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Research Article

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Variety in Fruit and Vegetable Consumption and the Risk of Lung Cancer in the European Prospective Investigation into Cancer and Nutrition

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Abstract

Background: We investigated whether a varied consumption of vegetables and fruits is associated with lower lung cancer risk in the European Prospective Investigation into Cancer and Nutrition study.

Methods: After a mean follow-up of 8.7 years, 1,613 of 452,187 participants with complete information were diagnosed with lung cancer. Diet diversity scores (DDS) were used to quantify the variety in fruit and vegetable consumption. Multivariable proportional hazards models were used to assess the associations between DDS and lung cancer risk. All models were adjusted for smoking behavior and the total consumption of fruit and vegetables.

Results: With increasing variety in vegetable subgroups, risk of lung cancer decreases [hazard ratios (HR), 0.77; 95% confidence interval (CI), 0.64-0.94 highest versus lowest quartile; *P* trend = 0.02]. This inverse association is restricted to current smokers (HR, 0.73; 95% CI, 0.57-0.93 highest versus lowest quartile; *P* trend = 0.03). In continuous analyses, in current smokers, lower risks were observed for squamous cell carcinomas with more variety in fruit and vegetable products combined (HR/two products, 0.88; 95% CI, 0.82-0.95), vegetable subgroups (HR/subgroup, 0.88; 95% CI, 0.79-0.97), vegetable products (HR/two products, 0.87; 95% CI, 0.79-0.96), and fruit products (HR/two products, 0.84; 95% CI, 0.72-0.97).

Conclusion: Variety in vegetable consumption was inversely associated with lung cancer risk among current smokers. Risk of squamous cell carcinomas was reduced with increasing variety in fruit and/or vegetable consumption, which was mainly driven by the effect in current smokers.

Impact: Independent from quantity of consumption, variety in fruit and vegetable consumption may decrease lung cancer risk. *Cancer Epidemiol Biomarkers Prev; 19(9); 2278–86. ©2010 AACR.*

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Introduction

Lung cancer is one of the most common cancers in humans. In high-income countries, due to declining smoking rates in the past decades, age-adjusted rates of lung cancer are decreasing among men, whereas rates are increasing in many low-income countries. In women, incidence rates are lower (globally, the age-standardized incidence rate is 12.1 per 100,000 women compared with 35.5 per 100,000 men; refs. 1, 2), but rates among women are rising in many countries (3). The major risk factor for lung cancer is tobacco smoking (3, 4).

Vegetable and fruit consumption has been hypothesized to influence lung cancer risk. The 2007 World Cancer Research Fund/American Institute for Cancer Research expert report "Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective" concluded that fruits probably protect against lung cancer and that there is only limited evidence suggesting that nonstarchy vegetables, selenium, and foods containing it protect against lung cancer (1). The relationship between lung cancer incidence and fruit and vegetable consumption was previously investigated within the European Prospective Investigation into Cancer and Nutrition (EPIC) study. A reduced risk of lung cancer was found with a high consumption of fruit (5-7). Also, a reduced risk was found with a high vegetable consumption in current smokers (6, 7). No clear relationship between fruit and vegetable consumption and histologic subtypes of lung cancer was observed (7). In current smokers, the consumption of vegetables and fruits seemed to slightly reduce lung cancer risk, in particular, the risk of squamous cell carcinomas, but residual confounding by smoking could not be ruled out.

None of the studies on fruit and vegetable consumption and lung cancer risk evaluated a potential role of the diversity in fruit and vegetable consumption. Different fruits and vegetables contain many different bioactive compounds. None of these bioactive compounds is found to be solely responsible for reducing cancer risk (1). Simply looking at the quantity of fruit and vegetable consumption might therefore not fully capture the mechanisms responsible for decreasing cancer risk. Looking at the diversity of fruit and vegetable consumption, reflecting an intake of many different bioactive compounds present in fruits and vegetables, might complement the research on fruit and vegetable consumption and cancer risk.

Diet diversity scores (DDS) are frequently used to measure diet variety. The DDS usually measures the number of different predefined food groups eaten over a certain period of time, but it can also be used to measure the variety within a specific food group (8). The DDS for total diet and specific food groups has already been associated with risks of several cancers like colorectal (8-11), gastric (12), breast (13), oral and pharyngeal cancer (14, 15), and squamous cell esophageal cancer (16). In all but one of these studies (11), decreased risks were reported with increased variety in diet especially with increased diversity in vegetable consumption.

