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

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Abstract

Introduction: Consumption of nuts, which contain multiple anti-carcinogenic components, has been inversely associated with colorectal cancer (CRC), particularly among women, but has not been investigated in relation to colorectal adenoma, the immediate precursor to most CRCs.

Methods: We pooled data from three case-control studies of incident, sporadic colorectal adenoma (n=785 cases, 2,107 controls) in which dietary intakes were assessed using food frequency questionnaires, and analyzed the data using multivariable unconditional logistic regression.

Results: Among men and women combined, 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. However, among women, the corresponding ORs and 95% CIs were 0.62 (0.40, 0.97), 0.57 (0.35, 0.94), and 0.78 (0.48, 1.25), respectively.

Conclusions: These results suggest that moderate nut consumption may be associated with lower risk for colorectal adenoma, primarily among women.

Keywords

Cancer risk; Diet; Colorectal cancer; Epidemiology; Case/Control

Introduction

Colorectal cancer is the second leading cause of cancer deaths in men and women combined in the United States (1–3). Marked differences in international incidence rates and the rapid increase in incidence among migrants from low- to high-risk countries, such as the United

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Declaration of Interest

The authors declare no conflicts of interest.

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States, point to the strong influence of environment—especially diet and lifestyle—on risk for the disease (4–7). Risk for the disease is also strongly linked to inflammation (8,9), and is increasingly linked to oxidative stress (10). Diet is increasingly found to be a source of inflammation and oxidative stress (4,7).

In general, nuts are rich in multiple macro- and micronutrients, such as fiber, unsaturated fats, B vitamins, vitamin E, minerals, polyphenols, folate, phytoestrogens, and other phytochemicals (11–13), many of which have anti-inflammatory and/or antioxidant properties, which have multiple anti-carcinogenic effects (14–17). Extensive research has indicated potential benefits of nut consumption for preventing several major diseases, particularly cardiovascular disease (18–20). Additionally, evidence from independent prospective studies and systematic reviews supports that frequent nut consumption may be inversely associated with body mass index (BMI) (21–24) and type 2 diabetes (25–29), both of which are risk factors for colorectal cancer (30–32). 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 (33).

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, the precursor to most colorectal cancers. Of the limited research, earlier studies reported no association of nut and legume intakes with colorectal cancer (34,35), while other studies suggested an inverse association of nut intakes with colorectal cancer among women (36–39). Most earlier studies grouped nuts with legumes and had a limited number of colorectal cancer cases (34,35). Some studies focused on only one sex (38), had only one type of nut intake (37), or only investigated colon cancer rather than colorectal cancer (34, 39). Moreover, among these epidemiological studies, none was focused on the association of nut intakes 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 incident, sporadic, colorectal adenomatous polyps: the Cancer Prevention Research Unit Study (CPRU; 1991–1994) (40) and the Markers of Adenomatous Polyps studies I (MAP I; 1995–1997) (41) and II (MAP II; 2002) (42), 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 colorectal 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 non-melanoma skin cancer), colorectal adenoma, inflammatory bowel disease, or a hereditary polyposis syndrome were eligible. The three studies had similar participation rates (68% to 76%). 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, alcohol and tobacco usage, diet, and, among women, reproductive history. Diet was assessed using semi-quantitative Willett food frequency questionnaires (FFQs) (43,44) 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. Participants were excluded from analysis if they did not answer 10% of the FFQ items or their total energy intake estimated from their FFQ responses was <600 or >5,000 kcal/day. The final combined sample size from all three case-control studies was 785 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), jam 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). A questionnaire-derived, equal-weight OBS was calculated as previously described (45, 46), and included pro-oxidant variables (smoking status, body mass index [BMI], and alcohol, saturated fat, and total iron intakes) and antioxidant variables (physical activity and total vitamin E, vitamin C, carotenoids, lutein, lycopene, vitamin E, omega-3 fatty acids, flavonoids, and glucosinolates intakes), such that a higher OBS represented higher antioxidant relative to pro-oxidant exposures. 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, aspirin/NSAID use, the OBS, and fruit and vegetable and jams and jelly intakes.

