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ARTICLE

Fruit and Vegetable Intake and Overall Cancer Risk in the European Prospective Investigation Into Cancer and Nutrition (EPIC)

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Background It is widely believed that cancer can be prevented by high intake of fruits and vegetables. However, inconsistent results from many studies have not been able to conclusively establish an inverse association between fruit and vegetable intake and overall cancer risk.

Methods We conducted a prospective analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to assess relationships between intake of total fruits, total vegetables, and total fruits and vegetables combined and cancer risk during 1992–2000. Detailed information on the dietary habit and lifestyle variables of the cohort was obtained. Cancer incidence and mortality data were ascertained, and hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox regression models. Analyses were also conducted for cancers associated with tobacco and alcohol after stratification for tobacco smoking and alcohol drinking.

Results Of the initial 142 605 men and 335 873 women included in the study, 9604 men and 21 000 women were identified with cancer after a median follow-up of 8.7 years. The crude cancer incidence rates were 7.9 per 1000 person-years in men and 7.1 per 1000 person-years in women. Associations between reduced cancer risk and increased intake of total fruits and vegetables combined and total vegetables for the entire cohort were similar (200 g/d increased intake of fruits and vegetables combined, HR = 0.97, 95% CI = 0.96 to 0.99; 100 g/d increased intake of total vegetables, HR = 0.98, 95% CI = 0.97 to 0.99); intake of fruits showed a weaker inverse association (100 g/d increased intake of total fruits, HR = 0.99, 95% CI = 0.98 to 1.00). The reduced risk of cancer associated with high vegetable intake was restricted to women (HR = 0.98, 95% CI = 0.97 to 0.99). Stratification by alcohol intake suggested a stronger reduction in risk in heavy drinkers and was confined to cancers caused by smoking and alcohol.

Conclusions A very small inverse association between intake of total fruits and vegetables and cancer risk was observed in this study. Given the small magnitude of the observed associations, caution should be applied in their interpretation.

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In 1990, the World Health Organization (1) recommended people to eat at least five portions (about 400 g) of fruits and vegetables a day to prevent cancer and other chronic diseases. However, despite considerable research in this direction, there is no conclusive evidence that high intake of fruits and vegetables reduces the risk of cancer development. Most available studies have concentrated on one or a few types of cancer, which complicates an overall assessment of the contribution of fruit and vegetable intakes in cancer risk. In a systematic review, published in 1997, the World Cancer Research Fund (2) claimed to have found convincing evidence for a protective effect of high intake of fruits and vegetables against a number of respiratory and digestive cancers. Most of this

CONTEXT AND CAVEATS

Prior knowledge

The association between high intake of fruits and vegetables and reduction in overall cancer risk is not conclusively established.

Study design

European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study was conducted between 1992 and 2000. Diet and lifestyle data were self-reported by the participants. Cancer incidence and mortality data were obtained from country-specific national and regional registries. Association between overall cancer risk and high intake of total fruits, total vegetables, and total fruits and vegetables combined was assessed. Estimated cancer risks were adjusted for smoking, alcohol consumption, and many other variables.

Contribution

High intake of vegetables, and fruits and vegetables combined, was associated with a small reduction in overall cancer risk. The association was stronger in heavy alcohol drinkers but was restricted to cancers caused by smoking and drinking.

Implications

This study reveals a very modest association between high intake of fruits and vegetables and reduced risk of cancer.

Limitations

The inverse association between overall cancer risk and high intake of fruits and vegetables was weak. Errors inherent to self-reported dietary habits may have resulted in bias.

From the Editors

evidence was based on results from case–control studies, which were the predominant types of study conducted at that time. In the past 15 years, results reported from prospective studies, mainly from North America, did not support a lower risk of cancer. Based on these studies, the International Agency for Research on Cancer (IARC) (3) classified the evidence as "limited" in 2003. In 2007, the World Cancer Research Fund (4) downgraded the strength of the evidence, which had been called convincing or probable in their earlier report (2), for most cancers.

The association between fruit and vegetable intake and overall cancer risk, rather than risk of specific cancers, has been less frequently studied. A total of six prospective studies that included more than 10 000 individuals have reported results on cancer incidence (5–9) or mortality (10). Of the six studies, one showed that mortality was lower in both men and women when higher amounts of green and yellow vegetables and fruits were consumed (10); three studies reported a lower incidence of cancer in women on high intake of fruits and vegetables (5,6,8); and the remaining two showed no association between cancer risk and fruit or vegetable intake. A few possible explanations for inconsistent results in the above-mentioned studies could be recall, selection bias in case–control studies, and inadequate exposure contrast and exposure misclassification in cohort studies (4).

