Association of Nut and Seed Intake with Colorectal Cancer Risk in the European Prospective Investigation into Cancer and Nutrition

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Abstract

A link between unsaturated fatty acids or phytonutrients and reduced risk of colorectal cancer has been suggested. However, the effects of higher intake of dietary sources of these nutrients, such as the nuts and seeds food group, are less clear. The objective of this study was to determine the effects of nut and seed intake on colorectal cancer risk within the European Prospective Investigation into Cancer and Nutrition study, a large prospective cohort study involving 10 European countries. Total nut and seed intake was determined from country-specific dietary questionnaires. The data set included 478,040 subjects (141,988 men, 336,052 women) with a total of 855 (327 men, 528 women) colon and 474 (215 men, 259 women) rectal cancer cases. A multivariate Cox proportional hazards model, stratified by center and controlled for fruit intake, dietary fiber, energy, height, weight, sex, age, physical activity, and smoking, was used. The data show no association between higher intake of nuts and seeds and risk of colorectal, colon, and rectal cancers in men and women combined, but a significant inverse association was observed in subgroup analyses for colon cancer in women at the highest (>6.2 g/d) versus the lowest (nonconsumers; hazard ratio, 0.69; 95% confidence interval, 0.50-0.95) category of intake and for the linear effect of log-transformed intake (hazard ratio, 0.89; 95% confidence interval, 0.80-0.98), with no associations in men. It is not evident from this data why there may be a stronger association in women or why it may be limited to the colon, suggesting that much further research is necessary. (Cancer Epidemiol Biomarkers Prev 2004;13(10):1595–603)

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Introduction

Nuts and seeds may be considered as an important component of a healthy diet. In general, they are nutrient

dense and provide protein, fat (mostly unsaturated fatty acids), dietary fiber, and many bioactive constituents, such as vitamins (e.g., folic acid, niacin, vitamin E, and vitamin B6), minerals (e.g., copper, magnesium, potassium, and zinc), antioxidants, phytoestrogens, and other phytochemicals (1). Given such density and variety of bioactive compounds, extensive research has focused on potential healthy effects of higher nut and seed consumption on the development of heart disease (2-4) and prostate cancer (5-7).

With respect to colorectal cancer (CRC), only limited data are available from one animal (8) and three human case-control studies, which show either no protective effects of combined higher intake of nuts and legumes (9, 10) or a significant linear dose-response protective effect with higher combined intake of pulses, nuts, and seeds in women but not in men (11). However, all of these studies combined intakes of nuts and seeds with legumes and did not measure the direct effects of intake of nuts or seeds as a unique food group, which may be one of the sources of variation observed in their results.

Data from the Adventist Health Study, a prospective observational cohort study, show a protective effect of nuts on colon cancer risk for intakes of one to four times per week compared with less than once per week [relative risk, 0.67; 95% confidence interval (95% CI), 0.45-0.98], but not for higher intakes, likely due to the small number of cases in the higher intake category (12). However, this study did not present data by gender and did not consider rectal cancer.

Due to these mixed results and the limited number of studies, the impact of nut and seed intake on CRC risk is far from being well defined. Thus, the objective of this study was to determine the effects of nut and seed intake on CRC risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) study. EPIC is an ongoing multicenter prospective cohort study, designed specifically to investigate a relationship between cancer and nutrition (13). Currently, the study has enrolled over 520,000 participants from 23 centers in 10 European countries. The strengths of the study lie in its very large size, in allowing comparisons between areas with varying cancer rates, and in its high degree of heterogeneity in dietary intake and variety of foods consumed. As such, it presents an appropriate setting for a study to contribute to the clarification of any potential influence of nuts and seeds on CRC risk.

Methods

Study Population. The rationale and methods of the EPIC study have been described previously in detail (13, 14). The EPIC cohort consists of 23 subcohorts in 10 European countries (Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom), providing a wide range of cancer occurrence rates, lifestyle, and dietary habits. The French and Norwegian cohorts as well as the Naples center of Italy and the Utrecht center in Netherlands are composed of women only. Country-specific dietary questionnaires as well as standardized lifestyle and personal questionnaires, various anthropometric measures, and blood samples have been collected from most participants. Country-specific dietary questionnaires were used to ensure high compliance and to obtain better measures of local dietary habits. In total, 521,468 subjects have been enrolled. For the present study, to reduce the effects of extreme values of intake, subjects in the top and bottom 1% of the ratio of energy intake to estimated energy requirement (calculated from age, sex, height, and body weight) as well as subjects with previous cancer diagnoses or with missing dietary data were excluded. Thus, for the present study, the database consisted of a total of 478,040 (141,988 men, 336,052 women) subjects, including a total of 855 colon cancer cases (327 men, 528 women; proximal: 127 men, 224 women; distal: 154 men, 237 women; unspecified or overlapping colon location: total of 113) and 474 rectal cancer cases (215 men, 259 women). Cases included only those with primary CRC, of which the majority (91%) are adenocarcinoma and the rest are other tumor types.

Follow-up is based on population cancer registries (Denmark, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom) and other methods such as health insurance records, pathology registries, and active contact of study subjects or next of kin (France, Germany, and Greece). The follow-up period for the present study was for data reports received at IARC to the end of October 2002, representing complete follow-ups until either December 2000 or December 2001 for all centers using cancer registry data and until 2002 for France, Germany, and Greece.

Definitions of colon and rectal cancers were as described previously (15). Tumors in the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0-C18.5) were defined as proximal (or right) colon tumors, whereas tumors in the descending and sigmoid colon (C18.6 and C18.7) were defined as distal (or left) colon tumors. Tumors that were overlapping or unspecified (C18.8 and C18.9) were not included in the assignment of proximal and distal colon tumors. Tumors for the proximal and distal colon as well as overlapping or unspecified tumors were combined to define the whole colon. Cancers of the rectum were defined as tumors occurring at the rectosigmoid junction (C19) or rectum (C20). Anal canal tumors were excluded from the analysis.