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 <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 overall estimated associations of total nut products, peanuts and other nuts, and peanut butter intakes with colorectal adenoma are shown in Table 2. In the multivariable-adjusted analysis, there was a suggestion of a U-shaped association of total nut products 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). There were no clear patterns to the separate associations of peanuts/other nuts or peanut butter with adenomas, and the confidence intervals for the odds ratios were quite wide.

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 apparent U-shaped association was more pronounced: risk was estimated to be 38%, 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, and 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. The estimated associations across the BMI strata were similar to each other.

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

Discussion

The results from this study suggest that moderate intakes of nuts may be associated with lower risk for colorectal adenoma, particularly among women, and possibly among 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 studies (34–39) 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) (36) found that consuming a mean of 15.7 g of nuts daily relative to consuming no nuts was associated with lower colon cancer risk among women (HR = 0.69; 95% CI = 0.50, 0.95; $P_{\text{trend}} = 0.04$), but not men (HR = 1.01; 95% CI = 0.67, 1.53; $P_{\text{trend}} = 0.50$). In a prospective cohort study (37) conducted in Taiwan, the estimated relative risks (RR) for associations of consuming peanuts 2 times/week relative to once/week with colorectal cancer risk among women and men were, respectively, 0.42 (95% CI = 0.21, 0.84) and 0.83 (95% CI = 0.50, 1.37). Similarly, in the all-female prospective Nurses' Health Study (n = 75,680) (38), 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; $P_{\text{trend}} = 0.06$). In the prospective Adventist Health Study (n = 32,051) (39), 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, among men and women combined; associations among men and women separately were not reported.

In our study, the estimated nut intake-adenoma association was more U-shaped than linear, whereas in the above-discussed studies of nut intake-CRC associations were more linear.

The reason(s) for the more U-shaped association in our study are unclear. The possibilities include chance and residual confounding.

The possible mechanisms of possible health benefits of nuts include that they contain phytochemicals with strong antioxidant and anti-inflammatory properties. Vinson and Cai (15) 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 IC₅₀ (the concentration at which oxidation was inhibited by 50%) for raw nuts was 4.3 ± 2.1 μ M, with walnuts having the highest efficacy. In a randomized crossover trial in Chinese patients with type 2 diabetes mellitus (n=22) (25), 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- α 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 (33) in a colon cancer cell line, fermented nuts reduced tumor-promoting deoxycholic acid (DCA), increased chemopreventive short chain fatty acids (SCFA), and prevented oxidative damage.

The strengths of our 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 some 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-shape of the 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 moderate nut intakes may be modestly inversely associated with risk for colorectal adenoma among women and other population subgroups. 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 with 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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References