The reduced cancer risk exerted by fruits and vegetables, if real, may operate via generic as well as cancer-specific mechanisms, including antioxidant activity, modulation of detoxification enzymes, stimulation of immunologic response, modulation of hormonal level, and antiproliferative activities (11). However, the identification of specific compounds in fruits and vegetables that are responsible for anticarcinogenic activities has remained elusive to date (3,4).

An assessment of the association between fruit and vegetable intake on overall cancer risk is important not only because it complements the observations on specific neoplasms and validates the claim but also because it is important for meaningful public health recommendations. The European Prospective Investigation into Cancer and Nutrition (EPIC) is a multicenter prospective study of diet and cancer conducted in 10 Western European countries with a great variability in fruit and vegetable intake between different populations. Results of detailed analyses on fruit and vegetable intake and risk of specific cancers within EPIC have been reported (12–23); however, none of the previous analyses of the combined dataset of the EPIC study provided results for overall cancer risk. In this study, we aimed to complement these results for specific cancers with an analysis of the association between overall cancer risk and intake of total fruits and vegetables.

Materials and Methods

Population and Study Design

We recruited 521 448 men and women, who were aged 25–70 years between January 1, 1992, and December 31, 2000. A combination of cohorts from 23 centers in Denmark (Aarhus and Copenhagen), France, Germany (Heidelberg and Potsdam), Greece, Italy (Florence, Naples, Ragusa, Turin, and Varese), the Netherlands (Bilthoven and Utrecht), Norway, Spain (Asturias, Granada, Murcia, Navarra, and San Sebastian), Sweden (Malmo and Umea), and United Kingdom (Cambridge and Oxford) were included in the study. The French cohort encompassed members of a health insurance scheme for school and university employees. Participants at the Spanish and Italian centers (except Florence) included blood donors, members of several health insurance programs, employees of several enterprises, civil servants, and the general population. In Utrecht and Florence, participants enrolled in mammographic screening programs were recruited for the study. In Oxford, most of the cohort consisted of "health conscious" subjects from England, Wales, Scotland, and Northern Ireland, many of whom were vegetarians. Participants were recruited from the general population in other centers. The cohorts of France, Norway, Utrecht, and Naples included only women. We obtained the approval of the relevant ethics committees and informed consent of the participants. We excluded 23 633 participants who were diagnosed with cancer (excluding nonmelanoma skin cancer) before enrollment. Participants with incomplete follow-up information (n = 9665) or with a ratio of energy intake vs energy expenditure in the top or bottom 1% (n = 9672) were also excluded. A total of 142 605 men and 335 873 women were included in the analysis. The details of the study design used in the EPIC study have been described elsewhere (24).

Exposure Assessment

For the baseline examination, we assessed the habitual diet of the participants for the past 12 months by using a country-specific food-frequency questionnaire. However, Spain and one Swedish

center were exceptions, where we used a modified diet history method (24). The questionnaire, validated within each country, was self-administered in all centers, except in Greece, two Italian centers, and Spain, where it was administered by the interviewers. In addition to the baseline dietary questionnaires, standardized, computer-based, 24-hour dietary recall measurements were administered to 8% of the study population, with the aim to calibrate measurements across countries based on this random sample (25,26).

For the present analysis, we evaluated associations between cancer and intake of total fruits, total vegetables, and total fruits and vegetables combined. Fresh fruits comprised approximately 90% of the total fruit intake. This category also included dried and canned fruits but not fruit juices. Fruit juices are nutritionally different from fresh fruits (eg, added sugars and vitamins could be diluted or prepared from concentrate) and are quantified in the liquid form, whereas total fruit and vegetable intake is expressed primarily as solid foods. Potatoes, other tubers, legumes, and vegetable juices were not included in the category of total vegetables.

Lifestyle questionnaires included information on education, medical history, tobacco smoking, alcohol intake, occupational and leisure time physical activities, menstrual and reproductive history, use of oral contraceptives, and hormonal therapy. Height and weight were measured at the baseline examination, except for one center in the United Kingdom and Norway and approximately two-thirds of the French cohort, for which self-reports were used.

Outcome Assessment

Cancer incidence data were obtained from population-based registries in Denmark, four Italian centers, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. An active follow-up study to confirm these data was conducted by contacting the study participants; in case of death, contacting the next of kin; searches through health insurance records and through additional cancer and pathology registries in France, Germany, one Italian center, and Greece. Mortality data were obtained from either the cancer or the mortality registries at the regional or national level. The follow-up ended between 2002 and 2005 in different countries; individuals were censored at the end of follow-up, last known contact, cancer diagnosis, or death.