Determination of Total Nut and Seed Intake. For determination of the total amount of nut and seed intake, this study used the value of total intake of pure nut and seed products (composed of at least 90% nuts and/or seeds) combined as determined from dietary questionnaires. The EPIC questionnaires have been validated by comparing questionnaire data to 12 monthly 24-hour recalls in a subsample of EPIC subjects. For total fruit intake, including nuts and seeds, the correlations range from 0.33 (German men) to 0.72 (Swedish men; ref. 16). Using the same procedure, the assessment of nuts and seeds has been validated in some EPIC cohorts, with correlations of 0.25 (men and women combined) in Germany (17) and 0.65 (men) and 0.38 (women) in Netherlands (18). In addition, we calculated the age-adjusted correlation coefficients between the mean intake of nuts and seeds from the EPIC diet questionnaires and the mean intake estimated from EPIC 24-hour dietary recalls, by sex and study center, in a subset of 36,000 EPIC subjects, to be 0.51 for men and 0.62 for women.

The EPIC diet questionnaires contain a range of questions on general intake of nuts and seeds, with most asking at least a general question about overall nut and seed intake. The amount of nut and seed intake and the types of nuts and seeds consumed throughout the EPIC centers vary widely. This wide range includes peanuts (and peanut butter), which are actually legumes but often identified by consumers as part of the nuts and seeds food group, and chestnuts, which are more starchy and have less fat content than most other nuts. Details of the dietary questionnaire items regarding nut and seed intake for each country (or center, if questionnaire questions were different for centers within a given country) are shown in Table 1. Questionnaires in the Malmö center of Sweden and in Spain were partly open ended (13), so specific items that appear in Table 1 for these centers represent details about nut and seed intake developed after asking a general question on overall consumption of nuts and seeds. Consumers were determined from the diet questionnaire and defined as those with an intake of nuts and seeds greater than zero.

Statistical Methods. The analyses were done using a multivariate Cox proportional hazards model (SAS statistical software, version 8e, SAS Institute, Cary, NC). To control for center effects such as follow-up procedures and questionnaire design, all analyses were stratified by center. Because the UK Oxford Center includes two very different populations (a health-conscious population and a general population), each was treated as a separate center.

Nut and seed intake data were divided into five categories with all nonconsumers (23.7% for men and 25.8% for women) placed in the first (reference) category. The consumers were divided by quartiles into the remaining four categories of intake (categories 2-5). Category cut points were defined across the entire cohort for men and women combined (grams of nut and seed intake per day): category 1 (nonconsumers; reference): 0.0 g/d, category 2: >0.0 to 0.8 g/d, category 3: >0.8 to 2.3 g/d, category 4: >2.3 to 6.2 g/d, and category 5: >6.2 g/d. The number of cases and noncases in each category of intake are listed in Table 2. Analyses were also done using gender-specific and gender and country–specific categories of intake, but as results were similar to those provided by non–gender and country–specific categories, the latter were used for all analyses presented. Analyses were also conducted by country and for the whole EPIC cohort, with nut and seed intake treated as a log-transformed (original value +1) continuous variable. Tests for interaction of nut and seed intake with country and by gender were also done.

In all models, age was used as the primary time variable. Risk estimates were computed using Cox regression by considering two different sets of adjusting variables and confounders: (*a*) energy-adjusted model: adjusted for gender, age, and intake of energy from fat, energy from alcohol, and energy from carbohydrates and proteins and (*b*) fully adjusted model: the same variables as in the energy-adjusted model plus additional inclusion of height, weight, total intake of fruits (without nuts and seeds), intake of total dietary fiber, physical activity at work, and duration of smoking (variable with separate categories of years of smoking for smokers and ex-smokers, including a category for nonsmokers). Because dietary folate may be a modulator of CRC risk, to take into account any potential confounding from this variable, dietary folate was additionally included as an adjustment variable in a large subset of EPIC subjects for whom dietary folate intake is available (1,182 cases, 412,085 noncases).

Total energy intake was partitioned into its components from fat, alcohol, and carbohydrate plus protein sources in all models used to improve the error correction with consideration of the high-fat content of nuts and seeds in general and the potential of both their fat and nonfat components to contribute to any possible cancer protective effects. Because alcohol is a rich source of energy and because its effect as a covariable was shown to be similar when it was included in the model either as a separate variable based on classes of amount of alcohol consumption, as a continuous variable, or as a component of total energy, it was deemed best to correct for alcohol consumption as a component of total energy.

Because previous methodologic studies indicate that weight is an important predictor of energy intake (19) and to control for body size, height and weight were adjusted for in all models. In these analyses, no differences were observed in the results when adjusting for height and weight in comparison with the body mass index alone or in combination with height or weight.

The same covariates were used in analysis models based on nut and seed intake as a continuous or categorical variable. In the categorical variable model, all covariates were categorical, whereas in the continuous variable models, all dietary intake variables were log transformed and continuous except for height, weight, physical activity, and smoking duration, which were modeled as categorical variables. For all models, linear trend tests were also done using a continuous variable scored from 1 to 5 according to the category interval in which an observation lay. To take into account possible deviations from linearity, an indicator variable (0 = nonconsumer, 1 = consumer) of nut intake was also included in models with nut and seed intake included as a continuous variable. However, this variable was not significantly associated with risk and the association between nut and seed intake and CRC incidence was not altered. Thus, only results without the indicator variable are presented.

