Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition[1–4]

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ABSTRACT

Background: A high consumption of fruit and vegetables is possibly associated with a decreased risk of colorectal cancer (CRC). However, the findings to date are inconsistent.

Objective: We examined the relation between self-reported usual consumption of fruit and vegetables and the incidence of CRC.

Design: In the European Prospective Investigation into Cancer and Nutrition (EPIC), 452,755 subjects (131,985 men and 320,770 women) completed a dietary questionnaire in 1992–2000 and were followed up for cancer incidence and mortality until 2006. A multivariate Cox proportional hazard model was used to estimate adjusted hazard ratios (HRs) and 95% CIs.

Results: After an average follow-up of 8.8 y, 2,819 incident CRC cases were reported. Consumption of fruit and vegetables was inversely associated with CRC in a comparison of the highest with the lowest EPIC-wide quintile of consumption (HR: 0.86; 95% CI: 0.75, 1.00; P for trend = 0.04), particularly with colon cancer risk (HR: 0.76; 95% CI: 0.63, 0.91; P for trend $<$ 0.01). Only after exclusion of the first 2 y of follow-up were these findings corroborated by calibrated continuous analyses for a 100-g increase in consumption: HRs of 0.95 (95% CI: 0.91, 1.00; P = 0.04) and 0.94 (95% CI: 0.89, 0.99; P = 0.02), respectively. The association between fruit and vegetable consumption and CRC risk was inverse in never and former smokers, but positive in current smokers. This modifying effect was found for fruit and vegetables combined and for vegetables alone (P for interaction $<$ 0.01 for both).

Conclusions: These findings suggest that a high consumption of fruit and vegetables is associated with a reduced risk of CRC, especially of colon cancer. This effect may depend on smoking status.

INTRODUCTION

Data suggest an up to 3-fold variation in colorectal cancer (CRC) incidence across Europe, with an estimated 372,000 new diagnoses (193,000 men and 179,000 women) and 203,000 deaths (102,000 men and 101,000 women) in 2002 (1). Substantial geographic variations and changes in incidence rates of CRC in the world, especially among migrants (2, 3), suggest the existence of modifiable lifestyle factors in the etiology of this disease.

Associations between the consumption of fruit and vegetables and CRC risk have been the focus of a large number of case-control and cohort studies. Nevertheless, a recent review by an international panel of experts concluded that the evidence of an inverse association with CRC risk of higher fruit and vegetables is limited (4); therefore, further studies are warranted.

Discrepancies in the cumulative results to date may be explained by differences in study design and the susceptibility of

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case-control studies to recall and selection biases (5). On the other hand, except for a few large-scale cohort studies, most of the cohort studies until now have been carried out in populations with relatively homogeneous dietary habits (4), so that the extent of measurement error may have obscured any but very large underlying diet-disease associations. One way of reducing the effect of measurement error is to study different populations with diverse dietary practices, which increases the between-person variance in diet and enables the detection of modest diet-cancer associations (6).

An intriguing hypothesis that may also explain the weak or absent relations between fruit and vegetable consumption and CRC risk seen thus far is that some factors may modify this association. Tobacco exposure has been shown to modify the effect of randomized supplementation of β-carotene on the recurrence of colorectal adenoma (7) and of dietary intake of β-carotene on smoking-related cancers (8). In these studies, β-carotene intake was inversely associated with risk among nonsmokers and was directly associated with risk among smokers. The association between fruit and vegetables and colon cancer risk has also been observed to vary by consumption of alcohol, in which an inverse association was apparent among nondrinkers, but not in drinkers, and by consumption of red meat, in which an inverse association was observed in low-to-moderate meat consumers but not in high meat consumers (9).

We investigated how the consumption of total fruit and vegetables is related to CRC risk in the European Prospective Investigation of Cancer and nutrition (EPIC) study—a large prospective collaborative project carried out in 10 different European countries (10, 11). It includes individuals living in 10 European countries spanning a wide range of fruit and vegetable consumption (12). Within this cohort study we also examined whether associations were modified by smoking status, meat consumption, alcohol consumption, or BMI.

SUBJECTS AND METHODS

Study population

EPIC is a multicenter prospective cohort study designed to investigate the relation between food habits, nutritional status, various lifestyle and environmental factors, and the incidence of different forms of cancer. It consists of cohorts from 10 European countries (with a total of 23 centers): Denmark (2 centers), France (1 center), Germany (2 centers), Greece (1 center), Italy (5 centers), the Netherlands (2 centers), Norway (1 center), Spain (5 centers), Sweden (2 centers), and the United Kingdom (2 centers). Dietary and lifestyle questionnaires and anthropometric measurements were collected from all subjects at the time of enrollment in the cohort. The full rationale and methods of the EPIC study were reported elsewhere (10, 11).

In brief, a total of 521,448 subjects, ≈70% women mostly aged 35–70 y, participated in the study. Most of the participants were recruited from the general population residing in a given geographic area, a town, or a province. Exceptions were the French cohort living throughout France (based on female members of the health insurance for school and university employees), the Florence (Italy) and Utrecht (Netherlands) cohorts (based on women attending breast cancer screening), components of the Italian and Spanish cohorts (mostly based on blood donors and their spouses), and the Oxford cohort living throughout the United Kingdom (based on vegetarian and health-conscious volunteers). The participants completed dietary and lifestyle questionnaires and had their anthropometric measurements recorded by trained health professionals (self-reported in France, Norway, and Oxford). All participants gave written informed consent, and the study was approved by the local ethics committee in the participating countries and the Internal Review Board of the International Agency for Research on Cancer.

Our study is based on data from 452,755 participants (131,985 men and 320,775 women) after a priori exclusion of subjects with any prevalent cancer at recruitment (n = 23,523) and subjects for whom dietary, nondietary, or endpoint information was not available (n = 9790). In addition, to reduce the effect on the analysis of implausible extreme values, observations in the top and bottom 1% of the ratio of energy intake to estimated energy requirement calculated from body weight, height, sex, and age were also excluded (n = 9674). We further excluded the subjects from Greece for whom values for dietary cereal fiber were missing, because this information was important for adequate adjustment in our analyses (n = 25,619) and cases who had in situ tumors or had no information on morphology characteristics (n = 87).

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Diet and lifestyle questionnaires

Diet was measured by country-specific validated dietary assessment methods designed to capture local dietary habits and to allow high compliance (10, 13). Extensive quantitative food-frequency questionnaires, containing up to 260 food items and systematically estimating individual portion sizes, were adopted in Germany, Greece, northern Italy, and the Netherlands, whereas questionnaires similar in content, but structured by meals, were used in France, Ragusa (Italy), and Spain (11). In Denmark, Naples (Italy), Norway, Umeå (Sweden), and the United Kingdom, a semiquantitative food-frequency questionnaire was used with the same standard portions for most of the foods. In Malmö (Sweden), a modified diet history was used, which combined a short non-quantitative food-frequency questionnaire with a 14-d record on hot meals. Face-to-face administration was adopted in Greece, Ragusa (Italy), Naples (Italy), and Spain, whereas, in all other centers, questionnaires were self-administered. All dietary measurements were validated previously (11, 14).