The purpose of this study is to evaluate the associations between the variety in fruit and vegetable consumption, independent from the total fruit and vegetable consumption and the risk of primary lung cancer among participants in the EPIC study.

Materials and Methods

Study participants

EPIC is an ongoing multicenter cohort study designed to investigate the relationships between diet, lifestyle and environmental factors, and the incidence of cancer. The total cohort consists of cohorts of men and women recruited from 23 centers in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. The populations and methods have been described in full elsewhere (17). In brief, the EPIC cohort consists of 521,468 subjects, mostly ages 25 to 70 years, recruited during the period 1991 to 2000 mostly from the general population residing in a specific geographic area, a town, or a province. As a rule, those who participated signed an informed consent form, and diet and lifestyle questionnaires were mailed to them, except in all Spanish centers, Greece, and Ragusa (Italy) where interviewer-administered questionnaires were used. In most countries, study subjects were invited to visit a center for blood collection and anthropometric measurements and to deliver the completed diet and lifestyle questionnaires (17).

Diet and lifestyle questionnaires

At baseline, usual diet before enrollment was measured by country-specific validated questionnaires designed to capture local dietary habits. Although the design of the questionnaires was based on the same general format, there were differences between the questionnaires used in several countries. Extensive self-administered quantitative dietary questionnaires were used in northern Italy, the Netherlands, Germany, and Greece. In France, Spain, and Ragusa (Italy), questionnaires similar to the dietary questionnaires, but structured by meals, were used. To increase compliance, the centers in Spain and Ragusa did a face-to-face dietary interview using a computerized dietary program. Semiquantitative food frequency questionnaires with the same standard portion assigned to all participants were used in Denmark, Norway, Naples (Italy), and Umeå (Sweden). In the United Kingdom, a semiquantitative food frequency questionnaire and a 7-day record were used (17). Details of food items included in the selected vegetables and fruits subgroups used in the analysis have been reported in full by Agudo et al. (18).

Lifestyle questionnaires included questions on education, occupation, medical history, lifetime history of consumption of tobacco, alcoholic beverages, and physical activity (17).

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DDS for vegetable and fruit consumption

Country-specific dietary questionnaires differed in the number of vegetables and fruits included. To improve between-country comparability of the scores, we decided to only select vegetable and fruit products asked about in four or more country-specific dietary questionnaires, this included the majority of products. We were not able to use data from the Malmö center (Sweden) because the frequency of consumption data was not available in the central data set.

Based on the baseline dietary questionnaires, four different DDS were calculated: DDSvegfr (range, 0-40) counts the total number of different vegetable and fruit products eaten at least once in 2 weeks. DDSveggr (range, 0-8) counts the total number of different vegetable subgroups eaten at least once in 2 weeks. The eight subgroups of vegetables used were: leafy vegetables, fruiting vegetables, root vegetables, cabbages, mushrooms, grain and pod vegetables, onion and garlic, and stalk vegetables (19). DDSvegpr (range, 0-26) counts the total number of different vegetable products eaten at least once in 2 weeks. DDSfr (range, 0-14) counts the total number of different fruit products eaten at least once in 2 weeks. The consumption of vegetables did not include legumes, potatoes, and other tubers. The consumption of fruit included fresh, dried, and canned fruits but excluded nuts, seeds, and olives.

End points

Follow-up was based on population-based cancer registries in seven of the participating countries: Denmark, Italy, Netherlands, Spain, Sweden, United Kingdom, and Norway. In France, Germany, and Greece, a combination of methods was used, including health insurance records, cancer and pathology hospital registries, and active follow-up. Mortality data were also collected from registries at the regional or national level (17). Censoring dates for complete follow-up were between December 2002 and December 2005. For Germany and Greece, the end of follow-up was considered to be the last known contact, the date of diagnosis or the date of death, whichever came first.

Cancer of the lung was defined as code C34 of the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death. Based on the morphology codes of the WHO International Histological Classification of Tumors histological types were classified into four major histological types: squamous cell carcinoma (8052, 8070-8073, 8075, and 8123), small cell carcinoma (8041-8045 and 8246), large cell carcinoma (8012, 8020-8021, and 8082), and adenocarcinoma (8140, 8143, 8200, 8211, 8230, 8250-8251, 8260, 8300, 8310, 8480-8481, 8490, and 8550). Other histologic types (8010-8011, 8022, 8030-8032, 8046, 8240, 8243, 8430, 8560, 8710, 8720, 8800-8801, 9120, 9133, 9590, 9591, 9671, and 9699) and unclassified histologic types of carcinomas (8000-8001 and missing histologic data) were placed into a miscellaneous category. Only first incident lung cancer cases were taken into account.

