IJC
International Journal of Cancer

Subtypes of fruit and vegetables, variety in consumption and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition

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Key words: fruits and vegetables, colorectal cancer, variety

Abbreviations: AICR: American Institute for Cancer Research; BMI: body mass index; CI: confidence interval; CRC: colorectal cancer; DDS: diet diversity score; DQ: dietary questionnaire; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; SD: standard deviation; WCRF: World Cancer Research Fund

Additional Supporting Information may be found in the online version of this article.

Conflicts of interest: Nothing to report
Grant sponsors: European Commission (DG-SANCO) and the International Agency for Research on Cancer (Coordination of EPIC)
DOI: 10.1002/ijc.29640
History: Received 20 Feb 2015; Accepted 20 Apr 2015; Online 11 June 2015

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Previously, a lower risk of colorectal cancer was observed with fruit and vegetable consumption in the European Prospective Investigation into Cancer and Nutrition within a follow-up period of 9 years which was not fully supported by a recent meta-analysis. Therefore, we were interested in the relation with extended follow-up, also focusing on single subtypes and a variety of intake of fruit and vegetables. Fruit and vegetable consumption was assessed at baseline. After an average of 13 years of follow-up, 3,370 participants were diagnosed with colon or rectal cancer. Diet diversity scores were constructed to quantify variety in fruit and vegetable consumption. A lower risk of colon cancer was observed with higher self-reported consumption of fruit and vegetable combined (HR Q4 *vs*. Q1 0.87, 95% CI 0.75–1.01, *p* for trend 0.02), but no consistent association was observed for separate consumption of fruits and vegetables. No associations with risk of rectal cancer were observed. The few observed associations for some fruit and vegetable subtypes with colon cancer risk may have been due to chance. Variety in consumption of fruits and vegetables was not associated with a lower risk of colon or rectal cancer. Although a lower risk of colon cancer is suggested with high consumption of fruit and vegetables, this study does not support a clear inverse association between fruit and vegetable consumption and colon or rectal cancer beyond a follow-up of more than 10 years. Attenuation of the risk estimates from dietary changes over time cannot be excluded, but appears unlikely.

What's new?

Eating a healthy diet loaded with fruits and vegetables will help you stave off cancer – that's the conventional wisdom. But the relationship between diet and cancer is complex. This study probed the effects of fruits and vegetables on colorectal cancer risk. The authors combed through data from the European Prospective Investigation into Cancer and Nutrition (EPIC) and analyzed total fruit and vegetable consumption as well as individual subtypes. Contrary to earlier results, they found no correlation between fruit and vegetable intake and colorectal cancer risk over a period of more than ten years.

Fruit and vegetable consumption is thought to be associated with colorectal cancer (CRC). In their 2011 report, the Continuous Update Project of the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) concluded that there is limited evidence for a role of fruits and nonstarchy vegetables in decreasing the risk of CRC, despite a convincing level of evidence for a reduced risk from dietary fiber.[1] Previously, within the European Prospective Investigation into Cancer and Nutrition (EPIC), an earlier analysis with less follow-up reported that participants in the highest quintile of vegetable or fruit consumption showed a 8 and 12% lower risk of developing CRC when compared to participants in the lowest quintile.[2] This study was also included in the WCRF/AICR report.

Fruits and vegetables are sources of dietary fiber and, when consumed in variety, of various vitamins, minerals and phytochemicals, all of them having potential anticarcinogenic properties.[3] The health benefits from fruits and vegetables are thought to be derived from a combination of these components.[3,4] For this reason, studying the overall consumption of fruit and vegetable may not fully clarify the underlying mechanisms responsible for the reduction in cancer risk. Studying consumption of specific fruits and vegetables and the diversity therein may complement the research on the association between fruits and vegetables and risk of (colorectal) cancer.

A diet diversity score (DDS) is commonly used to measure the variety of diets, by calculating the number of different food items consumed within a given time period.[5] These scores have been studied within EPIC before their association with bladder,[6] gastric[7] and lung cancer,[8] where an inverse association was observed with lung cancer only. Previous studies observed lower,[9,10] unaltered[5] or higher risks[11] of

CRC with a higher diversity in total diet, although diversity in fruit or vegetable consumption was consistently associated with a lower risk of CRC[5,9,10] in case–control studies. In our prospective cohort study, we examined the hypothesis that the consumption of separate subtypes of fruits and vegetables and the variety in fruits and vegetables in the diet decreased risk of colon and rectal cancer.