Cancer incidence data were coded according to the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10) (http://www.who.int./classifications/apps/icd/icd10online/) and the second revision of the International Classification of Diseases for Oncology (ICDO-2) (27). Mortality data were coded according to ICD-10. Only the first primary neoplasms were included in the analysis. Nonmelanoma skin cancer was excluded from the analysis.

Statistical Analysis

Multivariable Cox regression models were fitted to estimate cancer hazard ratios (HRs) and 95% confidence intervals (CIs) using the PHREG procedure in SAS, version 9.1 (SAS Institute, Cary, NC), with attained age as the primary time variable. Proportionality was verified using the analysis of residuals. Models were stratified by study center, sex, and age at recruitment (1-year categories). Linear calibration of the main exposure variables was based on a fixed-effect linear model in which sex- and country-specific 24-hour dietary recall data were regressed on dietary questionnaire measurements after controlling for the same variables included in the risk analysis (see below) (28). Models were fitted with intake of fruits and vegetables as continuous variables based on both calibrated and uncalibrated measurements and categorization of the uncalibrated variables in quintiles based on the distribution of the whole study population. In the latter approach, linear trends were tested by applying integer scores to the quintile categories and entering them as a continuous term in the regression models. The confidence intervals of the risk estimates, obtained using calibrated data, were estimated using bootstrap sampling to take into account the uncertainty related to measurement error correction. Unless stated otherwise, the results presented are based on the uncalibrated measurements.

The following covariates were measured at baseline—weight (kilogram, continuous), height (meter, continuous), energy from fat sources (kilocalories per day, continuous), energy from nonfat sources (kilocalories per day, continuous), physical activity (inactive, moderately inactive, moderately active, active, and missing), educational level (none or primary, technical or professional, secondary or university, and missing), and sex-specific alcohol drinking because of the different distributions of male and female drinkers (nondrinker, five categories of intensity for male drinkers [>0–6, 6.1–18, 18.1–30, 30.1–60, and >60 g/d], and four categories for female drinkers [>0–6, 6.1–18, 18.1–30, and >30 g/d]). To adjust for the potential confounding effect of tobacco smoking, we included in the regression models terms for current amount of smoking (1–14, 15–24, or ≥25 cigarettes per day), duration of smoking in 10-year categories (≤10, 11–20, 21–30, 31–40, 41–50, or >50 years), time since quitting (≤10, 11–20, and >20 years), smoking of pipe or cigar, and occasional smoking and missing smoking information. Additional covariates for women included menopausal status (pre-, peri-, and postmenopausal; surgical menopause; or missing), age at menarche (≤12, 13–14, ≥15 years, and missing), history of any full-term pregnancy, history of any use of oral contraceptives, and hormonal therapy. Furthermore, we made mutual adjustment for intake of fruits and vegetables. Adjustment for intake of red meat, processed meat, and fish was performed, but this did not affect the results. Adjustment for intake of cereal fiber, a variable missing for participants from Greece, also had no influence on the results. These variables were not included in the final regression models.

The primary analysis included all study participants. Secondary analyses were conducted after stratification by sex, country, region (North: Denmark, Germany, the Netherlands, Norway, Sweden, and United Kingdom; South: France, Greece, Italy, and Spain), and duration of follow-up (<2 and ≥2 years). Heterogeneity in risk estimates was assessed using Cochran Q statistics.

To explore the possible residual confounding of tobacco smoking and alcohol drinking, the analyses were stratified by these two habits, in addition to the original stratification by study center, sex, and age at recruitment. The stratification by tobacco smoking and alcohol drinking was carried out using different categories (never, current, and former smokers; men and women drinkers of <5 g/d ethanol, 5–30 g/d in women and 5–60 g/d in men and >30 g/d

in women and >60 g/d in men). Furthermore, the analyses were repeated separately for cancers associated with tobacco smoking or alcohol drinking and for cancers where causal association with tobacco smoking or alcohol drinking was not convincingly established. Smoking-associated cancers include cancers of the lung, kidney, upper aerodigestive tract, liver, stomach, pancreas, and bladder (29); alcohol-associated cancers include cancers of the upper aerodigestive tract, breast, liver, and colorectum (30).