A single 24-h diet recall measurement was collected from 36,000 study subjects sampled at baseline from the entire cohort to account for differences in the dietary questionnaires and to reduce measurement error of the food-frequency questionnaire by calibration (*see* Statistical analysis). The 24-h diet recalls were administered via a face-to-face interview with the use of a detailed, computerized method developed ad hoc, standardized across participating countries (15).

The main food groups of interest for the present study were all fruit and vegetables combined, all vegetables, and all fruit. All vegetables [leafy vegetables, fruiting vegetables, root vegetables, cabbages, onions and garlic, mushrooms, grain and pod vegetables (eg, peas), stalk vegetables and sprouts, mixed salads/mixed vegetables, and unclassified vegetables] and all fruit [fresh fruit (ie, citrus fruit, hard fruit, stone fruit, grapes, berries and other fruit; 96.5%), mixed fruit (ie, fresh and canned fruit; 1.6%), olives (0.2%), and nuts and seeds (1.7%)] were defined a priori on the basis of the food classification developed in the EPIC-SOFT system (16). The group of all vegetables does not include legumes or potatoes and other tubers, because they differ from vegetables in energy and carbohydrate contents and are frequently used as substitutes for cereals rather than vegetables. The group of all fruit does not include juices, because they are nutritionally different (eg, added sugars, vitamins) and because they were quantified in liquid form, whereas fruit consumption was mainly expressed as solid foods. The lifestyle questionnaires included detailed questions on the level of education, occupation, lifetime history of consumption of tobacco and alcoholic beverages, physical activity, and history of previous illnesses, disorders, or surgical procedures.

Endpoints

The follow-up was based on population cancer registries (Denmark, Italy, Norway, the Netherlands, Spain, Sweden, and the United Kingdom) or a combination of methods including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin (France, Germany, and Greece). Mortality data were also collected from either the cancer registry or mortality registries at the regional or national level.

This analysis included data on cancer cases assembled at the central database at the International Agency for Research on Cancer by March 2007. For selected centers and those with passive follow-up, specific censoring dates were established depending on the dates in which the cancer registries were considered complete: December 2002 (Granada, Spain), December 2003 (Florence, Varese, and Naples in Italy; Murcia, Spain; Bilthoven, Netherlands; and Denmark), December 2004 (Ragusa and Turin in Italy; Asturias and Navarra in Spain; United Kingdom; Utrecht, Netherlands; Malmö, Sweden; and Norway), June 2005 (France), December 2005 (Umeå, Sweden; and San Sebastian, Spain). For Germany and Greece, the end of follow-up was considered to be the last known contact, the date of diagnosis, or the date of death, whichever came first.

The 10th Revision of the International Classification of Diseases (ICD) for injuries and causes of death was used. Mortality data were coded following the rules of ICD-10, and cancer incidence data following ICD-Oncology. Right or proximal colon tumors included the cecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0–18.5). Left colon tumors included the descending (C18.6) and sigmoid (C18.7) colon. Overlapping lesions of the colon (C18.8) and colon NOS (C18.9) were grouped among all colon cancers only (C18.0-C18.9). Cancer of the rectum included tumors occurring at the rectosigmoid junction (C19) and rectum (C20). Anal canal tumors were excluded.

Statistical analysis

Sex-specific, age-standardized incidence rates were computed for each country, but were restricted to those aged 50–70 y, to ensure coherence across countries. Rates were obtained using the European standard population in 5-y age categories.

Distributions of characteristics are given for each quintile of combined fruit and vegetable consumption, using means with SDs or frequencies (where appropriate). A linear trend for characteristics across quintiles was tested by linear regression (continuous variables) or by the Cochrane-Armitage trend test (categorical variables; never smokers compared with former and current smokers).

Multivariable Cox proportional hazard models were used to assess the association of fruit and vegetable consumption with CRC risk. Fruit and vegetable consumption estimated from the dietary questionnaires was expressed in g/d. We analyzed the data using variables as categorical by EPIC-wide quintiles and as continuous (increment of 100 g/d). To calculate the P value for trend across quintiles, the median of each quintile was assigned to participants, and this variable was entered as a continuous term in the Cox regression models. Attained age was used as the primary time variable in all Cox regression models. Time at entry was the age at recruitment, and exit time was the age when participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. To control for differences in questionnaires, follow up procedures, and other center effects, all analyses were stratified by the centers. Models were further stratified by sex and by age at recruitment in 1-y categories.

The hazard ratios (HRs) were adjusted for body weight for the purpose of making isoenergetic comparisons (6). Estimated total energy intake was included to partially control for errors in the estimation of fruit and vegetable consumption, because there is a high correlation between the errors of estimation of different

dietary components. To improve this error correction, estimated energy intake was divided into energy from fat and energy from nonfat sources, because it is mostly the nonfat components of the diet that contribute to fruit and vegetable consumption.

To control for obesity and body size, weight and height in tertiles were included in the models. Also included in the models were smoking status in categories (never, former, and current), alcohol consumption (none, and 1–10, 11–20, 21–40, and >40 g/d ethanol for men; none and 1–5, 6–15, 16–25, and >25 g/d ethanol for women), processed and red meat consumption (continuous), fish consumption (continuous), and physical activity (inactive, moderately inactive, moderately active, and active based on work and leisure time physical activity) (17). Because a potential protective role of fiber from cereals on CRC risk has been observed in EPIC (18, 19), adjustment for dietary fiber from cereal sources (continuous) was performed to exclude residual confounding. The level of education and the intake of dietary calcium were not included in the final analysis because HR estimates were not substantially altered. Because most centers did not have information about family history of CRC, we were not able to include this into our model. Finally, to evaluate the explanatory power of fiber content, we tested whether gradients were attenuated when we included total fiber (continuous) in the models instead of cereal fiber. Risk estimates for vegetable consumption were adjusted for fruit consumption and vice versa.

To evaluate whether preclinical disease may have influenced results, additional analyses were conducted after exclusion of cases that were diagnosed within 2 y after recruitment. The heterogeneity of associations across countries was tested by using the interaction terms modeled as product terms of continuous consumption of fruit and vegetables with countries.

Effect modification (on the multiplicative scale) by smoking status, meat consumption, alcohol consumption, and BMI was tested by using the interaction term of tertiles of fruit and vegetable consumption with smoking status, tertiles of red and/or processed meat consumption, alcohol consumption, or BMI. For this analysis, a combined reference category of a high consumption of fruit and/or vegetables with never smokers, a low consumption of meat, a low consumption of alcohol, or a low BMI, respectively, was chosen.

Calibration

To correct for systematic over- or underestimation of dietary consumption and to improve the comparability of dietary data across the participating centers, a linear regression calibration model was used (20). The 24-h diet recall measurements were regressed on dietary questionnaire values for fruit and vegetables combined, vegetables, and fruit. Age at recruitment, center, energy from fat, energy from nonfat, height, weight, smoking status, physical activity, consumption of alcohol, red and processed meat, fish, and cereal fiber were included as covariates, and data were weighted by day of the week and season of the year on which the 24-h diet recall was collected. Country and sex-specific calibration models were used to obtain individual calibrated values of dietary exposure for all participants. Cox regression models for fruit and vegetables combined and separately were then fitted by using the predicted values on a continuous scale to compute measurement error–corrected (de-attenuated) HR estimates.

