Vegetables and Fruits in Relation to Cancer Risk: Evidence from the Greek EPIC Cohort Study

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Abstract

Introduction: **Vegetables and fruits have long been considered as conducive to cancer prevention, but this view has recently been challenged. We investigated the relation of vegetable and fruit intake with total cancer occurrence in the population-based cohort of the Greek component of the European Prospective Investigation into Cancer and nutrition (EPIC), which is characterized by high consumption of these foods.**
Materials and Methods: **For a median of 7.9 years, 25,623 participants (10,582 men, 15,031 women) were actively followed-up, contributing 188,042 person-years. Cancer at any site was diagnosed in 851 participants (421 men, 430 women). Dietary intakes were ascertained at enrollment through an extensive, validated, interviewer-administered food frequency questionnaire. Data were analyzed through Cox regression, controlling for potential confounders.**
Results: **An inverse association of cancer incidence with vegetables and fruits (mutually adjusted) was noted, reaching statistical significance for vegetables among women. When vegetables and fruits were combined, the inverse association with cancer occurrence was statistically significant for the entire cohort [hazard ratio per increasing quintile, 0.94; 95% confidence interval (95% CI), 0.88-0.99], as well as among women (hazard ratio per increasing quintile, 0.90; 95% CI, 0.83-0.98), but not among men (hazard ratio per increasing quintile, 0.95; 95% CI, 0.87-1.04).**
Conclusions: **In a general population-based Greek cohort, we have found evidence that consumption of vegetables and fruits is inversely associated with incidence of cancer overall, although the associations seem to be weaker than expected on the basis of case-control studies previously undertaken in Greece.** (Cancer Epidemiol Biomarkers Prev 2008;17(2):387–92)

Introduction

Whether diet is responsible for almost 35% of total cancer mortality, as the classic report by Doll and Peto (1) postulated, or for ~15% to 20%, as it was more recently suggested (2, 3), plant foods have been assumed to have considerable beneficial effects for cancer prevention. Indeed, in 1997, the World Cancer Research Fund summarized the published data as indicating that for five cancer sites (mouth and pharynx, esophagus, lung, stomach, and large bowel) there was ''convincing'' evidence that vegetables and/or fruits have a protective effect, whereas for another 11 cancer sites the existing evidence was either ''probable'' (larynx, pancreas, breast, and urinary bladder) or ''possible'' (corpus uteri, cervix uteri, kidney, liver, ovary, prostate, and thyroid gland) (4). Since 1997, inverse associations of vegetables and/or fruits with various cancer sites have been reported either from large case-control studies (5, 6) or from large cohort investigations (7-11), although in a major report from the International Agency for Research on Cancer (IARC) no association of any particular cancer with fruits and vegetables was considered as firmly established (12). It is also worth noting that although several null studies for particular cancer sites have been reported, no positive associations of any cancer site with either vegetables or fruits have been documented in any epidemiologic investigation. Thus, it was surprising that a combined analysis of two major cohorts, the Nurses' Health Study composed of 71,910 female participants and the Health Professionals' Follow-up Study with 37,725 male participants, indicated no association of fruit and vegetable intake with the incidence of all cancers (13).

In Greece, inverse associations of vegetables and/or fruits with several forms of cancer have been reported over the years from moderately sized case-control investigations (14-17). We have thus examined the association between these food categories and cancer occurrence overall in a general, population-based, cohort in Greece, which constitutes the Greek component of the European Prospective Investigation into Cancer and nutrition (EPIC). This component cohort of EPIC is characterized by high consumption of vegetables and fruits as well as considerable variation in intake, and ascertainment of dietary exposures was done by specially trained personnel in face-to-face interviews. Moreover, the Greek EPIC cohort is population based, allowing approximate estimations of population attributable rates.

