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Associations of Nut Intakes with Incident Sporadic Colorectal Adenoma Risk:

A Pooled Case-Control Study

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By

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Bachelor of Arts

China Pharmaceutical University

2015

Faculty Thesis Advisor: Roberd M. Bostick, MD, MPH

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Abstract

Associations of Nut Intakes with Incident Sporadic Colorectal Adenoma Risk:

A Pooled Case-Control Study

By Xin Yin

Nuts are rich in phytochemicals with antioxidant and anti-inflammatory properties, suggesting that consumption of them may reduce risk for colorectal carcinogenesis. However, there are few published reports on associations of nut intakes with colorectal adenoma, the immediate precursor to most colorectal cancers. To investigate an association of nut intakes with incident, sporadic colorectal adenoma, we pooled data from three case-control studies of incident, sporadic colorectal adenoma (n=785 cases, 2,107 controls), and analyzed them using multivariable unconditional logistic regression. The multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association of total nut product (all nuts and peanut butter combined) intakes, for those who consumed 0.5 – 1.5, 2.0 – 5.5, and ≥ 6 servings/week relative to no nut consumption were 0.81 (0.58, 1.12), 0.86 (0.61, 1.23), and 0.93 (0.65, 1.31), respectively (p_{trend} = 0.66). The corresponding ORs and 95% CIs among women were 0.62 (0.40, 0.97), 0.57 (0.35, 0.94), and 0.78 (0.48, 1.25), respectively (p_{trend} = 0.86). Findings similar to those for women were noted among those who were <56 years old, had a family history of colorectal cancer in a first degree relative, regularly took aspirin or other non-steroidal anti-inflammatory drugs, and those who had a lower balance of anti- to pro-oxidant exposures. These results suggest a possible U-shaped association of total nut product intakes with risk for colorectal adenoma, possibly limited to women and other population subgroups. The possible reasons for the estimated U-shaped association are unclear, and investigation in other populations/studies is needed.

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CHAPTER I: BACKGROUND/LITERATURE REVIEW

Colorectal Cancer

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer death in the US.[1-3] In 2014, there were approximately 1.3 million people living with colon or rectal cancer in the United States.[1] Although the rates for death and new colon cancer cases have been falling slowly and continuously during the past decade, colon cancer still causes great morbidity and mortality in the United States.[1-2] Colorectal cancer mostly begins with the growth of an adenomatous polyp on the inner lining of the colon or rectum. Adenomas may serve as a biological marker of higher colon cancer risk. [2, 4-5] Although not all adenomas progress to cancer, the risk of developing colon cancer increases with the size and number of adenomas.[4] Nonmodifiable risk factors for colorectal cancer include age, sex, family history and inherited genetic conditions. Modifiable risk factors that might increase the risk for developing adenomas or colorectal cancer are increased body mass index (IBM), physical inactivity, type 2 diabetes, certain types of diets, smoking and heavy alcohol use. Among these risk factors, obesity, physical inactivity, diets high in red and processed meats are considered as major factors that may raise colorectal cancer risk.[6-9] Particularly, colorectal cancer is one of the cancers that is most associated with diet. Considerable studies provided evidence of lower risk for colorectal cancer of higher intake of foods containing dietary fiber [10-14] and phytochemicals with antioxidant/anti-inflammatory properties.[15-19]

Nuts and Antioxidant/Anti-inflammatory Effects

Nuts are high in vegetable protein, fiber, monounsaturated fatty acids, B vitamins, vitamin E, polyphenols, folate and phytoestrogen, although the concentrations vary among different types of nuts.[14, 18, 20] The phytochemicals found in tree nuts have been associated with antioxidant, anti-inflammatory, anti-proliferative, antiviral and chemopreventive properties, all of which can impact several pathogenic processes.[18, 21-24] Particularly, more and more studies suggest that oxidative stress and inflammatory effects play important roles in colorectal carcinogenesis. For example, a case-control study[25] in the European Prospective Investigation into Cancer and Nutrition cohort (n= 1064 cases and 1064 matched controls) examined the association of oxidative stress indicators with the risk for colorectal cancer, and concluded that pre-diagnostic serum ROM levels were associated with higher CRC risk in subjects with relatively short follow-up. A large amount of research has addressed a role for phytochemical antioxidants, such as vitamins C and E and polyphenols in reducing oxidative stress, which is often referred to as an imbalance of oxidants relative to antioxidants in the human body.[15, 21-22] A 4-week randomized crossover trail[19] (n=27) found that full-dose almonds (taken as snacks) had antioxidant action, as indicated by reducing serum concentrations of malondialdehyde (MDA) (P=0.04) and urinary isoprostanes (P=0.03), compared to the control group who took low-saturated fat (<5% energy) whole-wheat muffins. Another randomized crossover trial[24] (n=22) in Chinese patients with type 2 diabetes mellitus found that a diet rich in almonds could ameliorate inflammation and oxidant stress. Comparing to the control diet which provided daily calories from carbohydrate, protein, and fat at 56, 17, and 27 % respectively, an almond diet which incorporated roasted, unsalted whole