To take into account the additional variability introduced by the calibration model, the SE of the de-attenuated coefficients was corrected through bootstrap sampling ($n = 10$ repetitions). The P value for trend for the de-attenuated coefficients was calculated by dividing the de-attenuated β by the bootstrap-derived SE and by calculating the associated percentile referring to the standardized normal distribution (20). All analyses were performed by using SAS software (version 9.1; SAS Institute Inc, Cary, NC). For all analyses 2-sided P values <0.05 were considered statistically significant.

RESULTS

Since 1992, after an average follow-up of 8.7 y in men and 8.8 y in women, 3,978,204 person-years of observation have been accrued among 452,755 cohort participants. The present study is based on 2819 first incident cases of CRC (1152 men and 1667 women) and 449,936 noncases. Of the 2819 CRC cases, 1828 tumors were located in the colon, of which 783 were proximal, 790 were distal, and 255 were overlapping or unspecified colon tumors. There were 991 rectal tumors.

The numbers of CRC cases and incidence rates according to country, age, and sex are shown in **Table 1**. A difference in incidence rates computed for the common age band of 50–69 y of age was seen between countries, but a north-south gradient across Europe was not observed. Incidence rates were higher for men than for women, and they increased with age.

The observed range of fruit and vegetable intakes within each EPIC-wide quintile of consumption as well as selected characteristics across quintiles of usual consumption of fruit and vegetables combined, for men and women separately, are shown in **Table 2**. Both men and women with higher reported levels of consumption of fruit and vegetables were slightly older, shorter in stature, somewhat lower in weight, reported higher energy intakes from fat and nonfat, reported lower intakes of red and processed meat, reported higher intakes of fish and total fiber, were less likely to be ever smokers, and were more physically active. Men with higher levels of consumption of fruit and vegetables also reported higher cereal fiber intakes.

Fruit and vegetables combined

The number of cases, person-years, and estimated HRs per EPIC-wide quintile and per 100-g increase in fruit and vegetable intakes combined by cancer site are shown in **Table 3**. Crude HRs, overall adjusted HRs, and adjusted HRs for subgroups of smoking status are shown.

The adjusted model showed an inverse association with CRC and colon cancer, but not with rectal cancer. The continuous calibrated analyses, however, did not result in statistically significant findings for CRC, colon cancer, or rectal cancer. The test for heterogeneity between countries was not statistically significant ($P = 0.06$), with all countries except Norway (HR: 1.12; 95% CI: 0.99, 1.27; $P = 0.07$) showing nonsignificant risk estimates of ≤ 1.

In a comparison of the highest with the lowest quintile, no substantial difference was observed between proximal colon cancer (HR: 0.77; 95% CI: 0.58, 1.02; P for trend $= 0.10$) and distal colon cancer (HR: 0.70; 95% CI: 0.53, 0.93; P for trend $= 0.01$). The results for CRC were similar for men (HR: 0.91; 95% CI: 0.72, 1.15; P for trend $= 0.40$) and women (HR: 0.82; 95% CI: 0.68, 1.00; P for trend $= 0.04$) separately (P for interaction $=$ 0.97).

TABLE 1
Description of the cohorts participating in the European Prospective Investigation into Cancer and Nutrition by country and age

	Cohort numbers		Colorectal cancer cases		Person-years		Incidence rate per 100,000 person-years	
	Men	Women	Men	Women	Men	Women	Men	Women
Country								
Denmark	26,283	28,735	265	218	195,551	215,966	129.3[1]	90.6[1]
France	.	67,992	.	351	.	740,903		50.0[1]
Germany	21,579	27,915	166	97	174,164	227,268	116.1[1]	60.4[1]
Italy	14,017	30,495	110	172	118,707	257,232	133.2[1]	88.8[1]
Netherlands	9777	26,512	38	186	81,345	228,914	111.6[1]	86.4[1]
Norway	.	35,227	.	100	.	210,300	.	86.2[1]
Spain	15,151	24,857	133	99	153,845	241,319	112.5[1]	60.9[1]
Sweden	22,309	26,380	231	198	229,535	271,071	103.2[1]	72.8[1]
United Kingdom	22,869	52,657	209	246	190,441	441,645	102.8[1]	64.6[1]
Age band								
<35 y	7602[2]	18,203[2]	1[3]	1[3]	38,057	95,533	2.6	1.1
35–44 y	22,339[2]	62,862[2]	12[3]	25[3]	113,982	298,650	10.5	8.4
45–54 y	47,954[2]	135,751[2]	121[3]	257[3]	326,861	930,695	37.0	27.6
55–64 y	45,696[2]	86,288[2]	496[3]	716[3]	443,615	1,020,732	111.8	70.2
≥65 y	8394[2]	17,666[2]	522[3]	668[3]	221,856	490,950	235.3	136.1
All	131,985[2]	320,770[2]	1152[3]	1667[3]	1,143,587	2,834,617	100.7	58.8

[1] For each country (5 y), age-standardized (European standard population) incidence rates were computed for the common age band of 50–69 y of age.
[2] Based on age at recruitment.
[3] Based on age at diagnosis.

In a subgroup analysis by smoking status, a decreasing trend over quintiles for CRC and colon cancer was seen for never and former smokers, and an increasing trend in risk of rectal cancer was shown for current smokers. A similar pattern was shown when a single reference category was chosen and joint effects were determined for tertiles of fruit and vegetables in combination with categories of smoking status in relation to CRC risk (**Figure 1**; P for interaction < 0.01), colon cancer risk (P for interaction $= 0.02$), and rectal cancer risk (P for interaction < 0.01).

The association between total fruit and vegetable intake and the risk of CRC or any subtype of this cancer did not vary by alcohol. However, the association differed by consumption of red and processed meat for CRC (P for interaction $= 0.03$), colon cancer (P for interaction $= 0.05$), and especially proximal colon cancer (P for interaction $= 0.01$). In particular, an inverse association was apparent among individuals in the highest tertile of red and processed meat consumption, for which the HRs from the lowest tertile to the middle and highest tertiles of combined fruit and vegetable consumption in relation to CRC were 1.28 (95% CI: 1.07, 1.52), 1.14 (95% CI: 0.96, 1.35), and 0.97 (95% CI: 0.81, 1.17). The association also varied by BMI for CRC (P for interaction $= 0.01$) and especially rectal cancer (P for interaction < 0.01), in which an inverse association was also most apparent in the highest tertile of BMI.

Vegetables

There was no evidence of an inverse association between vegetable consumption and CRC, colon cancer, or rectal cancer risk in the categorical, observed continuous, or calibrated continuous analysis (**Table 4**).