1. Siegel R, Miller K, Fedewa S, Ahnen D, Meester R, et al. Colorectal Cancer Statistics, 2017. *CA Cancer J Clin* 67, 177–193, 2017. doi: 10.3322/caac.21395. [PubMed: 28248415]
2. Edwards B, Ward E, Kohler B, Ehemann C, Zauber A, et al. Annual Report to the Nation on the Status of Cancer, 1975–2006, Featuring Colorectal Cancer Trends and Impact of Interventions (Risk Factors, Screening, and Treatment) to Reduce Future Rates. *Cancer* 116 (3), 544–573, 2010. doi: 10.1002/cncr.24760. [PubMed: 19998273]
3. Hagggar FA & Boushey RP. Colorectal Cancer Epidemiology: Incidence, Mortality, Survival, and Risk Factors. *Clinics in Colon and Rectal Surgery* 22(4), 191–197, 2009. doi: 10.1055/s-0029-1242458. [PubMed: 21037809]
4. Marmot M, Atinmo T, Byers T, Chen J, Hirohata T, et al. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: World Cancer Research Fund/American Institute for Cancer Research. American Institute for Cancer Research; 2007.
5. Vargas AJ & Thompson PA. Diet and Nutrient Factors in Colorectal Cancer Risk. *Nutrition in Clinical Practice* 27(5), 613–623, 2012. doi: 10.1177/0884533612454885. [PubMed: 22892274]
6. Corrêa Lima MP, Gomes-da-Silva MH. Colorectal Cancer: Lifestyle and Dietary Factors. *Nutr Hosp* 20(4), 235–41, 2005 [PubMed: 16045124]
7. Huxley RR, Ansary-Moghaddam A, Clifton P, Czernichow S, Parr CL, Woodward M. The Impact of Dietary and Lifestyle Risk Factors on Risk of Colorectal Cancer: A Quantitative Overview of the Epidemiological Evidence. *Int. J. Cancer* 125, 171–180, 2009. [PubMed: 19350627]
8. Terzic J, Grivennikov S, Karin E, Karin M. Inflammation and Colon Cancer. *Gastroenterology* 138(6), 2101–2114.e5, 2010. doi: 10.1053/j.gastro.2010.01.058. [PubMed: 20420949]
9. Cytokines Klampfer L., Inflammation and Colon Cancer. *Current Cancer Drug Targets* 11(4), 451–464, 2011. doi: 10.2174/156800911795538066. [PubMed: 21247378]
10. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? *Free Radical Biology and Medicine* 49(11), 1603–1616, 2010. [PubMed: 20840865]
11. Alasalvar C, Bolling BW. Review of Nut Phytochemicals, Fat-soluble Bioactives, Antioxidant Components and Health Effects. *British Journal of Nutrition* 113, S68–S78, 2015. [PubMed: 26148924]
12. Dreher ML, Maher CV, Kearney P. The Traditional and Emerging Role of Nuts in Healthful Diets. *Nutr Rev* 54, 241–245, 1996. [PubMed: 8961751]
13. Gonzalez CA, Salas-Salvado J. The Potential of Nuts in the Prevention of Cancer. *Br J Nutr* 96 (Suppl. 2), S87–S94, 2006. [PubMed: 17125538]
14. Bolling BW, Chen CY, McKay DL, Blumberg LB. Tree Nut Phytochemicals: Composition, Antioxidant Capacity, Bioactivity, Impact Factors. A Systematic Review of Almonds, Brazils, Cashews, Hazelnuts, Macadamias, Pecans, Pine Nuts, Pistachios and Walnuts. *Nutrition Research Reviews* 24, 244–275, 2011. [PubMed: 22153059]
15. Vinson JA, Cai Y. Nuts, Especially Walnuts, Have Both Antioxidant Quantity and Efficacy and Exhibit Significant Potential Health Benefits. *Food & Function* 3, 134–140, 2012. [PubMed: 22187094]
16. Gonzalez CA, Salas-Salvado J. The Potential of Nuts in the Prevention of Cancer. *Br J Nutr* 96 (Suppl. 2), S87–S94, 2006. [PubMed: 17125538]
17. Jiang R, Jacobs DR Jr, Mayer-Davis E, Szklo M, Herrington D, Jenny NS, et al. Nut and Seed Consumption and Inflammatory Markers in the Multi-ethnic Study of Atherosclerosis. *Am J Epidemiol* 163, 222–31, 2006. [PubMed: 16357111]
18. Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, et al. Effects of a Mediterranean-style Diet on Cardiovascular Risk Factors: A Randomized Trial. *Ann Intern Med* 145, 1–11, 2006. [PubMed: 16818923]

