Nut Consumption and Survival in Patients With Stage III Colon Cancer: Results From CALGB 89803 (Alliance)

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ABSTRACT

Purpose
Observational studies have reported increased colon cancer recurrence and mortality in patients with states of hyperinsulinemia, including type 2 diabetes, obesity, sedentary lifestyle, and high glycemic load diet. Nut intake has been associated with a lower risk of type 2 diabetes, metabolic syndrome, and insulin resistance. However, the effect of nut intake on colon cancer recurrence and survival is not known.

Patients and Methods
We conducted a prospective, observational study of 826 eligible patients with stage III colon cancer who reported dietary intake on food frequency questionnaires while enrolled onto a randomized adjuvant chemotherapy trial. Using Cox proportional hazards regression, we assessed associations of nut intake with cancer recurrence and mortality.

Results
After a median follow-up of 6.5 years, compared with patients who abstained from nuts, individuals who consumed two or more servings of nuts per week experienced an adjusted hazard ratio (HR) for disease-free survival of 0.58 (95% CI, 0.37 to 0.92; \( P_{\text{trend}} = .03 \)) and an HR for overall survival of 0.43 (95% CI, 0.25 to 0.74; \( P_{\text{trend}} = .01 \)). In subgroup analysis, the apparent benefit was confined to tree nut intake (HR for disease-free survival, 0.54; 95% CI, 0.34 to 0.85; \( P_{\text{trend}} = .04 \); and HR for overall survival, 0.47; 95% CI, 0.27 to 0.82; \( P_{\text{trend}} = .04 \)). The association of total nut intake with improved outcomes was maintained across other known or suspected risk factors for cancer recurrence and mortality.

Conclusion
Diets with a higher consumption of nuts may be associated with a significantly reduced incidence of cancer recurrence and death in patients with stage III colon cancer.

INTRODUCTION

Recent prospective observational studies among patients with colon cancer suggest that diet and lifestyle factors may significantly influence the risk of colon cancer recurrence and death.\(^1\)\(^-\)\(^6\) In aggregate, these studies indicate that states of energy excess, including type 2 diabetes (T2D),\(^7\) obesity,\(^6\) sedentary lifestyle,\(^2\)\(^,\)\(^5\) Western-pattern diet,\(^3\)\(^,\)\(^5\) increased dietary glycemic load,\(^1\) and high intake of sugar-sweetened beverages,\(^8\) are associated with an increased risk of colon cancer recurrence and mortality. Moreover, increased cancer mortality was observed among patients with colorectal cancer with elevated plasma C-peptide or low insulin-like growth factor–binding protein-1 levels,\(^9\) suggesting that the association between energy excess and increased risk of colon cancer recurrence may be mediated, in part, by long-term hyperinsulinemia. In fact, increased coffee intake, which has been associated with decreased risk of T2D,\(^10\)\(^-\)\(^14\) lower plasma C-peptide levels,\(^15\)\(^,\)\(^16\) and increased insulin sensitization,\(^17\)\(^,\)\(^18\) conferred improved disease-free survival (DFS) in patients with stage III colon cancer.\(^19\)

In prospective cohort studies, increased nut intake has been associated with a reduced risk of T2D and metabolic syndrome\(^20\)\(^-\)\(^23\) and a reduction in insulin resistance.\(^24\)\(^-\)\(^27\) Nuts are nutrient-dense foods that are rich in unsaturated...
fatty acids, fiber, vitamins, minerals, and other bioactive substances such as phenolic antioxidants and phytosterols.28-30

In light of evidence supporting a link between excess energy balance, hyperinsulinemia, and increased recurrence in patients with colon cancer, we prospectively examined the association of nut intake with cancer recurrence and mortality in a cohort of patients with stage III colon cancer enrolled onto a National Cancer Institute–sponsored randomized clinical trial of adjuvant chemotherapy. In the trial, detailed data on pathologic stage, performance status, postoperative treatment, and follow-up were prospectively captured. In addition, comprehensive data on diet and lifestyle were collected before any documentation of cancer recurrence.

**PATIENTS AND METHODS**

**Study Population**

Patients in this prospective cohort participated in the National Cancer Institute–sponsored Cancer and Leukemia Group B (now Alliance for Clinical Trials in Oncology) 89803 adjuvant therapy trial for stage III colon cancer, comparing therapy with weekly fluorouracil and leucovorin to weekly irinotecan, fluorouracil, and leucovorin (ClinicalTrials.gov identifier: NCT000038350). Between April 1999 and May 2001, 1,264 patients were enrolled. An amendment was introduced after enrolling 87 patients that required enrollees to complete a self-administered semiquantitative food frequency questionnaire (FFQ) that captured diet and lifestyle habits. The questionnaires were administered midway through adjuvant therapy (4 months after surgery; questionnaire 1 [Q1]) and again 6 months after completion of treatment (14 months after surgery; questionnaire 2 [Q2]).