Statistical methods

Cox proportional hazards regression was used to analyze the association between the variety in fruit and vegetable consumption and risk of lung cancer. Age was used as the primary time variable in the models with entry time defined as age at recruitment and exit time as age at diagnosis, age at death or age at end of follow-up, whichever came first. All analyses were stratified by age at recruitment (in 1-year categories) to control for length of follow-up, and by gender and center to control for country effects such as follow-up procedures and questionnaire design. The proportional hazard assumption was tested by introducing an interaction term between time and the exposure variable. Cases diagnosed after censoring date were considered as noncases.

A total of 453,460 participants provided data for the construction of the four DDS and did not have a history of cancer at baseline. We excluded participants with incomplete nondietary information (n = 784), participants with missing data on dietary information (n = 30), and participants within the extreme 1% percentiles of the distribution of the estimated energy intake to energy expenditure of the total EPIC cohort (in our study, n = 459). A total of 452,187 participants were left for analysis.

The DDS were divided into quartiles according to the distribution observed in the study population, with the lowest quartile as reference category. In addition, we did continuous analysis with increments of two products for DDSvegfr, DDSvegpr, and DDSfr and with increments of one group for DDSveggr. To analyze the associations between the variety in fruit and vegetable consumption and lung cancer risk independent of the amount of fruit and vegetables consumed, we adjusted the variety of vegetable and fruit consumption (DDSvegfr) for the amount of vegetable and fruit consumption, the variety of vegetable consumption (DDSveggr and DDSvegpr) for the amount of vegetable consumption, and the variety of fruit consumption (DDSfr) for the amount of fruit consumption.

In the overall model, we controlled for smoking status (current, former, never), duration of smoking (continuous in years), lifetime intensity of smoking (continuous in cigarettes per day), the number of cigarettes smoked at baseline (continuous in cigarettes per day). Additionally, we included the lifetime number of cigarettes squared. Indicator variables were used for missing values related to the intensity (11% missing values) and duration (5% missing values) of smoking. Individuals with unknown smoking status (n = 6,258; 1.4%) were excluded from the Cox regression analyses. All models additionally included body mass index (kg/m^2), energy intake from fat and nonfat sources (continuous in kcal/d). All covariates were included as separate variables on a continuous scale unless stated otherwise. The following variables were tested in the model but showed no effect on the model parameters and are therefore not included in the final model: consumption of red and processed meat, alcohol consumption, physical activity, and educational level.

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We derived probability values for a linear trend across quartiles from regression models using the median consumption within the quartiles as a continuous variable, hereby taking the unequal distances of the quartiles into account (20).

Analyses were also done separately by smoking status. Interaction (on the multiplicative scale) was tested using the interaction term of fruit and/or vegetable variety (in quartiles) with smoking status.

Additionally, we analyzed whether there were differences between the four main histologic subtypes of lung cancer, i.e., adenocarcinomas, small cell, large cell, and squamous cell carcinomas. When analyzing the different histologic subgroups of lung cancers, the histologic subtypes of no interest were censored at the time of diagnosis.

To evaluate whether preclinical disease might have influenced results, additional analyses were conducted after the exclusion of cases that were diagnosed within 2 years after recruitment. All analyses were done using SAS version 9.1 (SAS Institute, Inc.).

Results

After a mean follow-up of the cohort of 8.7 years, 1,613 participants were newly diagnosed with a first primary incident lung cancer: 503 were classified as adenocarcinomas, 250 as small cell carcinomas, 87 as large cell carcinomas, and 326 as squamous cell carcinomas; 250 cases had other specified histologies and the histology was not specified for 197 participants. Tumors (78%) were microscopically confirmed, 86% of which were histologically confirmed (67% of the total number of cases). Table 1 shows the frequency of lung cancer and the histologic subtypes of lung cancer, stratified by country, included in the analysis.

Selected characteristics across quartiles of variety in vegetable and fruit consumption are shown in Table 2. The quantity of vegetable and fruit consumption and energy intake increased with increasing variety in fruit and vegetable consumption. Those reporting higher variety in vegetable and fruit consumption were leaner, more likely to be female, and never smokers.