Material and Methods

Study population

The EPIC cohort includes 521,448 participants from ten European countries (Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom).[12,13] Participants were recruited by 23 centers between 1992 and 2000 and are from the general population. Exceptions were the French cohort, which included women from a national health insurance plan covering school teachers and coworkers, the Ragusa and Turin (Italy) and Spanish cohorts, which included blood donors, the Florence (Italy) and Utrecht (the Netherlands) cohorts, which included women attending mammographic screening programs and the Oxford (UK) cohort, which included vegetarians and other health-conscious participants. The French, Utrecht and Norwegian cohorts included women only. Anthropometric measurements were measured or reported at baseline and participants were asked to complete dietary and lifestyle questionnaires. All participants gave their informed consent and the study was approved by the relevant ethics committees in participating countries and the Internal Review Board of the International Agency for Research on Cancer.

Exposure assessment

At baseline, the diet of participants reflecting the past 12 months was assessed by center-specific dietary questionnaires (DQ) designed to reflect local dietary patterns.[13,14] A DQ was combined with a 7-day record in the UK and Malmö (Sweden) cohorts. Information on validity of the DQ has been published previously.[15,16] Baseline information on lifestyle was obtained using lifestyle questionnaires with questions on smoking habits, alcohol consumption, physical activity, education and medical history. This study focuses on consumption of five subtypes of fruits (berries, citrus fruits, grapes, hard fruits, stone fruits) and eight vegetables (cabbages, fruiting vegetables, grain and pod vegetables, leafy vegetables, mushrooms, onion and garlic, root vegetables, stalk vegetables) (Supporting Information Table 1).[17] Fruit consumption included fresh, dried and canned fruits. Nuts, seeds and olives were excluded. The DQ differed in number of included vegetables and fruits between centers. Centers that did not ask about a specific subtype were excluded from the analysis.

For the analysis on variety in fruit and vegetable consumption, fruit and vegetable items were included if they were included in at least four country-specific DQ. This was done to improve the comparability of variety scores between the countries. Each fruit or vegetable item that was consumed at least once every 2 weeks was added into a DDS. Four DDS were calculated: one for all 49 fruit and vegetable items, one for all 16 fruit items, one for all 33 vegetable items and one for the eight subtypes of vegetables as given above (Supporting Information Table 1).[8] Correlations between absolute consumption and variety in related consumption was examined using Spearman's correlation analysis.

Outcome assessment

Incident cancer cases were identified through population cancer registries (Denmark, Italy except Naples, The Netherlands, Norway, Spain, Sweden and United Kingdom; complete follow-up for cancer incidence ranging from December 2004 to December 2008) or by active follow-up (France, Germany, Greece and Naples; complete follow-up ranging from December 2006 to June 2010), consisting of a combination of methods including health insurance records, cancer and pathology registries and active follow-up of study subjects and their next of kin.

Colon cancers were defined as malignant, primary adenocarcinomas of the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending and sigmoid colon (C18.0–C18.7 according to the tenth revision of the International Statistical Classification of Diseases and Related Health Problems) and overlapping or unspecified origin tumors (C18.8 and C18.9). Colon cancers were classified as proximal colon (C18.0–C18.5) or distal colon cancers (C18.6 and C18.7), thus providing the possibility to stratify analyses by subsite. Rectal cancers were defined as malignant, primary adenocarcinomas in the rectosigmoid junction (C19) or rectum (C20).

Statistical analysis

Hazard ratios (HR) with 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards models with age as underlying time variable. Gender, center and age at recruitment were used as stratification variables. Consumption of fruit and vegetable subtypes was modeled continuously using increments of subtype-specific standard deviations, including nonconsumers, and using EPIC-wide quartiles for consumers and an additional nonconsumers group. Tests for trend were performed using quartile medians modeled continuously in consumers only. Variety in consumption was modeled continuously (per two items consumed every 2 weeks) and using EPIC-wide quartiles of the DDS.

Cox regression analyses were adjusted for height (cm) and weight (kg), dietary calcium intake (g/day), alcohol consumption (g/day), cereal fiber intake (g/day), physical activity according to the Cambridge Physical Activity Index[18] and smoking status (never, former and current smokers). In addition, lifetime tobacco exposure, smoking duration (years) for both current and former smokers, time since stopped smoking (years) for former smokers and number of cigarettes per day for current smokers were added to the models as

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covariates. Participants with missing values for these variables (ranging between 0.5 and 1.9% of the total study population) were kept in the analysis through missing indicator variables. Variables for dietary intake of sugar, red meat, processed meat and dairy, the use of postmenopausal hormone therapy and the highest level of education were assessed for possible confounding bias and were not included, because additional adjustments did not appear to affect the risk estimates.