almonds (56 g/day, on average) with skins into meals to replace 20% calories of the control diet decreased IL-6 by a median 10.3%, CPR by a median 10.3%, TNF-a by a median 15.7 %, plasma protein carbonyl by a median 28.2 % and enhanced the resistance of LDL against Cu^{2+}-induced oxidation by a median 16.3 %, indicating the benefits of almond intake in diminishing oxidative stress and inflammation. In a PREDIMED study[26] reductions in circulating inflammatory biomarkers (interleukin-6) and cell adhesion molecules (ICAM-1 & VCAM-1) concentrations was observed in the case group who were on a diet supplemented with nuts 30 g/d (n=258) relative to the control group who were assigned to a low-fat diet (n=257), supporting the anti-inflammatory effects of the nuts diet. Furthermore, in The Multi-Ethnic Study of Atherosclerosis (MESA) study (n=6080),[27] the data analysis demonstrated an inverse association between frequent total nut and seed consumption and inflammatory biomarkers including plasma levels of C-reactive protein ($r = 0.06$, $p < 0.001$), interleukin-6 ($r = -0.05$, $p < 0.001$), and fibrinogen ($r = -0.07$, $p < 0.001$) in age-adjusted models. After adjusting for all potentially confounding variables including BMI, the associations were moderately attenuated, but the inverse relations were still observed. In a research on *in vitro* fermented nuts,[28] the analysis confirmed that fermentation supernatants of nuts, particularly walnuts, had higher antioxidant capacities than ground nuts. *In vitro* fermented nuts presented chemopreventive effects on colon cancer cells by reducing tumor-promoting deoxycholic acid (DCA) (8.20–88.65 mM), increasing chemopreventive short chain fatty acids (SCFA) (67·83–85·93 mmol/l), and preventing oxidative damage. Vinson and Cai[22] measured the antioxidant efficacy of nuts and found that the antioxidant capacity of the various raw nuts was, in order of decreasing capacity: walnuts > cashews > hazelnuts >

pecans > almonds > macadamias > pistachios > Brazil nuts > peanuts. They also found a 37% decrease on average (but not significant, p=0.14) in antioxidant efficacy for the roasted counterparts.

Nuts and Body Mass Index (BMI)

There is evidence suggesting that frequent nut consumption is inversely associated with body mass index (BMI), contrary to the common belief that nuts could cause obesity because of their high energy and fat content.[29-32] The SUN prospective cohort[29] assessed nut consumption and its association with risk of weight gain (≥5 kg) or the risk of becoming overweight in a Mediterranean population. Data were collected from 8,865 adults who completed a 2-year follow-up questionnaire (a median of 28 months after baseline). Frequent nut consumption was statistically significantly associated with a lower risk of weight gain of ≥5 kg. After adjustment for other established risk factors, participants who ate nuts at least two times a week were 30% less likely to gain weight than those who rarely ate them. Similarly, another prospective study, the NHS II cohort,[30] investigated an association of nut consumption with long-term weight change in women (n= 51,188). Nut consumption ≥2 times/wk relative to never or seldom consumption was associated with a slightly lower risk of weight increase (HR: 0.77; 95% CI: 0.57, 1.02; P for trend = 0.003). The results were similar when total nut consumption was subdivided into peanuts and tree nuts, and the findings were also similar in normal-weight, overweight, and obese participants.

Nuts and Type 2 Diabetes

Other than being helpful in controlling weight, nut consumption may be inversely associated with risk for type 2 diabetes (T2D).[33-36] The prospective Nurses' Health

Study[33] with a 16-year follow-up (n= 83,818 women) identified a statistically significant inverse association of nut consumption with type 2 diabetes after adjusting for known or suspect risk factors of T2D. Specifically, women who ate nuts ≥5 times/wk in relative to those who never or almost never ate nuts had 26% lower risk (RR: 0.74, 95% CI: 0.61, 0.89). Also, women who ate peanut butter ≥5 times/wk relative to women who never or almost never ate peanut butter had 21% lower risk for type 2 diabetes (RR: 0.79, 95% CI: 0.68–0.91). The PREDIMED study[36] was a Mediterranean diet intervention trial with 4 years of follow-up data in 418 nondiabetic participants (but at high risk of cardiovascular disease). Those on the Mediterranean diet supplemented with nuts (50% walnuts, 25% almonds, and 25% hazelnuts) had a 52% lower diabetes incidence than the control group who were on an advised low-fat diet.

Nuts and Colorectal Cancer

Given the accumulating evidence of nuts' antioxidant/anti-inflammatory effects, and that nut consumption is inversely associated with the risk of overweight and type II diabetes, which are recognized risk factors for colon cancer,[6-7, 37-39] it appears plausible that nut consumption may help lower the risk of incident colorectal neoplasms. However, few studies reported on an association of nut consumption with colorectal cancer, and even fewer studies reported on a nut intake-colorectal adenoma association. The results from the limited number of reported studies were inconsistent regarding a nut consumption-colorectal cancer association. The prospective EPIC cohort study[40] of 478,040 (141,988 men, 336,052 women) subjects from 10 European countries over an average of 4.8 years of follow-up, a total of 855 colon cancer cases and 474 rectal cancer cases were documented. After controlling for known and suspect risk factors, there was