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Table 1. Baseline characteristics of 25,623 study participants and 851 incident cancer cases, by gender, from the Greek component of the EPIC study

Baseline characteristics	Study population		Cancer cases	
	Men (n = 10,582)	Women (n = 15,041)	Men (n = 421)	Women (n = 430)
	Median (25th, 75th centiles)			
Age (y)	52.2 (42.3, 64.3)	53.8 (43.3, 63.9)	64.6 (56.6, 69.8)	59.6 (48.5, 67.1)
Formal education (y)	6 (6, 12)	6 (3, 12)	6 (6, 12)	6 (3, 12)
Height (cm)	170.0 (165.0, 174.8)	156.0 (152.0, 160.5)	168.0 (164.0, 173.0)	156.0 (151.0, 160.0)
Body mass index (kg/m^2)	27.9 (25.6, 30.4)	28.6 (25.2, 32.1)	27.4 (25.1, 30.3)	29.2 (25.7, 32.7)
Physical activity (MET-h/d)	34.1 (31.2, 38.5)	35.1 (32.7, 37.7)	32.8 (30.1, 36.3)	34.8 (32.7, 37.6)
	n (%)			
Smoking status				
Never	2,691 (25)	11,232 (75)	77 (18)	334 (78)
Former	3,667 (35)	1,171 (8)	166 (40)	32 (7)
Current	4,224 (40)	2,638 (17)	178 (42)	64 (15)
Ethanol intake (g/d)				
<10	5,232 (49)	13,775 (92)	236 (56)	394 (92)
10-<30	3,383 (32)	1,132 (7)	109 (26)	32 (7)
≥30	1,967 (19)	134 (1)	76 (18)	4 (1)
Supplement intake				
No	10,031 (95)	12,231 (81)	393 (93)	342 (79)
Yes	551 (5)	2,810 (19)	28 (7)	88 (21)

Materials and Methods

Recruitment and Approval. The enrollment of participants in the Greek component of EPIC took place between 1994 and 1999. A total of 28,572 participants from all over Greece were recruited. EPIC is a prospective cohort study conducted in 23 research centers in 10 European countries with the aim of investigating the role of biologic, dietary, lifestyle, and environmental factors in the etiology of cancer and other chronic diseases (18, 19). All procedures were in accordance with the Helsinki Declaration, all participants provided written informed consent, and the study protocol was approved by the ethics committees both at the IARC (a key participant in EPIC) and at the University of Athens Medical School.

Data on Diet. Usual dietary intake during the year preceding enrollment was assessed through a validated, semiquantitative, food frequency questionnaire including ~150 foods and beverages, as well as several complex recipes (20, 21). The questionnaire, which was administered in person by specially trained interviewers, comprised 63 entries for vegetables, 5 entries for legumes, and 19 entries for fruits, including the entries from complex recipes. Because vegetables are consumed in much higher quantities than legumes (at least 50 times higher) and the two food groups are frequently not distinguished in the literature, we have integrated legumes into the vegetable group.

For each dietary item, participants were asked to report their frequency of consumption and portion size. This information was used for the estimation of consumed quantities (in grams per day) and, on the basis of a food composition data base that has been modified to accommodate the particularities of the Greek diet (22), for the estimation of total energy intake (in kilocalories per day).

Data on Other Variables. At enrollment, several sociodemographic and lifestyle characteristics, including detailed smoking and alcohol drinking habits, as well as dietary supplement intake, were recorded. Anthropometric measurements were also undertaken using standardized procedures and allowing the calculation of body mass index (in kilograms per square meter). Finally, on the basis of the frequency and duration of participation in occupational and leisure-time physical activities, an overall metabolic equivalent (MET)-hour per day index was calculated, expressing the average daily energy expenditure level (19, 23, 24).

Participants and Follow-up. From the original cohort of 28,572 participants, 1,696 (5.9%) were excluded because information from follow-up was not available. An additional 383 participants (1.3%) were excluded because they had prevalent cancer (excluding nonmelanoma skin cancer) and another 870 (3.0%) because they had missing values in one or more of the variables used in the analyses. Thus, information from a total of 25,623 participants was evaluated in this study.

Follow-up was active and conducted at regular time intervals through telephone contacts with the participants or, in case of death, their next of kin. A structured form was filled in by specially trained health professionals, and when an incident cancer was reported, verification was sought through pathology reports, medical records, discharge diagnoses, or death certificates according to the IARC guidelines for the collection of end-point data. Classification of cancer cases was done on the basis of the International Classification of Diseases for Oncology (ICD-O-2) (25). The median duration of follow-up was 7.9 years, for a total of 188,042 person-years. The outcome studied was the first diagnosis of any cancer (excluding nonmelanoma skin cancer). In some instances, when diagnosis of incident cancer was not reported, death from cancer was recorded (110 cases).

