 1 to 3 times a month, once a week, 2 to 4 times a week, 5 to 6 times a week, once a day, 2 to 3 times a day, 4 to 6 times a day, or more than 6 times a day. In the subsequent questionnaires, the question for nuts was split into peanuts and other nuts. Total nut consumption was the sum of peanuts and other nuts intakes. We also assessed peanut butter consumption (serving size, 15 mL [1 tablespoon]) every 2 to 4 years using the same 9 responses. A validation study of the NHS food-frequency questionnaire demonstrated that nut and peanut butter intakes were reported with

reasonable accuracy; the correlation coefficients were 0.75 for nuts and 0.75 for peanut butter between intakes assessed by the 1980 questionnaire and by dietary records collected over four weeks[20].

In all questionnaires, women were asked about their history of smoking, including smoking status, time since quitting and average number of cigarettes smoked daily. Information on physical activity was assessed at baseline and updated every 2 to 4 years. Body mass index (BMI) was calculated from self-reported height at baseline and weight updated every 2 years. Information on family history of colorectal cancer, use of aspirin and multivitamin, and history of diabetes (incident cases during follow-up), ulcerative colitis, polyps, and lower endoscopy were updated every 2 to 4 years.

Identification of Colorectal Cancer Cases

Participants were asked to report specified medical conditions, including cancers, that were diagnosed in the 2-year period between each follow-up questionnaire. Whenever a participant (or next of kin for decedents) reported a diagnosis of colorectal cancer, we asked for permission to access the participant's medical records. We also searched the National Death Index to identify deaths among non-respondents. This method has been shown to capture >98% of deaths[21]. Study physicians who were blinded to participants' risk factor status reviewed medical records and assigned cancer diagnoses and causes of death.

Statistical Analysis

The follow-up started from the return date of the 1980 questionnaire to the date of colorectal cancer diagnosis, death from any cause, or the end of follow-up (May 31st, 2010),

whichever came first. The cumulative average of nut consumption were calculated from all available dietary questionnaires, using methods for repeated measures, as described previously[22]. Briefly, we used data from the 1980 questionnaire for the follow-up period from 1980 to 1984, the average of 1980 and 1984 for the interval from 1984 to 1986, and the average of 1980, 1984, and 1986 for the interval from 1986 to 1990, and so forth. For analyses of total nuts, peanuts, other nuts, and peanut butter, we divided women into 4 groups according to their frequency of nut consumption: never/almost never (the reference group), 1 to 3 times a month, once a week, and at least 2 times a week.

Cox proportional hazards models were used to estimate relative risk (RR) and 95% confidence intervals (CIs). In multivariable analyses, we adjusted for potential confounding variables including age, physical activity, family history of colorectal cancer, history of previous lower endoscopy, history of ulcerative colitis, history of polyps, aspirin use, multivitamin use, smoking, alcohol intake, and total energy intake. Separately, we then adjusted for BMI and diabetes to see if the observed association was independent of these potential mediators or confounding factors for the association between nut intake and colorectal cancer risk. Additional adjustment for postmenopausal hormone use, red meat, fruits and vegetables, dietary fiber, folate, calcium, vitamin D, or the Mediterranean diet score did not appreciably change the results; thus these variables were omitted from the final models. *P* values for trend were calculated by the Wald test of a score variable that contained median values of intake categories.

To test the robustness of our results, we conducted sensitivity analyses excluding individuals with diabetes or ulcerative colitis at baseline. To address the concern of any effect of subclinical colorectal cancer on nut intake, we added a 4-year lag period between nut intake assessment and each follow-up period (follow-up started in 1984 for this analysis), i.e., we used

146 nut intake from the 1980 questionnaire for the follow-up period from 1984 to 1988, the 1984
147 questionnaire for the period from 1988-1992 and so forth.

148 We examined whether the associations of interest were modified by BMI and physical
149 activity. Tests for interaction were performed by the Wald test of cross-product terms. All
150 statistical analyses were performed with the SAS 9.1 statistical package (SAS Institute, Cary,
151 North Carolina) and all *P* values are two sided.

152

153 **RESULTS**

154 Nut consumption remained relatively constant during study follow-up. At baseline,
155 women with higher nut consumption were leaner, less likely to smoke, and more likely to
156 exercise, have lower endoscopy, and take aspirin on a regular basis (Table **1**). They also tended
157 to consume more alcohol, multivitamin supplements, fruits, vegetables as well as calcium, fiber
158 and folate.