Patients were eligible if they underwent a complete surgical resection of the primary tumor within 56 days before trial entry, had no prior chemotherapy or radiation therapy for treatment of the tumor, had regional lymph node metastases without evidence of distant metastases, had a baseline Eastern Cooperative Oncology Group performance status of 0 to 2,29 and had adequate bone marrow, renal, and hepatic function.30 Because of possible dietary modifications immediately after colectomy, we a priori limited the primary analysis to nut intake reported on Q2. Patients were excluded if they reported significantly abnormal caloric intake (< 600 or > 4,200 calories per day for men; < 500 or > 3,500 calories per day for women), left > 70 food items blank, or left blank the nut consumption–related questions on Q2. Finally, patients were excluded if they had cancer recurrence or death before completion of Q2 or within 60 days of completing Q2 to avoid misattribution bias. The resulting cohort included 826 eligible patients (Fig 1). The protocol was reviewed by the institutional review board of each participating center, and all patients provided study-specific informed consent.

**Dietary Assessment**

Patients in this analysis completed semiquantitative FFQs that included 131 food items, vitamin and mineral supplements, and open-ended sections for other supplements and foods not specifically listed.34,35 Participants were asked how often, on average, over the previous 3 months they consumed a specific food portion size, with up to nine possible responses, which ranged from never to six or more times per day. We computed nutrient intake by multiplying the frequency of consumption of each food by the nutrient content of the specified portions.36 Nutrient values were energy adjusted using the residuals methods.37

On the questionnaire, we separately assessed self-reported intake of 1-oz servings of tree nuts and peanuts with the following eight ordered categories for intake: none; less than once per month; one to three servings per month; one serving per week; two to four servings per week; five to six servings per week; one serving per day; and two or more servings per day.

Total nut intake was calculated as the weighted proportional summation of tree nuts and peanuts. We similarly assessed self-reported peanut butter intake. In a previous cohort study evaluating the validity of our FFQ in measuring intake of nuts and peanut butter, the correlation coefficients between dietary records and the FFQs were 0.75 and 0.75, respectively.38

**Tumor Assessments for KRAS, BRAF, PIK3CA, and TP53 Mutations, Microsatellite Instability, and PTGS2 Expression**

Polymerase chain reaction (PCR) and pyrosequencing targeted for mutation hotspots in PIK3CA exons 9 and 20,39 BRAF codon 600,40 and
KRA5 codons 12 and 13 were performed, as previously described.41,42 Mutations in TP53 exons 5 to 8 were determined by Sanger sequencing and sequencing by hybridization, as previously described.43 Microsatellite instability (MSI) was assessed by PCR for 10 microsatellite markers; tumors with instability in ≥ 50% of the loci were classified as MSI-high; for 28 patients without PCR MSI results, those with loss of MLH1 or MSH2 expression were classified as MSI-high, as previously described.44 PTGS2 (COX-2) expression was assessed by immunohistochemistry, as previously described.45

**Study End Points**

The primary end point was DFS, defined as time from completion of Q2 to tumor recurrence, occurrence of a new primary colon tumor, or death from any cause. We also assessed recurrence-free survival (RFS), defined as time from completion of Q2 to tumor recurrence or occurrence of a new primary colon tumor. For RFS, patients who died without known tumor recurrence were censored at last documented physician evaluation. Finally, we assessed overall survival (OS), defined as the time from completion of Q2 to death from any cause.

**Statistical Analysis**

There was no statistically significant difference in OS or DFS in both arms of the randomized trial.31 Therefore, patient data from both arms were combined and analyzed according to frequency categories of dietary intake. The primary analysis was done with total nut intake, combining intake of tree nuts and peanuts. For consistency with prior published studies on nut intake and to conserve statistical power for the analysis, categories of nut intake were consolidated into the following five ordered categories: never, less than one serving per month, one to three servings per month, one serving per week, and two or more servings per week.46-49 Differences in distribution of baseline characteristics by nut consumption categories were evaluated using the χ² test, except for continuous variables, which were evaluated using the Kruskal-Wallis test.