To determine whether the effect of (variety in) fruit and vegetable consumption was additional (*i.e.*, consumed in addition to other food items) or substitutional (*i.e.*, consumed instead of other food items), we estimated models for fruit and vegetable subtypes both with and without energy adjustment and using the nutrient residual method (only for models of subtypes of fruits and vegetables).[19] In addition, models for variety in consumption were estimated with and without adjustment for consumption of absolute consumption of fruits and vegetables. Models for absolute consumption of fruits or vegetables were estimated with and without adjustment for all other fruit and vegetable consumption. To rule out reverse causation, sensitivity analyses were performed by excluding participants with less than 2 or 5 years of follow-up.

Effect modification of associations by gender, smoking status, BMI, alcohol consumption and meat consumption was examined for overall fruit and vegetable consumption and the various DDS. Participants were cross-classified according to quartiles of consumption or DDS and categories of gender, smoking status (never, former and current smokers), BMI (<25, 25–30 and >30 kg/m^2), alcohol consumption [low (<3 g/day for women, <6 g/day for men), moderately low (3–<12 g/day for women, 6–<24 g/day for men), moderately high (12–30 g/day for women, 24–60 g/day for men) and high consumption (>30 g/day for women, >60 g/day for men)] or meat consumption (tertiles: <48 g/day, 48–88 g/day, >88 g/day). Models with and without a multiplicative interaction term were compared using a likelihood ratio test to determine deviation from multiplicative interaction. Heterogeneity in the association between countries was assessed using a meta-analytical approach, pooling center-specific estimates of continuous risk estimates.

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Results

After exclusion of participants without information on diet, lifestyle or cancer ($n = 40{,}880$), participants in the lowest or highest 1% of the distribution of the ratio of reported energy intake to required energy ($n = 9{,}880$), participants with an unknown cancer morphology ($n = 104$), participants in the highest or lowest 0.5% of the distribution of BMI ($n = 990$) and participants without information on the frequency of diet intake ($n = 26{,}542$, including the entire Malmö cohort), 442,961 participants were included in this study, including 2,128 colon cancer (of which 954 proximal and 965 distal) and 1,242 rectal cancer cases (Supporting Information Table 2). Colon and rectal cancer was cytologically or histologically confirmed in 87 and 88% of the cases, respectively.

Median consumption of fruit and vegetable was 397 g/day and median number of different fruit and vegetable items consumed every 2 weeks was eight (data not shown). A higher variety in consumption of fruit and vegetable was accompanied with a higher absolute consumption of fruits and vegetables, a higher proportion of women and never smokers, a higher consumption of red meat and lower consumption of processed meat (Table 1). The correlation between absolute consumption of fruit and vegetable was 0.40. Correlations between absolute consumption and related variety were 0.49 for fruit and 0.60 for vegetables (data not shown).

A lower risk of colon cancer was observed with higher consumption of fruit and vegetables combined (p for trend 0.02), but there was no association for rectal cancer. Neither fruit nor vegetable consumption alone was associated with a lower risk of colon or rectal cancer (Tables 2 and 3, Supporting Information Table 3). When cross-classified with categories of smoking, an increased risk of rectal cancer was suggested with higher fruit consumption in current smokers (p for interaction 0.03, Supporting Information Table 4). No differences in associations between categories of gender, BMI, alcohol consumption or meat consumption were observed (data not shown).

When analyzed by subtypes of fruits or vegetables, a lower risk of colon cancer was observed for high cabbage consumption and a higher risk was observed for high mushroom consumption (Table 2). Both associations were only apparent when consumption was analyzed as continuous variable. For every 36.7 g/day higher cabbage consumption, the risk of colon cancer was 7% lower (95% CI 1–12%). Similar associations (albeit not statistically significant) were seen for proximal colon cancer (Supporting Information Table 5). The risk of colon cancer was 5% higher (95% CI 0–10%) with every 8.8 g/day higher mushroom consumption. This association was also seen in distal colon cancer. Also, a 7% (95% CI 0–14%) higher risk of distal colon cancer was observed for every 12.9 g/day increase in consumption of stalk vegetables (only when analyzed continuously). A J-shaped association was seen for the risk of proximal colon cancer with consumption of grapes. Nonconsumers had a 35% higher risk of proximal colon cancer (95% CI 3–77%) when compared to the first quartile of consumers, whereas a trend for higher risk of proximal colon cancer was observed over all quartiles of grape consumption (p for trend 0.01) and a 6% higher risk (95% CI 0–12%) was seen for every 16.6 g/day higher consumption.