Results

Based on the 24-hour recall data, the median intake of fruits and vegetables was 335 g/d in the entire cohort of 142 605 men and 335 873 women; country-specific medians ranged from 231 g/d in Sweden to 511 g/d in Spain. In general, intake was higher in Southern European countries than in Northern European countries. The overall median intake of total fruits was 170 g/d and that of total vegetables was 134 g/d (Table 1). High intake of fruits and vegetables was also associated with female sex, higher education, physical activity, low alcohol intake, and never-smoking status (Supplementary Table 1, available online). After a median follow-up time of 8.7 years, 9604 men and 21 000 women were diagnosed with cancer. The crude cancer incidence rates were 7.9 per 1000 person-years in men and 7.1 per 1000 person-years in women. Country-specific rates in men ranged from 3.8 per 1000 person-years in the Netherlands to 10.1 per 1000 person-years in Denmark; in women, they ranged from 3.1 per 1000 person-years in Greece to 8.8 per 1000 person-years in France. A statistically significant reduction in overall cancer risk was associated with increased intake of fruits and vegetables (200 g/d increase in intake of fruits and vegetables, HR = 0.97, 95% CI = 0.96 to 0.99) (Table 2). Adjustment for age, sex, and center did not change the estimates (HR = 0.97, 95% CI = 0.96 to 0.98, data not shown), demonstrating a lack of confounding effect by variables other than age, sex, and center (Table 2). In the categorical analysis for total fruit and vegetable intake, there was a decreased overall cancer risk for the second to the fifth quintiles of the distribution compared with the first quintile (HR = 0.95, 95% CI = 0.92 to 0.99; HR = 0.91, 95% CI = 0.88 to 0.95; HR = 0.93, 95% CI = 0.89 to 0.97; HR = 0.89, 95% CI = 0.85 to 0.93; $P_{trend} < .001$) (Table 2).

The results of 100 g/d increase in total vegetable intake were similar to those of fruits and vegetables combined (HR = 0.98, 95% CI = 0.97 to 0.99) (Table 2). In the categorical analysis, a monotonous decrease in overall cancer risk was observed for the second through the fifth quintiles vs first quintile of the distribution of total vegetable intake (HR = 0.97, 95% CI = 0.94 to 1.01; HR = 0.97, 95% CI = 0.93 to 1.00; HR = 0.95, 95% CI = 0.91 to 0.98; HR = 0.93, 95% CI = 0.89 to 0.97; $P_{trend} < .001$).

The results for 100 g/d increase of total fruit intake suggested a weaker inverse association with cancer risk compared with total vegetable intake (HR = 0.99, 95% CI = 0.98 to 1.00). In the categorical analysis, a decrease in overall cancer risk was observed for second through the fifth quintiles vs first quintile of the distribution of total fruit intake (HR = 0.96, 95% CI = 0.93 to 0.99; HR = 0.94, 95% CI = 0.91 to 0.97; HR = 0.95, 95% CI = 0.91 to 0.98; HR = 0.94, 95% CI = 0.90 to 0.98; $P_{trend} < .001$).

Results were comparable in men and women, although the precision of the risk estimates was greater in women because of the larger number of cancers. Tests for heterogeneity by sex, using continuous exposure variables, showed no statistically significant heterogeneity across the combined fruit and vegetable, vegetable, and fruit intake groups ($P_{heterogeneity}$ = .08, = .99, and = .08, respectively) (Table 2).

The results of the analysis based on the calibrated data were similar to those based on the uncalibrated data (200 g/d increase in the intake of fruits and vegetables, HR = 0.96, 95% CI = 0.94 to 0.98). A lower hazard ratio for higher intake of fruits and vegetables was observed in nine of the 10 participating countries, although statistical significance was not reached in most cases when individual countries were analyzed (Table 3). Results were comparable in men and women ($P_{heterogeneity}$ = .30 overall, = .33 in men, and = .55 in women). When countries were combined according to geographic region, the decrease in overall cancer risk for a 200 g/d increase in intake of fruits and vegetables was similar in the Northern countries (HR = 0.98, 95% CI = 0.96 to 0.99) and in the Southern countries (HR = 0.97, 95% CI = 0.96 to 0.99). Tests for heterogeneity showed that there was no difference between the geographic regions ($P_{heterogeneity}$ = .38).