Cox proportional hazards regression analysis was used to determine the simultaneous affect of other variables potentially associated with each outcome.26 The covariates in the model were fixed as measured on Q2. To account for the caloric content of nuts, our initial model adjusted for total calorie intake.37 The final model further adjusted for potential confounders including age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, body mass index (calculated as weight in kilograms divided by height in meters squared), physical activity (measured in metabolic equivalent task hours per week), aspirin use, and glycemic load (as previously described).1 Selection of covariates for the final model was based on clinical significance, previous studies, and degree of correlation with the exposure. Covariates with missing variables were coded with indicator variables.

The statistical analysis was performed using nut consumption as a continuous measure to minimize bias created by selected categorization. We tested for linear trends across frequency categories of intake by assigning each participant the median value for each frequency category and modeling this value as a continuous variable, consistent with prior studies.3,20,28,46 P values for trend were calculated using the Wald test of the score variable. Secondary exploratory analysis was performed individually for peanuts and tree nuts; we further collapsed intake into four categories to conserve power (never, < one serving per month, one to three servings per month, and ≥ one serving per week). Stratified exploratory analyses were also performed for other risk factors; the likelihood ratio test was used to test for interaction. In addition, we performed several sensitivity analyses to confirm the robustness of the results. The Cox regression models were tested for and met the assumption of proportionality by both time-dependent covariate and Schoenfeld residuals methods. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A threshold level of significance of \( P < .05 \) was considered statistically significant. All \( P \) values are two-sided and were not adjusted for multiple comparisons. Data collection and management were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. All analyses were based on the study database frozen on November 9, 2009. See the Appendix (online only) for additional analyses.

**RESULTS**

**Baseline Characteristics**

Baseline characteristics by frequency of total nut consumption are listed in Table 1. Patients who consumed more nuts were more frequently male, consumed more alcohol, and had a lower glycemic load diet. Although nut users consumed greater total calories, nut users did not present with a higher body mass index. There were statistical differences in age, Western and prudent dietary patterns, and dietary glycemic load by categories of nut intake, although clear trends in these factors by nut intake were less apparent.

**Impact of Nut Intake on Cancer Recurrence and Death**

Median follow-up time from completion of Q2 was 6.5 years. During follow-up, 199 of the 826 patients experienced cancer recurrence or developed new primary tumors. Of the 826 patients, 177 patients died; of those, 39 patients died without documented cancer recurrence.

Increasing total nut intake was associated with significant reduction in recurrence and mortality after adjusting for other predictors of cancer recurrence (Table 2). Compared with patients who abstained, individuals who consumed diets with two or more servings of nuts per week experienced an adjusted hazard ratio (HR) for DFS of 0.58 (95% CI, 0.37 to 0.92; \( P_{trend} = .03 \)). Higher nut intake was also associated with a significant improvement in OS (HR, 0.43; 95% CI, 0.25 to 0.74; \( P_{trend} = .01 \)) and a trend toward improved RFS, which did not reach statistical significance (HR, 0.70; 95% CI, 0.42 to 1.16; \( P_{trend} = .15 \)). Unadjusted survival curves are presented in Appendix Figures A1, A2, and A3 (online only).

We further examined the associations with nut intake models after controlling for other possible confounders (Western and prudent dietary patterns, race, smoking, and alcohol use) and found that our findings were largely unchanged (Appendix Table A1, online only).

**Sensitivity Analyses**

Because of possible dietary modifications immediately after colectomy,31 we a priori limited the primary analysis to nut intake reported on Q2. Nonetheless, we repeated our analyses using the cumulative average of nut intake on Q1 and Q2 and found that the association with DFS was unchanged (Appendix Tables A2 and A3, online only).

We considered the possibility that changes in dietary habits could reflect occult cancer or impending death; as such, our primary analyses excluded patients who developed cancer recurrence or died within 60 days of completing Q2. To further address this issue, we repeated the models after excluding recurrences or deaths within 180 days of Q2 completion (n = 783), and our results remained largely unchanged (HR, 0.54; 95% CI, 0.32 to 0.89; \( P_{trend} = .02 \)).

Furthermore, we considered that nut intake may be a marker of dentition and oral health, potential confounders that were not
assessed in this cohort. To address this issue, we ran the models using a new reference group that combined the lowest intake strata of other potential predictors and confounders of patient outcome, comparing patients with an intake of two or more servings per week to nonconsumers (Fig 2). In this exploratory analysis, the association between total nut intake and DFS was consistent across strata of patient, disease, and treatment characteristics; these included strata of clinically relevant genomic alterations (MSI and KRAS, BRAF, and PIK3CA mutations). However, in these stratified analyses, statistical power to adequately detect differences was limited by the sample size, and such analyses should be considered exploratory.