Statistical Analysis. All analyses were done with the use of STATA.7 statistical package. Frequency distributions were used for descriptive purposes. Medians and quartiles were used for dietary variables including energy intake. The date of first diagnosis of incident cancer (or the date of death from incident cancer when the date of diagnosis was not reported) was used for the

Table 2. Distribution of incident cancer cases, by major sites, among 25,623 men and women (188,042 person-years) in the Greek component of the EPIC study

Cancer site	ICD-O-2 codes	Men (n = 421)	Women (n = 430)
Stomach	C16	35	13
Large bowel	C18-21	38	38
Liver	C22	19	9
Pancreas	C25	18	17
Lung	C34	116	19
Hematopoietic system	C42	25	18
Breast	C50	0	158
Cervix uteri	C53	0	21
Corpus uteri	C54	0	15
Ovary	C56	0	34
Prostate	C61	48	0
Kidney	C64	15	7
Bladder	C67	27	9
Brain	C71	11	14
Thyroid gland	C73	2	13
Lymph nodes	C77	16	15
All other sites		50	30
Total		421	430

calculation of time to event (cancer occurrence, death from causes other than cancer, or last contact till March 2007). Time to event was modeled through Cox proportional hazards regression, using as the main predictor variables vegetables (including legumes) and fruits, and in a separate model, the combination of vegetables and fruits in a single variable. All models were stratified by sex and adjusted simultaneously for age (<35, 35-44, 45-54, 55-64, and >65 years; categorically), years of formal education (≤5, 6-11, 12, and ≥13 years; categorically), smoking status (never smoker, former smoker, and five categories of current smoker: 1-10, 11-20, 21-30, 31-40, and ≥41 cigarettes per day; ordered), body mass index (in ordered quintiles), height (in ordered quintiles), physical activity expressed in MET-hours per day (in ordered quintiles), daily alcohol intake (per 10 g of ethanol; continuously), supplement intake (no, yes), and total energy intake (in ordered quintiles). In the Cox models, the assumption of proportionality was met (assessed through Schoenfeld goodness-of-fit test), no time-dependent covariates were used, and there was no colinearity among the variables.

Results

During 188,042 person-years of follow-up, a total of 851 cases of incident cancer were recorded.

Table 1 shows baseline characteristics of the study population and the cancer cases. The data in this table serve only descriptive purposes because mutual confounding and time to event are not accounted for. Of interest is the high body mass index among both men and women in this population. A high proportion of men and a substantial proportion of women are current smokers, whereas intake of dietary supplements is not uncommon among women, but it is rather limited among men.

Table 2 shows the distribution of incident cancer cases by gender and major cancer sites. Among men, cancer of the lung (116 cases) predominates, followed by cancers of the prostate (48 cases), large bowel (38 cases), and stomach (35 cases). Among women, cancer of the breast predominates (158 cases), followed by cancers of the large bowel (38 cases), ovary (34 cases), and uterus (36 cases, slightly more common in the cervix). It should be noted that there were more women than men in the Greek EPIC cohort, and therefore cancer occurrence differences between the two sexes cannot be directly assessed from this table.

In Table 3, daily intake of vegetables (including legumes) and fruits in grams, as well as total energy intake in kilocalories, is shown. The very high intake of vegetables and to a lesser extent of fruits in the Greek population is evident in these data.

In Table 4, study participants are categorized into sex-specific quintiles of intake of vegetables (including legumes) and, separately, fruits. Cases of incident cancer, person-time by sex and quintile of intake, as well as hazard ratios for each quintile in comparison with the first one and per increasing quintile, orderly, are shown. In all models, fruits and vegetables are mutually adjusted for, and when both sexes are studied together, sex is stratified for. Adjustment is also made for several potential confounding variables as indicated in the footnote of the table. An inverse association of cancer incidence with vegetables and fruits is noted, but it reaches statistical significance only with respect to vegetables among women. The interaction terms of sex by intake, however, are not statistically significant (P value for interaction of sex by vegetable intake is 0.893 and by fruit intake is 0.524).