To address the residual confounding by major causes of cancer, namely tobacco smoking and alcohol drinking, we repeated the main analysis after stratification for tobacco smoking and alcohol

Table 1. Number of study participants by sex and country and median intake of fruits and vegetables (grams per day) by country*

Country	Men (n)	Women (n)	Median (10th–90th percentiles)		
			Fruits and vegetables	Vegetables	Fruits
Denmark	26283	28736	264 (37–650)	114 (0–313)	126 (0–443)
France	0	68049	420 (150–805)	184 (30–432)	206 (0–493)
Germany	21584	27915	328 (80–728)	135 (0–351)	160 (0–497)
Greece	10601	15019	404 (124–855)	189 (24–494)	172 (0–506)
Italy	14017	30497	500 (164–997)	156 (17–416)	307 (12–714)
The Netherlands	9784	26529	270 (55–613)	113 (0–265)	145 (0–429)
Norway	0	35227	244 (53–547)	101 (0–268)	124 (0–370)
Spain	15152	24857	511 (125–1061)	172 (7–463)	313 (0–748)
Sweden	22308	26380	231 (48–511)	97 (0–255)	114 (0–345)
United Kingdom	22876	52664	317 (95–693)	151 (12–353)	144 (0–425)
Overall	142605	335873	335 (77–772)	134 (0–364)	170 (0–510)

* Results based on uncalibrated 24-hour recall data.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident cancer and distribution of incident cancers excluding nonmelanoma skin cancer by sex and vegetable, fruit, and combined fruit and vegetable intake

	Men		Women		Overall	
Food group	**n**	**HR (95% CI)***	**n**	**HR (95% CI)***	**n**	**HR (95% CI)***
Fruit and vegetable intake						
Continuous (200 g/d, uncalibrated)	9604	0.96 (0.94 to 0.98)	21 000	0.98 (0.97 to 0.99)	30 604	0.97 (0.96 to 0.99)
Continuous (200 g/d, calibrated)	9604	0.95 (0.92 to 0.99)	21 000	0.96 (0.93 to 0.98)	30 604	0.96 (0.94 to 0.98)
Categorical						
Quintile 1 (0–226 g/d)	2988	1.00 (reference)	3174	1.00 (reference)	6163	1.00 (reference)
Quintile 2 (227–338 g/d)	2260	0.98 (0.92 to 1.03)	3934	0.94 (0.90 to 0.99)	6194	0.95 (0.92 to 0.99)
Quintile 3 (339–462 g/d)	1729	0.93 (0.87 to 0.97)	4534	0.91 (0.87 to 0.96)	6263	0.91 (0.88 to 0.95)
Quintile 4 (463–646 g/d)	1351	0.88 (0.82 to 0.94)	5131	0.95 (0.90 to 0.99)	6482	0.93 (0.89 to 0.97)
Quintile 5 (≥647 g/d)	1276	0.89 (0.82 to 0.97)	4226	0.90 (0.85 to 0.95)	5502	0.89 (0.85 to 0.93)
P_{trend}†		<.001		.002		<.001
Vegetable intake						
Continuous (100 g/d, uncalibrated)	9604	0.98 (0.96 to 1.00)	21 000	0.98 (0.97 to 0.99)	30 604	0.98 (0.97 to 0.99)
Continuous (100 g/d, calibrated)	9604	1.02 (0.97 to 1.07)	21 000	0.95 (0.92 to 0.98)	30 604	0.97 (0.94 to 0.99)
Categorical						
Quintile 1 (0–97 g/d)	2810	1.00 (reference)	3466	1.00 (reference)	6276	1.00 (reference)
Quintile 2 (98–146 g/d)	2126	0.99 (0.93 to 1.05)	3867	0.97 (0.92 to 1.01)	5993	0.97 (0.94 to 1.01)
Quintile 3 (147–208 g/d)	1854	0.97 (0.91 to 1.03)	4355	0.97 (0.92 to 1.01)	6209	0.97 (0.93 to 1.00)
Quintile 4 (209–306 g/d)	1506	0.92 (0.85 to 0.97)	4830	0.95 (0.91 to 1.00)	6336	0.95 (0.91 to 0.98)
Quintile 5 (≥307 g/d)	1308	0.95 (0.87 to 1.03)	4482	0.92 (0.87 to 0.97)	5787	0.93 (0.89 to 0.97)
P_{trend}†		.04		.005		<.001
Fruit intake						
Continuous (100 g/d, uncalibrated)	9604	0.98 (0.97 to 1.00)	21 000	1.00 (0.99 to 1.01)	30 604	0.99 (0.98 to 1.00)
Continuous (100 g/d, calibrated)	9604	0.98 (0.96 to 1.01)	21 000	0.99 (0.97 to 1.01)	30 604	0.99 (0.98 to 1.00)
Categorical						
Quintile 1 (0–90 g/d)	2884	1.00 (reference)	3339	1.00 (reference)	6223	1.00 (reference)
Quintile 2 (91–162 g/d)	2212	0.97 (0.91 to 1.02)	3974	0.96 (0.92 to 1.01)	6186	0.96 (0.93 to 0.99)
Quintile 3 (163–246 g/d)	1765	0.94 (0.88 to 1.00)	4554	0.95 (0.90 to 0.99)	6319	0.94 (0.91 to 0.97)
Quintile 4 (247–366 g/d)	1388	0.90 (0.84 to 0.97)	5001	0.97 (0.92 to 1.02)	6389	0.95 (0.91 to 0.98)
Quintile 5 (≥367 g/d)	1355	0.89 (0.82 to 0.97)	4132	0.97 (0.92 to 1.02)	5487	0.94 (0.90 to 0.98)
P_{trend}†		<.001		.5		.006