**Stratified Analyses**

We evaluated the influence of total nut intake on DFS across strata of other potential predictors and confounders of patient outcome, comparing patients with an intake of two or more servings per week to nonconsumers (Fig 2). In this exploratory analysis, the association between total nut intake and DFS was consistent across strata of patient, disease, and treatment characteristics; these included strata of clinically relevant genomic alterations (MSI and KRAS, BRAF, and PIK3CA mutations). However, in these stratified analyses, statistical power to adequately detect differences was limited by the sample size, and such analyses should be considered exploratory.

**Subgroup Analyses**

In separate analyses of the subtypes of nuts, we observed a significant improvement in both DFS and OS with increasing tree servings per week to nonconsumers (Fig 2). In this exploratory analysis, the association between total nut intake and DFS was consistent across strata of patient, disease, and treatment characteristics; these included strata of clinically relevant genomic alterations (MSI and KRAS, BRAF, and PIK3CA mutations). However, in these stratified analyses, statistical power to adequately detect differences was limited by the sample size, and such analyses should be considered exploratory.

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**Table 1. Baseline Characteristics: Total Nut Consumption (N = 826)**

| Characteristic | servings of Nuts | P* |
|---------------|-----------------|----|
|                | Never (n = 145) | ≥ 2 per Week (n = 158) |
| Median nut intake, servings per week (IQR) | 0 (0-0) | 3.5 (3.0-6.0) |
| Median age, years (IQR) | 64 (54-70) | 62 (53-69) |
| Male | 74 (51.0) | 103 (65.2) |
| Race | White | 125 (86.2) |
| | Black | 11 (7.6) |
| | Other | 9 (6.2) |
| Performance status‡ | 0 | 103 (71.0) |
| | 1-2 | 39 (26.9) |
| | Unknown | 3 (2.1) |
| No. of positive nodes | 1-3 | 94 (64.8) |
| | ≥ 3 | 48 (33.1) |
| | Unknown | 3 (2.1) |
| Tumor stage§ | T1, 2 | 29 (20.0) |
| | T3, 4 | 116 (80.0) |
| | Unknown | 0 (0.0) |
| Differentiation | Well/moderate | 108 (74.5) |
| | Poor/undifferentiated | 34 (23.4) |
| | Unknown | 3 (2.1) |
| Obstruction | 32 (22.1) |
| Perforation | 4 (2.8) |
| Treatment | FU+LV | 82 (56.6) |
| | CPT-11+FU+LV | 63 (43.4) |
| | CPT-11+LV | 14 (9.8) |
| | LV | 8 (5.5) |
| | Other | 52 (35.9) |
| | Unknown | 3 (2.1) |
| Characteristic | Servings of Nuts | P* |
|---------------|-----------------|----|
| Never (n = 145) | < 1 per Month (n = 98) | ≥ 2 per Week (n = 158) |
| Median calorie consumption, kcal/d (IQR) | 1,624 (1,298-2,034) | 2,162 (1,970-2,630) |
| Median BMI, kg/m² (IQR) | 28.7 (24.8-32.5) | 28.8 (25.3-33.1) |
| Median physical activity, MET-h/wk (IQR) | 10.8 (6.7-25.2) | 12.9 (8.0-26.4) |
| Median SSB, servings per week (IQR) | 0.7 (0.0-3.4) | 1.2 (0.0-4.0) |
| Race | White | 11 (7.6) |
| | Black | 11 (7.6) |
| | Other | 9 (6.2) |
| White | 125 (86.2) |
| | Black | 11 (7.6) |
| | Other | 9 (6.2) |
| Performance status‡ | 0 | 103 (71.0) |
| | 1-2 | 39 (26.9) |
| | Unknown | 3 (2.1) |
| No. of positive nodes | 1-3 | 94 (64.8) |
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| | CPT-11+FU+LV | 63 (43.4) |
| | CPT-11+LV | 14 (9.8) |
| | LV | 8 (5.5) |
| | Other | 52 (35.9) |
| | Unknown | 3 (2.1) |

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: BMI, body mass index; CPT-11, irinotecan; FU, fluorouracil; IQR, interquartile range; LV, leucovorin; MET, metabolic equivalent task; SSB, sugar-sweetened beverage.

*By χ² test unless otherwise noted.
†By Kruskal-Wallis nonparametric test.
‡Baseline performance status: 0 indicates fully active; 1 indicates restricted in physically strenuous activity but ambulatory and able to carry out light work; 2 indicates ambulatory and capable of all self-care but unable to carry out any work activities, up and about 50% of waking hours.
§T1, 2 indicates level of invasion through the bowel wall not beyond the muscle layer; T3, 4 indicates level of invasion through the bowel wall beyond the muscle layer.