no association of higher intake of nuts and seeds with CRC (colon and rectum cancer) among men and women combined. However, among women, there was an estimated 31% lower risk in colon cancer for a daily consumption of more than 6.2g nuts, while there was no observable association among men, nor for rectal cancer for either sex. In another prospective cohort study conducted in Taiwan[41] (n = 22115 men and women) with a 10-year follow-up, frequent peanut intake was found inversely associated with the risk for colorectal cancer among women only (RR: 0.42; 95% CI = 0.21-0.84). In the Nurses' Health Study [42](n= 75680 women who were free of cancer at baseline), 1,503 colorectal cancer cases were documented during 30 years of follow-up. Women who consumed nuts 2 or more times per week (⩾56g per week) had a 13% lower risk of colorectal cancer, but the association was not statistically significant (RR: 0.87; 95% CI: 0.72–1.05; P-trend: 0.06).

In summary, we reviewed 6 observational studies (4 prospective cohort studies and 2 case-control studies) that investigated nut intake-colorectal cancer associations. Two[42-43] reported nonsignificant inverse associations among all subjects, two[40-41] reported statistically significant inverse associations among women, and two[44-45] reported no association. There were some limitations in these studies, including grouping nuts with seeds and legumes,[44-45] having only one type of nut intake,[41] focusing only on one sex,[42] or having a limited number of colorectal cancer cases.[44-45] To address these gaps in knowledge, we examined the association of nut intakes with risk of incident, sporadic colorectal adenoma in men and women.

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CHAPTER II: MANUSCRIPT

Associations of Nut Intakes with Incident Sporadic Colorectal Adenoma Risk: A Pooled Case-Control Study

ABSTRACT

Nuts are rich in phytochemicals with antioxidant and anti-inflammatory properties, suggesting that consumption of them may reduce risk for colorectal carcinogenesis. However, there are few published reports on associations of nut intakes with colorectal adenoma, the immediate precursor to most colorectal cancers. To investigate an association of nut intakes with incident, sporadic colorectal adenoma, we pooled data from three case-control studies of incident, sporadic colorectal adenoma (n=785 cases, 2,107 controls), and analyzed them using multivariable unconditional logistic regression. The multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association of total nut product (all nuts and peanut butter combined) intake, for those who consumed 0.5 – 1.5, 2.0 – 5.5, and ≥ 6 servings/week relative to no nut consumption were 0.81 (0.58, 1.12), 0.86 (0.61, 1.23), and 0.93 (0.65, 1.31), respectively (p_{trend} = 0.66). The corresponding ORs and 95% CIs among women were 0.62 (0.40, 0.97), 0.57 (0.35, 0.94), and 0.78 (0.48, 1.25), respectively (p_{trend} = 0.86). Findings similar to those for women were noted among those who were <56 years old, had a family history of colorectal cancer in a first degree relative, regularly took aspirin or other non-steroidal anti-inflammatory drugs, and those who had a lower balance of anti- to pro-oxidant exposures. These results suggest a possible U-shaped association of total nut product intakes with risk for colorectal adenoma, possibly limited to women and other population

subgroups. The possible reasons for the estimated U-shaped association are unclear, and investigation in other populations/studies is needed.

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer deaths in men and women combined in the United States.[1-2] Beyond well-known risk factors, such as age, family history of colorectal cancer, and inherited genetic conditions,[3-4] risk of colorectal cancer has also been found to be higher among individuals who are obese[5-6] or have type II diabetes mellitus.[7] Colorectal cancer is one of the cancers that is most associated with diet.[8-10] Dietary fiber, physical activity, and non-steroid anti-inflammatory drug use are consistently inversely associated with colon cancer, while red and processed meats, alcohol and smoking are directly associated with the disease.[3-4, 8-10]

In general, nuts are rich in protein, dietary fiber, unsaturated fat, B vitamins, vitamin E, minerals, polyphenols, folate, phytoestrogen, and other phytochemicals.[10-12] Extensive research has indicated potential benefits of nut consumption for preventing several major diseases, particularly cardiovascular disease.[13-16] Additionally, evidence from independent prospective studies and systematic reviews supports that frequent nut consumption may be inversely associated with lower body mass index (BMI)[17-20] and type 2 diabetes,[21-24] both of which are risk factors for colorectal cancer. [3-7] Moreover, there is evidence suggesting that antioxidant and anti-inflammatory exposures have multiple anti-carcinogenic effects.[25-28] Fermented nuts were reported to have chemopreventive effects on colon cancer cells *in vitro* by reducing tumor-promoting deoxycholic acid (DCA), increasing chemopreventive short chain fatty acids (SCFA), and preventing oxidative stress[29]

However, few epidemiologic studies investigated an association of nut consumption with colorectal cancer, and to our knowledge, there are no reports of an association of nut intakes with incident, sporadic colorectal adenomas, an important precursor to most colorectal cancers. Of the limited research, earlier studies reported no association of nut and legume intakes with colorectal cancer,[30-31] while other studies suggested an inverse association of nut intake with colorectal cancer among women.[32-35] Nonetheless, most earlier studies grouped nuts with legumes and had a limited number of colorectal cancer cases.[30-31] Some studies focused on only one sex,[34] had only one type of nut intake,[33] or only investigated colon cancer rather than colorectal cancer.[30, 35] Moreover, among these epidemiological studies, none was focused on the association of nut intake with incident, sporadic colorectal adenomas. To address this gap in the literature, herein we report the results of an analysis of data pooled from three case-control studies to investigate an association of nut consumption with incident, sporadic colorectal adenoma in men and women.