In a comparison of the highest with the lowest quintile, no difference was observed between proximal colon cancer risk (HR: 0.86; 95% CI: 0.65, 1.14; P for trend $= 0.53$) and distal colon cancer risk (HR: 0.86; 95% CI: 0.66, 1.14; P for trend $= 0.24$). No clear distinction for CRC could be made between men (HR: 0.84; 95% CI: 0.67, 1.07; P for trend $= 0.21$) and women (HR: 0.97; 95% CI: 0.80, 1.18; P for trend $= 0.58$) separately (P for interaction $= 0.72$).

Effect modification by smoking for vegetables alone was similar, but was stronger than for fruit and vegetables combined and was statistically significant for risk of CRC (P for interaction < 0.01), colon cancer (P for interaction $= 0.03$), and rectal cancer (P for interaction < 0.01). When the subgroup of current smokers was further subdivided into mild smokers and heavy smokers on the basis of sex-specific medians of number of cigarettes per day (15 cigarettes for men and 10 for women), mild smokers showed a smaller risk of CRC than did heavy smokers in a comparison of the lowest tertile of vegetable consumption with the combined reference category of highest tertile of vegetable consumption in never smokers (HR: 1.21; 95% CI: 0.93, 1.58 and HR: 1.77; 95% CI: 1.37, 2.29, respectively). Similarly, when the subgroup of former smokers was further subdivided into long-term quitters (>5 y) and recent quitters (<5 y), the direction of the effect estimates for CRC, although not statistically significant, was as one would expect in a comparison of the lowest tertile of vegetable consumption with the combined reference category of highest tertile of vegetable consumption in never smokers: long-term quitters (HR: 1.14; 95% CI: 0.96, 1.35) and recent quitters (HR: 1.33; 95% CI: 0.97, 1.82). These findings were similar for colon and rectal cancer (data not shown).

Tertiles of red and processed meat or alcohol did not modify the association between vegetable consumption and the risk of

TABLE 2
Observed range of fruit and vegetable intakes and distribution of selected characteristics by European Prospective Investigation into Cancer and Nutrition–wide quintile (Q) of fruit and vegetable consumption combined and by sex

Characteristics[1]	Q1	Q2	Q3	Q4	Q5
Fruit and vegetables (g/d)[2–4]	<221.1	221.1–326.2	326.2–441.6	441.6–603.6	>603.6
Vegetables (g/d)[2,4,5]	<95.1	95.1–141.0	141.0–197.5	197.5–284.4	>284.4
Fruit (g/d)[2,6]	<92.8	92.8–156.0	156.0–235.3	235.3–342.7	>342.7
Men					
No. of subjects	39,691	29,620	23,987	19,787	18,900
Age (y)	51.2 ± 9.9	52.4 ± 9.9	52.8 ± 9.9	52.7 ± 10.0	52.1 ± 9.8
Height (cm)	175.9 ± 6.9	175.8 ± 7.1	175.2 ± 7.2	174.3 ± 7.4	172.9 ± 7.3
Weight (kg)	81.1 ± 12.2	81.2 ± 12.0	80.6 ± 11.8	80.4 ± 11.7	80.6 ± 11.9
BMI (kg/m^2)	26.2 ± 3.6	26.3 ± 3.6	26.3 ± 3.5	26.5 ± 3.6	27.0 ± 3.8
Energy from fat (kcal)	800.1 ± 282.6	847.3 ± 283.4	862.6 ± 289.8	879.0 ± 297.8	927.1 ± 326.7
Energy from nonfat (kcal)	1418.0 ± 406.2	1545.0 ± 399.9	1606.3 ± 409.1	1676.6 ± 432.4	1793.9 ± 467.1
Alcohol (g/d)	21.7 ± 25.7	21.6 ± 23.1	20.7 ± 22.1	20.8 ± 22.5	20.6 ± 23.4
Red and processed meat (g/d)	107.3 ± 59.0	110.2 ± 62.1	104.0 ± 63.2	97.5 ± 64.7	91.2 ± 66.0
Fish (g/d)	27.0 ± 26.5	33.6 ± 29.3	38.9 ± 33.9	43.8 ± 37.5	54.4 ± 47.3
Total fiber (g/d)	18.5 ± 6.23	22.4 ± 6.4	24.9 ± 6.8	28.0 ± 7.6	35.2 ± 10.6
Cereal fiber (g/d)	10.4 ± 5.5	11.1 ± 5.6	11.3 ± 6.0	11.5 ± 6.6	11.5 ± 7.6
Never smokers (%)	31.9	33.5	34.4	35.5	36.7
Former smokers (%)	32.3	37.7	39.5	40.6	39.9
Current smokers (%)	35.8	28.9	26.1	24.0	23.4
Physically active (%)[7]	47.9	49.5	50.2	51.3	54.0
Women					
No. of subjects	50,860	60,931	66,564	70,764	71,651
Age (y)	49.2 ± 9.4	50.2 ± 9.6	50.9 ± 9.7	51.3 ± 9.5	51.3 ± 9.8
Height (cm)	163.6 ± 6.5	163.4 ± 6.5	162.7 ± 6.6	162.1 ± 6.5	161.5 ± 6.5
Weight (kg)	66.3 ± 12.0	66.0 ± 11.7	65.4 ± 11.5	64.9 ± 11.4	65.0 ± 11.4
BMI (kg/m^2)	24.8 ± 4.4	24.8 ± 4.3	24.7 ± 4.2	24.7 ± 4.3	24.9 ± 4.4
Energy from fat (kcal)	604.0 ± 207.9	649.8 ± 214.4	680.2 ± 222.9	715.2 ± 236.7	767.8 ± 267.6
Energy from nonfat (kcal)	1044.4 ± 292.1	1158.7 ± 298.9	1240.7 ± 317.7	1315.3 ± 334.8	1437.5 ± 375.4
Alcohol (g/d)	8.1 ± 12.8	8.5 ± 12.1	8.6 ± 11.9	8.5 ± 11.5	7.8 ± 11.2
Red and processed meat (g/d)	67.9 ± 39.2	69.6 ± 40.3	68.7 ± 42.4	67.2 ± 44.1	64.1 ± 47.7
Fish (g/d)	33.5 ± 36.6	36.5 ± 38.2	37.7 ± 37.2	39.2 ± 35.1	43.6 ± 37.4
Total fiber (g/d)	15.5 ± 4.9	18.7 ± 4.9	21.2 ± 5.2	24.1 ± 5.7	30.7 ± 8.0
Cereal fiber (g/d)	8.1 ± 4.1	8.4 ± 4.2	8.4 ± 4.4	8.3 ± 4.6	8.4 ± 5.0
Never smokers (%)	43.6	51.0	56.5	60.9	64.0
Former smokers (%)	22.0	24.8	24.7	24.0	23.7
Current smokers (%)	34.4	24.2	18.8	15.1	12.3
Physically active (%)[7]	43.4	44.5	44.3	44.2	47.1

[1] A linear trend for characteristics across quintiles was tested by linear regression (continuous variables) or by the Cochrane-Armitage trend test (categorical variables; never smokers compared with former and current smokers). P for trend < 0.01 for all characteristics.
[2] The ranges are based on the food-frequency questionnaires.
[3] Calibrated interquintile range: 261.0–494.2 g/d.
[4] The following information was incomplete or absent in the following centers: leafy vegetables, mushrooms, onion and garlic, and soups in Norway; cabbages, mushrooms, and onion and garlic in Umeå; onion and garlic in France; soups in Denmark; and nuts and soups in Naples.
[5] Calibrated interquintile range: 121.7–209.0 g/d.
[6] Calibrated interquintile range: 130.4–295.2 g/d.
[7] After the exclusion of missing values: housework in Italy, home repair and stair climbing in Malmö, and all leisure variables in Umeå and Norway.