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nut consumption, whereas the associations with peanut intake did not reach statistical significance (Table 3). We similarly examined the influence of peanut butter consumption on patient outcome and found no association between peanut butter intake and DFS ($P_{\text{trend}} = .15$), OS ($P_{\text{trend}} = .12$), or RFS ($P_{\text{trend}} = .09$).

### DISCUSSION

In this prospective cohort of patients with stage III colon cancer who received adjuvant chemotherapy, a diet with increased total nut intake was associated with a significant improvement in cancer recurrence or mortality (DFS) and all-cause mortality (OS). Moreover, these associations seemed to be independent of other predictors of patient outcome, diet, and lifestyle factors, and the effect of total nut consumption was maintained across other known or suspected risk factors of cancer recurrence. In contrast to tree nuts, we did not observe a significant association with peanuts, which are legumes, although the statistical power to assess peanut intake was limited.

To our knowledge, this is the first study to examine the association between nut intake and colon cancer recurrence and survival. Prior observational cohort studies have explored the relationship between nut intake and risk of developing colorectal cancer, finding inconsistent results.46,51,52 Other studies have reported reduced cancer-related mortality in association with increased nut intake49,53-55; however, the attributable mortality reductions in colorectal cancer or other individual cancer types were not described in these studies.

Our data are consistent with a wealth of existing observational and clinical trial data reporting health benefits of nut consumption on many chronic diseases, including reductions in the risk of T2D, insulin resistance, metabolic syndrome, cardiovascular disease, and all-cause mortality.46,56-65 Nutrients in nuts, such as unsaturated fatty acids, high-quality protein, fiber, vitamins, minerals, phytochemicals, and other bioactive substances, may confer potential anticarcinogenic, anti-inflammatory, and antioxidant properties.28-30 Clinical trials have demonstrated beneficial effects of nuts on relevant intermediate markers including oxidation,25,66 endothelial dysfunction,67 hyperglycemia,25 and insulin resistance.20,68 In addition, preclinical studies suggest that the contents of nuts may inhibit the growth of a colon cancer cell line69 and may decrease the rate of colorectal cancer growth and angiogenesis in mice.70

Multiple prior observational studies in patients with colorectal cancer, including analyses from our study population, suggest that states of excess energy balance (eg, obesity, T2D, sedentary lifestyle, Western-pattern diet, greater glycemic load diet, and high sugar-sweetened beverage intake) are associated with greater risk of cancer recurrence and mortality.1-3,8 Therefore, we hypothesize that the effect of nuts on hyperinsulinemia and energy balance may, in part, explain the association between nut intake and improved patient outcome in our study. Nonetheless, there might be other possible mechanisms through which nut intake may influence survival in patients with colon cancer.

There are several strengths of our analysis. Embedding the cohort within a randomized trial ensures equal distribution of potential confounders. All patient had stage III colon cancer, minimizing the effect of heterogeneity of the disease stage on the outcomes. Treatment and patient follow-up were rigorous because they were prescribed and monitored by the clinical trial; the outcomes of death and cancer recurrence were prospectively collected through regular detailed medical examinations during the course of the follow-up period. Furthermore, detailed information about potential founders and effect modifiers was collected prospectively.

However, our study has a few limitations. Nut intake was self-reported, potentially subject to measurement errors, and somewhat limited in range of intake in this patient population. However, in previous validation studies, nut intake as recorded on our questionnaire showed good concordance with independent dietary records.35 Moreover, because dietary data were collected prospectively, any misclassification of nut intake would underestimate a true association. Given the observational nature of this study, we cannot exclude the possibility that the associations between nut intake and improved outcome are a result of confounding variables or that error in the measurement of adjusted confounding variables could result in residual confounding. However, these...
associations persisted even after controlling for known or suspected predictors of patient outcome. Furthermore, the associations remained largely consistent on multiple sensitivity analyses.

Our cohort did not collect data on dentition. Poor dentition may influence the intake of foods such as nuts, which are hard and require significant mastication. Observational studies have shown an association between dental disease and increased incidence and mortality of cardiovascular disease.\textsuperscript{71-77} Periodontal disease has also been linked with a higher incidence of some solid cancers,\textsuperscript{78-85} although studies on the association with colon cancer incidence have yielded conflicting results\textsuperscript{79,82,86} and the effect on colon cancer outcomes is largely unknown. Our additional sensitivity analysis to address this potential confounder, collapsing the two lowest categories into a new control group, yielded consistent results.
results. Nonetheless, as with many nutritional epidemiology studies, the potential for residual confounding remains.