MATERIALS AND METHODS

Study Population

Data for this study were pooled from three colonoscopy-based case-control studies of risk factors for adenomatous polyps: the Cancer Prevention Research Unit Study (CPRU; 1991–1994), the Markers of Adenomatous Polyps studies I (MAP I; 1995–1997)[36] and II (MAP II; 2002),[37] conducted in Minnesota, North Carolina, and South Carolina, respectively. Participants were recruited when scheduled for outpatient, elective colonoscopies at large private gastroenterology clinics, using the same data collection

protocol. The CPRU study was primarily colonoscopy-based but had two additional control groups: 1) patients being screened for colon cancer using flexible sigmoidoscopy, and 2) individuals randomly selected (from driver's license tapes, with frequency matching to the cases on 5-year age intervals, sex, and zip code) from the general population in the Minneapolis metropolitan region. The studies used identical eligibility criteria for recruitment—English-speaking individuals aged 30-74 with no history of cancer (except nonmelanoma skin cancer), colorectal neoplasms, or inflammatory bowel disease were eligible. Cases were those with adenomatous polyps diagnosed at the elective outpatient colonoscopy. Controls were patients who were free of adenomatous or hyperplastic polyps at colonoscopy (all studies) or were CPRU sigmoidoscopy or community controls who reported no history of colorectal neoplasms. Non-cases found to have hyperplastic polyps were excluded from analyses. All self-reported data, including demographic, dietary, lifestyle, and medical and family history, were collected before case/control status was determined. All subjects provided written informed consent, and the protocols were approved by the institutional review boards of the respective institutions.

Dietary Assessment

All participants completed questionnaires on demographic and socioeconomic factors, family history of colorectal cancer in first degree relatives, physical activity (via a Paffenbarger physical activity questionnaire), alcohol and tobacco usage, diet, and, among women, reproductive history. Diet was assessed using semi-quantitative Willett food frequency questionnaires that referenced each participant's usual intakes over the previous 12 months. In the CPRU and MAP I studies, questions related to nut

consumption included how often participants consumed nuts (referencing 1 oz. per serving) and peanut butter (referencing 1 tablespoon per serving), with the following response choices: never or less than once per month, 1-3 times per month, once a week, 2-4 times per week, 5-6 times per week, once a day, 2-3 a day, 4-5 a day, or 6+ times a day. In the MAP II study, participants were asked about their consumption of peanuts (referencing 1 oz. per serving), other nuts (referencing 1 oz. per serving), and peanut butter (referencing 1 tbs. per serving), with the follow response choices: never, less than once per month, 1-3 times per month, once a week, 2-4 times per week, 5-6 times per week, once a day, and 2 or more times per day. Other key measurements included self-reported height, weight, and waist and hip circumferences.

Statistical Analyses

We combined data from the three studies described above, since the studies had almost identical protocols. For the present analysis, all cases were combined into one case group and all controls were combined into one control group. The initial sample sizes were 564 cases and 1,737 controls in the CPRU study; 184 cases and 236 controls in the MAP I study; and 49 cases and 154 controls in the MAP II study. Subjects were excluded if their total energy intake estimated from the Willett semi-quantitative food frequency questionnaires (FFQ) was >5,000 or <600 kilocalories daily, or if ≥10% of their FFQ data were missing. The final combined sample size from all three case-control studies was 785 incident, sporadic colorectal adenoma cases and 2,107 controls. The characteristics of the cases and controls were compared using Pearson's chi-square test for categorical variables and the Student t-test for continuous variables. Total nut product intakes (peanuts, other nuts, and peanut butter), nut intakes and peanut butter intakes

were all categorized into the following four categories: none, 0.5-1.5 servings/week, 2-5.5 servings/week, and ≥ 6 servings/week based on the study-specific distributions among the controls. Multivariable unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations of the categorized exposure variables of interest with adenomas.

Potential confounding variables, selected based on biological plausibility and previous literature, included age, sex, family history of colorectal cancer in a first-degree relative, total energy intake (continuous), total fruit and vegetable intakes (continuous), red and processed meat intakes (continuous), total calcium intake (continuous), jams or jelly intakes (categorical), regular (≥ once per week) aspirin or nonsteroidal anti-inflammatory drug (NSAID) use (yes/no), and an oxidative balance score (OBS; continuous). Inclusion of covariates in the final models was based on the following considerations: 1) biological plausibility, 2) previous literature, 3) their associations with the primary exposure and outcome variables, and 4) whether inclusion of the variable in the models changed the logistic regression coefficient of the primary exposure variable by ≥10%. Initial models were adjusted for age and total energy intake, and the final full models were additionally adjusted for sex, family history of colorectal cancer, fruit and vegetable intake, jams and jelly intake, the OBS, and aspirin/NSAID use.