CRC or any subtype of this cancer, whereas BMI did modify the association just as was seen for fruit and vegetables combined, and which was statistically significant for CRC (P for interaction = 0.03) and rectal cancer (P for interaction = 0.05).

Fruit

No association between fruit consumption and CRC, colon cancer, or rectal cancer was observed in the categorical, observed continuous, or calibrated continuous analysis (**Table 5**). In a comparison of the highest with the lowest quintile, no substantial difference was observed between proximal colon cancer (HR: 0.81; 95% CI: 0.62, 1.05; P for trend = 0.19) and distal colon cancer (HR: 0.84; 95% CI: 0.64, 1.09; P for trend = 0.08). The results for CRC were similar for men (HR: 0.89; 95% CI: 0.72, 1.12; P for trend = 0.56) and for women (HR: 0.87; 95% CI: 0.72, 1.04; P for trend = 0.18) separately (P for interaction = 0.68).

No associations were observed in the different subgroups of smoking status. No effect modification by smoking status, alcohol, or BMI was shown, but, just as for fruit and vegetables combined, red and processed meat did modify the association with fruit, which

TABLE 3
Risk of colorectal cancer by European Prospective Investigation into Cancer and Nutrition (EPIC)–wide quintile (Q) of fruit and vegetable consumption combined and by site and smoking status

	EPIC-wide quintiles of consumption (g/d)						For every 100-g increase			
Dietary variable	Q1	Q2	Q3	Q4	Q5	*P* for trend (median)	Observed	*P*	Calibrated	*P*
Colorectal cancer										
Total no. of cases	574	581	575	575	514		2,819		2,819	
Person-years	761,221	764,509	790,797	818,639	843,038		3,978,204		3,978,204	
Crude HR[1]	1.00	0.97 (0.86,1.09)	0.93 (0.82,1.05)	0.93 (0.82,1.06)	0.85 (0.74,0.97)	0.02	0.98 (0.96,1.00)	0.02	0.96 (0.92,0.99)	0.02
Adjusted HR[2]	1.00	0.98 (0.87,1.11)	0.95 (0.83,1.07)	0.94 (0.82,1.07)	0.86 (0.75,1.00)	0.04	0.98 (0.97,1.00)	0.09	0.97 (0.93,1.01)	0.11
Never smokers[2]	1.00	0.91 (0.75,1.11)	0.88 (0.72,1.08)	0.85 (0.69,1.05)	0.80 (0.64,1.01)	0.07	0.98 (0.95,1.01)	0.16	0.96 (0.91,1.03)	0.27
Former smokers[2]	1.00	0.89 (0.73,1.09)	0.81 (0.66,1.00)	0.79 (0.63,0.99)	0.75 (0.59,0.97)	0.03	0.97 (0.94,1.00)	0.08	0.95 (0.89,1.02)	0.16
Current smokers[2]	1.00	1.20 (0.95,1.50)	1.21 (0.94,1.56)	1.33 (1.01,1.74)	1.11 (0.81,1.53)	0.37	1.01 (0.97,1.06)	0.51	0.99(0.91,1.07)	0.75
Colon cancer										
Total no. of cases	1828	358	374	376	350		1,828		1,828	
Crude HR[1]	1.00	0.89 (0.76,1.03)	0.86 (0.74,1.00)	0.84 (0.72,0.99)	0.78 (0.66,0.92)	<0.01	0.97 (0.95,1.00)	0.02	0.95 (0.90,0.99)	0.02
Adjusted HR[2]	1.00	0.89 (0.76,1.03)	0.85 (0.73,1.00)	0.82 (0.69,0.97)	0.76 (0.63,0.91)	<0.01	0.97 (0.95,1.00)	0.02	0.96 (0.91,1.01)	0.10
Never smokers[2]	1.00	0.84 (0.66,1.07)	0.79 (0.62,1.02)	0.73 (0.56,0.94)	0.75 (0.57,0.98)	0.07	0.98 (0.94,1.01)	0.22	0.98 (0.90,1.06)	0.56
Former smokers[2]	1.00	0.82 (0.63,1.05)	0.80 (0.62,1.04)	0.75 (0.57,1.00)	0.66 (0.48,0.90)	0.02	0.95 (0.91,1.00)	0.04	0.92 (0.84,1.00)	0.06
Current smokers[2]	1.00	1.03 (0.76,1.38)	0.93 (0.67,1.29)	1.10 (0.78,1.55)	0.84 (0.55,1.26)	0.53	0.99 (0.93,1.04)	0.63	0.96 (0.86,1.07)	0.50
Rectal cancer										
Total no. of cases	204	223	201	199	164		991		991	
Crude HR[1]	1.00	1.13 (0.93,1.37)	1.06 (0.86,1.30)	1.12 (0.90,1.38)	0.99 (0.78,1.24)	0.75	0.99 (0.96,1.02)	0.43	0.97 (0.91,1.03)	0.34
Adjusted HR[2]	1.00	1.17 (0.96,1.42)	1.13 (0.92,1.40)	1.20 (0.96,1.50)	1.09 (0.85,1.40)	0.67	1.00 (0.97,1.04)	0.81	0.99 (0.92,1.05)	0.67
Never smokers[2]	1.00	1.07 (0.76,1.52)	1.08 (0.76,1.55)	1.17 (0.81,1.68)	0.92 (0.61,1.38)	0.58	0.96 (0.93,1.03)	0.48	0.94 (0.84,1.05)	0.26
Former smokers[2]	1.00	1.04 (0.76,1.43)	0.81 (0.59,1.27)	0.86 (0.59,1.27)	0.99 (0.65,1.51)	0.77	1.00 (0.94,1.06)	0.98	1.01 (0.90,1.14)	0.86
Current smokers[2]	1.00	1.51 (1.05,2.19)	1.78 (1.20,2.63)	1.77 (1.14,2.75)	1.74 (1.05,2.90)	0.02	1.06 (0.99,1.13)	0.08	1.04 (0.91,1.18)	0.61

[1] Cox proportional hazard ratios (HRs) from a regression stratified by age at entry, sex, and center.

[2] Cox proportional HRs from a regression stratified by age at entry, sex, and center and adjusted for energy from fat (in quintiles or continuous if main variable was modeled as continuous), energy from nonfat (in quintiles or continuous if main variable was modeled as continuous), weight in tertiles, height in tertiles, physical activity, smoking status, alcohol consumption, red and processed meat consumption (continuous), fish consumption (continuous), and dietary fiber from cereal sources (continuous).