Finally, patients in randomized trials may differ from the population at large. However, the distribution of dietary and lifestyle habits reported by our cohort was similar to that of other US cohorts,87 supporting generalizability of our results. Still, it is imperative to replicate our findings in other cohorts. In conclusion, this prospective study of patients with stage III colon cancer suggests that a diet with increased nut consumption is associated with a significant reduction in cancer recurrence and mortality. Although the findings of our observational study do not establish causality, the results offer further support of the role of diet and lifestyle as modifiable risk factors of outcomes in patients with colon cancer.

Table 3. Associations Between Colon Cancer Recurrence and Mortality by Nut Subtype: Tree Nuts and Peanuts

| Categories of Intake (servings) | Outcome | Never | < 1 per Month | 1-3 per Month | ≥ 1 per Week | \( P_{\text{trend}} \)* |
|---------------------------------|---------|-------|---------------|---------------|-------------|----------------|
| Tree nuts                       | DFS     |       |               |               |             |                |
| No. of events/total No. of patients | 96/267 | 77/287 | 40/152 | 25/120 |             |                |
| HR (95% CI), adjusted 1†       | Ref     | 0.72 (0.53 to 0.97) | 0.66 (0.46 to 0.96) | 0.53 (0.34 to 0.84) | .02          |
| HR (95% CI), adjusted 2‡       | Ref     | 0.68 (0.51 to 0.93) | 0.66 (0.45 to 0.96) | 0.54 (0.34 to 0.85) | .04          |
| RFS                            |         |       |               |               |             |                |
| No. of events/total No. of patients | 78/267 | 71/287 | 32/152 | 20/120 |             |                |
| HR (95% CI), adjusted 1†       | Ref     | 0.84 (0.61 to 1.16) | 0.67 (0.44 to 1.02) | 0.55 (0.33 to 0.91) | .03          |
| HR (95% CI), adjusted 2‡       | Ref     | 0.79 (0.57 to 1.10) | 0.66 (0.43 to 1.01) | 0.56 (0.33 to 0.94) | .06          |
| OS                             |         |       |               |               |             |                |
| No. of events/total No. of patients | 77/267 | 55/287 | 28/152 | 17/120 |             |                |
| HR (95% CI), adjusted 1†       | Ref     | 0.65 (0.46 to 0.92) | 0.61 (0.39 to 0.94) | 0.47 (0.27 to 0.80) | .02          |
| HR (95% CI), adjusted 2‡       | Ref     | 0.62 (0.44 to 0.88) | 0.58 (0.37 to 0.91) | 0.47 (0.27 to 0.82) | .04          |
| Peanuts                        | DFS     |       |               |               |             |                |
| No. of events/total No. of patients | 70/215 | 78/280 | 51/183 | 39/148 |             |                |
| HR (95% CI), adjusted 1†       | Ref     | 0.84 (0.61 to 1.16) | 0.83 (0.58 to 1.19) | 0.78 (0.52 to 1.17) | .41          |
| HR (95% CI), adjusted 2‡       | Ref     | 0.87 (0.63 to 1.21) | 0.85 (0.59 to 1.23) | 0.81 (0.53 to 1.23) | .46          |
| RFS                            |         |       |               |               |             |                |
| No. of events/total No. of patients | 55/215 | 66/280 | 44/183 | 34/148 |             |                |
| HR (95% CI), adjusted 1†       | Ref     | 0.91 (0.64 to 1.30) | 0.92 (0.62 to 1.37) | 0.90 (0.58 to 1.40) | .76          |
| HR (95% CI), adjusted 2‡       | Ref     | 0.94 (0.66 to 1.35) | 0.93 (0.62 to 1.39) | 0.97 (0.61 to 1.53) | .98          |
| OS                             |         |       |               |               |             |                |
| No. of events/total No. of patients | 57/215 | 57/280 | 37/183 | 26/148 |             |                |
| HR (95% CI), adjusted 1†       | Ref     | 0.75 (0.52 to 1.08) | 0.73 (0.48 to 1.10) | 0.62 (0.39 to 1.01) | .15          |
| HR (95% CI), adjusted 2‡       | Ref     | 0.77 (0.53 to 1.12) | 0.73 (0.48 to 1.11) | 0.60 (0.37 to 0.98) | .11          |

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival; Ref, reference; RFS, recurrence-free survival.

*Two-sided P value. Trend across consumption levels with the categorical median.
†Model adjusted 1: Adjusted using Cox proportional hazards regression for calorie intake.
‡Model adjusted 2: Adjusted using Cox proportional hazards regression further for age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, body mass index, physical activity, aspirin use, and glycemic load.

Disclosures provided by the authors are available with this article at jco.org.