The lowest category of each exposure variable was used as the referent category. All statistical analyses were conducted using Statistical Analysis Software (SAS, Version 9.2). All tests were 2-sided, and a two-sided P value of <0.05 or a 95% CI that did not contain 1.00 was considered statistically significant.

RESULTS

Selected characteristics of the study participants are presented in Table 1. Cases were more likely to be male, current smokers, to currently drink alcohol, and to not regularly take aspirin or other NSAIDs. On average, cases consumed slightly more total energy, total fat, and red and processed meats, but less total calcium, especially supplemental calcium. Cases were also, on average, 4 years older and had a slightly higher BMI.

The estimated associations of total nut products, peanuts and other nuts, or peanut butter intakes with colorectal adenoma were close to the null, and none was statistically significant (Table 2). In the multivariable-adjusted analysis, there was a suggestion of a U-shaped association of total nut products (and, to a lesser extent, peanut butter intakes), with incident, sporadic colorectal adenomas, with approximately 19%, 14%, and 7% estimated lower risk among those in the second, third, and fourth categories, respectively, relative to those who did not eat nuts or peanut butter (none of these estimates was statistically significant).

Differences in the associations of nut intakes with colorectal adenoma according to various demographic and lifestyle risk factors are shown in Table 3. Among women, the suggestion of a U-shaped association was more pronounced: risk was estimated to be 28%, 43%, and 22% lower among those in the second, third, and fourth categories, respectively, relative to those who did not consume nuts or peanut butter (the estimates for categories 2 and 3 were statistically significant). Findings similar to those for women were noted among those who were <56 years old, had a family history of colorectal cancer in a first degree relative, regularly took aspirin or other non-steroidal anti-

inflammatory drugs, and those who had a lower balance of anti- to pro-oxidant exposures. No strong or consistent patterns to indicate effect modification were found by family history of colorectal cancer in a first-degree relative or BMI.

Associations of total nut intakes with various categories of colorectal adenoma are shown in Table 4. The roughly U-shaped pattern of the total nuts-adenoma association seen for adenomas overall tended to be slightly more pronounced for proximal, sessile, small, tubular, and single adenomas, although none of the findings was statistically significant.

DISCUSSION

The results from this study suggest that there may be a modest U-shape association of total nut intakes with colorectal adenoma, particularly among women, those less than 56 years of age, those with a family history of colorectal cancer in a first degree relative, those who regularly take aspirin or other non-steroidal anti- inflammatory drugs, and those with a lower balance of anti- to pro-oxidant exposures. To the best of our knowledge, this is the first report of a possible association of nut intakes with colorectal adenoma.

Several previous[30-35] studies investigated associations of nut intakes with colorectal cancer, mostly finding inverse associations, particularly among women. The prospective EPIC study (European Prospective Investigation into Cancer and Nutrition) study (n = 478,040)[32] found that for those who consumed a mean of 15.7 g/d nuts relative to those who consumed no nuts, nut intakes were inversely associated with colon cancer risk, but among women (HR, 0.69; 95% CI, 0.50-0.95; $p_{trend} = 0.04$), but not men (HR, 1.01; 95%

CI, 0.67-1.53; $p_{trend} = 0.50$). In a prospective cohort study in Taiwan[33] the estimated relative risks (RR) for associations of consuming peanuts ≥2 times/week relative to ≤once/week with colorectal cancer risk among men and women were, respectively, 0.83 (95% CI: 0.50-1.37; p = 0.45) and 0.42 (95% CI: 0.21–0.84; p = 0.01). Similarly, in the all-female prospective Nurses' Health Study (n = 75,680),[34] the RR for colorectal cancer among those who ate nuts ≥2 times/week relative to those who did not eat nuts was 0.87 (95% CI: 0.72–1.05; p = 0.06). In the prospective Adventist Health Study (n = 32,051),[35] the RRs for colon cancer for those who consumed 1 – 3.5 and ≥ 4 servings of nuts per week relative to non-consumers were 0.67 (95% CI: 0.45, 0.98) and 0.68 (95% CI: 0.45, 1.04) respectively ($p_{trend} = 0.22$) among men and women combined; associations among men and women separately were not reported.

The possible mechanisms of possible health benefits of nuts need to be further investigated. Present evidence indicates that nuts contain phytochemicals with strong antioxidant and anti-inflammatory properties. Vinson and Cai[26] investigated the antioxidant efficacy of nine types of nuts and two types of peanut butter by measuring the ability of the free polyphenol nut extracts to inhibit the oxidation of lower density lipoproteins (LDL + VLDL). The average IC_{50} (the concentration at which oxidation was inhibited by 50%) for raw nuts was 4.3 ± 2.1 μM, with walnuts having the highest efficacy. In a randomized crossover trial in Chinese patients with type 2 diabetes mellitus (n=22),[28] a diet rich in almonds decreased circulating concentrations of IL-6 by a median 10.3%, C-reactive protein by a median 10.3%, TNF-a by a median 15.7 %, and protein carbonyl by a median 28.2%, and enhanced the resistance of LDL against Cu2+-induced oxidation by a median 16.3%. In an *in vitro* study[30] in a colon cancer cell line, fermented

nuts reduced tumor-promoting deoxycholic acid (DCA) (8.20–88.65 Mm relative to the blank control of 125.05 mM), increased chemopreventive short chain fatty acids (SCFA) (67.83–85.93 mM relative to the blank control of 32.15 mM), and prevented oxidative damage.