The same set of models was run for colorectal, colon (whole, proximal, and distal sections), and rectal cancers. Due to potential differences between men and women in nut and seed intake patterns, variation in types of nuts and seeds consumed, and with regard to purported gender differences in incidence of CRC (20, 21), all analyses were also conducted by gender.

As described previously (22), 24-hour diet recalls have been collected from a subset (8% random sample; total of 36,000 subjects) of all EPIC cohorts for the purpose of calibrating dietary questionnaire data to counter estimation errors and differences in questionnaire design and application among centers, allowing for estimation of food intakes on a common scale, hence enabling better comparisons of cancer risk among the EPIC centers. A common strategy of calibration procedures is to adjust for center-specific errors in estimating the true mean intake of the food group of interest (22). This was done in this study by centering the mean intake for nuts and

Table 1. Listing of items for nuts and seeds from the list of items in the EPIC baseline dietary questionnaires, percentage of nut and seed consumers, average daily intake from both diet questionnaire and 24-hour recalls by country, HR and 95% CI for association of nuts and seeds for men and women combined, by country, and contribution of each country to the entire EPIC cohort and CRC cases

EPIC country and/or study center	Questionnaire food item concerning intake of nuts and/or seeds	Percentage of consumers*	Mean intake (g/d)†		24-hour recall mean intake (g/d)‡		HR of nut and seed intake§	Total person years	CRC cases (*n*)
			Males	Females	Males	Females			
Denmark	Peanuts	74.2	2.0 ± 4.4	1.5 ± 3.7	1.4 ± 9.2	1.2 ± 8.1	1.21 (0.97-1.51)	182,176	177
France	Nuts, nonspecific‖	71.7	—	5.5 ± 8.4	—	3.6 ± 15.6	0.85 (0.72-1.00)	437,420	174
Germany	Nuts, nonspecific‖; seeds, nonspecific‖; peanut butter	91.3	6.3 ± 11.0	5.2 ± 9.0	2.5 ± 11.6	2.7 ± 12.0	0.97 (0.78-1.17)	209,262	114
Greece	Nuts, nonspecific,‖ with salt; nuts, nonspecific,‖ without salt	92.9	7.2 ± 9.4	4.9 ± 7.3	3.5 ± 15.9	3.2 ± 14.3	0.98 (0.64-1.50)	92,661	24
Italy		89.0	0.9 ± 1.8	0.9 ± 2.1	3.0 ± 16.5	3.4 ± 18.1	0.92 (0.61-1.39)	186,919	101
Italy North (Florence, Turin, and Varese)	Walnuts; hazelnuts; almonds; peanuts								
Ragusa	Nuts, nonspecific‖								
Naples	Walnut								
Norway	Peanuts	47.2	—	2.2 ± 3.6	—	2.8 ± 12.7	0.90 (0.52-1.55)	57,423	20
Netherlands	Nuts, nonspecific, eaten at dinner‖; peanut butter; peanuts, cocktail nuts, and other nuts	94.1	12.4 ± 16.6	7.5 ± 10.6	10.0 ± 26.7	5.5 ± 15.9	0.87 (0.72-1.11)	161,194	97
Spain	Almond; chestnut; coconut; hazelnut; other nuts, nonspecific‖; peanut; pine nut; pistachio nut; seed, sunflower/ pumpkin; walnut	38.0	5.0 ± 13.0	3.9 ± 9.7	6.8 ± 24.9	4.4 ± 15.1	0.98 (0.81-1.18)	236,108	110
Sweden		62.6	1.1 ± 3.7	0.8 ± 3.1	1.0 ± 6.9	1.0 ± 6.0	0.89 (0.72-1.10)	368,594	272
Malmö	Almonds; cashew nuts; chestnuts, roasted; hazelnuts; nuts/ almonds; peanut butter; peanuts; peanuts, roasted salted; pecan nuts; pistachio nuts; pumpkin kernels; pumpkin/squash seeds, dried; walnuts								
Umeå	Peanuts, salted								
United Kingdom	Peanut butter, peanuts, or other nuts	84.6	6.7 ± 13.8	5.6 ± 10.6	5.5 ± 20.4	4.6 ± 15.6	1.10 (0.97-1.26)	351,401	240

*Defined as those with nut and seed intakes >0 from diet questionnaire.
†Unadjusted means ± SD from EPIC diet questionnaires, including nonconsumers.
‡Unadjusted means ± SD from EPIC 24-hour recalls in 38,000 EPIC subjects, including nonconsumers.
§HR and 95% CI for association of nut and seed intake with CRC risk for men and women combined, by country, with intake presented as a log-transformed continuous variable, using a model stratified by center with age as the primary time variable and adjusted for age, gender, height (categorical), weight (categorical), energy from alcohol (log-transformed continuous), energy from fat (log-transformed continuous), energy from carbohydrates and proteins (log-transformed continuous), fruit intake (without nuts and seeds; log-transformed), dietary fiber intake (log-transformed), physical activity (categorical), and smoking duration (categorical).
‖"Nonspecific" implies intake of any kind of nuts.

seeds obtained from questionnaire data on nut and seed intake data obtained from the 24-hour recalls (values shown in Table 1) using an additive approach. Cox regression models were re-run using calibrated data. The calibrated intake of nuts and seeds was again divided into cohort-wide categories of intake with all nonconsumers in the first (reference) category and the consumers divided as equally as possible among the remaining four categories with cut points defined as follows: category 1 (nonconsumers; reference): 0.0 g/d, category 2: >0.0 to 1.2 g/d, category 3: >1.2 to 3.5 g/d, category 4: >3.5 to 7.1 g/d, and category 5: >7.1 g/d. Intake of total fruits (without nuts and seeds) and dietary fiber as well as intake of energy from fat, energy from alcohol, and energy from carbohydrates and proteins were also calibrated in the same manner described above and then