Excluding adjustment for consumption of other fruits and vegetables did not affect the observed HRs, neither did adjusting for total energy intake (absolute or using the nutrient residual method) or excluding participants with <2 or 5 years follow-up. However, excluding cases with a follow-up longer than 10 years (approximating the set of cases used in

Table 1. Baseline characteristics by quartiles of the diet diversity score for all fruit and vegetable items combined: The European Prospective Investigation into Cancer and Nutrition, 1992–2010

	Full cohort	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Number of participants	442,961	116,714	99,985	121,005	105257
Female (%)	70.7	58.8	71.3	77.2	75.5
Age at recruitment (years)	51.2 (38.3–63.0)	50.4 (37.4–61.5)	51.3 (38.3–62.7)	51.6 (39.1–63.6)	51.6 (38.4-64.4)
Body mass index (kg/m^2)	24.8 (20.6–31.0)	24.9 (20.7–30.7)	24.6 (20.6–30.5)	24.6 (20.5–30.8)	25.2 (20.7-31.8)
Observed vegetable consumption (g/day)	177.2 (70.9–401.9)	92.7 (38.3–153.5)	155.1 (83.8–243.9)	222.4 (115.5–342.8)	351.1 (174.2-579.3)
Observed fruit consumption (g/day)	197.0 (52.5–461.7)	75.2 (19.4–137.1)	162.5 (80.0–249.2)	254.5 (141.4–372.5)	415.4 (242.7-689.7)
Observed red meat consumption (g/day)	35.0 (3.7–91.2)	30.5 (7.2–90.8)	35.1 (4.8–92.2)	36.8 (2.9–90.6)	38.0 (1.4-90.9)
Observed processed meat consumption (g/day)	23.6 (1.9–66.5)	32.8 (8.5–79.8)	26.5 (4.2–69.1)	21.1 (1.7–60.1)	14.2 (0.1–53.1)
Observed cereal fiber consumption (g/day)	7.8 (3.4–15.3)	8.4 (3.6–15.6)	8.2 (3.6–15.7)	7.5 (3.4–15.2)	7.0 (3.1–14.6)
Alcohol status					
Consumption (g/day)	5.6 (0.0–33.2)	6.1 (0.1–40.0)	6.1 (0.1–34.0)	5.6 (0.0–30.7)	4.4 (0.0–29.4)
Nonconsumers (%)	5.0	5.2	4.5	4.7	5.5
Smoking status					
Never smokers (%)	50.8	40.5	49.1	55.4	58.1
Former smokers (%)	26.7	26.8	28.1	26.7	25.1
Time since stopped smoking (years)	14.0 (2.5–29.0)	13.5 (2.0–28.0)	14.5 (2.5–29.0)	14.5 (3.0–29.5)	13.5 (2.5–29.0)
Smoking duration (years)	17.0 (4.0–34.0)	17.0 (4.0–34.0)	17.0 (4.0–33.0)	17.0 (4.0–33.0)	17.0 (5.0–34.0)
Current smokers (%)	22.5	32.7	22.8	17.9	16.8
Smoking duration (years)	30.5 (17.0–42.5)	31.5 (18.5–43.0)	31.0 (17.5–43.0)	30.0 (16.5–42.5)	27.5 (14.0–41.5)
Cigarettes/day (no.)	14.0 (3.0–25.0)	15.0 (5.0–25.0)	12.0 (3.0–23.0)	11.0 (2.5–25.0)	12.0 (2.5–30.0)
Highest education level					
None/primary school (%)	29.4	29.1	25.9	28.1	34.7
Technical/professional school (%)	22.3	30.4	25.5	19.2	13.9
Secondary school (%)	21.0	17.7	20.7	23.3	22.3
University (%)	23.9	21.1	24.8	25.2	24.5
Unknown/missing (%)	3.4	1.7	3.1	4.2	4.7
Physical activity					
Inactive (%)	20.6	17.0	17.7	21.7	25.9
Moderately inactive (%)	31.2	29.1	30.8	32.5	32.2
Moderately active (%)	22.3	20.8	21.9	23.0	23.7
Active (%)	17.3	17.7	18.2	16.9	16.2
Unkown/missing (%)	8.7	15.4	11.4	5.9	2.0

Values are given as median (10th–90th percentile) or percentage, where applicable.

Table 2. Hazard ratios for the consumption of vegetable and fruit subtypes with risk of colon cancer, according to quartiles and continuously modeled consumption (per SD): The European Prospective Investigation into Cancer and Nutrition, 1992–2010