The strengths of this study include a relatively large sample size, inclusion of both sexes, the separate examination of peanuts and peanut butter, completion of study questionnaires prior to colonoscopy (thus reducing bias), and collection of extensive information on potential confounding and effect modifying factors. The study also had several limitations. First, although we investigated peanuts, peanut butter, and other nuts separately, it was not possible to determine the exact types of other nuts, such as walnuts or almonds, that may have contributed to the reported total nut intakes. Thus, further epidemiologic research into associations of different varieties of nuts with colorectal adenoma and other outcomes is needed. Likewise, more basic science research into the phytochemical contents of different varieties of nuts is needed to guide future epidemiologic investigations. Other limitations of this study included the general limitations of case-control studies (e.g., inability to assess temporality) and the known limitations of FFQs (e.g., recall error, limited number of food items). Also, over 80% of our study participants were white, thus limiting the generalizability of our findings to non-white racial groups. Finally, given the unexpected, estimated modest U-shaped association found in this study and the lack of a possible biological explanation for it, residual confounding by other possible risk factors is possible.

In summary, our findings taken together with findings from previous studies of nut-colorectal cancer associations, suggest that nut intakes may be modestly inversely

associated with risk for colorectal adenoma among women. However, given that our observed association was more U-shaped than linear; that this was the first study, to our knowledge, of a nut-adenoma association; and the limitations of assessing nut intakes in currently used major FFQs, further study of nut-colorectal adenoma and carcinoma associations overall, by sex, and by other population characteristics is needed.

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TABLES

Table 1. Selected characteristics of participants in a pooled case-control study of incident, sporadic colorectal adenomas

Characteristics [a]	Cases (n = 785)	Controls (n = 2,107)	P value [b]
Demographics			
Age (yr)	58.1 (9.3)	54.6 (10.8)	<0.0001
Male (%)	61.3	43.4	<0.0001
White (%)	90.2	90.1	0.95
College education or higher (%)	28.6	31.7	0.12
Family history [c] (%)	13.0	27.3	<0.0001
Lifestyle factors			
Current smoker (%)	24.2	14.8	<0.0001
Current drinker (%)	23.0	20.8	<0.0001
Body mass index (kg/m^2)	27.5 (5.2)	26.9 (5.1)	0.004
Physical activity (MET-hr/wk)	34.4 (35.3)	34.5 (32.8)	0.90
Take NSAID/aspirin (%) [d]	32.2	39.1	0.0002
HRT use (% females)	30.9	44.3	0.0001
Dietary Factors			
Total energy (kcal/day)	2,069 (769)	1,986 (713)	0.01
Total fat (% total kcals)	31.3 (6.7)	30.3 (6.9)	0.0004
Total calcium (mg/day)	910.9 (508.4)	965.6 (520.3)	0.01
Dietary calcium (mg/day)	807.3 (430.5)	814.7 (428.3)	0.70
Supplemental calcium (mg/day)	103.6 (274.8)	150.9 (324.6)	<0.0001
Total nut products (servings/week)	4.5 (7.1)	4.1 (6.7)	0.21
Peanuts and other nuts (servings/week)	2.7 (4.3)	2.4 (4.0)	0.12
Peanut butter (servings/week)	1.8 (3.1)	1.7 (3.0)	0.48

Oxidative balance score [e]	0.1 (5.5)	-0.7 (5.1)	0.0002
Total fruits (servings/week)	17.6 (13.3)	19.6 (13.7)	0.0003
Total vegetables (servings/week)	27.5 (16.8)	27.9 (17.1)	0.56
Red meat (servings/week)	4.8 (3.8)	4.4 (3.5)	0.01
Processed meat (servings/week)	2.8 (3.8)	2.1 (3.0)	<0.0001

Abbreviations: MET, metabolic equivalents of task; NSAID, nonsteroidal anti-inflammatory drug; HRT, hormone replacement therapy.

[a] Values presented are mean (standard deviation) unless otherwise specified.

[b] From Student t-test for continuous variables and chi-square test for categorical variables.

[c] Family history of colorectal cancer in a first-degree relative.

[d] Regularly take aspirin or NSAID ≥ once per week.

[e] A composite of 15 anti- and pro-oxidant dietary and lifestyle exposures; a higher score represents higher anti-oxidant relative to pro-oxidant dietary and lifestyle exposures.

Table 2. Multivariable-adjusted associations of nut intakes with incident, sporadic colorectal adenomas in a pooled case-control study.