Table 2. Description of the study population

	Whole cohort	Category of nut and seed intake*				
		1 (Reference; nonconsumers)	2 (>0-2.8 g/d)	3 (>0.8-2.3 g/d)	4 (>2.3-6.2 g/d)	5 (>6.2 g/d)
Dietary variables						
Nuts and seeds (g/d)†						
All subjects	4.2 ± 8.8	0.0	0.3 ± 0.2	1.4 ± 0.6	4.0 ± 1.0	16.7 ± 14.6
Men	4.6 ± 10.4	0.0	0.3 ± 0.2	1.3 ± 0.5	4.1 ± 1.0	19.1 ± 17.6
Women	4.1 ± 8.1	0.0	0.3 ± 0.2	1.5 ± 0.6	4.0 ± 1.0	15.7 ± 13.0
Total energy (MJ)†,‡						
All subjects	8.8 ± 2.7	8.5 ± 2.7	8.5 ± 2.7	9.0 ± 2.6	8.7 ± 2.5	9.6 ± 2.7
Men	10.3 ± 2.9	10.4 ± 2.9	9.7 ± 2.9	10.4 ± 2.7	10.3 ± 2.8	10.9 ± 3.0
Women	8.2 ± 2.3	7.8 ± 2.2	7.8 ± 2.3	8.3 ± 2.2	8.2 ± 2.2	9.0 ± 2.4
Fruits (g/d)†,§						
All subjects	244.1 ± 196.4	231.3 ± 186.9	264.7 ± 211.0	216.9 ± 168.2	258.1 ± 206.7	255.5 ± 206.1
Men	222.4 ± 207.5	214.0 ± 196.5	236.1 ± 214.8	171.6 ± 150.4	257.9 ± 237.0	247.2 ± 230.5
Women	253.3 ± 190.8	237.9 ± 182.6	279.8 ± 207.5	239.3 ± 172.0	258.1 ± 196.1	259.1 ± 194.7
Dietary fiber intake (g/d)†						
All subjects	22.4 ± 8.0	21.8 ± 8.0	21.5 ± 8.8	21.3 ± 7.3	22.7 ± 7.4	25.2 ± 8.0
Men	23.9 ± 9.2	23.8 ± 9.2	23.1 ± 10.3	21.6 ± 7.7	24.2 ± 8.4	27.1 ± 9.0
Women	21.8 ± 7.4	21.1 ± 7.3	20.6 ± 7.8	21.1 ± 7.1	22.2 ± 7.0	24.3 ± 7.4
Nondietary variables						
Colon cancer cases (*n*)						
All subjects	855	299	148	181	124	103
Men	327	116	59	75	40	37
Women	528	183	89	106	84	66
Rectal cancer cases (*n*)						
All subjects	474	175	69	90	59	81
Men	215	76	40	38	28	33
Women	259	99	29	52	31	48
Subjects (*n*)						
All subjects	478,040	119,890	87,120	92,532	88,963	89,535
Men	141,988	33,276	30,171	30,536	21,324	26,681
Women	336,052	86,614	56,949	61,996	67,639	62,854
Age (y)†						
All subjects	51.2 ± 9.9	54.0 ± 8.4	49.5 ± 10.9	52.6 ± 9.2	49.9 ± 9.8	49.0 ± 10.4
Men	52.2 ± 10.1	56.0 ± 8.4	49.7 ± 10.6	54.0 ± 8.3	51.2 ± 10.5	48.9 ± 11.2
Women	50.8 ± 9.8	53.2 ± 8.3	49.3 ± 11.1	51.9 ± 9.5	49.5 ± 9.6	49.0 ± 10.1
Height (cm)†						
All subjects	166.0 ± 9.0	164.9 ± 8.5	165.9 ± 9.5	167.1 ± 9.1	165.6 ± 8.7	166.9 ± 9.1
Men	174.8 ± 7.4	173.1 ± 7.2	174.7 ± 7.5	176.0 ± 6.8	174.8 ± 7.6	175.7 ± 7.7
Women	162.3 ± 6.8	161.8 ± 6.8	161.2 ± 6.9	162.7 ± 6.5	162.8 ± 6.8	163.2 ± 6.8
Weight (kg)†						
All subjects	70.6 ± 13.7	70.9 ± 13.7	71.3 ± 13.5	71.4 ± 14.1	69.5 ± 13.5	69.8 ± 13.5
Men	81.3 ± 12.0	81.4 ± 12.0	80.4 ± 11.7	82.1 ± 12.1	81.7 ± 12.0	80.9 ± 12.0
Women	66.1 ± 11.8	66.9 ± 12.1	66.4 ± 11.9	66.1 ± 11.8	65.6 ± 11.6	65.1 ± 11.2

NOTE: Average no. years of follow-up: category 1: all subjects $n = 5.1$, men $n = 5.5$, women $n = 4.9$; category 2: all subjects $n = 5.1$, men $n = 5.3$, women $n = 5.1$; category 3: all subjects $n = 4.4$, men $n = 4.0$, women $n = 4.6$; category 4: all subjects $n = 4.5$, men $n = 4.3$, women $n = 4.5$; and category 5: all subjects $n = 4.7$, men $n = 4.4$, women $n = 4.9$. Average no. proximal colon cancer cases (not including overlapping or unspecified tumors): category 1: all subjects $n = 117$, men $n = 46$, women $n = 71$; category 2: all subjects $n = 57$, men $n = 18$, women $n = 39$; category 3: all subjects $n = 84$, men $n = 36$, women $n = 48$; category 4: all subjects $n = 55$, men $n = 15$, women $n = 40$; and category 5: all subjects $n = 38$, men $n = 12$, women $n = 26$. Average no. distal colon cancer cases (not including overlapping or unspecified tumors): category 1: all subjects $n = 175$, men $n = 76$, women $n = 99$; category 2: all subjects $n = 69$, men $n = 40$, women $n = 29$; category 3: all subjects $n = 90$, men $n = 38$, women $n = 52$; category 4: all subjects $n = 59$, men $n = 28$, women $n = 31$; and category 5: all subjects $n = 81$, men $n = 33$, women $n = 48$.