159 During 30 years of follow-up (2,103,037 person-years), we documented 1,503 colorectal
160 cancer cases. The multivariable RR of colorectal cancer for women consuming nuts 2 times or
161 more per week versus women rarely consuming nuts was 0.86 (95% CI: 0.72, 1.04; *P*
162 trend=0.04) (Table **2**). The inverse association attenuated after further adjusting for BMI and
163 diabetes (RR: 0.87; 95% CI: 0.72, 1.05; *P* trend=0.06) (Table **2**). Separate analyses of colon and
164 rectal cancer showed no substantial differences in relation to nut intake, although the *P* value for
165 trend was statistically significant for colon cancer (RR: 0.86; 95% CI: 0.70, 1.07; *P* trend=0.04)
166 (Table **2**). We further divided colon cancer into proximal and distal colon cancer. The RRs
167 comparing 2 or more times per week with never were 0.95 (95% CI: 0.72, 1.27; *P* trend=0.10)
168 for proximal colon cancer and 0.78 (95% CI: 0.56, 1.10; *P* trend=0.20) for distal colon cancer (*P*

for heterogeneity=0.99). No association was observed between peanut butter and colorectal cancer risk (RR comparing 2 or more times per week with never: 0.94; 95% CI: 0.80, 1.11; *P* trend=0.72).

The association between nut consumption and colorectal cancer risk remained virtually unchanged when we excluded diabetes at baseline, when we restricted to those without ulcerative colitis at baseline, or when we excluded the first 4 years of follow-up and added a 4-year lag period between nut intake assessment and each follow-up period (Supplementary Table **1**). Moreover, the association was not different across strata of BMI and physical activity (*P* for interaction≥0.14) (Table **3**). In separate analyses of the types of nuts consumed (assessed in 1986), the RRs comparing 2 or more times per week with never were 0.85 (95% CI: 0.66, 1.09) for peanuts and 0.93 (95% CI: 0.71, 1.23) for other nuts (*P* for heterogeneity=0.98) (Supplementary Table **2**).

DISCUSSION

In this large prospective cohort of women, frequent nut consumption was not significantly associated with colorectal cancer risk after adjusting for other known or suspected risk factors of colorectal cancer, although an inverse association was suggested. This observation is compatible with previous prospective cohort studies. The Adventist Health Study found a suggestive lower risk of colon cancer with higher nut intake (RR comparing >4 times/week with never to <once/week: 0.68; 95% CI: 0.45, 1.04; *P* trend=0.22)[16]. The European Prospective Investigation into Cancer and Nutrition (EPIC) study found that among women, the consumption of nuts and seeds was associated with a nonsignificant reduction in colorectal cancer risk (RR comparing >6.2 g/d with 0 g/d: 0.81; 95% CI: 0.63, 1.04; P trend=0.07) and a significant

reduction in colon cancer risk (RR comparing >6.2 g/d with 0 g/d: 0.69; 95% CI: 0.50, 0.95; *P* trend: 0.04)[17]. In contrast, no association was observed among men. Similarly, a Taiwan study reported that frequent intake of peanut and its products was associated with a significantly reduced risk of colorectal cancer among women only (RR comparing ≥2 times/week with ≤once/week: 0.42; 95% CI: 0.21, 0.84; *P* trend = 0.01)[18].

The mechanisms underlying the health benefits of nuts are unclear and need to be elucidated[23]. However, nuts are rich sources of unsaturated fatty acids, fibers, vitamins, minerals, and phytochemicals, which may provide antioxidant, anti-inflammatory, and anticarcinogenic properties[24]. Indeed, intervention studies have demonstrated beneficial effects of nuts on intermediate markers of cancer, including oxidative stress[25, 26], inflammation[27], and insulin resistance[4, 5]. Moreover, observational studies have also shown that increasing nut intake was associated with reduced waist circumference[28] and a reduced risk of obesity[7], metabolic syndrome[29], and type 2 diabetes[8-10], all of which are risk factors for colorectal cancer.