	Nonconsumers	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend	Continuous (per SD)
Vegetables (total)	–	1.00 (ref.)	1.01 (0.90–1.13)	1.05 (0.93–1.18)	0.90 (0.78–1.05)	0.17	0.97 (0.91–1.03)
Cabbages	1.08 (0.89–1.31)	1.00 (ref.)	1.19 (1.05–1.36)	1.18 (1.03–1.36)	0.98 (0.83–1.17)	0.24	0.93 (0.88–0.99)
Fruiting vegetables	1.25 (0.75–2.08)	1.00 (ref.)	1.10 (0.98–1.23)	0.98 (0.86–1.12)	1.09 (0.94–1.27)	0.49	1.06 (0.99–1.14)
Grain and pod vegetables[1]	0.99 (0.84–1.18)	1.00 (ref.)	1.02 (0.91–1.16)	1.05 (0.91–1.20)	1.03 (0.88–1.22)	0.76	1.00 (0.95–1.06)
Leafy vegetables[2]	1.08 (0.88–1.33)	1.00 (ref.)	1.03 (0.90–1.19)	0.97 (0.82–1.16)	0.94 (0.76–1.16)	0.39	0.99 (0.92–1.06)
Mushrooms	0.97 (0.82–1.15)	1.00 (ref.)	1.11 (0.98–1.26)	1.10 (0.95–1.27)	1.13 (0.96–1.33)	0.35	1.05 (1.00–1.10)
Onion and garlic	0.95 (0.72–1.25)	1.00 (ref.)	1.00 (0.88–1.14)	1.03 (0.90–1.18)	1.01 (0.85–1.18)	0.95	0.99 (0.94–1.05)
Root vegetables	1.01 (0.81–1.26)	1.00 (ref.)	1.05 (0.94–1.19)	1.03 (0.90–1.17)	0.99 (0.86–1.15)	0.63	1.01 (0.96–1.05)
Stalk vegetables[1]	0.94 (0.76–1.17)	1.00 (ref.)	0.96 (0.85–1.09)	1.01 (0.89–1.15)	1.04 (0.90–1.20)	0.37	1.03 (0.98–1.08)
Fruits (total)	–	1.00 (ref.)	1.03 (0.92–1.16)	0.96 (0.85–1.09)	0.98 (0.86–1.13)	0.61	0.99 (0.94–1.04)
Berries[2,3]	0.99 (0.80–1.23)	1.00 (ref.)	1.02 (0.88–1.18)	1.09 (0.93–1.27)	1.04 (0.88-1.24)	0.70	1.01 (0.96–1.06)
Citrus fruits	1.10 (0.93–1.31)	1.00 (ref.)	1.03 (0.91–1.17)	0.96 (0.85–1.10)	1.02 (0.88–1.17)	0.94	1.01 (0.96–1.06)
Grapes[1,4]	1.12 (0.93–1.35)	1.00 (ref.)	0.98 (0.83–1.15)	1.13 (0.96–1.34)	1.15 (0.97–1.37)	0.06	1.03 (0.98–1.07)
Hard fruits	0.96 (0.78–1.18)	1.00 (ref.)	0.92 (0.80–1.05)	0.94 (0.82–1.07)	1.01 (0.88–1.16)	0.43	1.02 (0.98–1.06)
Stone fruits[1,2]	1.15 (0.97–1.37)	1.00 (ref.)	1.01 (0.88–1.15)	1.06 (0.91–1.24)	0.97 (0.81–1.15)	0.57	0.99 (0.94–1.05)
Fruits and vegetables combined	–	1.00 (ref.)	1.07 (0.95–1.20)	0.96 (0.84–1.09)	0.87 (0.75–1.01)	0.02	0.97 (0.92–1.02)

Analyses were adjusted for all other fruit and vegetable consumption, height, weight, dietary calcium consumption, dietary alcohol consumption, dietary cereal fiber consumption, smoking status, time since stopped smoking, duration of smoking, number of cigarettes smoked per day and physical activity. Medians of consumption per quartiles were: vegetables (79, 142, 221, 373 g/day), cabbages (3, 13, 26, 62 g/day), fruiting vegetables (14, 37, 65, 133 g/day), grain and pod vegetables (1, 4, 10, 25 g/day), leafy vegetables (2, 10, 28, 77 g/day), mushrooms (0.5, 2, 6, 19 g/day), onion and garlic (2, 5, 12, 31 g/day), root vegetables (4, 13, 29, 61 g/day), stalk vegetables (2, 5, 10, 22 g/day), fruits (64, 149, 250, 427 g/day), berries (1, 4, 8, 21 g/day), citrus fruits (7, 21, 49, 110 g/day), grapes (1, 5, 13, 32 g/day), hard fruits (10, 36, 73, 153 g/day), stone fruits (2, 10, 30, 83 g/day) and fruits and vegetables combined (181, 323, 480, 750 g/day). Standard deviations of consumption were: vegetables (146 g/day), cabbages (37 g/day), fruiting vegetables (77 g/day), grain and pod vegetables (14 g/day), leafy vegetables (40 g/day), mushrooms (9 g/day), onion and garlic (14 g/day), root vegetables (31 g/day), stalk vegetables (13 g/day), fruits (184 g/day), berries (11 g/day), citrus fruits (65 g/day), grapes (17 g/day), hard fruits (85 g/day), stone fruits (43 g/day) and fruits and vegetables combined (273 g/day). Results for colorectal cancer (*i.e.*, colon and rectal cancer combined) are given in Supporting Information Table 6.