*Non–sex-specific category cut points were defined across the entire cohort.

†Values are means ± SD and are not adjusted by any variable.

‡In men, 35.5% of total energy are from fats, 58.5% from carbohydrates and proteins, and 5.9% from alcohol. In women, 35.9% of total energy are from fats, 61.3% from carbohydrates and proteins, and 2.8% from alcohol.

§Not including intake of nuts and seeds.

redivided into EPIC-wide quintiles of intake. Analysis models for calibrated data were similar to the fully adjusted model described above for the noncalibrated (original) data in categories of intake.

Results

Table 1 lists the percentage of nut and seed consumers and the average amount of nut and seed intake by country as well as the extent of the contribution, in terms of the number of subjects, of each country to the entire cohort. It shows a wide degree of variation in intake of nuts and seeds, as derived from dietary questionnaires, among the EPIC countries, with the mean intake ranging from a low of 0.8 g/d (women in Sweden) to a high of 12.4 g/d (men in Netherlands). The total intake of nuts and seeds ranged from 0 to 300.2 g/d for men and 0 to 265.5 g/d for women. From Table 1, it is clear that a large percentage of subjects in most countries consume some nuts and seeds with the highest in Netherlands (94.1%). Table 1 also lists the mean intake of nuts and seeds derived from 24-hour recalls taken from a subset of the EPIC cohort and used in the calibration of the intake data, as described in more detail in Methods. The average percentage of consumers in all EPIC cohorts together was 76.6% and 74.2% for men and women, respectively, and 74.9% for all subjects combined. Table 1 also shows the hazard ratios (HR) for the association of nut and seed intake with CRC in each individual country. The results show variations in direction and magnitude of the risk by country. In addition, tests for interaction of nut and seed intake with country did not show any significant interactions.

A description of the study population is given in Table 2. Follow-up consisted of 2,294,592 person-years of follow-up (average 4.8 years per subject) with 478,040 subjects and a total of 1,329 cases of CRC.

Table 2 shows that the average unadjusted daily intake of nuts and seeds was 4.6 g for men and 4.1 g for women in the whole cohort. Table 2 also shows the average amount of nut and seed consumption per category of intake. Comparing the second category to the highest category, the intake of nuts and seeds showed over a 55-fold increase across category means (Table 2). Average total intakes in the whole cohort adjusted for energy were much higher for women (4.44 g/d) than for men (3.63 g/d).

The HRs for risk of colorectal, colon, and rectal cancers associated with total intake of nuts and seeds for categorical and continuous data for both energy-adjusted and fully adjusted analysis models are shown in Table 3. No meaningful differences were observed between energy-adjusted and fully adjusted analysis models. No associations between nut and seed intake and incidence of colorectal, colon, or rectal cancers were observed in men and women combined or in men alone in any of the analysis models (Table 3). However, subgroup analyses by gender show that in women, but not men, the highest category of nut and seed intake was associated with a reduced incidence of colon cancer (HR, 0.69; 95% CI, 0.50-0.95; fully adjusted model), particularly distal colon cancer (HR, 0.52; 95% CI, 0.32-0.85; fully adjusted model), with a mean intake of 15.7 g/d compared with nonconsumers. This is supported by P's for trend (P = 0.03; Table 3). No statistical significant association was observed in men. The same pattern is observed when the nut and seed intake data are presented as a log-transformed continuous variable (Table 3), with a reduced incidence of colon cancer (HR, 0.89; 95% CI, 0.80-0.98; fully adjusted model), particularly distal colon cancer (HR, 0.83; 95% CI, 0.70-0.97; fully adjusted model), in women and no associations in men. However, tests for interaction of nut and seed intake with gender did not show a significant difference in effect for CRC by gender (P = 0.18). No significant association of nut and seed intake with incidence of rectal cancer was observed for either gender (Table 3).

To fully explore the confounding effect of energy, models were also run with total energy or with energy partitioned into its components, as described in Methods. There was little difference in the results, however, and so the components of energy were used as confounders. No meaningful differences in results were observed when energy variables were adjusted for as either categorical or log-transformed continuous variables in the analysis models.

No relevant changes in results were observed with adjustments for dietary folate (Table 3). Furthermore, intakes of vegetables, legumes, meat and meat products, cereals and cereal products, dairy products, fish/shellfish, and vitamin E were also tested as potential covariates in the analysis models. However, the results were not modified after their inclusion. Because nuts and seeds are rich in polyunsaturated and monounsaturated fatty acids, the models were also tested correcting for ratios of either (*a*) polyunsaturated to saturated, (*b*) monounsaturated to saturated, or (*c*) monounsaturated to polyunsaturated fatty acids. However, none of these altered the results obtained.

Figure 1 shows the HRs for CRC risk of increased nut and seed intake for men and women based on calibrated compared with noncalibrated (original) data of categories of nut and seed intake from Table 3 (fully adjusted model). Calibrated results for men are very similar to the original data, with no significant effects at any level of intake. However, for women, calibration heightens the strength of the inverse association between increased nut and seed intake and CRC with a significant reduction in the two highest categories of intake.