Adjusted hazard ratios (HR) for lung cancer by quartiles of DDS for the whole cohort and by smoking status are presented in Table 3. With increasing variety in the consumption of vegetable subgroups, the overall risk of lung cancer decreased. The HR for the highest quartile compared with the lowest quartile is 0.77 with 95% confidence interval (CI) of 0.64 to 0.94, and P for trend is 0.02. Every additional different vegetable subgroup eaten decreases the risk of lung cancer by 4% (HR, 0.96; 95% CI, 0.93-1.00). The other DDS for fruit and vegetable consumption did not show clear associations with lung cancer risk.

Analyses stratified by smoking status show a borderline statistically significant 3% reduction with every two additional different types of vegetable and fruit products in current smokers, whereas no associations were found in former and never smokers. We observed that reduced lung cancer risk with an increased number of different vegetable subgroups eaten, was only present among current smokers, although the continuous estimate is borderline statistically significant. With increasing variety in fruit consumption, we observed a borderline statistically significant 6% lower lung

Table 1. Incidence of lung cancer (the EPIC cohort study)

Country	Person-years	First primary lung cancer	Histology of the tumor n (%)				
			Adenocarcinomas	Squamous cell carcinomas	Small cell carcinomas	Large cell carcinomas	Other and not specified histologies
Denmark	410,382	463	157 (34)	102 (22)	84 (18)	20 (4)	100 (22)
France*	736,299	113	42 (37)	3 (3)	12 (11)	5 (4)	51 (45)
Germany	401,155	186	60 (32)	31 (17)	46 (24)	7 (4)	42 (23)
Greece	180,851	90	22 (24)	15 (17)	12 (13)	2 (2)	39 (43)
Italy	375,858	137	56 (41)	26 (19)	18 (13)	4 (3)	33 (24)
The Netherlands*	310,014	136	54 (40)	27 (20)	23 (17)	21 (15)	11 (8)
Norway*	210,208	68	29 (43)	7 (10)	15 (22)	0 (0)	17 (25)
Spain	394,264	132	41 (31)	31 (23)	18 (14)	24 (18)	18 (14)
Sweden	257,130	58	26 (45)	16 (28)	8 (14)	4 (7)	4 (7)
United Kingdom	626,441	230	55 (24)	71 (31)	26 (11)	5 (2)	73 (32)
Total	3,902,602	1,613	542 (34)	329 (20)	262 (16)	92 (6)	388 (24)

*The French, Norwegian, and Utrecht (the Netherlands) cohorts consisted of women only.

Table 2. Baseline characteristics by quartiles of observed variety in total vegetable and fruit consumption (DDSvegfr) as mean (standard deviation) except otherwise stated (the EPIC Cohort Study)

	Full cohort	DDSvegfr			
		1	2	3	4
Number of different items eaten at least once in 2 wk (range)	—	0-10	11-15	16-22	23-40
General characteristics					
Men (%)	29	33	37	33	14
Age at recruitment (y)	51 (9.9)	50 (8.7)	52 (9.2)	52 (10.6)	50 (10.7)
Height (cm)	165.8 (8.9)	167.2 (8.8)	166.2 (9.3)	165.7 (9.3)	164.1 (7.8)
Weight (kg)	70.1 (13.7)	71.3 (13.9)	72.5 (13.5)	71.3 (13.4)	64.9 (12.4)
BMI (kg/m^2)	25.4 (4.3)	25.4 (4.2)	26.2 (4.3)	25.9 (4.3)	24.0 (4.0)
Physically active (%)*	43	41	42	44	44
Diet					
Energy (kcal/d)	2,077.8 (621.1)	1,907.5 (615.8)	2,079.3 (626.1)	2,153.0 (614.6)	2,181.1 (588.9)
Energy from fat sources (kcal/d)	744.2 (272.7)	680.4 (262.7)	738.2 (263.0)	777.9 (267.6)	782.9 (284.8)
Energy from nonfat sources (kcal/d)	1,333.6 (408.3)	1,227.1 (402.2)	1,341.2 (415.8)	1,375.1 (414.5)	1,398.1 (376.4)
Consumption of vegetables (g/d)	214.2 (147.8)	134.7 (109.9)	174.8 (107.1)	234.8 (134.7)	316.9 (165.0)
Consumption of fruit (g/d)	241.4 (197.1)	148.3 (135.1)	213.4 (170.5)	288.2 (203.3	318.6 (222.4)
Alcohol nonconsumers (%)	7	10	9	5	2
Alcohol consumption (g/d)†	6.4	4.6	7.4	7.2	6.7
Red and processed meat (g/d)	75.8 (51.5)	75.2 (50.6)	86.1 (52.5)	78.0 (50.8)	64.3 (50.2)
Smoking status (%)					
Never smokers	50	46	45	48	62
Former smokers	27	26	28	28	25
Lifetime number of cigarettes (cigarettes/d)	9.4 (9.8)	8.2 (9.4)	10.8 (9.5)	11.1 (9.9)	7.3 (9.7)
Current smokers	22	27	26	23	12
Lifetime number of cigarettes (cigarettes/d)	10.9 (8.5)	10.6 (8.6)	12.0 (7.9)	11.6 (8.4)	8.1 (9.1)
Smoke duration (y)	29.3 (10.9)	29.9 (9.8)	30.4 (10.5)	29.3 (11.5)	25.7 (11.9)
Unknown	1	2	1	1	1
Educational level (%)					
None	4	4	8	5	1
Primary school	23	28	29	24	10
Technical/professional school	23	26	26	25	13
Secondary school	24	22	18	23	33
University degree	24	20	19	21	37
Not specified	2	0	1	3	6