[1]The Umeå cohort was excluded, because no information on this consumption was available.

[2]The Norway cohort was excluded, because no information on this consumption was available.

[3]The United Kingdom cohorts were excluded, because no information on this consumption was available.

[4]The Danish cohorts were excluded, because no information on this consumption was available.

Table 3. Hazard ratios for the consumption of vegetable and fruit subtypes with risk of rectal cancer, according to quartiles and continuously modeled consumption (per SD): The European Prospective Investigation into Cancer and Nutrition, 1992–2010

	Nonconsumers	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend	Continuous (per SD)
Vegetables, total	–	1.00 (ref.)	1.10 (0.94–1.28)	1.12 (0.95–1.33)	1.08 (0.88–1.31)	0.57	1.03 (0.95–1.11)
Cabbages	1.19 (0.90–1.57)	1.00 (ref.)	1.14 (0.97–1.35)	1.22 (1.02–1.47)	1.24 (0.99–1.54)	0.12	1.01 (0.94–1.08)
Fruiting vegetables	1.54 (0.78–3.02)	1.00 (ref.)	1.02 (0.88–1.18)	1.03 (0.87–1.22)	1.11 (0.91–1.37)	0.30	1.07 (0.97–1.18)
Grain and pod vegetables[1]	1.04 (0.82–1.33)	1.00 (ref.)	1.09 (0.92–1.28)	1.25 (1.05–1.49)	1.17 (0.94–1.46)	0.20	1.05 (0.98–1.12)
Leafy vegetables[2]	0.94 (0.72–1.22)	1.00 (ref.)	0.92 (0.76–1.11)	0.95 (0.75–1.20)	0.89 (0.67–1.19)	0.56	0.97 (0.89–1.07)
Mushrooms	1.17 (0.92–1.49)	1.00 (ref.)	1.08 (0.90–1.29)	1.05 (0.86–1.27)	1.01 (0.81–1.26)	0.70	0.97 (0.90–1.04)
Onion and garlic	1.34 (0.92–1.94)	1.00 (ref.)	1.11 (0.93–1.32)	1.21 (1.00–1.47)	1.16 (0.92–1.45)	0.62	0.98 (0.91–1.05)
Root vegetables	1.13 (0.83–1.54)	1.00 (ref.)	1.04 (0.89–1.22)	1.12 (0.95–1.33)	1.03 (0.85–1.25)	0.88	0.99 (0.93–1.05)
Stalk vegetables[1]	1.14 (0.85–1.54)	1.00 (ref.)	1.00 (0.84–1.19)	1.19 (1.00–1.41)	1.15 (0.95–1.40)	0.09	1.04 (0.98–1.10)
Fruits, total	–	1.00 (ref.)	1.06 (0.91–1.23)	1.14 (0.97–1.34)	1.09 (0.91–1.31)	0.32	1.01 (0.95–1.08)
Berries[2,3]	0.80 (0.59–1.08)	1.00 (ref.)	1.00 (0.84–1.20)	1.04 (0.86–1.28)	1.04 (0.83–1.30)	0.73	0.99 (0.92–1.06)
Citrus fruits	0.93 (0.73–1.19)	1.00 (ref.)	1.18 (1.00–1.38)	1.19 (1.00–1.40)	1.15 (0.95–1.38)	0.36	1.02 (0.95–1.09)
Grapes[1,4]	1.00 (0.78–1.30)	1.00 (ref.)	0.92 (0.74–1.15)	1.17 (0.94–1.46)	0.98 (0.78–1.25)	0.85	1.00 (0.93–1.06)
Hard fruits	0.88 (0.65–1.19)	1.00 (ref.)	1.15 (0.97–1.36)	1.14 (0.96–1.36)	1.11 (0.92–1.34)	0.57	1.01 (0.96–1.07)
Stone fruits[1,2]	1.16 (0.93–1.45)	1.00 (ref.)	1.12 (0.95–1.32)	1.07 (0.88–1.31)	1.19 (0.94–1.50)	0.24	1.02 (0.94–1.11)
Fruits and vegetables combined	–	1.00 (ref.)	1.14 (0.99–1.33)	1.07 (0.90–1.27)	1.12 (0.92–1.35)	0.44	1.03 (0.96–1.11)

Analyses were adjusted for all other fruit and vegetable consumption, height, weight, dietary calcium consumption, dietary alcohol consumption, dietary cereal fiber consumption, smoking status, time since stopped smoking, duration of smoking, number of cigarettes smoked per day and physical activity. Medians per quartile and standard deviations are given in Table 2. Results for colorectal cancer (*i.e.*, colon and rectal cancer combined) are given in Supporting Information Table 6.
[1]The Umeå cohort was excluded, because no information on this consumption was available.
[2]The Norway cohort was excluded, because no information on this consumption was available.
[3]The United Kingdom cohorts were excluded, because no information on this consumption was available.
[4]The Danish cohorts were excluded, because no information on this consumption was available.