Discussion

EPIC is one of the largest prospective cohort studies ever conducted on diet and cancer. The results of this present study show no significant protective associations on CRC risk for men and women combined. However, the results of subgroup analyses by gender suggest that a modest intake of an average of ~16 g of nuts and seeds daily is associated with reduced incidence of colon cancer in women relative to nonconsumers, with no observable effects in men, or rectal cancer for either gender. Adjusting for measurement error of nut and seed intake by calibrating diet questionnaire values against values obtained from a 24-hour intake measurement in a subset of the EPIC cohort (23) shows a heightened inverse association with CRC risk of increased nut and seed intake in women (Fig. 1), suggesting a potential improvement of intake estimation with calibration.

It is not clear why this study suggests an association for women but not for men, although the same has been observed for the intake of pulses, nuts, and seeds combined (10) in a case-control study. Nuts and seeds have been suggested to be rich sources of many phytochemicals (1, 24-26) and it is possible to speculate that hormonally active components may affect colon cancer risk differently in women versus men. Indeed,

Table 3. Multivariate-adjusted HR of categories of nut and seed intake and risk of colorectal, colon, and rectal cancers

	HR and 95% CI for category of nut and seed intake*					*P* for trend†	Continuous (Log)‡	Continuous (Log) with folate adjusted§
	1 (Reference)	2	3	4	5			
CRC								
Energy-adjusted model‖								
All subjects	1.00	0.95 (0.77-1.18)	0.98 (0.83-1.16)	0.93 (0.77-1.12)	0.89 (0.73-1.08)	0.23	0.97 (0.91-1.03)	0.98 (0.92-1.05)
Men	1.00	1.10 (0.79-1.55)	1.02 (0.78-1.32)	1.12 (0.83-1.51)	1.06 (0.78-1.43)	0.60	1.04 (0.94-1.14)	1.06 (0.95-1.18)
Women	1.00	0.87 (0.65-1.15)	0.95 (0.77-1.18)	0.83 (0.65-1.05)	0.79 (0.61-1.01)	0.04	0.92 (0.84-0.99)	0.93 (0.84-1.02)
Fully adjusted model¶								
All subjects	1.00	0.95 (0.76-1.18)	0.99 (0.84-1.17)	0.94 (0.78-1.14)	0.91 (0.75-1.11)	0.39	0.98 (0.92-1.05)	0.99 (0.92-1.07)
Men	1.00	1.10 (0.78-1.54)	1.03 (0.79-1.34)	1.13 (0.84-1.53)	1.09 (0.81-1.49)	0.42	1.06 (0.95-1.17)	1.07 0.96-1.19)
Women	1.00	0.87 (0.64-1.15)	0.96 (0.77-1.20)	0.84 (0.67-1.07)	0.81 (0.63-1.04)	0.07	0.93 (0.85-1.01)	0.94 (0.85-1.03)
Colon cancer								
Energy-adjusted model‖								
All subjects	1.00	1.04 (0.80-1.36)	1.07 (0.87-1.32)	1.01 (0.80-1.27)	0.80 (0.62-1.02)	0.18	0.94 (0.87-1.03)	0.93 (0.85-1.02)
Men	1.00	1.09 (0.70-1.67)	1.17 (0.84-1.62)	1.17 (0.80-1.72)	1.00 (0.67-1.50)	0.63	1.04 (0.92-1.18)	1.03 (0.90-1.18)
Women	1.00	1.01 (0.72-1.41)	1.00 (0.77-1.31)	0.91 (0.69-1.21)	0.68 (0.50-0.93)	0.03	0.88 (0.79-0.97)	0.86 (0.76-0.96)