19. O'Neil CE, Keast DR, Nicklas TA, Fulgoni VF. Nut Consumption Is Associated with Decreased Health Risk Factors for Cardiovascular Disease and Metabolic Syndrome in U.S. Adults: NHANES 1999–2004. *Journal of the American College of Nutrition* 30(6), 502–510, 2011. [PubMed: 22331685]
20. Kris-Etherton PM, Hu FB, Ros E, Sabate J. The Role of Tree Nuts and Peanuts in the Prevention of Coronary Heart Disease: Multiple Potential Mechanisms. *The Journal of Nutrition* 138(9), 1746S–1751S, 2008. [PubMed: 18716180]
21. Bes-Rastrollo M, Sabate J, Gomez-Gracia E, Alonso A, Martinez JA, Martinez-Gonzalez, MA. Nut Consumption and Weight Gain in a Mediterranean Cohort: the SUN Study. *Obesity (Silver Spring)* 15(1), 107–116, 2007. [PubMed: 17228038]
22. Bes-Rastrollo M, Wedick NM, Martinez-Gonzalez MA, Li TY, Sampson L, Hu FB. Prospective Study of Nut Consumption, Long-term Weight Change, and Obesity Risk in Women. *Am J Clin Nutr* 89, 1913–9, 2009. [PubMed: 19403639]
23. Jackson CL, Hu FB. Long-term Associations of Nut Consumption with Body Weight and Obesity. *The American Journal of Clinical Nutrition* 100(1), 408S–411S, 2014. doi:10.3945/ajcn.113.071332. [PubMed: 24898229]
24. Sabate J Nut Consumption and Body Weight. *Am J Clin Nutr* 78(3), 647S–650S, 2003. [PubMed: 12936960]
25. Liu JF, Liu YH, Chen CM, Chang WH, Chen CY. The Effect of Almonds on Inflammation and Oxidative Stress in Chinese Patients with Type 2 Diabetes Mellitus: A Randomized Crossover Controlled Feeding Trial. *Eur J Nutr* 52(3), 927–35, 2013. doi: 10.1007/s00394-012-0400-y. [PubMed: 22722891]
26. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and Peanut Butter Consumption and Risk of Type 2 Diabetes in Women. *JAMA* 288(20), 2554–2560, 2002. [PubMed: 12444862]
27. Pan A, Sun Q, Manson JE, Willett WC, Hu FB. Walnut Consumption is Associated with Lower Risk of Type 2 Diabetes in Women. *J Nutr* 143, 512–518, 2013. [PubMed: 23427333]
28. Wu L, Wang Z, Zhu J, Murad AL, Prokop LJ, Murad MH. Nut Consumption and Risk of Cancer and Type 2 Diabetes: A Systematic Review and Meta-analysis. *Nutr Rev* 73(7), 409–25, 2015. doi: 10.1093/nutrit/nuv006. [PubMed: 26081452]
29. Salas-Salvadó J, Bullo M, Babio N, Martinez-Gonzalez MA, Ibarrola-Jurado N, et al. Reduction in the Incidence of Type 2 Diabetes with the Mediterranean Diet: Results of the PREDIMED-Reus Nutrition Intervention Randomized Trial. *Diabetes Care* 34(1), 14–9, 2011. doi: 10.2337/dc10-1288. [PubMed: 20929998]
30. Shaikat A, Dostal A, Menk J, Church TR. BMI Is a Risk Factor for Colorectal Cancer Mortality. *Dig Dis Sci*. 2017. doi: 10.1007/s10620-017-4682-z.
31. Bardou M, Barkun AN, Martel M. Obesity and Colorectal Cancer. *Gut* 62(6), 933–947, 2013. doi: 10.1136/gutjnl-2013-304701. [PubMed: 23481261]
32. Larsson SC, Orsini N, Wolk A. Diabetes Mellitus and Risk of Colorectal Cancer: A Meta-analysis. *J Natl Cancer Inst* 97(22), 1679–1687, 2005. [PubMed: 16288121]
33. Lux S, Scharlau D, Schlormann W, Birringer M, Gleis M. In vitro Fermented Nuts Exhibit Chemopreventive Effects in HT29 Colon Cancer Cells. *Br J Nutr* 108, 1177–1186, 2012. [PubMed: 22172380]
34. Peters RK, Pike MC, Garabrant D, Mack TM. Diet and Colon Cancer in Los Angeles County, California. *Cancer Causes Control* 3, 457–473, 1992. [PubMed: 1525327]
35. Pickle LW, Greene MH, Ziegler RG, Toledo A, Hoover R, Lynch HT et al. Colorectal Cancer in Rural Nebraska. *Cancer Res* 44, 363–369, 1984. [PubMed: 6690049]
36. Jenab M, Ferrari P, Slimani N, Norat T, Casagrande C, et al. Association of Nut and Seed Intake with Colorectal Cancer Risk in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* 13(10), 1595–603, 2004. [PubMed: 15466975]
37. Yeh CC, You SL, Chen CJ, Sung FC. Peanut Consumption and Reduced Risk of Colorectal Cancer in Women: A Prospective Study in Taiwan. *World J Gastroenterol* 12, 222–227, 2006. [PubMed: 16482621]