* Cox regression model stratified by center (23 categories) and sex (male or female) and adjusted for age (continuous), current amount of smoking (1–14, 15–24, or ≥25 cigarettes per day), duration of smoking (≤10, 11–20, 21–30, 31–40, 41–50, or >50 years), time since quitting (≤10, >10–20, or >20 years), smoking of pipe or cigar, occasional smoking and missing smoking information, alcohol intake (never-drinker, five categories of intensity for male drinkers [>0–6, >6–18, >18–30, >30–60, and >60 g/d] and four categories for female drinkers [>0–6, >6–18, >18–30, and >30 g/d]), physical activity (inactive, moderately active, active, or missing), educational level (none or primary, technical or professional, secondary or university, or missing), height (meter, continuous), weight (kilogram, continuous), energy from fat sources (kilocalories per day, continuous), energy from nonfat sources (kilocalories per day, continuous), as well as, for women, age at menarche (≤12, 13–14, ≥15 years, or missing), pregnancy (ever or never), oral contraceptive (ever or never), use of hormone replacement therapy (ever or never), and menopausal status (pre-, peri-, and postmenopausal; surgical menopause; or missing).

† P_{trend} values were calculated using two-sided test for linear trend.

drinking (Table 4). The results of the main analysis (Table 2) were confirmed in all categories of smokers; however, in many of them, we could not formally exclude the possibility of chance factor because of relatively small number of cancers. Stratification by alcohol drinking suggested a stronger association in heavy drinkers than in moderate or weak drinkers. When cancers were stratified according to the presence of a causal association with tobacco smoking or alcohol drinking (Table 5), the inverse association with higher intake of fruits and vegetables was restricted to cancers associated with the two habits (mainly respiratory and the digestive organ cancers). The duration of follow-up did not change the results (data not shown).

Discussion

Our analysis of a prospective study from 10 European countries showed an inverse association between cancer risk and higher intake of fruits and vegetables, notably intake of vegetables. However, in this population, a higher intake of fruits and vegetables was also associated with other lifestyle variables, such as lower intake of alcohol, never-smoking, short duration of tobacco smoking, and higher level of physical activity, which may have contributed to a lower cancer risk. Although the multivariable analysis was adjusted for these factors, we cannot rule out the possibility of residual confounding because of exposure measurement error in dietary and other variables and the inability of statistical models to capture complex relationships between exposure variables. The analysis restricted to never-smokers, however, argues against a substantial residual confounding by tobacco smoking, as does the sensitivity analysis in which individual covariates were excluded from the regression model. However, a stratified analysis on alcohol drinking in different categories of drinkers revealed heterogeneity in the association with high fruit and vegetable intake. These findings might suggest residual confounding

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident cancer per increasing fruit and vegetable intake (200 g/d, continuous) and distribution of incident cancer cases (excluding nonmelanoma skin cancer) by sex and country*

	Men		Women		Overall	
Country	**n**	**HR (95% CI)†**	**n**	**HR (95% CI)†**	**n**	**HR (95% CI)†**
Denmark	1875	0.92 (0.87 to 0.97)	2161	0.98 (0.93 to 1.03)	4036	0.94 (0.91 to 0.97)
France	—	—	6514	0.99 (0.96 to 1.01)	—	—
Germany	1395	0.94 (0.86 to 1.04)	1299	0.99 (0.91 to 1.09)	2694	0.97 (0.91 to 1.03)
Greece	337	0.96 (0.89 to 1.03)	338	0.92 (0.85 to 1.00)	675	0.94 (0.89 to 0.99)
Italy	735	1.00 (0.94 to 1.06)	1676	0.95 (0.90 to 0.99)	2411	0.96 (0.93 to 1.00)
The Netherlands	311	0.90 (0.76 to 1.06)	1667	0.99 (0.93 to 1.06)	1978	0.97 (0.91 to 1.03)
Norway	—	—	1153	0.99 (0.91 to 1.08)	—	—
Spain	938	0.94 (0.89 to 0.98)	999	1.01 (0.97 to 1.06)	1937	0.97 (0.94 to 1.00)
Sweden	2324	0.99 (0.94 to 1.05)	2286	1.01 (0.95 to 1.06)	4610	1.00 (0.96 to 1.04)
United Kingdom	1689	0.98 (0.94 to 1.03)	2907	0.99 (0.96 to 1.02)	4596	0.99 (0.96 to 1.01)