Fully adjusted model¶								
All subjects	1.00	1.03 (0.79-1.35)	1.07 (0.87-1.32)	1.01 (0.80-1.27)	0.81 (0.63-1.04)	0.28	0.96 (0.88-1.04)	0.94 (0.86-1.03)
Men	1.00	1.09 (0.70-1.69)	1.17 (0.84-1.63)	1.17 (0.80-1.73)	1.01 (0.67-1.53)	0.50	1.06 (0.93-1.21)	1.05 (0.91-1.20)
Women	1.00	1.01 (0.72-1.41)	1.01 (0.77-1.32)	0.92 (0.70-1.23)	0.69 (0.50-0.95)	0.04	0.89 (0.80-0.98)	0.87 (0.77-0.98)
Proximal colon cancer								
Energy-adjusted model‖								
All subjects	1.00	1.23 (0.80-1.88)	1.36 (1.00-1.87)	1.22 (0.86-1.73)	0.79 (0.52-1.18)	0.74	0.95 (0.84-1.08)	0.94 (0.82-1.08)
Men	1.00	0.96 (0.44-2.07)	1.58 (0.96-2.59)	1.13 (0.61-2.11)	0.78 (0.39-1.56)	0.96	0.96 (0.78-1.19)	0.96 (0.77-1.19)
Women	1.00	1.39 (0.83-2.33)	1.24 (0.82-1.85)	1.24 (0.81-1.90)	0.76 (0.46-1.26)	0.59	0.93 (0.791.09)	0.92 (0.77-1.10)
Fully adjusted model¶								
All subjects	1.00	1.21 (0.79-1.86)	1.35 (0.99-1.86)	1.22 (0.86-1.73)	0.80 (0.53-1.21)	0.87	0.96 (0.85-1.10)	0.95 (0.82-1.10)
Men	1.00	0.95 (0.44-2.06)	1.55 (0.94-2.56)	1.11 (0.60-2.08)	0.77 (0.38-1.56)	0.91	0.97 (0.78-1.20)	0.96 (0.77-1.20)
Women	1.00	1.38 (0.83-2.31)	1.24 (0.82-1.86)	1.26 (0.82-1.93)	0.80 (0.48-1.33)	0.73	0.95 (0.81-1.12)	0.93 (0.78-1.12)
Distal colon cancer								
Energy-adjusted model‖								
All subjects	1.00	0.88 (0.59-1.30)	0.94 (0.69-1.27)	0.90 (0.64-1.26)	0.71 (0.49-1.03)	0.13	0.93 (0.82-1.05)	0.91 (0.80-1.05)
Men	1.00	1.09 (0.58-2.05)	0.99 (0.62-1.60)	1.01 (0.57-1.79)	1.05 (0.59-1.87)	0.87	1.08 (0.90-1.30)	1.09 (0.89-1.33)
Women	1.00	0.74 (0.44-1.24)	0.88 (0.60-1.30)	0.81 (0.53-1.24)	0.53 (0.33-0.87)	0.03	0.82 (0.70-0.97)	0.79 (0.66-0.95)
Fully adjusted model¶								
All subjects	1.00	0.88 (0.60-1.31)	0.94 (0.70-1.28)	0.91 (0.65-1.28)	0.70 (0.48-1.02)	0.17	0.94 (0.83-1.06)	0.92 (0.81-1.06)
Men	1.00	1.11 (0.59-2.10)	1.01 (0.63-1.64)	1.04 (0.58-1.85)	1.07 (0.60-1.92)	0.69	1.11 (0.92-1.34)	1.11 (0.90-1.36)
Women	1.00	0.74 (0.44-1.24)	0.88 (0.59-1.30)	0.82 (0.54-1.25)	0.52 (0.32-0.85)	0.03	0.83 (0.70-0.97)	0.80 (0.67-0.96)
Rectal cancer								
Energy-adjusted model‖								
All subjects	1.00	0.81 (0.59-1.18)	0.84 (0.63-1.11)	0.81 (0.59-1.11)	1.04 (0.77-1.42)	0.83	1.01 (0.91-1.12)	1.07 (0.96-1.20)
Men	1.00	1.13 (0.67-1.93)	0.81 (0.52-1.25)	1.06 (0.66-1.68)	1.17 (0.71-1.77)	0.80	1.03 (0.88-1.20)	1.10 (0.93-1.30)
Women	1.00	0.60 (0.35-1.02)	0.86 (0.59-1.25)	0.67 (0.43-1.04)	1.01 (0.67-1.52)	0.70	1.00 (0.87-1.16)	1.06 (0.91-1.24)
Fully adjusted model¶								
All subjects	1.00	0.82 (0.56-1.18)	0.86 (0.65-1.14)	0.83 (0.61-1.15)	1.10 (0.81-1.50)	0.95	1.03 (0.92-1.14)	1.08 (0.97-1.21)
Men	1.00	1.13 (0.67-1.92)	0.82 (0.53-1.27)	1.08 (0.68-1.72)	1.20 (0.75-1.90)	0.63	1.05 (0.90-1.23)	1.11 (0.94-1.31)
Women	1.00	0.61 (0.36-1.03)	0.88 (0.61-1.28)	0.69 (0.44-1.07)	1.05 (0.70-1.58)	0.99	1.01 (0.88-1.17)	1.07 (0.92-1.25)