Table 4. Hazard ratios for the diet diversity scores with risk of colon and rectal cancer, according to quartiles and continuously modeled consumption: The European Prospective Investigation into Cancer and Nutrition, 1992–2010

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p* for trend	Continuous (per two items)
Colon cancer						
Variety in fruit and vegetable items	1.00 (ref.)	1.09 (0.96–1.23)	1.08 (0.94–1.24)	0.96 (0.79–1.16)	0.68	1.01 (0.97–1.04)
Variety in fruit items	1.00 (ref.)	0.97 (0.86–1.09)	0.99 (0.86–1.14)	0.87 (0.73–1.03)	0.10	1.04 (0.96–1.14)
Variety in vegetable items	1.00 (ref.)	1.09 (0.96–1.23)	1.08 (0.94–1.25)	1.07 (0.88–1.30)	0.49	1.00 (0.95–1.06)
Variety in vegetable groups	1.00 (ref.)	0.96 (0.85–1.09)	1.05 (0.91–1.22)	1.08 (0.92–1.28)	0.34	1.04 (0.87–1.24)
Rectal cancer						
Variety in fruit and vegetable items	1.00 (ref.)	1.24 (1.04–1.46)	1.24 (1.03–1.50)	1.26 (0.97–1.63)	0.09	1.01 (0.99–1.04)
Variety in fruit items	1.00 (ref.)	1.20 (1.02–1.40)	1.41 (1.16–1.70)	1.41 (1.11–1.78)	<0.01	1.08 (1.03–1.13)
Variety in vegetable items	1.00 (ref.)	1.05 (0.88–1.24)	1.08 (0.89–1.29)	0.88 (0.68–1.14)	0.62	0.99 (0.96–1.02)
Variety in vegetable groups	1.00 (ref.)	1.07 (0.90–1.27)	1.00 (0.82–1.22)	0.98 (0.78–1.22)	0.72	0.98 (0.89–1.07)

Analyses were adjusted for fruit and vegetable consumption, height, weight, dietary calcium consumption, dietary alcohol consumption, dietary cereal fiber consumption, smoking status, time since stopped smoking, duration of smoking, number of cigarettes smoked per day and physical activity. Diet diversity scores (DDS) include each fruit or vegetable item/group consumed at least once every 2 weeks.

the previous EPIC study) resulted in decreased risk estimates similar to those of Van Duijnhoven *et al.*[2] (data not shown). Adjustment for total fiber consumption attenuated the significant trend observed for combined consumption of fruit and vegetable (adjusted *p* for trend 0.09).

Variety in consumption of fruits and vegetables was not associated with the risk of developing colon cancer, but an increased risk of rectal cancer was observed with a high variety in consumption of fruit items. Participants consuming more than eight different fruit items every 2 weeks had a 41% higher risk (95% CI 11–78%) of developing rectal cancer than participants consuming less than three different fruit items. For every two additional fruit items per 2 weeks, an 8% higher risk (95% CI 3–13) was observed (Table 4). No associations were observed between any of the DDS and proximal or distal colon cancer (data not shown). Although some associations were statistically significantly modified by categories of smoking status, alcohol consumption and BMI, no clear differences in associations were observed (not shown). Lastly, no heterogeneity in associations between countries was observed, except for the association between variety in fruit and vegetable items and rectal cancer (*p* for heterogeneity 0.03, Supporting Information Fig. 1).

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Discussion

The results of this study do not support a clear inverse association between fruit and vegetable consumption and colon or rectal cancer, although a lower risk of colon cancer was suggested with high consumption of fruit and vegetables. When consumption was analyzed according to subtypes, an inverse association with colon cancer was suggested for cabbage consumption, while an increased risk was suggested for high mushroom consumption. Surprisingly, a higher variety of fruit items consumed was associated with a higher risk of rectal cancer.