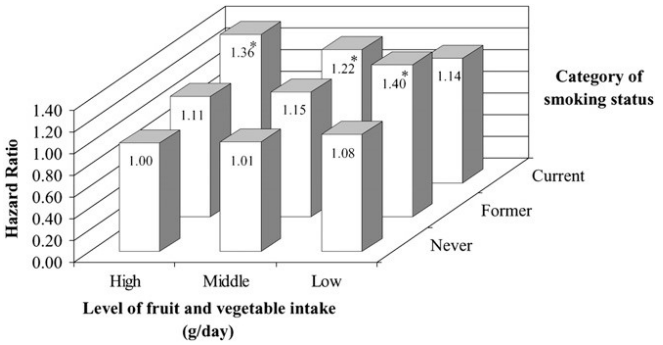

FIGURE 1. Relation of colorectal cancer risk with consumption of fruit and vegetables combined and smoking status. Bars represent the hazard ratios of the joint effect of tertiles of combined fruit and vegetable consumption with smoking status for men and women combined. Cox proportional hazard regression with interaction terms of tertiles of fruit and vegetable consumption with smoking status were used, stratified by age at entry, sex, and center and adjusted for energy from fat and energy from nonfat in quintiles, weight in tertiles, height in tertiles, physical activity, alcohol consumption, red and processed meat consumption, fish consumption, and dietary fiber from cereal sources. Intakes of fruit and vegetable combined (g/d) were <290.7 for the low tertile, 290.7–487.2 for the middle tertile, and >487.2 for the high tertile. $P < 0.01$ for interaction of tertiles of combined fruit and vegetable consumption with smoking status. *$P < 0.05$ for the hazard ratio of each separate bar compared with the reference bar (high fruit and vegetable consumption in never smokers).

was statistically significant for CRC (P for interaction < 0.01), colon cancer (P for interaction < 0.01), and proximal colon cancer (P for interaction < 0.01).

Adjustment for total fiber

When total fiber was included in the adjusted models instead of cereal fiber, the estimate for the relation between fruit and vegetables combined and CRC reached the null value, whereas the estimate for colon cancer was still below one in a comparison of the highest with the lowest quintile (HR: 0.90; 95% CI: 0.72, 1.12; P for trend $= 0.44$). Nevertheless, effect modification by smoking status, red and processed meat consumption, and BMI remained statistically significant.

Influence of preclinical disease

Exclusion of the first 2 y of follow-up did not materially change the results for most of the associations (data not shown). However, the observed and calibrated continuous analyses of fruit and vegetables combined became statistically significant in relation to CRC (HR: 0.95; 95% CI: 0.91, 1.00; $P = 0.04$) and colon cancer (HR: 0.94; 95% CI: 0.89, 0.99; $P = 0.02$). Furthermore, in a comparison of the highest with the lowest quintile, the exclusion of the first 2 y of follow-up did strengthen the risk gradients for the relation between vegetable consumption and CRC (HR: 0.83; 95% CI: 0.71, 0.98; P for trend $= 0.02$) and colon cancer (HR: 0.76; 95% CI: 0.62, 0.93; P for trend < 0.01). Effect modification by smoking status and red and processed meat consumption remained, whereas that for BMI disappeared.

DISCUSSION

Our results suggest that usual consumption of fruit and vegetables combined is weakly inversely associated with risk of CRC and, in particular, colon cancer. However, this effect was attenuated by adjustment for total fiber. The association between risk of CRC and fruit and vegetables combined and vegetables alone was modified by smoking.

The association between the consumption of fruit and vegetables combined and the risk of CRC disappeared with adjustment for total fiber instead of cereal fiber, whereas the risk estimate for colon cancer lost its statistical significance, but was still below one in a comparison of the highest with the lowest quintile (HR: 0.90; 95% CI: 0.72, 1.12; P for trend $= 0.44$). This 10% nonsignificant risk reduction may imply that dietary fiber explains the effect of fruit and vegetables, but we cannot exclude a role for other bioactive compounds in fruit and vegetables highly correlated with dietary fiber. For instance, fruit and vegetable fiber (21), but also fruit and vegetable subgroups high in β-carotene (22) or lycopene (22), have been suggested to be related to a lower risk of colon cancer. However, on the basis of questionnaire information alone, it is difficult to disentangle the relative importance of each constituent.

The consumption of vegetables alone did not show a statistically significant association with CRC risk. However, an inverse association was found when we excluded the first 2 y of follow-up. This may suggest that subjects who received a diagnosis of CRC within 2 y after recruitment might have changed their diet to offset prediagnostic abdominal complaints. Because this effect was not apparent for fruit consumption, it may indicate that especially the consumption of vegetables might have increased because of these prediagnostic complaints.

A weak inverse association of fruit and vegetable consumption was observed with colon, but not with rectal cancer, which has been shown in other studies (4, 23). Although colon and rectal cancers may have different etiologies (24, 25), the potential mechanisms accounting for these differences have not been unraveled yet. Proximal and distal colon cancers are also considered as 2 different categories of CRC, and their tumors have different molecular characteristics (26). Our results do not show a difference between these subsites, which suggests that a diet rich in fruit and vegetables may be involved in preventing the molecular changes leading to cancers arising in the distal and proximal colon.

The relation between fruit and vegetables and the risk of CRC differed according to smoking status, in which an inverse association for never and former smokers and a statistically nonsignificant positive association for current smokers was observed. This pattern was even more pronounced for vegetable consumption. The associations between vegetables and CRC risk were larger for heavy smokers and recent quitters than for mild smokers and long-term quitters. This pattern seems to be consistent with effect modification by smoking status, which thus suggests that smoking may negate the potential beneficial effect of vegetables on CRC risk. Confirmation in other studies, however, is warranted. A recent pooled analysis of cohort studies did not show effect modification by smoking status, categorized as never, former, and current smokers (9). The Nurses' Health Study and the Health Professionals Follow-Up Study in the United States, which are both included in the Pooling Project, did not observe differential effects by smoking status (27). The absence of effect modification in these latter 2 studies may in part be explained by grouping former and current smokers with potentially opposing trends in a single category of ever smokers.

TABLE 4
Risk of colorectal cancer by European Prospective Investigation into Cancer and Nutrition (EPIC)–wide quintile (Q) of vegetable consumption by site and smoking status