*Values are HRs derived from models as described above, with all covariates presented as categorical variables. Non–sex-specific category cut points were defined across the entire cohort: category 1 (reference): 0.0 g/d, category 2: 0.0-0.8 g/d, category 3: >0.8-2.3 g/d, category 4: >2.3-6.2 g/d, and category 5: >6.2 g/d.

†*P* of χ^2 test for trend using a continuous variable with 1 *df*.

‡Values are HRs derived from models as described above, with all covariates presented as log-transformed continuous variables, except height, weight, physical activity, and duration of smoking (categorical).

§Values are HRs derived from models as described above with further adjustments for intake of folate, with all covariates presented as log-transformed variables, except height, weight, physical activity, and duration of smoking (categorical), from a large subset of EPIC subjects (men: cases n = 496, noncases n = 119,876; women: cases n = 686, noncases n = 292,209).

‖Energy-adjusted model: stratified by center with age as the primary time variable and adjusted for age, gender, energy from alcohol, energy from fat, and energy from carbohydrates and proteins.

¶Fully adjusted model: stratified by center with age as the primary time variable and adjusted for all the same variables as the energy-adjusted model plus adjustments for height, weight, intake of fruits (without nuts and seeds), intake of dietary fiber, physical activity, and duration of smoking.

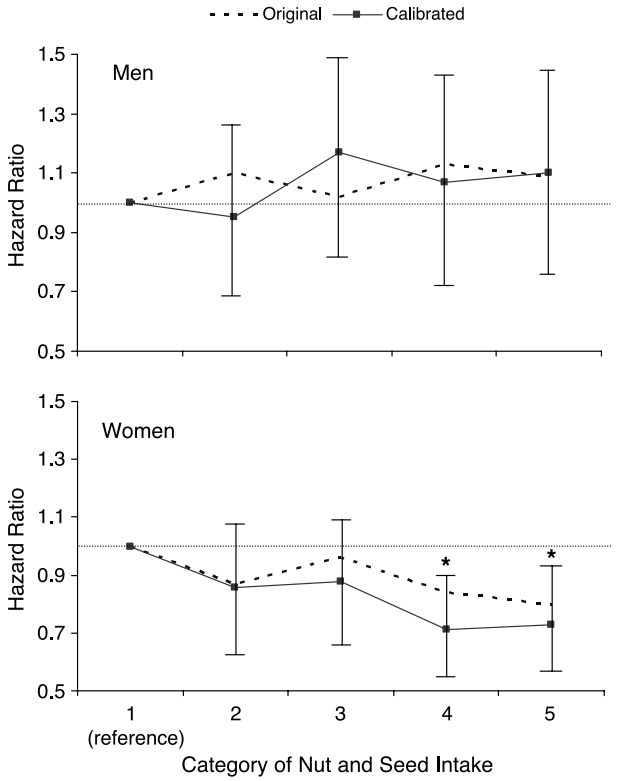

Figure 1. HRs for the risk of CRC in men and women associated with intake of nuts and seeds, original versus calibrated data. *Dotted line,* original HRs for noncalibrated dietary data and CRC risk, which are given and described in Table 3. *Solid line,* calibrated HRs with 95% CIs (*bars*). Calibrated HRs were derived from dietary questionnaire nut and seed intake values centered on 24-hour recall means for nut and seed intake, stratified by center with age as the primary variable and adjusted for age, gender, height (categorical), weight (categorical), energy from alcohol (categorical), energy from fat (categorical), energy from carbohydrates and proteins (categorical), fruit intake (without nuts and seeds; categorical), dietary fiber intake (categorical), physical activity (categorical), and duration of smoking (categorical). Cut points for the noncalibrated data are described in Tables 2 and 3. For calibrated data, non–sex-specific category cut points were redefined after calibration across the entire cohort: category 1 (nonconsumers; reference): 0.0 g/d, category 2: >0.0 to 1.2 g/d, category 3: >1.2 to 3.5 g/d, category 4: >3.5 to 7.1 g/d, and category 5: >7.1 g/d; *, $P < 0.05$, significant difference from reference category.

gender differences in colon cancer risk factors are thought to possibly have a hormonal basis (27) and cancerous and normal bowel tissue may express both types of estrogen receptors (28), suggesting that dietary phytoestrogens may be able to influence colon cancer development. That nuts and seeds, as a food group, may be capable of exerting a possible physiologic hormonal effect is suggested by the observation that increased nut and seed intake can delay the age of menarche in Spanish teenage girls (29). In the present study, to determine if varying hormonal milieus possibly play a role in determining a stronger effect in women, attempts were made to separate women based on their menopausal status, but this did not show any meaningful differences between premenopausal and menopausal women.

Different patterns of nut and seed consumption between men and women may also be a determining factor in the results of this study, although little descriptive information exists. It must also be noted that this study contained much more women subjects and cancer cases, which may strengthen the observation of associations in women versus men. Nonetheless, the apparent differences in effect between men and women observed in this study should, at this stage, only provide a basis for further research and requires clear confirmation.

In this study, it is also interesting that the protective association observed in women was observed in the distal (left) colon. This is not an unusual observation because other epidemiologic studies have also shown a differing effect of various dietary variables on proximal versus distal colon cancers (30, 31). Additionally, in this study, no effect of increased nut and seed intake was observed on the incidence of rectal cancer in either gender. Colon and rectal cancers may have different etiologies, and components of diet have been shown to affect colon cancer but not rectal cancer (32-34), whereas some environmental factors may affect colon and rectal cancers differently in men and women (35). It may, however, also be argued that a limitation of this study is the smaller number of rectal versus colon cancer cases for each gender and hence a reduced statistical power to observe any effects. Nonetheless, the site-specific associations observed in this study require further confirmation.

It may be suggested that nuts and seeds are acting as a marker of consumption of fruits and vegetables or just a generally healthier diet and that the observations of this study may be attributable to these factors instead of an effect of nuts and seeds as a food group. However, this does not seem to be the case because (*a*) adjustments for vegetables, legumes, meats and meat products, and cereals and cereal products, either individually or in combination, did not alter the results and (*b*) total intake of nuts and seeds was not highly correlated with intake of either dietary fiber, vegetables, legumes, fruits, cereals, vitamin E, or any other major food component.

As has been suggested to be the case for their effects on heart disease (2-4), part of the potential cancer protective effects of nuts and seeds may be attributable to their high content of unsaturated fatty acids. In this study, the persistence of a protective effect when intakes of energy from fats were included as covariates in the analysis model suggests that the fat profile of nuts and seeds as a whole may play a role in the observed associations. However, these remained unchanged after adjusting for the ratio of polyunsaturated or monounsaturated to saturated fatty acids, suggesting that the observations of this study may not be entirely due to the unsaturated fatty acid components of nuts and seeds.

From the EPIC dietary questionnaires, it is not possible to determine the exact types of nuts or seeds that are contributing to the overall intakes determined in this analysis; thus, further research is necessary to determine the exact type of nuts and seeds consumed by Europeans. Likewise, due to the small amount of information currently available regarding the phytochemical contents

of different varieties of nuts and seeds, much further research is necessary to detail the bioactive profiles of different varieties and to establish their contribution to the observations of this study.

The total amount of nut and seed intake used in this study does not include foods such as turron (a nut candy popular in Spain), marzipan (almond paste), nut-chocolate spreads, or other products that contain nuts. The contribution of these foods to overall nut and seed consumption in the EPIC database is very low and the testing of their inclusion as part of the nuts and seeds group did not at all affect the results of this study. However, chestnuts are included in this database as part of total nut and seed intake for Spain and the Malmö center of Sweden, whose partly open-ended questionnaires picked up chestnut consumption, and they may also be included for those countries whose questionnaires asked about nonspecific nut and seed intake (Table 1). Although chestnuts are tree nuts by definition, they do not have the same fat and phytochemical profile as other nuts; hence, their inclusion in this study may have reduced the power of the analyses. However, removal of chestnuts as part of the total nut and seed intake values from Spain and the Malmö center of Sweden, where their intake is readily identifiable, did not change the results of this study in any way.

In conclusion, the EPIC study has shown that higher intake of nuts and seeds is not associated with a CRC protective effect in men and women combined. However, subgroup analyses by gender suggest that it may be associated with a reduced incidence of colon cancer in women with no observed effects on rectal cancer for either gender. The potential gender and site–specific associations observed in this study require further confirmation before any recommendations can be made about increasing intake of nuts and seeds in the general population.

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Association of Nut and Seed Intake with Colorectal Cancer Risk in the European Prospective Investigation into Cancer and Nutrition

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