38. Yang M, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, et al. Nut Consumption and Risk of Colorectal Cancer in Women. *European Journal of Clinical Nutrition* 70, 333–337, 2016. [PubMed: 25944181]
39. Singh PN, Fraser GE. Dietary Risk Factors for Colon Cancer in a Low-risk Population. *Am J Epidemiol* 148, 761–774, 1998. [PubMed: 9786231]
40. Potter JD, Bigler J, Fosdick L, et al. Colorectal Adenomatous and Hyperplastic Polyps: Smoking and N-acetyltransferase 2 Polymorphisms. *Cancer Epidemiol Biomarkers Prev* 8 (1), 69–75, 1999. [PubMed: 9950242]
41. Boyapati SM, Bostick RM, McGlynn KA, Fina MF, Roufail WM, et al. Calcium, Vitamin D, and Risk for Colorectal Adenoma: Dependency on Vitamin D Receptor BsmI Polymorphism and Nonsteroidal Anti-inflammatory Drug Use? *Cancer Epidemiol Biomarkers Prev* 12, 631–637, 2003. [PubMed: 12869402]
42. Daniel CR, Bostick RM, Flanders WD, Long Q, Fedirko V, et al. TGF- α Expression as a Potential Biomarker of Risk Within the Normal-appearing Colorectal Mucosa of Patients with and without Incident Sporadic Adenoma. *Cancer Epidemiol Biomarkers Prev* 18, 65–73, 2009. doi: 10.1158/1055-9965.EPI-08-0732. [PubMed: 19124482]
43. Smith-Warner SA, Elmer PJ, Fosdick L, Randall B, Bostick RM, et al. Fruits, Vegetables, and Adenomatous Polyps: the Minnesota Cancer Prevention Unit Case-control study. *Am J Epidemiol* 155, 1104–1113, 2002. [PubMed: 12048224]
44. Smith-Warner SA, Elmer PJ, Fosdick L, Tharp TM, Randall B. Reliability and Comparability of Three Dietary Assessment Methods for Estimating Fruit and Vegetable Intakes. *Epidemiology* 8(2), 196–201, 1997. [PubMed: 9229214]
45. Dash C, Goodman M, Flanders WD, Mink PJ, McCullough ML, Bostick RM. Using pathway-specific comprehensive exposure scores in epidemiology: application to oxidative balance in a pooled case-control study of incident, sporadic colorectal adenomas. *Am J Epidemiol* 178(4), 610–24, 2013. [PubMed: 23639935]
46. Dash C, Bostick RM, Goodman M, Flanders WD, Patel R, Shah R, Campbell PT, McCullough ML. Oxidative balance scores and risk of incident colorectal cancer in a U.S. prospective cohort study. *Am J Epidemiol* 181, 584–94, 2015. [PubMed: 25693772]

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
<i>Demographics</i>			
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
<i>Lifestyle factors</i>			
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
<i>Dietary Factors</i>			
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
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 meats (servings/week)	4.8 ± 3.8	4.4 ± 3.5	0.01
Processed meats (servings/week)	2.8 ± 3.8	2.1 ± 3.0	<0.0001
Oxidative balance score ^e	0.1 ± 5.5	-0.7 ± 5.1	0.0002

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

^aValues presented are means ± standard deviations unless otherwise specified.

^bFrom Student t-test for continuous variables and chi-square test for categorical variables.

^cFamily history of colorectal cancer in a first-degree relative.

^dRegularly take aspirin or NSAID once per week.