Abbreviation: BMI, body mass index.

*The Cambridge Physical Activity Index incorporates occupational and nonoccupational physical activity.

†Median consumption of alcohol excluding nonconsumers.

cancer risk among current smokers (HR, 0.94; 95% CI, 0.89-1.00), but in the categorical analyses, no clear downward trend is seen. Again, no associations were seen in former and never smokers. The interaction with smoking status was only statistically significant for the association of different types of vegetable and fruit products and lung cancer risk ($P = 0.01$).

In Table 4, HRs are given for the different DDS for fruit and vegetable consumption as measured with continuous variables and the risk of three main histologic subtypes of lung cancer, for the whole cohort, and stratified by smoking status. We observed lower risks for squamous cell carcinomas with more variety in fruit and vegetable products (HR/two products, 0.91; 95% CI, 0.86-0.96), more variety in vegetable subgroups (HR/one subgroup increment, 0.87; 95% CI, 0.80-0.95), and more variety in vegetable products (HR/two products, 0.88; 95% CI, 0.82-0.95). Lower risks for squamous cell carcinomas were restricted to current smokers (HR, 0.88; 95% CI, 0.82-0.95; HR, 0.88; 95% CI, 0.79-0.97; and HR, 0.87; 95% CI, 0.79-0.96 for DDSvegfr, DDSveggr, and DDSvegpr, respectively). Lower risks were not observed among former smokers. There were too few squamous cell carcinomas to calculate reliable HRs among never

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smokers. Interaction with smoking status was not statistically significant (with P values for interaction ranging from 0.13 for DDSfr to 0.85 for DDSveggr). With increasing variety in fruit consumption, the findings suggest a lower risk of squamous cell carcinomas (HR/two products, 0.90; 95% CI, 0.80-1.01) which is statistically significant among current smokers (HR/two products, 0.84; 95% CI, 0.72-0.97). None of the DDS for fruit and vegetable consumption are found to be associated with risk of adenocarcinomas or small cell carcinomas. For large cell

Table 3. Adjusted HRs and 95% CI for lung cancer by quartiles of the four different diversity scores for the full cohort and by smoking status (the EPIC cohort study)