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Nut Consumption and Stage III Colon Cancer Outcome

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Appendix

Methods

In supplemental analyses, we offer additional multivariable models using Cox proportional hazards regression, whereby additional covariates were added as part of sensitivity analyses. In successive models, Western and prudent dietary patterns (model 3) and race (as a categorical variable: white, black, or other), smoking as binary (ever or never), and alcohol (as a continuous variable in grams per day; model 4) were added to the final model that included age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, body mass index (calculated as weight in kilograms divided by height in meters squared), physical activity (measured in metabolic equivalent task hours per week), aspirin use, and glycemic load. Glycemic load and Western and prudent dietary patterns were determined by methods previously described by our study cohort (Wu K, et al: Cancer Causes Control 15:853-862, 2004; Fung T, et al: Arch Intern Med 163:309-314, 2003).1,3

Because of possible dietary modifications immediately after colectomy, we a priori limited the primary analysis to nut intake reported on questionnaire 2 (Q2). In secondary analyses, we repeated the models using cumulative nut intake from questionnaire 1 (Q1) and Q2. Cumulative nut exposure average was calculated based on weighting proportional to the time between Q1 and Q2, and then the time between Q2 and the outcome survival period, using previously published methods (Hu FB, et al: Am J Epidemiol 149:531-540, 1999).1 In this analysis, the follow-up period began from the completion of Q1. Consistent with previous analyses in our study cohort, patients were excluded if they experienced cancer recurrence or death within 90 days of completing Q1 to prevent misattribution bias.1,8,18 Survival estimate curves for disease-free survival, recurrence-free survival, and overall survival by nut intake categories were calculated using the Kaplan-Meier methods, and the log-rank testing was used to compare survival between groups (Kaplan EL, Meier P: J Am Stat Assoc 53:457-481, 1958).

![Fig A1. Kaplan-Meier curves for disease-free survival (DFS) by total nut consumption. Curves depict survival for five categories of total nut intake (never, less than one serving per month, one to three servings per month, one serving per week, and two or more servings per week).](image-url)
Fig A2. Kaplan-Meier curves for recurrence-free survival (RFS) by total nut consumption. Curves depict survival for five categories of total nut intake (never, less than one serving per month, one to three servings per month, one serving per week, and two or more servings per week).

Fig A3. Kaplan-Meier curves for overall survival (OS) by total nut consumption. Curves depict survival for five categories of total nut intake (never, less than one serving per month, one to three servings per month, one serving per week, and two or more servings per week).
### Table A1. Sensitivity Analyses Further Controlling for Additional Confounders: Dietary Pattern, Race, Smoking, and Alcohol Use

| Outcome | Total Nut Consumption Categories of Intake (servings) |
|---------|-----------------------------------------------------|
|         | Never | < 1 per Month | 1-3 per Month | 1 per Week | ≥ 2 per Week | \(P_{\text{trend}}^*\) |
| DFS     | No. of events/total No. of patients                  | 52/145 | 36/98 | 56/211 | 58/214 | 36/158 |
|         | HR (95% CI), model 3†                               | Ref    | 1.03 (0.67 to 1.59) | 0.71 (0.48 to 1.05) | 0.71 (0.48 to 1.04) | 0.60 (0.38 to 0.95) | .05            |
|         | HR (95% CI), model 4‡                               | Ref    | 1.02 (0.66 to 1.57) | 0.69 (0.47 to 1.02) | 0.69 (0.47 to 1.02) | 0.59 (0.37 to 0.93) | .05            |
| RFS     | No. of events/total No. of patients                  | 39/145 | 31/98 | 51/211 | 47/214 | 31/158 |
|         | HR (95% CI), model 3†                               | Ref    | 1.15 (0.71 to 1.86) | 0.84 (0.55 to 1.29) | 0.76 (0.49 to 1.18) | 0.72 (0.43 to 1.20) | .18            |
|         | HR (95% CI), model 4‡                               | Ref    | 1.13 (0.70 to 1.82) | 0.82 (0.53 to 1.25) | 0.75 (0.48 to 1.16) | 0.70 (0.42 to 1.17) | .16            |
| OS      | No. of events/total No. of patients                  | 44/145 | 27/98 | 43/211 | 39/214 | 24/158 |
|         | HR (95% CI), model 3†                               | Ref    | 0.94 (0.58 to 1.54) | 0.65 (0.42 to 0.99) | 0.55 (0.35 to 0.85) | 0.45 (0.26 to 0.78) | .01            |
|         | HR (95% CI), model 4‡                               | Ref    | 0.92 (0.56 to 1.50) | 0.64 (0.41 to 0.98) | 0.54 (0.34 to 0.85) | 0.46 (0.26 to 0.78) | .01            |

**Abbreviations:** BMI, body mass index; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; Q2, questionnaire 2; Ref, reference; RFS, recurrence-free survival.