	EPIC-wide quintiles of consumption (g/d)						For every 100-g increase			
Dietary variable	Q1	Q2	Q3	Q4	Q5	*P* for trend (median)	Observed	*P*	Calibrated	*P*
Colorectal cancer										
Total no. of cases	607	561	584	561	506		2,819		2,819	
Person-years	779,076	763,003	778,423	809,438	848,264	3,978,204	3,978,204		3,978,204	
Crude HR[1]	1.00	0.95 (0.85,1.07)	0.98 (0.87,1.10)	0.96 (0.85,1.09)	0.89 (0.78,1.02)	0.13	0.98 (0.95,1.01)	0.25	0.95 (0.85,1.06)	0.35
Adjusted HR[2]	1.00	0.97 (0.86,1.09)	1.01 (0.89,1.14)	0.99 (0.87,1.13)	0.92 (0.79,1.06)	0.27	0.99 (0.95,1.03)	0.57	1.00 (0.91,1.10)	0.98
Never smokers[2]	1.00	0.96 (0.79,1.17)	1.01 (0.83,1.22)	0.94 (0.76,1.16)	0.88 (0.70,1.10)	0.20	0.97 (0.92,1.03)	0.37	1.01 (0.86,1.19)	0.89
Former smokers[2]	1.00	0.85 (0.70,1.04)	0.88 (0.71,1.08)	0.75 (0.60,0.94)	0.69 (0.53,0.89)	<0.01	0.94 (0.88,1.01)	0.09	0.85 (0.70,1.02)	0.09
Current smokers[2]	1.00	1.13 (0.88,1.44)	1.19 (0.92,1.53)	1.58 (1.22,2.06)	1.41 (1.03,1.93)	<0.01	1.08 (1.00,1.17)	0.05	1.17 (0.95,1.44)	0.13
Colon cancer										
Total no. of cases	390	361	375	367	335		1,828		1,828	
Crude HR[1]	1.00	0.93 (0.81,1.08)	0.95 (0.82,1.10)	0.93 (0.80,1.09)	0.85 (0.72,1.01)	0.09	0.97 (0.93,1.01)	0.16	0.93 (0.81,1.06)	0.27
Adjusted HR[2]	1.00	0.94 (0.81,1.09)	0.97 (0.83,1.12)	0.95 (0.81,1.12)	0.85 (0.71,1.02)	0.11	0.97 (0.93,1.02)	0.23	0.98 (0.86,1.12)	0.79
Never smokers[2]	1.00	0.89 (0.70,1.12)	0.91 (0.72,1.16)	0.88 (0.69,1.13)	0.83 (0.63,1.09)	0.24	0.97 (0.90,1.03)	0.32	1.00 (0.80,1.26)	0.97
Former smokers[2]	1.00	0.93 (0.72,1.20)	0.93 (0.72,1.21)	0.83 (0.63,1.11)	0.67 (0.49,0.93)	0.01	0.94 (0.86,1.02)	0.12	0.82 (0.65,1.03)	0.09
Current smokers[2]	1.00	1.04 (0.76,1.42)	1.11 (0.80,1.53)	1.63 (0.97,1.92)	1.27 (0.85,1.90)	0.12	1.05 (0.95,1.16)	0.37	1.15 (0.90,1.48)	0.26
Rectal cancer										
Total no. of cases	217	200	209	194	171		991		991	
Crude HR[1]	1.00	0.98 (0.81,1.20)	1.04 (0.85,1.27)	1.02 (0.83,1.26)	0.97 (0.77,1.22)	0.82	1.00 (0.94,1.06)	0.98	0.99 (0.83,1.18)	0.90
Adjusted HR[2]	1.00	1.02 (0.84,1.25)	1.08 (0.88,1.33)	1.06 (0.85,1.33)	1.04 (0.81,1.33)	0.80	1.02 (0.96,1.09)	0.51	1.04 (0.87,1.23)	0.69
Never smokers[2]	1.00	1.14 (0.81,1.60)	1.24 (0.88,1.74)	1.09 (0.75,1.57)	0.99 (0.67,1.48)	0.61	1.00 (0.90,1.10)	0.93	1.02 (0.77,1.35)	0.90
Former smokers[2]	1.00	0.75 (0.54,1.03)	0.79 (0.57,1.11)	0.61 (0.41,0.90)	0.74 (0.49,1.13)	0.17	0.96 (0.85,1.07)	0.44	0.89 (0.66,1.20)	0.45
Current smokers[2]	1.00	1.29 (0.87,1.92)	1.32 (0.87,2.00)	2.00 (1.32,3.04)	1.64 (0.99,2.73)	0.02	1.14 (1.01,1.29)	0.04	1.24 (0.88,1.76)	0.22

[1] Cox proportional hazard ratios (HRs) from a regression stratified by age at entry, sex, and center.

[2] Cox proportional HRs from a regression stratified by age at entry, sex, and center and adjusted for energy from fat (in quintiles or continuous if main variable was modeled as continuous), energy from nonfat (in quintiles or continuous if main variable was modeled as continuous), weight in tertiles, height in tertiles, physical activity, smoking status, alcohol consumption, red and processed meat consumption (continuous), fish consumption (continuous), dietary fiber from cereal sources (continuous), and consumption of fruit.

TABLE 5
Risk of colorectal cancer by European Prospective Investigation into Cancer and Nutrition (EPIC)–wide quintile (Q) of fruit consumption by site and smoking status

	EPIC-wide quintiles of consumption (g/d)						For every 100-g increase			
Dietary variable	Q1	Q2	Q3	Q4	Q5	*P* for trend (median)	Observed	*P*	Calibrated	*P*
Colorectal cancer										
Total no. of cases	588	551	548	581	551		2819		2819	
Person-years	765,557	773,766	793,915	819,641	825,325		3,978,204		3,978,204	
Crude HR[1]	1.00	0.90 (0.80,1.01)	0.86 (0.77,0.97)	0.90 (0.80,1.01)	0.84 (0.74,0.95)	0.02	0.97 (0.95,0.99)	0.02	0.95 (0.91,0.99)	0.03
Adjusted HR[2]	1.00	0.92 (0.82,1.04)	0.89 (0.78,1.01)	0.93 (0.81,1.05)	0.88 (0.76,1.01)	0.15	0.98 (0.96,1.01)	0.14	0.97 (0.92,1.02)	0.19
Never smokers[2]	1.00	0.92 (0.75,1.13)	0.93 (0.76,1.13)	0.92 (0.75,1.13)	0.90 (0.72,1.12)	0.47	0.98 (0.94,1.02)	0.37	0.95 (0.87,1.04)	0.28
Former smokers[2]	1.00	0.97 (0.79,1.18)	0.82 (0.66,1.02)	0.95 (0.77,1.19)	0.89 (0.70,1.13)	0.44	0.99 (0.94,1.03)	0.54	1.02 (0.93,1.11)	0.72
Current smokers[2]	1.00	0.87 (0.69,1.10)	0.89 (0.69,1.14)	0.93 (0.71,1.22)	0.83 (0.62,1.12)	0.32	0.98 (0.92,1.04)	0.43	0.93 (0.83,1.03)	0.16
Colon cancer										
Total no. of cases	359	364	343	389	373		1828		1828	
Crude HR[1]	1.00	0.94 (0.81,1.09)	0.83 (0.71,0.97)	0.89 (0.76,1.03)	0.82 (0.70,0.96)	0.02	0.97 (0.94,1.00)	0.03	0.94 (0.89,1.00)	0.04
Adjusted HR[2]	1.00	0.96 (0.82,1.11)	0.84 (0.72,0.99)	0.90 (0.77,1.06)	0.84 (0.71,1.00)	0.07	0.97 (0.94,1.01)	0.11	0.96 (0.90,1.02)	0.22
Never smokers[2]	1.00	1.01 (0.78,1.30)	0.96 (0.74,1.24)	0.98 (0.75,1.26)	0.94 (0.72,1.24)	0.60	0.99 (0.94,1.03)	0.54	0.98 (0.88,1.09)	0.66
Former smokers[2]	1.00	0.94 (0.73,1.20)	0.74 (0.57,0.97)	0.92 (0.70,1.20)	0.78 (0.58,1.06)	0.17	0.97 (0.91,1.03)	0.26	0.98 (0.88,1.10)	0.75
Current smokers[2]	1.00	0.91 (0.68,1.23)	0.76 (0.55,1.06)	0.77 (0.54,1.09)	0.75 (0.52,1.09)	0.11	0.95 (0.88,1.03)	0.22	0.90 (0.78,1.13)	0.13
Rectal cancer										
Total no. of cases	229	187	205	192	178		991		991	
Crude HR[1]	1.00	0.82 (0.68,1.00)	0.93 (0.77,1.13)	0.92 (0.75,1.12)	0.88 (0.71,1.09)	0.53	0.98 (0.94,1.02)	0.30	0.96 (0.89,1.04)	0.33
Adjusted HR[2]	1.00	0.87 (0.71,1.06)	0.98 (0.80,1.20)	0.97 (0.78,1.20)	0.96 (0.76,1.21)	0.92	0.99 (0.95,1.04)	0.80	0.98 (0.89,1.07)	0.60
Never smokers[2]	1.00	0.77 (0.55,1.09)	0.87 (0.62,1.21)	0.83 (0.58,1.17)	0.83 (0.57,1.20)	0.60	0.97 (0.91,1.05)	0.46	0.91 (0.78,1.05)	0.19
Former smokers[2]	1.00	1.02 (0.74,1.41)	0.99 (0.69,1.40)	1.04 (0.71,1.51)	1.15 (0.77,1.72)	0.49	1.03 (0.95,1.11)	0.54	1.08 (0.93,1.25)	0.30
Current smokers[2]	1.00	0.79 (0.54,1.16)	1.11 (0.76,1.62)	1.25 (0.83,1.89)	0.99 (0.61,1.59)	0.59	1.02 (0.93,1.11)	0.74	0.97 (0.82,1.16)	0.75