	Range	Full cohort (*n* = 445,923)*		Current smokers (*n* = 100,488)		Former smokers (*n* = 120,064)		Never smokers (*n* = 225,371)	
		Lung cancer	HR (95% CI)	Lung cancer	HR (95% CI)	Lung cancer	HR (95% CI)	Lung cancer	HR (95% CI)
DDS vegetable and fruit products[†,‡]									
Q1	0-10	507	1	386	1	82	1	39	1
Q2	11-15	438	0.91 (0.79-1.04)	279	0.82 (0.69-0.98)	127	1.26 (0.93-1.72)	32	1.07 (0.62-1.86)
Q3	16-22	465	0.94 (0.80-1.10)	276	0.85 (0.70-1.04)	144	1.22 (0.87-1.71)	45	1.08 (0.62-1.87)
Q4	23-40	197	0.96 (0.75-1.21)	80	0.83 (0.59-1.16)	66	1.43 (0.89-2.29)	51	1.06 (0.61-1.85)
P trend			0.65		0.16		0.35		0.89
Continuous per two products increment			0.99 (0.97-1.01)		0.97 (0.95-1.00)		1.01 (0.96-1.05)		1.00 (0.96-1.05)
DDS vegetable subgroups[‡]									
Q1	0-4	380	1	264	1	80	1	36	1
Q2	5-6	545	0.92 (0.80-1.06)	359	0.91 (0.77-1.09)	129	0.81 (0.60-1.10)	57	1.43 (0.87-2.36)
Q3	7	358	0.86 (0.73-1.02)	215	0.89 (0.72-1.11)	93	0.80 (0.56-1.14)	50	1.04 (0.61-1.76)
Q4	8	324	0.77 (0.64-0.94)	183	0.73 (0.57-0.93)	117	0.86 (0.59-1.26)	24	0.81 (0.42-1.59)
P trend			0.02		0.04		0.70		0.90
Continuous per 1 product group increment			0.96 (0.93-1.00)		0.96 (0.92-1.01)		0.95 (0.88-1.03)		0.99 (0.89-1.10)
DDS vegetable products[‡]									
Q1	0-6	436	1	312	1	85	1	39	1
Q2	7-10	475	0.96 (0.84-1.11)	319	0.93 (0.78-1.10)	115	0.91 (0.67-1.23)	41	1.41 (0.83-2.39)
Q3	11-15	488	0.90 (0.77-1.05)	309	0.88 (0.72-1.07)	143	0.94 (0.68-1.31)	36	0.82 (0.47-1.43)
Q4	16-26	208	0.94 (0.74-1.18)	81	0.77 (0.55-1.08)	76	1.09 (0.70-1.69)	51	1.15 (0.66-1.98)
P trend			0.31		0.11		0.61		0.89
Continuous per two products increment			0.99 (0.96-1.02)		0.98 (0.94-1.02)		0.99 (0.93-1.06)		1.00 (0.94-1.07)
DDS fruit products[†]									
Q1	0-2	493	1	368	1	96	1	29	1
Q2	3-5	567	0.97 (0.85-1.10)	360	0.92 (0.79-1.08)	155	1.09 (0.83-1.44)	52	1.26 (0.74-2.12)
Q3	6-8	335	0.92 (0.78-1.10)	192	0.87 (0.70-1.08)	112	1.22 (0.87-1.71)	31	0.87 (0.48-1.56)
Q4	9-14	212	0.94 (0.76-1.17)	101	0.91 (0.68-1.23)	56	1.14 (0.74-1.78)	55	1.12 (0.66-1.91)
P trend			0.42		0.24		0.20		0.95
Continuous per two products increment			0.98 (0.94-1.02)		0.94 (0.89-1.00)		1.05 (0.96-1.15)		1.02 (0.93-1.12)

NOTE: Cox regression model stratified by age at recruitment, gender, and center and adjusted for duration of smoking, lifetime number of cigarettes, current number of cigarettes, body mass index, and energy intake from fat and nonfat sources.

*Cox regression model additionally adjusted for smoking status.

[†]Cox regression model additionally adjusted for fruit consumption.

[‡]Cox regression model additionally adjusted for vegetable consumption.

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Table 4. Adjusted continuous HRs and 95% CI for lung cancer and histologic subgroups of lung cancer per two products increment for DDSvegfr, DDSvegpr, and DDSfr and per one product group increment for DDSveggr