*Two-sided \(P\) value. Trend across consumption levels with the categorical median.

†Model 3: Cox proportional hazards regression adjusting for age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, and aspirin use (Q2), BMI (Q2), physical activity (Q2), dietary glycemic load (Q2), calorie intake (Q2), Western dietary pattern (Q2), and prudent dietary pattern.

‡Model 4: Cox proportional hazards regression adjusting for age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, and aspirin use (Q2), BMI (Q2), physical activity (Q2), glycemic load (Q2), and calorie intake (Q2), plus race (white, black, or other), smoking (never or ever), and alcohol (grams per day, Q2).

### Table A2. Consumption of Nuts on Q1 and Q2 in Servings per Day

| Nut Type     | Q1 Mean (95% CI) | Q1 Median | Q2 Mean (95% CI) | Q2 Median | \(P^*\) |
|--------------|------------------|-----------|------------------|-----------|-------|
| Peanuts      | 0.09 (0.08 to 0.11) | 0.03 | 0.10 (0.09 to 0.11) | 0.03 | < .001 |
| Tree nuts    | 0.07 (0.05 to 0.08) | 0.03 | 0.08 (0.07 to 0.09) | 0.03 | < .001 |
| Peanut butter| 0.28 (0.25 to 0.32) | 0.07 | 0.23 (0.21 to 0.26) | 0.07 | < .001 |

**NOTE.** \(P\) value generated from the paired Wilcoxon test for non-normality.

### Table A3. Association Between Colon Cancer Recurrence and Mortality by Cumulative Average Total Nut Consumption of Q1 and Q2

| Outcome | Total Nut Consumption Categories of Intake (servings) |
|---------|-----------------------------------------------------|
|         | Never | < 1 per Month | 1-3 per Month | 1 per Week | ≥ 2 per Week | \(P_{\text{trend}}^*\) |
| DFS     | No. of events/total No. of patients                  | 89/152 | 43/117 | 99/260 | 81/251 | 81/236 |
|         | HR (95% CI), model 1†                               | Ref    | 0.49 (0.34 to 0.70) | 0.51 (0.39 to 0.69) | 0.41 (0.30 to 0.56) | 0.44 (0.32 to 0.60) | .008            |
|         | HR (95% CI), model 2†                               | Ref    | 0.53 (0.36 to 0.76) | 0.51 (0.38 to 0.68) | 0.41 (0.30 to 0.56) | 0.45 (0.33 to 0.62) | .01             |
| RFS     | No. of events/total No. of patients                  | 78/152 | 39/117 | 90/260 | 71/251 | 71/236 |
|         | HR (95% CI), model 1†                               | Ref    | 0.52 (0.35 to 0.76) | 0.55 (0.40 to 0.74) | 0.42 (0.30 to 0.58) | 0.45 (0.33 to 0.63) | .01             |
|         | HR (95% CI), model 2†                               | Ref    | 0.54 (0.36 to 0.79) | 0.53 (0.39 to 0.73) | 0.42 (0.30 to 0.58) | 0.46 (0.32 to 0.64) | .02             |
| OS      | No. of events/total No. of patients                  | 74/152 | 32/117 | 78/260 | 62/251 | 64/236 |
|         | HR (95% CI), model 1†                               | Ref    | 0.44 (0.29 to 0.66) | 0.49 (0.36 to 0.68) | 0.38 (0.27 to 0.54) | 0.43 (0.30 to 0.60) | .02             |
|         | HR (95% CI), model 2†                               | Ref    | 0.48 (0.32 to 0.73) | 0.48 (0.34 to 0.66) | 0.38 (0.26 to 0.53) | 0.43 (0.30 to 0.61) | .03             |

**NOTE.** Survival time starts at Q1, and patients with events within 90 days of Q1 were excluded.

**Abbreviations:** DFS, disease-free survival; HR, hazard ratio; OS, overall survival; Q1, questionnaire 1 (midway through adjuvant therapy); Q2, questionnaire 2 (6 months after completion of adjuvant therapy).

*Two-sided \(P\) value. Trend across consumption levels with the categorical median.

†Model 1: Cox proportional hazards regression adjusting for time-varying calorie consumption.

‡Model 2: Cox proportional hazards regression adjusting for age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, regular aspirin use (both Q1 and Q2), and time-varying calorie consumption, body mass index, physical activity, and glycemic load.