Categories	No. of cases/controls (n=785/2,107)	Initial model[a]		Full Model[b]	
		OR	95% CI	OR	95% CI
Total nut products					
1 (Never)	125/336	1.00 (ref)		1.00 (ref)	
2 (0.5-1.5 servings/week)	244/694	0.91	0.71, 1.18	0.81	0.58, 1.12
3 (2.0-5.5 servings/week)	173/482	0.88	0.66, 1.16	0.86	0.61, 1.23
4 (≥6 servings/week)	241/587	0.95	0.73, 1.24	0.93	0.65, 1.31
P_{trend}[c]		*0.45*		*0.66*	
Peanuts and other nuts					
1 (Never)	134/381	1.00 (ref)		1.00 (ref)	
2 (0.5-1.5 servings/week)	61/206	0.77	0.54, 1.11	0.99	0.63, 1.57
3 (2.0-5.5 servings/week)	197/476	1.08	0.82, 1.42	1.13	0.80, 1.60
4 (≥6 servings/week)	119/258	1.09	0.79, 1.51	1.11	0.74, 1.66
P_{trend}[c]		*0.23*		*0.52*	
Peanut Butter					
1 (Never)	258/663	1.00 (ref)		1.00 (ref)	
2 (0.5-1.5 servings/week)	294/873	0.85	0.70, 1.04	0.89	0.69, 1.14
3 (2.0-5.5 servings/week)	173/443	0.94	0.74, 1.19	0.94	0.69, 1.27
4 (≥6 servings/week)	59/120	1.04	0.73, 1.49	1.12	0.70, 1.76
P_{trend}[c]		*0.56*		*0.58*	

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

[a] Unconditional logistic regression model adjusted for age and total energy intake.

[b] Unconditional logistic regression model adjusted for age, total energy per day, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, regular use (≥ 1/week) of aspirin or nonsteroidal anti-inflammatory drugs, total fruit and vegetable intake, total energy intake.

[c] P_{trend} calculated using sex-specific median of each category

Table 3. Multivariable-adjusted associations[a] of nut intakes with incident, sporadic colorectal adenomas, stratified by sex, age, BMI, aspirin/NSAID use and oxidative balance score

	Categories of total nut products (servings/week)				
	Q1 (Never)	Q2 (0.5-1.5 servings/week)	Q3 (2.0-5.5 servings/week)	Q4 (≥6 servings/week)	
	No. of cases/controls (n = 125/336)	No. of cases/controls (n = 244/694)	No. of cases/controls (n = 173/482)	No. of cases/controls (n = 241/587)	P_{trend} [b]
Sex					
Male	1.00 (ref)	1.13 (0.70, 1.82)	1.40 (0.83, 2.35)	1.20 (0.73, 1.99)	0.73
Female	1.00 (ref)	0.62 (0.40, 0.97)	0.57 (0.35, 0.94)	0.78 (0.48, 1.25)	0.86
Age, yrs.					
< 56	1.00 (ref)	0.55 (0.34,0.90)	0.69 (0.40, 1.18)	0.70 (0.41, 1.19)	0.92
≥ 56	1.00 (ref)	1.08 (0.69, 1.68)	1.01 (0.63, 1.63)	1.11 (0.70, 1.77)	0.68
Family history [c]					
Yes	1.00 (ref)	0.52 (0.24, 1.09)	0.82 (0.37, 1.83)	0.84 (0.38, 1.85)	0.60
No	1.00 (ref)	0.89 (0.67, 1.19)	0.98 (0.69, 1.39)	0.98 (0.59, 1.63)	0.81
Body mass index					
< 25kg/m^2	1.00 (ref)	0.86 (0.49, 1.49)	0.94 (0.51, 1.73)	1.06 (0.60, 1.90)	0.98
≥ 25kg/m^2	1.00 (ref)	0.82 (0.53, 1.24)	0.83 (0.53, 1.31)	0.85 (0.54, 1.33)	0.60
Aspirin/NSAID use [d]					
Yes	1.00 (ref)	0.58 (0.33, 1.02)	0.77 (0.43, 1.38)	0.67 (0.37, 1.21)	0.74
No	1.00 (ref)	0.98 (0.65, 1.48)	0.96 (0.61, 1.52)	1.11 (0.72, 1.73)	0.44

Oxidative balance score [e]					
< -0.54	1.00 (ref)	0.60 (0.37, 0.98)	0.84 (0.49, 1.44)	0.69 (0.41, 1.15)	0.65
≥ -0.54	1.00 (ref)	1.00 (0.63, 1.59)	0.84 (0.51, 1.38)	1.04 (0.69, 1.85)	0.46

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug.

[a] Unconditional logistic regression model adjusted for age, total energy per day, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, fruit and vegetable intake, and total energy intake.

[b] P_{trend} calculated using sex-specific median of each category as a continuous variable.

[c] Family history of colorectal cancer in a first-degree relative.

[d] Regularly take aspirin or other NSAID ≥ once per week.

[e] A composite of 15 anti- and pro-oxidant dietary and lifestyle exposures; a higher score represents higher anti-oxidant relative to pro-oxidant dietary and lifestyle exposures.

Table 4. Multivariable-adjusted associations[a] of total nut product intakes with incident, sporadic colorectal adenomas, by characteristics of the largest adenoma.