	Full cohort (*n* = 445,923)*		Current smokers (*n* = 100,488)		Former smokers (*n* = 120,064)		Never smokers (*n* = 225,371)	
	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
DDS vegetable and fruit products† ‡								
Lung cancer	1,607	0.99 (0.97-1.01)	1,021	0.97 (0.95-1.00)	419	1.01 (0.96-1.05)	167	1.00 (0.96-1.05)
Adenocarcinomas	542	1.00 (0.97-1.04)	302	0.99 (0.93-1.05)	150	1.02 (0.95-1.10)	90	1.02 (0.96-1.08)
Small cell carcinomas	258	1.01 (0.95-1.07)	215	1.00 (0.94-1.07)	42	1.02 (0.89-1.17)	1	—
Squamous cell carcinomas	328	0.91 (0.86-0.96)	224	0.88 (0.82-0.95)	94	0.98 (0.88-1.08)	10	—
DDS vegetable subgroups‡								
Lung cancer	1,607	0.96 (0.93-1.00)	1,021	0.96 (0.92-1.01)	419	0.95 (0.88-1.03)	167	0.99 (0.89-1.10)
Adenocarcinomas	542	0.97 (0.91-1.04)	302	0.97 (0.89-1.06)	150	0.95 (0.83-1.08)	90	1.05 (0.90-1.24)
Small cell carcinomas	258	0.97 (0.88-1.06)	215	0.96 (0.87-1.07)	42	0.91 (0.71-1.17)	1	—
Squamous cell carcinomas	328	0.87 (0.80-0.95)	224	0.88 (0.79-0.97)	94	0.87 (0.74-1.02)	10	—
DDS vegetable products‡								
Lung cancer	1,607	0.99 (0.96-1.02)	1,021	0.98 (0.94-1.02)	419	0.99 (0.93-1.06)	167	1.00 (0.94-1.07)
Adenocarcinomas	542	1.03 (0.97-1.08)	302	1.03 (0.95-1.12)	150	1.04 (0.94-1.16)	90	1.02 (0.93-1.13)
Small cell carcinomas	258	0.99 (0.91-1.07)	215	0.98 (0.90-1.08)	42	0.97 (0.81-1.18)	1	—
Squamous cell carcinomas	328	0.88 (0.82-0.95)	224	0.87 (0.79-0.96)	94	0.92 (0.81-1.05)	10	—
DDS fruit products†								
Lung cancer	1,607	0.98 (0.94-1.02)	1,021	0.94 (0.89-1.00)	419	1.05 (0.96-1.15)	167	1.02 (0.93-1.12)
Adenocarcinomas	542	0.96 (0.89-1.03)	302	0.90 (0.81-1.01)	150	0.99 (0.86-1.15)	90	1.03 (0.90-1.17)
Small cell carcinomas	258	1.06 (0.94-1.18)	215	1.04 (0.91-1.18)	42	1.16 (0.87-1.55)	1	—
Squamous cell carcinomas	328	0.90 (0.80-1.01)	224	0.84 (0.72-0.97)	94	1.11 (0.89-1.37)	10	—

NOTE: Cox regression model stratified by age at recruitment, gender, and center and adjusted for duration of smoking, lifetime number of cigarettes, current number of cigarettes, body mass index, and energy intake from fat and nonfat sources.
*Cox regression model additionally adjusted for smoking status.
†Cox regression model additionally adjusted for fruit consumption.
‡Cox regression model additionally adjusted for vegetable consumption.

carcinomas, we did not have enough cases to perform these analyses. The HRs do not change when the analyses are repeated with the exclusion of the first 2 years of follow-up.

Discussion

More variety in vegetable consumption, as represented by the number of different vegetable subgroups eaten was associated with a lower risk of lung cancer. This lower risk was only seen among current smokers. When analyzed by subtype of lung cancer, higher variety in fruit and vegetable consumption (combined and separately) was inversely associated with risk of squamous cell carcinomas, which was mainly driven by the effect among current smokers. For adenocarcinomas and small cell carcinomas, no associations with variety in vegetable and/or fruit consumption were observed.

Previously, we described the associations between the quantity of fruit and vegetable consumption (g/d) and lung cancer risk and its histologic subtypes (7). We found inverse associations between the consumption of vegetables and fruits combined and lung cancer and between fruits and risk of lung cancer. In current smokers, we found that consumption of vegetables and fruits, both combined and separately, may reduce lung cancer risk, in particular, the risk of squamous cell carcinoma (7). Our current results suggest that, over and above the inverse association with quantity, the variety in vegetable consumption might reduce lung cancer risk in the full cohort, especially among current smokers. On the other hand, inverse associations between risk of lung cancer and the quantity of fruit and vegetable consumption combined and for fruits alone reported previously, were not consistently linked to associations with the variety of intakes. Both studies consistently showed the strongest reduced risks among current smokers and squamous cell carcinomas. It should be kept in mind, however, that irrespective of adjustment for total quantity, individuals with a more varied fruit and vegetable consumption are in general also the individuals consuming more fruits and vegetables, and these individuals are probably also comparable for other lifestyle

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factors. Although we adjust for several of these factors, residual confounding cannot be ruled out.

Vegetables and their consumption are generally considered as food items that are not very easy to assess in food frequency questionnaires (as well as in other methods of dietary assessment). Indeed, within the EPIC validation studies, which compared the food frequency questionnaires with the average of 12 24-hour recalls, the correlation coefficients for relative validity of total vegetable consumption were in general lower (between 0.30 among Italian men and 0.54 among French women) than those for fruits (between 0.33 among German men and 0.79 among Spanish men; ref. 21). In this study, we observed inverse associations with more variety in vegetable consumption and lung cancer risk. This may indicate that the quantity of vegetables is poorly assessed in the EPIC dietary questionnaires due to difficulties in assessing portion size, but that the frequency of consumption of types of vegetables is better assessed. Alternatively, a varied consumption of vegetables may be more etiologically relevant than the quantity of vegetable consumption in reducing lung cancer risk because a more varied consumption of vegetables results in a more varied intake of the bioactive compounds present in fruits and vegetables. In addition, we observed stronger inverse associations with increasing diversity in vegetable subgroups compared with increased diversity in vegetable products. This can be explained by the fact that an increment in different vegetable subgroups eaten probably reflects a much greater diversity than increments in vegetable products eaten.