Table 5 follows the rationale of Table 4, but in this table intake of fruits and vegetables is combined into a single variable. When vegetables and fruits are combined into a single variable, the inverse association with cancer occurrence is statistically significant among women as well as for the overall cohort. The interaction term of sex by vegetable and fruit intake combined, however, is not statistically significant (P = 0.694).

There was no evidence that the association between vegetables and/or fruits, on the one hand, and cancer occurrence, on the other, is different among dietary supplement users and nonusers—if anything, the inverse association was slightly more evident among the users (data not shown).

Discussion

In a cohort study undertaken among volunteers from the general population of Greece, consumption of vegetables (including legumes) and fruits combined was significantly inversely associated with cancer occurrence in the

Table 3. Median daily intake (and 25th and 75th centiles) of vegetables, fruits and energy intake in the Greek component of the EPIC study

Food group intake	Men (n = 10,582)	Women (n = 15,041)
Vegetables* (g/d)	555 (440, 690)	502 (390, 640)
Fruits (g/d)	335 (233, 456)	335 (234, 449)
Energy intake (kcal/d)	2293 (1,868, 2,798)	1831 (1,502, 2,214)

*Legumes are included.

Table 4. Hazard ratios (95% confidence intervals) for incident cancer and distribution of incident cancer cases (excluding nonmelanoma skin cancer) and corresponding person-time, by sex and sex-specific quintile of intake of vegetables (including legumes) and fruits; data from 25,623 adults of the Greek component of the EPIC study

	Sex-specific quintiles of the corresponding variable					Ordered quintiles
	Q1	Q2	Q3	Q4	Q5	
				Men (n = 10,582)		
Vegetables*						
Quintile median	*344*	*464*	*555*	*656*	*855*	
Person-time	14,976	15,130	15,237	15,065	15,653	
Incident cancers	94	95	82	76	74	
HR (95% CI)	1	1.11 (0.83-1.49)	0.99 (0.72-1.36)	0.92 (0.66-1.29)	0.98 (0.68-1.41)	0.98 (0.90-1.06)
Fruits						
Quintile median	*147*	*256*	*335*	*428*	*595*	
Person-time	14,871	15,181	15,267	15,294	15,448	
Incident cancers	100	87	68	87	79	
HR (95% CI)	1	0.83 (0.62-1.12)	0.67 (0.49-0.92)	0.83 (0.61-1.14)	0.86 (0.61-1.19)	0.97 (0.89-1.04)
				Women (n = 15,041)		
Vegetables*						
Quintile median	*301*	*414*	*502*	*607*	*801*	
Person-time	21,928	22,345	22,374	22,490	22,843	
Incident cancers	110	77	91	76	76	
HR (95% CI)	1	0.70 (0.52-0.94)	0.85 (0.63-1.14)	0.69 (0.49-0.95)	0.64 (0.44-0.93)	0.91 (0.84-0.99)
Fruits						
Quintile median	*150*	*256*	*335*	*423*	*588*	
Person-time	22,006	22,118	22,380	22,534	22,942	
Incident cancers	98	90	79	75	88	
HR (95% CI)	1	0.93 (0.70-1.24)	0.83 (0.61-1.13)	0.80 (0.58-1.10)	0.95 (0.69-1.32)	0.97 (0.90-1.05)
				Overall (n = 25,623)		
Vegetables*						
Person-time	36,904	37,475	37,611	37,555	38,496	
Incident cancers	204	172	173	152	150	
HR (95% CI)	1	0.90 (0.73-1.11)	0.93 (0.75-1.16)	0.82 (0.65-1.04)	0.83 (0.64-1.07)	0.96 (0.90-1.01)
Fruits						
Person-time	36,877	37,299	37,647	37,828	38,390	
Incident cancers	198	177	147	162	167	
HR (95% CI)	1	0.89 (0.73-1.10)	0.76 (0.61-0.95)	0.85 (0.68-1.05)	0.93 (0.74-1.18)	0.98 (0.93-1.03)

NOTE: Data were adjusted for age (<35, 35-44, 45-54, 55-64, and >65 y; categorically), formal education (≤5, 6-11, 12, and ≥13 y; categorically), smoking status (never smoker, former smoker, and five categories of current smoker: 1-10, 11-20, 21-30, 31-40, and ≥41 cigarettes/d; ordered), body mass index (in ordered quintiles), height (in ordered quintiles), physical activity expressed in MET-hours per day (in ordered quintiles), alcohol intake (per 10 g/d; continuously), supplement intake (no, yes), and total daily energy intake (in ordered quintiles). For both genders overall stratified by sex. Fruits and vegetables are mutually adjusted for.
Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.
*Legumes are included.

total cohort, after adjustment for several potential confounding variables including age, educational level, tobacco smoking, physical activity, and total energy intake. When vegetables and fruits were examined separately, indicative inverse associations with cancer occurrence were observed, which reached statistical significance for vegetables among women.