[1] Cox proportional hazard ratios (HRs) from a regression stratified by age at entry, sex, and center.

[2] Cox proportional HR from a regression stratified by age at entry, sex, and center and adjusted for energy from fat (in quintiles or continuous if main variable was modeled as continuous), energy from nonfat (in quintiles or continuous if main variable was modeled as continuous), weight in tertiles, height in tertiles, physical activity, smoking status, alcohol consumption, red and processed meat consumption (continuous), fish consumption (continuous), dietary fiber from cereal sources (continuous), and consumption of vegetables.

Because cigarette smoking was found to modify the effect of supplementation with 25 mg β-carotene on the risk of colorectal adenoma in the same manner (7), β-carotene may be a candidate compound underlying our observation. The mechanism behind the interplay between β-carotene and smoking in relation to CRC is not well understood. In vitro models have shown that β-carotene may serve as an antioxidant but also as a pro-oxidant, depending on the amount of β-carotene and on the redox potential of the biologic environment in which it acts (28). Furthermore, β-carotene may enhance DNA oxidative damage and modify p53-related pathways of cell proliferation and apoptosis in cultured cells when these cells are exposed to tobacco smoke condensate (29). However, it should be kept in mind that these in vitro studies are based on pharmacologic doses of β-carotene, which may result in different effects than physiologic doses. Furthermore, a recent pooled analysis of 11 cohort studies, in which dietary intake of β-carotene in relation to CRC risk was investigated, did not observe effect modification by smoking status (30). This may indicate that substances other than β-carotene within fruit and vegetables might also increase the carcinogenic potential of tobacco smoke, rather than reduce it. If the effect modification by smoking holds in future studies, however, this may explain the weak or absent associations with fruit and vegetables observed thus far in the epidemiology of CRC. Furthermore, it should further reinforce recommendations to quit smoking to enable fruit and vegetables to exert their full protective potential on CRC risk.

In the present study, the consumption of fruit and vegetables combined and of fruit alone showed an inverse association with CRC, colon cancer, and proximal colon cancer risk among individuals with elevated intakes of red and processed meat. Although this may have been a chance finding, a comparable interaction was observed in a nested case-control study within EPIC, in which the effect of plasma vitamin C was more apparent in subjects with medium and high intakes of red and processed meat in relation to gastric cancer risk (31). It is thought that vitamin C inhibits the formation of endogenous *N*-nitroso compounds (32), which is stimulated with a high consumption of red and processed meats (33). Nevertheless, the observed effect modification by meat does warrant further study. The same recommendation applies to the observed effect modification by BMI, which was present for CRC and rectal cancer in the overall analyses, but disappeared after the exclusion of the first 2 y of follow-up.

Among the strengths of the present study was its prospective design and the large number of CRC cases that developed after almost 10 y of follow-up. Moreover, EPIC is characterized by a large heterogeneity of exposure, with a 2–3-fold difference in observed mean consumption of fruit and of vegetables across participating centers (12). Moreover, confounder distributions substantially differ across Europe.

A limitation of our study was that the food-frequency questionnaire was only used during the baseline examination to obtain individuals' habitual intake consumption during the previous year and has not been repeated during follow-up. Although it is not expected that middle-aged participants, the majority of the EPIC study participants, change their dietary habits over the years, this single food-frequency questionnaire may not perfectly represent long-term intake.

Furthermore, although our dietary assessment methods are validated (14), they do contain measurement errors. The number and detail of questions about the consumption of specific foods was adapted to local habits, because dietary habits vary substantially between countries (34). To adjust for possible center-specific systematic misclassification in dietary measurements, a calibration approach was used (15). The calibration method assumes that the 24-h diet recall method measures aggregate consumption without bias and that the measurement errors of the 24-h recalls are independent of true consumption, and of that of the dietary questionnaire. In practice, however, there was evidence that the individual errors of dietary measurements obtained with dietary questionnaires and 24-h diet recalls tend to be positively correlated (35). Limitations of the EPIC calibration study have been addressed in detail (20). Briefly, in a very simple scenario, with one variable measured with errors, error correlation would lead to an underestimation of the deattenuation factor, thus determining a conservative correction of HR estimates toward the null value. In this study, a multivariate calibration model was used with a supposedly fairly complicated measurement error structure. Although error correlation between fruit and vegetable consumption and energy components are not likely to be sizeable, thus calling for stability of the linear calibration model, the calibrated HR estimates should be interpreted with caution (20).

It is possible that only specific types of fruit and vegetables or their related nutrients confer protection against CRC risk. There may be a protective effect of certain fruit or vegetable subgroups or anticarcinogenic food constituents that is diluted when food groups are considered as a whole. Future analyses of CRC risk in EPIC will, therefore, aim to examine the associations of risk with specific subgroups and nutrients.

In summary, our findings indicate that a higher consumption of fruit and vegetables may protect against the development of CRC, especially colon cancer. This association was stronger in never and former smokers, whereas current smokers showed, if any, a positive association. To investigate whether these opposed directions of associations may explain the weak or absent relations between fruit and vegetable consumption and CRC risk, future evaluations of potential effect modifiers in other studies should be carried out.

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