* — = Not applicable.

† Cox regression model stratified by center and sex and adjusted for age, duration of smoking, smoking status, alcohol intake, education, height, weight, energy from fat sources, energy from nonfat sources, physical activity, as well as, for women, age at menarche, pregnancy, oral contraceptive, use of hormone replacement therapy, and menopausal status.

but could also point to an interaction between the dietary risk factors.

The results of analyses not including adjustment for alcohol drinking or tobacco smoking indicated only a modest confounding effect of these factors. No reciprocal confounding of fruit and vegetable intake was observed. The hazard ratios for either fruit or vegetable group were virtually unchanged when intake of the other group was excluded from the regression model.

We performed several secondary analyses to assess the validity of our results. The estimates were not affected by the duration of follow-up, which suggests that reverse causality (changes in dietary habits because of early symptoms of an undetected cancer) was unlikely, and the classification of subjects at baseline with respect to their intake of fruits and vegetables remained valid throughout the study period.

The consistency of results by country was particularly noteworthy. Although absolute intake level varied greatly among the countries included in our analysis, no heterogeneity was observed in the inverse association between high intake of fruits and vegetables and overall cancer risk. Furthermore, because of the magnitude of the inverse association, most of the country-specific results were not statistically significant, thus emphasizing the need for a large number of events in such analysis.

The inverse association of fruit and vegetable intake on overall cancer risk was reported earlier in a Greek EPIC cohort study (5). The results of this study, which are based on a smaller number of events in the Greek cohort, are in close agreement with our present analysis. Whole EPIC cohort analyses have been published for several cancers, which include prostate (12), lung (13,22), breast (14), ovary (19), upper aerodigestive tract (15), kidney (16), stomach (17), pancreas (20), colorectal (21), and bladder (23). However, the number of observed cases of cancer was not large enough in most of these analyses to detect a weak association between fruit and vegetable intake and

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident cancer per increasing vegetable, fruit, and combined fruit and vegetable intake and distribution of incident cancers (excluding nonmelanoma skin cancer) by categories of tobacco smoking and alcohol drinking

Category of intake	**Never-smokers, HR (95% CI)***	**Former smokers, HR (95% CI)***	**Current smokers, HR (95% CI)***	**Heterogeneity†**
No. of cancers	13728	8832	7388	
Fruits and vegetables (200 g/d, continuous)	0.98 (0.96 to 0.99)	0.98 (0.96 to 1.00)	0.96 (0.93 to 0.98)	.20
Vegetables (100 g/d, continuous)	0.97 (0.96 to 0.99)	0.98 (0.96 to 1.00)	0.97 (0.95 to 0.98)	.66
Fruits (100 g/d, continuous)	1.00 (0.99 to 1.01)	0.99 (0.98 to 1.01)	0.98 (0.97 to 1.00)	.18
Category of intake	Weak drinkers‡, HR (95% CI)*	Moderate drinkers‡, HR (95% CI)*	Heavy drinkers‡, HR (95% CI)*	Heterogeneity†
No. of cancers	10935	13110	2442	
Fruits and vegetables (200 g/d, continuous)	0.99 (0.97 to 1.01)	0.97 (0.96 to 0.99)	0.90 (0.86 to 0.94)	<.001
Vegetables (100 g/d, continuous)	0.99 (0.97 to 1.00)	0.99 (0.97 to 1.00)	0.93 (0.89 to 0.97)	.16
Fruits (100 g/d, continuous)	1.00 (0.99 to 1.01)	0.99 (0.97 to 1.00)	0.96 (0.93 to 1.00)	.09

* Cox regression model stratified by center and sex and adjusted for age, duration of smoking, smoking status, alcohol intake, education, height, weight, energy from fat sources, energy from nonfat sources, physical activity, as well as, for women, age at menarche, pregnancy, oral contraceptive, hormone replacement therapy use, and menopausal status.