The findings from this study confirm the conclusion by the Continuous Update Project of the WCRF and AICR that there is limited evidence for an inverse association between fruit and vegetable consumption and CRC[1] and are supported by the lack of association with colon and rectal cancer for plasma carotenoids and vitamins in the same population as the present investigation.[20] However, the results were remarkably less obvious when compared with the previous findings of an inverse association between (fruit and) vegetable consumption and colon cancer within the EPIC study.[2] The increase in number of cases (3,370 *vs.* 2,819) and longer follow-up (11.2 *vs.* 8.8 years) in our study in relation to the previous EPIC publication may explain this attenuation of the earlier effect estimates. Study populations were not identical as the previous EPIC study excluded subjects from Greece due to missing information on dietary cereal fiber, whereas our study excluded subjects from Malmö due to missing information on frequency of consumption. Additionally, analysis methods differed in groups of exposure (quartiles *vs.* quintiles) and in variables included as possible confounders. However, when performing the analysis using quintiles and similar covariables as were used by Van Duijnhoven *et al.* the results still did not approximate the reported risk estimates [HR for risk of colon cancer in highest quintile of combined fruit and vegetable consumption 0.87 (0.74–1.03) *versus* reported 0.76 (0.63–0.91), data not shown]. Excluding cases with a follow-up longer than 10 years—thereby approximating the set of cases used in the previous study—resulted however in similar risk estimates. Because the dietary measurement was performed only once, changes in fruit and vegetable consumption over time may have occurred, thereby possibly causing attenuation of the risk estimates. However, it appears unlikely that the observed attenuation is caused by a change in diet, as little changes in dietary patterns are seen in adulthood while aging.[21]

The observed decreased risk of colon cancer with increased consumption of cabbage (analyzed as continuous variable) may be explained by the anticancer effects attributed to glucosinolates.[22] However, most prospective cohort studies have until now not reported inverse associations between consumption of cruciferous vegetables and CRC.[22] The observed increased risks of colon cancer in the continuous analyses of consumption of mushrooms (overall and distal colon), stalk vegetables (distal colon) and grapes (proximal colon) did not match our hypotheses of inverse associations. Studies on the effects of mushroom consumption on cancer are scarce, but based on animal models a beneficial effect from mushrooms could be expected due to the presence of phytochemicals with antitumor and immune-modulating properties.[23] However, previous studies have reported higher risks of CRC[24] and rectal cancer (in women)[25] with high mushroom consumption. Grapes are thought to reduce the risk of CRC through the presence of resveratrol and proanthocyanidin, which have antiproliferative effects *in vitro*,[26,27] but again increased risks have been observed in a previous cohort study.[28] Stalk vegetables are notably rich in dietary fiber, an established protective factor for CRC.[1] We have no clear explanations for the observed increased risk of (distal) colon cancer, although a chance finding cannot be excluded. It should be noted that because of the many analyses performed in this study, the chance of observing false associations has been increased. This could explain these unexpected associations. Similarly, the observed increased risk of colon and rectal cancer associated with consumption of a high variety of fruit and vegetables was surprising, considering our hypothesis of an inverse association. Considering the inverse associations previously observed in other studies,[5,9,10] a chance finding may be a likely explanation.

A limitation of this study was the way that diet and diversity of consumption was measured. First, consumption of fruits and vegetables was measured using a single questionnaire at study enrolment. Validation studies in the EPIC cohort measured correlations of questionnaire data with data from single 24-hr recalls. For fruits and vegetables, these correlations were 0.45 and 0.56, respectively, when averaged over subgroups by country and gender.[16] Measurement errors in exposure may attenuate risk estimates[29] and may have resulted in false-negative results in our study. It is possible that measurement errors in the quantity of consumption of fruits and vegetables also caused false-negative results in the analyses regarding diet diversity. Second, the dietary questionnaires differed between EPIC centers. Although the Cox regression was performed stratified by center, therefore preventing the occurrence of direct comparisons between participants from different centers, bias may have been introduced by limiting the analysis to food items that were included in at least four questionnaires. This made the DDS better comparable between centers, but may have caused underestimation of diet diversity of participants consuming more rare food items. It should be noted that no heterogeneity in associations was observed between countries.

In conclusion, our findings do not support a clear inverse association between fruit and vegetable consumption and the risk of colon or rectal cancer. Additionally, a high variety in consumption of fruits and vegetables does not appear to be associated with a lower risk of colon or rectal cancer.

Acknowledgements

The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); Ministry of Health and Social Solidarity, Stavros Niarchos Foundation and Hellenic Health Foundation (Greece); Italian Association for Research on Cancer (AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch Zorg Onderzoek Nederland (ZON), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); ERC-2009-AdG 232997 and Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway); Health Research Fund (FIS), Regional Governments of Andalucía, Asturias, Basque Country, Murcia (N° 6236) and Navarra, Instituto de Salud Carlos III - Red Temática de Investigació Cooperativa en Cancer (RD06/0020/0091) (Spain); Cancer Research UK, Medical Research Council, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency and Wellcome Trust (United Kingdom).

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