Until recently, it has generally been assumed that vegetables and/or fruits are inversely associated with cancer at several sites with supporting evidence mostly derived from case-control studies (1, 2, 4, 26, 27). Plausible mechanisms through which these food groups could convey protection against a spectrum of malignancies have also been proposed (28, 29).

Results from large cohort studies, focusing on specific cancer sites and reported with increasing frequency during the last decades, have supported a role of vegetables and/or fruits against the occurrence of cancer at certain sites (9, 10, 30-33). Nevertheless, the inverse associations observed in the cohort studies were generally weaker than those reported from the case-control investigations, the discrepancies being due to either recall and selection biases in case-control studies or imprecise dietary measurements in cohort investigations (34). Indeed, in a major report by IARC, no cancer site was deemed to be conclusively inversely related to intake of fruits and/or vegetables, although no evaluation for overall cancer occurrence was attempted (12). Moreover, recently, combined results from two major U.S. cohorts, the Nurses' Health Study and the Health Professionals' Follow-up Study, indicated no association between intake of vegetables and fruits and overall cancer occurrence (13).

Unlike that of Hung et al. (13), our data indicated a significant, albeit weak, inverse association between combined intake of vegetables and fruits and cancer occurrence. The association was stronger among women, although the interaction terms of intake by sex were not statistically significant. There are several possible explanations for the discrepancy of our results from those of Hung and colleagues. Schatzkin and Kipnis (35) noted that the null results reported by Hung and colleagues could reflect exposure misclassification in their study because the assessment tool used is subject to error, both random and systematic. They point out that because dietary exposures are examined in conjunction with

Table 5. Hazard ratios (95% confidence intervals) for incident cancer and distribution of incident cancer cases (excluding nonmelanoma skin cancer) and corresponding person-time, by sex and sex-specific quintile of vegetable and fruit intakes combined; data from 25,623 adults of the Greek component of the EPIC study

	Sex-specific quintiles of the corresponding variable					
	Q1	Q2	Q3	Q4	Q5	Ordered quintiles
			Men (*n* = 10,582)			
Vegetables* and fruits						
Quintile median	*567*	*758*	*905*	*1069*	*1371*	
Person-time	14,819	15,179	15,184	15,238	15,641	
Incident cancers	93	98	84	77	69	
HR (95% CI)	1	1.10 (0.82-1.48)	0.93 (0.67-1.28)	0.89 (0.63-1.26)	0.87 (0.59-1.27)	0.95 (0.87-1.04)
			Women (*n* = 15,041)			
Vegetables* and fruits						
Quintile median	522	704	847	1011	1314	
Person-time	21,858	22,210	22,372	22,480	23,060	
Incident cancers	104	84	89	81	72	
HR (95% CI)	1	0.79 (0.59-1.06)	0.84 (0.62-1.13)	0.74 (0.53-1.03)	0.61 (0.41-0.90)	0.90 (0.83-0.98)
			Overall (*n* = 25,623)			
Vegetables* and fruits						
Person-time	36,677	37,389	37,556	37,718	38,701	
Incident cancers	197	182	173	158	141	
HR (95% CI)	1	0.95 (0.77-1.16)	0.91 (0.73-1.13)	0.84 (0.66-1.07)	0.77 (0.59-1.01)	0.94 (0.88-0.99)