As far as we know, this is the first attempt to specifically evaluate the role of the diversity of fruit and vegetable consumption on lung cancer risk. Different fruit and vegetable products contain different bioactive compounds like carotenoids and vitamins. A greater variety in fruit and vegetable consumption therefore represents a more varied intake of these substances. Alternatively, the consumption of many different kinds of fruit and vegetable products makes it more likely to consume specific bioactive compounds that might reduce (lung) cancer risk. As individuals consuming a wide variety of fruit and vegetable products are also more likely to consume more fruit and vegetables, we adjusted our analyses for the overall fruit and vegetable consumption.

Because the dietary questionnaires differed slightly between the different EPIC centers, we calculated the DDS based on fruit and vegetable products included in four or more dietary questionnaires. This makes the DDS better comparable between countries because if more fruit and vegetable products are included in the questionnaires, individuals are more likely to report eating them. However, it also induces bias. We therefore also calculated DDS based on all fruit and vegetable products included in the dietary questionnaires. HRs are similar using these DDS compared with those reported in this article.

DDS have previously been used to describe the variety within diets or food groups. Jansen et al. looked specifically at the diversity of fruit and vegetable consumption in relation to cancer risk in the Zutphen cohort study and found decreased overall cancer risks among individuals with a higher variety in vegetable consumption which was adjusted for total vegetable consumption (20). Nine case-control studies, of which seven were from the same study base in Italy (9, 10, 12-16) and two from the United States (8, 11), looked at the relationship between diversity in overall diet and within specific food groups and the risk of several cancers (8-16). Four of these case-control studies focused on colorectal cancer, with three of those studies finding a reduced colorectal cancer risk with higher variety in total diet (8-10). All studies found lower risks of colon cancer with increased variety in vegetable consumption (8-11). Also for gastric cancer (12), oral and pharyngeal cancer (14, 15), breast cancer (14), and squamous cell carcinoma of the esophagus (16), protective effects were found for a more diverse diet, especially for a more diverse consumption of fruits and vegetables, although only three studies (10, 11, 13) adjusted specifically for the total number of fruit and vegetable servings consumed.

Few cohort studies have analyzed the effect of fruits and vegetables on different histologic subtypes of lung tumors (22-26). Most studies have divided lung tumors into two groups: Kreyberg I (comprising small cell carcinomas, squamous cell carcinomas, and large cell carcinomas) and Kreyberg II (adenocarcinomas). There were indications that fruits and vegetables were more protective for nonadenocarcinomas (Kreyberg I) than for adenocarcinomas (Kreyberg II; refs. 25, 27, 28). In both our previous and in our current study on the quantity and variety of vegetable and fruit consumption, and the risk on the different histologic subtypes of lung cancer, we found associations for squamous cell carcinomas and no associations for the other histologic subtypes of lung cancer.

Several studies have indicated a protective effect of fruits and vegetables on lung cancer risk among current smokers only (24, 29, 30). It is argued that the inverse association among current smokers seen in some studies might be due to residual confounding by smoking (25). Although we have paid special attention to control for smoking behavior, residual confounding by smoking also cannot be excluded in our study. Conversely, these studies suggested that antioxidants from vegetables and fruits strongly reduce oxidative stress due to smoking. Because of the large number of bioactive constituents in fruits and vegetables, other biological mechanisms may explain our findings such as counteracting nitrosation and influencing bioactive transformations.

The important advantages of our cohort study are its size and the large heterogeneity of fruit and vegetable consumption, lung cancer incidence, and other lifestyle habits caused by the recruitment of participants living in countries from the North to the South of Europe.

In conclusion, we found inverse associations between the variety in vegetable consumption and lung cancer risk in EPIC. These associations were restricted to current smokers. A varied consumption of fruit and vegetables combined and alone reduced the risk of squamous cell carcinomas, which was mainly driven by the effect in current smokers. The greater variety in fruit and/or vegetable consumption was not related to lung cancer risk in former and never smokers nor was it related to the risk of adenocarcinomas and small cell carcinomas. Because smoking is the predominant risk factor, the primary focus for public health in reducing lung cancer incidence should continue to be smoking prevention and cessation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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