The strengths of this study include its prospective design, large sample size, 30 years of follow-up with excellent follow-up rate, and repeated measures of diet and lifestyle variables. In addition, the inverse association trend persisted for colon cancer when we added a 4-year lag period between nut intake and each follow-up period. Our study also has limitations. Self-reported dietary data has inherent measurement error. Nevertheless, we were able to reduce the error by averaging nut intake cumulatively. In addition, although we examined peanuts and tree nuts separately, we were not able to examine different types of tree nuts, such as walnuts, in this analysis. Moreover, although we cannot eliminate residual confounding by other risk factors for colorectal cancer, our study provided detailed information on diet and lifestyle, and we were also

able to adjust for dietary patterns. Restriction to female nurses could reduce the generalizability of the results, but it also potentially minimizes residual confounding by socioeconomic status.

In conclusion, frequent nut consumption was not significantly associated with colorectal cancer risk in this large prospective cohort of women, although a possible inverse association was suggested. Further studies are warranted.

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CONFLICT OF INTEREST

Dr. Bao reported receiving a research grant from the International Tree Nut Council Nutrition Research & Education Foundation. The sponsors did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. Dr. Yang, Dr. Hu, Dr. Giovannucci, Dr. Stampfer, Dr. Willett, Dr. Fuchs and Dr. Wu declare no potential conflict of interest.

Supplementary information is available at European Journal of Clinical Nutrition's website.

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Table **1**. Characteristics of person-years by nut consumption*

	Frequency of nut consumption (28g serving)			
	Never	1-3 times/month	Once/week	≥ 2 times/week
Nut intake, servings/d	0	0.01-0.09	0.10-0.19	≥ 0.20
Person-years	363,578	936,896	396,362	406,201
Age, y, mean (SD)	55.8(10.9)	59.3(10.8)	60.4(10.8)	61.0(10.7)
BMI, kg/m^2, mean (SD)	26.1(5.3)	26.2(5.2)	25.9(5.0)	25.3(4.8)
Physical activity, metabolic equivalents-hours/week, mean (SD)	13.8(20.5)	15.6(20.9)	17.4(22.1)	19.5(25.0)
Current smoking, %	20.7	15.5	13.8	13.5
Family history of colorectal cancer, %	11.3	12.6	12.7	12.6
History of previous lower endoscopy, %	11.7	15.2	16.8	16.5
History of diabetes mellitus, %	7.8	7.0	6.6	6.0
Multivitamin use, %	32.6	42.4	46.5	50.0
Aspirin use, %	43.2	48.6	49.7	50.3
Red meat, servings/d, mean (SD)	1.1(0.7)	1.1(0.6)	1.1(0.6)	1.1(0.6)
Vegetables, servings/d, mean (SD)	2.3(1.2)	2.6(1.2)	2.8(1.2)	3.0(1.3)
Fruits, servings/d, mean (SD)	2.0(1.2)	2.1(1.1)	2.3(1.2)	2.5(1.3)
Alcohol, g/d, mean (SD)	5.2(9.4)	5.6(9.0)	6.6(9.3)	7.3(10.2)
Vitamin D, IU/d, mean (SD)	344 (237)	345(212)	349(223)	362(225)
Calcium, mg/d, mean (SD)	870(366)	915(349)	925(342)	942(345)
Folate, μg/d, mean (SD)	406(249)	438(250)	457(261)	481(267)
Fiber, g/d, mean (SD)	14.0(4.7)	15.8(4.3)	16.3(4.2)	17.4(4.6)

*All variables (except age) are age-standardized. IU: international unit.

Table **2**. Relative risks (RR) and 95% confidence intervals (CIs) for colorectal cancer according to total nut consumption