† P values for test for heterogeneity across strata were calculated using the χ^2 test.

‡ Weak drinkers: <5 g/d; moderate drinkers: 5–60 g/d (men) and 5–30 g/d (women); heavy drinkers: >60 g/d (men) and >30 g/d (women).

Table 5. Hazard ratios (HRs) and 95% confidence intervals (CIs) for incident cancers associated or not associated with tobacco smoking or alcohol drinking per increasing vegetable, fruit, and combined fruit and vegetable intake

Group of cancers	Associated, HR (95% CI)*	Not associated, HR (95% CI)*
Association with tobacco smoking†		
Number of cancer cases	5034	25570
Fruits and vegetables (200 g/d, continuous)	0.92 (0.90 to 0.95)	0.98 (0.97 to 1.00)
Vegetables (100 g/d, continuous)	0.96 (0.93 to 0.99)	0.98 (0.97 to 0.99)
Fruits (100 g/d, continuous)	0.96 (0.94 to 0.98)	1.00 (0.99 to 1.01)
Association with alcohol drinking‡		
Number of cancer cases	11340	17434
Fruits and vegetables (200 g/d, continuous)	0.97 (0.95 to 0.99)	0.99 (0.97 to 1.00)
Vegetables (100 g/d, continuous)	0.97 (0.95 to 0.99)	0.99 (0.97 to 1.00)
Fruits (100 g/d, continuous)	0.99 (0.98 to 1.00)	1.00 (0.99 to 1.01)

* Cox regression model stratified by center and sex and adjusted for age, duration of smoking, smoking status, alcohol intake, education, height, weight, energy from fat sources, energy from nonfat sources, physical activity, as well as, for women, age at menarche, pregnancy, oral contraceptive, use of hormone replacement therapy, and menopausal status.

† Smoking-associated cancers of the lung, kidney, upper aerodigestive tract, liver, stomach, pancreas, and bladder.

‡ Alcohol-associated cancers of the upper aerodigestive tract, breast, liver, and colorectum.

cancer risk, and updated analyses of risk of specific cancers are under way.

This study has a few major methodological strengths. The number of cancers included in the study is larger and the range in fruit and vegetable intake is greater, to our knowledge, than most previous studies (eg, fivefold variation in the median fruit and vegetable intake values between the lowest and the highest quintiles compared with no more than fourfold variation in previous prospective studies) (6). In addition, our analysis made a special effort to increase the validity of dietary exposure assessment by including a calibration approach to adjust for the systematic and random intraindividual error as well as intercenter errors.

There are potential limitations in this study. Systematic and random errors may still be present in the 24-hour dietary recall, which would affect the validity of the calibration of dietary intake (31). The fact that uncalibrated and calibrated results are similar adds to the validity of the dietary assessment, although this can also be because of a similar error structure in the two dietary assessment methods. In addition to misclassification inherent in the use of self-reported nutritional habits (31), dietary habits measured only at enrollment may have changed during follow-up and resulted in exposure misclassification. The risk of cancer and other chronic diseases might also be associated with changes in dietary habits during follow-up, particularly in high-risk individuals (eg, those overweight and obese), who are more prone to modify their diet than others. This possible source of bias is likely to increase with the duration of follow-up. Also, we did not take into account the differences in crop production and food preparation, which can result in differences in the composition of fruits and vegetables (32) and contribute to dietary assessment misclassification. Additional limitations are the limited follow-up duration and the lack of information on dietary habits earlier in life.

If the modest inverse association between high intake of fruits and vegetables and cancer risk is deemed to be causal, it is possible to estimate the proportion of cancers that could theoretically be avoided according to counterfactual exposure scenarios, that is, assuming that a different distribution of fruit and vegetable intake had taken place in this population (33). A straightforward counterfactual scenario could be based on a shift of the study population across various exposure spectra. As an example, under the assumption that study subjects shift one quintile upward in the distribution of fruit and vegetable intake corresponding to an average increase of approximately 150 g/d, 2.6% cancers in men and 2.3% cancers in women could be avoided.

In conclusion, our study supports the notion of a modest cancer preventive effect of high intake of fruits and vegetables and we can exclude chance as a likely factor. The analysis suggested little confounding by body weight, physical activity, smoking, and several other factors that were examined. Nevertheless, the observed association of cancer risk overall with vegetable and fruit intake was very weak, and we cannot entirely rule out the possibility of residual confounding by these or other factors. Given the small magnitude of the observed associations, caution should be applied in interpretation of the results.

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Notes

S. Bingham: deceased.

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