NOTE: Data were adjusted for age (<35, 35-44, 45-54, 55-64, and >65 y; categorically), formal education (≤5, 6-11, 12, and ≥13 y; categorically), smoking status (never smoker, former smoker, and five categories of current smoker: 1-10, 11-20, 21-30, 31-40, and ≥41 cigarettes/d; ordered), body mass index (in ordered quintiles), height (in ordered quintiles), physical activity expressed in MET-hours per day (in ordered quintiles), alcohol intake (per 10 g/d; continuously), supplement intake (no, yes), and total daily energy intake (in ordered quintiles). For both genders overall stratified by sex.
*Legumes are included.

energy intake and other covariates that have their own errors and may be variably correlated among themselves, an attenuation of a modest inverse association of vegetables and fruits with cancer occurrence cannot be excluded. Dekker and Verkerk (36) postulate that protection of vegetables and fruits is conveyed by certain components within them and that these components may have variable effects with variable latencies with respect to the various outcomes (cancer in different sites). Potter (37) speculates about genuine exposure variability over time and points out that when cancer is considered as a consolidated outcome, one has to take into account that some cancers may be strongly related to vegetables and fruits, and others not at all. Finally, Hung and colleagues argue that perhaps cancer risk is elevated only in individuals with low intake of vegetables and fruits and that supplement intake may distort the association of vegetables and fruits with cancer—the latter argument is also supported by the data of Olsen et al. (38). In our study, however, there was no evidence that the inverse association pattern was more evident among supplement nonusers than among users.

It is possible that the results of Hung et al. (13) approximate reality better and that the findings from the Greek EPIC cohort are an aberration. Selection and information bias, however, cannot be invoked to explain the findings of our study given its prospective cohort design and that possible confounders, including age, tobacco smoking, educational lever, physical activity, supplement intake, and energy intake, have been controlled for. Chance, although it cannot be completely dismissed, is an unlikely explanation of our findings given the overall pattern presented in Tables 4 and 5.

There are other potential explanations for the discrepancy noted between our results and those of Hung and colleagues. Dietary ascertainment in the Greek EPIC cohort was based on an interviewer-administered questionnaire, whereas the dietary questionnaires in the Nurses' Health Study and in the Health Professionals' Follow-up Study were self-administered. There is no evidence, however, that the Greek, interviewer-administered, questionnaire has generated more valid results than the self-administered one used in the American cohorts. It is also possible that the high consumption of fruits and, particularly, vegetables in certain segments of the Greek population facilitates the documentation of a log-linear association; it may be of importance that when vegetables and fruits were combined, the reduction of cancer risk was particularly evident in the upper two quintiles (Q4 and Q5). Finally, consumption of seasonal fresh vegetables and fruits is more likely in the Greek rather than the American population.

Strengths of our investigation are its prospective design, the employment of interviewer-administered validated research instruments, and the use as outcome of medically confirmed cases of incident cancer. Limitations of our study are the inability to separately examine individual cancer sites in relation to vegetable and fruit intake because of power limitations. This could lead to underestimation of the strength of association between vegetables and fruits and genuinely related cancer sites because overall cancer occurrence incorporates the occurrence of tumor sites for which there has been little or no evidence for an association with these foods (e.g., lymphoid neoplasms and prostate cancer). The use of time of cancer death as substitute for the time of cancer diagnosis for 110 of the 851 incident cancer cases is also a limitation. It should be noted, however, that in many instances in Greece, cancer diagnosis is hidden from the patient so that sensitivity of ascertainment is somewhat reduced, although specificity is very high because medical confirmation is required.

Calculation of cancer rates attributable to reduced consumption of vegetables and fruits would be of obvious importance. These calculations are hindered by the fact that attributable rates must rely on both the hazard ratios and the prevalence of the exposure (here reduced vegetable and fruit consumption), each of which has its own chance variation. Moreover, attributable rates are strictly interpretable when they rely on a random sample of the population. The Greek EPIC cohort, although population based, relies on volunteers. Nevertheless, we have attempted calculation of attributable rates using a simple procedure suggested by Wahrendorf (39). If every participant in the Greek EPIC cohort was consuming the quantities of vegetables and fruits of the upper (highest) quartile, then cancer incidence would be reduced by 4.5% among men and by 26% among women.

In conclusion, we have found evidence from a cohort study based on the general population of Greece that consumption of vegetables, and perhaps fruits, is inversely associated with cancer incidence. The association, however, seems to be somewhat weaker than would have been expected on the basis of case-control studies previously undertaken in Greece.

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