	Categories[b]	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI
Atypia			Mild			> Mild	
	1	78/336	1.00 (ref)		46/336	1.00 (ref)	
	2	145/694	0.83	0.56, 1.22	90/694	0.86	0.55, 1.34
	3	107/482	0.93	0.62, 1.41	65/482	0.87	0.54, 1.40
	4	146/587	0.93	0.62, 1.40	93/587	0.96	0.61, 1.54
Location			Proximal[c]			Distal[d]	
	1	25/336	1.00 (ref)		98/336	1.00 (ref)	
	2	39/694	0.75	0.40, 1.42	195/694	0.83	0.59, 1.18
	3	23/482	0.59	0.29, 1.20	149/482	0.96	0.66, 1.40
	4	38/587	0.75	0.39, 1.46	199/587	0.98	0.68, 1.41
Shape			Pedunculated			Sessile	
	1	27/336	1.00 (ref)		80/336	1.00 (ref)	
	2	57/694	0.92	0.53, 1.58	130/694	0.72	0.49, 1.06
	3	48/482	1.17	0.66, 2.07	100/482	0.80	0.53, 1.22
	4	64/587	1.13	0.65, 1.97	130/587	0.79	0.52, 1.18
Size			< 1 cm			≥ 1 cm	
	1	31/336	1.00 (ref)		87/336	1.00 (ref)	
	2	53/694	1.02	0.54, 1.91	165/694	0.76	0.53, 1.09
	3	26/482	0.65	0.31, 1.35	135/482	0.92	0.63, 1.35
	4	37/587	0.65	0.34, 1.38	179/587	0.93	0.64, 1.36
Subtype			Tubular			Villous/tubulovillous	
	1	97/336	1.00 (ref)		26/336	1.00 (ref)	
	2	178/694	0.81	0.57, 1.16	56/694	0.92	0.54, 1.58
	3	119/482	0.82	0.56, 1.21	52/482	1.18	0.67, 2.08
	4	172/587	0.90	0.62, 1.32	67/587	1.13	0.65, 1.96
Multiplicity			1			> 1	

1	66/336	1.00 (ref)		26/336	1.00 (ref)	
2	112/694	0.66	0.45, 0.96	69/694	1.23	0.72, 2.08
3	95/482	0.80	0.53, 1.21	43/482	1.12	0.63, 1.99
4	123/587	0.79	0.53, 1.18	75/587	1.61	0.93, 2.77

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

[a] Unconditional logistic regression model adjusted for age, sex, oxidative balance score, family history of colorectal cancer in first-degree relative, regular use of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake and fruit and vegetable intake.

[b] 1: never; 2: 0.5-1.5 servings/week; 3: 2.0-5.5 servings/week; 4: ≥ 6 servings/week.

[c] Cecum, ascending colon, hepatic flexure.

[d] Transverse colon, splenic flexure, descending colon, sigmoid colon, rectum

CHAPTER III: SUMMARY, PUBLIC HEALTH IMPLICATIONS, POSSIBLE FUTURE DIRECTIONS

In this pooled case-control study, we found a modest U-shaped association of total nut product intakes with risk for colorectal adenoma, particularly among women. The odds ratios (OR) and 95% confidence intervals (CI) for the association of total nut product (all nuts and peanut butter combined) intake, for those who consumed 0.5 – 1.5, 2.0 – 5.5, and ≥ 6 servings/week relative to no nut consumption were 0.81 (0.58, 1.12), 0.86 (0.61, 1.23), and 0.93 (0.65, 1.31), respectively (p_{trend} = 0.66). The corresponding ORs and 95% CIs among women were 0.62 (0.40, 0.97), 0.57 (0.35, 0.94), and 0.78 (0.48, 1.25), respectively (p_{trend} = 0.86).

Further investigation is needed into 1) the possible mechanisms underlying the possible health benefits of nuts, especially among women, 2) details of the phytochemical contents of nuts which may contribute to the present observations, and 3) associations of different varieties of nuts with colorectal adenoma, colorectal carcinoma, and other health outcomes. These questions could be addressed via 1) more detailed questionnaires that include questions on specific types and amounts of nuts consumed, and 2) large clinical trials of different varieties of nuts to test their effects on the risk of colorectal adenoma.

APPENDIX

Appendix I. Summary of studies that examined associations between nuts intakes and incident colorectal cancer

Author	Study Type	Population	Exposure	Outcome	Participant number	OR/RR/HR	Comments
Pickle et al., 1984	Case-control study	Hospital-based; Nebraska	Nuts, legumes	Incident colorectal cancer	Control: 197 Case: 96	OR: 1.08 (colon) OR: 2.04 (rectum)	
Peters et al., 1992	Case-control study	Population-based; California, Los Angeles county	Peanut butter, nuts and other legumes	Incident colon cancer	Control: 746 Case: 746	RR: 0.98 (all subjects)	No association
Singh & Fraser, 1998	Prospective cohort study	the Adventist Health Study; California, 1976-1982	Nuts	Incident colon cancer	34198	RR: 0.68 (all subjects)	
Janeb et al., 2004	Prospective cohort study	Population-based; 10 European countries	Nut and seed	Incident colorectal cancer	478040	RR: 0.89 (all subjects) RR: 0.79 (women)	Statistically significant in women
Yeh et al., 2006	Prospective cohort study	Community-based; Taiwan	Peanut	Incident colorectal cancer	22115	RR: 0.73 (men) RR: 0.42 (women)	Statistically significant in women
Yang et al., 2016	Prospective cohort study	Hospital-based	Nut intake and peanut butter	Incident colorectal cancer	75680	RR: 0.87 (women)	Not Statistically significant; Inverse association suggested