	Frequency of nut consumption (28g/serving)				
	Never	1-3 times/month	Once/week	≥ 2 times/week	P_{trend}
Nut intake, servings/d	0	0.01-0.09	0.10-0.19	≥ 0.20	
Person-years	363,578	936,896	396,362	406,201	
Colorectal					
No, of cases (n=1,503)	231	698	293	281	
Age-adjusted	1.00	1.01 (0.87, 1.17)	0.98 (0.82, 1.17)	0.87 (0.73, 1.04)	0.04
Multivariable I*	1.00	1.00 (0.86, 1.16)	0.97 (0.81, 1.17)	0.86 (0.72, 1.04)	0.04
Multivariable II †	1.00	1.00 (0.86, 1.16)	0.98 (0.82, 1.17)	0.87 (0.72, 1.05)	0.06
Colon					
No, of cases (n=1,147)	169	540	226	212	
Age-adjusted	1.00	1.06 (0.89, 1.26)	1.02 (0.83, 1.25)	0.88 (0.72, 1.09)	0.05
Multivariable I*	1.00	1.04 (0.87, 1.24)	1.00 (0.81, 1.23)	0.86 (0.69, 1.06)	0.03
Multivariable II †	1.00	1.04 (0.87, 1.24)	1.00 (0.81, 1.23)	0.86 (0.70, 1.07)	0.04
Rectum					
No, of cases (n=323)	55	147	60	61	
Age-adjusted	1.00	0.92 (0.67, 1.26)	0.89 (0.61, 1.29)	0.85 (0.59, 1.23)	0.43
Multivariable I*	1.00	0.93 (0.68, 1.28)	0.92 (0.63, 1.34)	0.88 (0.60, 1.30)	0.60
Multivariable II †	1.00	0.93 (0.67, 1.28)	0.92 (0.62, 1.34)	0.89 (0.60, 1.31)	0.64

* Adjusted for age (month), physical activity (metabolic-equivalents/week, quintiles), family history of colorectal cancer (yes/no), history of previous lower endoscopy (yes/no), history of ulcerative colitis (yes/no), history of polyps (yes/no), aspirin use (<1, 1-3, 3.1-7, >7 tablets/week), multivitamin use (yes/no), pack-years of smoking (never smoker, 1-9, 10-24,25-44, and ≥ 45 pack-years), alcohol intake (never, 0.1-5, 5.1-15, > 15 g/d), and total energy intake (kcal, continuous).

† Multivariable I plus body-mass index (<22, 22-22.9, 23-24.9, 25-28.9, ≥29 kg/m^2) and history of diabetes mellitus (yes/no).

Table **3**. Total nut consumption and risk of colorectal cancer, stratified by BMI and physical activity *

			Frequency of nut consumption (28g serving)					
	Cases	Person-years	Never	1-3 times/month	Once/week	≥ 2 times/week	P_{trend}	$P_{interaction}$
Nut intake, servings/d			0	0.01-0.09	0.10-0.19	≥ 0.20		
Body mass index (BMI)								0.14
< 25 kg/m^2	603	943,976	1.00	0.85 (0.66, 1.08)	0.88 (0.67, 1.17)	0.91 (0.69, 1.20)	0.93	
≥ 25kg/m^2	733	905,415	1.00	1.13 (0.90, 1.42)	1.11 (0.85, 1.45)	0.82 (0.62, 1.09)	0.01	
Physical activity†								0.20
High physical activity	693	1,080,247	1.00	0.97 (0.77, 1.24)	0.95 (0.72, 1.25)	0.78 (0.59, 1.03)	0.02	
Low physical activity	755	910,096	1.00	1.04 (0.84, 1.30)	1.04 (0.80, 1.34)	1.01 (0.78, 1.32)	0.89	
BMI and Physical activity								0.94
BMI<25 and high physical activity	318	565,384	1.00	0.90 (0.63, 1.27)	0.80 (0.53, 1.19)	0.78 (0.53, 1.17)	0.27	
Intermediate group	603	800,522	1.00	1.00 (0.78, 1.29)	1.13 (0.84, 1.50)	0.96 (0.71, 1.30)	0.72	
BMI≥25 and low physical activity	399	458,321	1.00	1.07 (0.79, 1.44)	1.01 (0.71, 1.45)	0.78 (0.53, 1.15)	0.07	

*****Adjusted for age (month), physical activity (metabolic-equivalents/week, quintiles), family history of colorectal cancer (yes/no), history of previous lower endoscopy (yes/no), history of ulcerative colitis (yes/no), history of polyps (yes/no), aspirin use (<1, 1-3, 3.1-7, >7 tablets/week), multivitamin use (yes/no), pack-years of smoking (never smoker, 1-9, 10-24,25-44, and ≥ 45 pack-years), alcohol intake (never, 0.1-5, 5.1-15, > 15 g/d), and total energy intake (kcal, continuous), body-mass index (<22, 22-22.9, 23-24.9, 25-28.9, ≥29 kg/m^2), and history of diabetes mellitus (yes/no).

† High physical activity group was defined by metabolic-equivalents/week more than the median level; low physical activity group was defined by metabolic-equivalents per week less than or equal to median level.