^eA composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); 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/wk)	244/694	0.91	0.71, 1.18	0.81	0.58, 1.12
3 (2.0 – 5.5 servings/wk)	173/482	0.88	0.66, 1.16	0.86	0.61, 1.23
4 (≥ 6 servings/wk)	241/587	0.95	0.73, 1.24	0.93	0.65, 1.31
<i>P_{trend}</i> ^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/wk)	61/206	0.77	0.54, 1.11	0.99	0.63, 1.57
3 (2.0 – 5.5 servings/wk)	197/476	1.08	0.82, 1.42	1.13	0.80, 1.60
4 (≥ 6 servings/wk)	119/258	1.09	0.79, 1.51	1.11	0.74, 1.66
<i>P_{trend}</i> ^c		0.23		0.52	
Peanut Butter					
1 (Never)	258/663	1.00 (ref)		1.00 (ref)	
2 (0.5 – 1.5 servings/wk)	294/873	0.85	0.70, 1.04	0.89	0.69, 1.14
3 (2.0 – 5.5 servings/wk)	173/443	0.94	0.74, 1.19	0.94	0.69, 1.27
4 (≥ 6 servings/wk)	59/120	1.04	0.73, 1.49	1.12	0.70, 1.76
<i>P_{trend}</i> ^c		0.56		0.58	

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

^aUnconditional logistic regression models adjusted for age and total energy intake.

^bUnconditional logistic regression models adjusted for age, sex, family history of colorectal cancer in first-degree relative, regular use (≥ 1/week) of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fruit and vegetable intakes, and an oxidative balance score ^d.

^c*P_{trend}* calculated using sex-specific median of each category.

^dA composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text).

Table 3.

Multivariable-adjusted associations^a of nut intakes with incident, sporadic colorectal adenomas, stratified by selected participant characteristics.

	Categories of total nut products				<i>P</i> _{trend} ^b
	Q1 (Never) No. of cases/controls (n = 125/336)	Q2 (0.5 – 1.5 servings/wk) No. of cases/controls (n = 244/694)	Q3 (2.0 – 5.5 servings/wk) No. of cases/controls (n = 173/482)	Q4 (≥ 6 servings/wk) No. of cases/controls (n = 241/587)	
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					
< 25 kg/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
≥ 25 kg/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.

^aUnconditional logistic regression models adjusted for age, sex, family history of colorectal cancer in first-degree relative, regular use (≥ 1/week) of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fruit and vegetable intakes, and an oxidative balance score^e.

^b*P*_{trend}/calculated using sex-specific median of each category as a continuous variable.

^cFamily history of colorectal cancer in a first-degree relative.

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^d Regularly take aspirin or other NSAID once per week.

^e A composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text); 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 adenoma multiplicity and the characteristics of the largest adenoma.

	Nut intake categories ^b	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI
Multiplicity	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
Size ^c	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	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
Atypia	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	1	33/336	1.00 (ref)		90/336	1.00 (ref)	
	2	55/694	0.76	0.40, 1.42	179/694	0.85	0.59, 1.18
	3	38/482	0.77	0.29, 1.20	134/482	0.94	0.66, 1.40
	4	58/587	0.90	0.39, 1.46	179/587	0.95	0.68, 1.41
Shape	1	33/336	1.00 (ref)		90/336	1.00 (ref)	
	2	55/694	0.76	0.40, 1.42	179/694	0.85	0.59, 1.18
	3	38/482	0.77	0.29, 1.20	134/482	0.94	0.66, 1.40
	4	58/587	0.90	0.39, 1.46	179/587	0.95	0.68, 1.41

Nut intake categories ^b	No. of cases/controls	OR	95% CI	No. of cases/controls	OR	95% CI
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

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

^aUnconditional logistic regression models adjusted for age, sex, family history of colorectal cancer in first-degree relative, regular use (1/week) of aspirin or nonsteroidal anti-inflammatory drugs, total energy intake, total fruit and vegetable intakes, and an oxidative balance score ^f.

^b1: never; 2: 0.5 – 1.5 servings/week; 3: 2.0 – 5.5 servings/week; 4: 6 servings/week.

^cLargest *in vivo* diameter.

^dCecum, ascending colon, hepatic flexure, transverse colon.

^eSplenic flexure, descending colon, sigmoid colon, rectum.

^fA composite of 15 anti- and pro-oxidant dietary and lifestyle exposures (see text).