Fruit and vegetable consumption and lung cancer risk: Updated information from the European Prospective Investigation into Cancer and Nutrition (EPIC)

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The association of fruit and vegetable consumption and lung cancer incidence was evaluated using the most recent data from the European Prospective Investigation into Cancer and Nutrition (EPIC), applying a refined statistical approach (calibration) to account for measurement error potentially introduced by using food frequency questionnaire data. Between 1992 and 2000, detailed information on diet and life-style of 478,590 individuals participating in EPIC was collected. During a median follow-up of 6.4 years, 1,126 lung cancer cases were observed. Multivariate Cox proportional hazard models were applied for statistical evaluation. In the whole study population, fruit consumption was significantly inversely associated with lung cancer risk while no association was found for vegetable consumption. In current smokers, however, lung cancer risk significantly decreased with higher vegetable consumption; this association became more pronounced after calibration, the hazard ratio (HR) being 0.78 (95% CI 0.62–0.98) per 100 g increase in daily vegetable consumption. In comparison, the HR per 100 g fruit was 0.92 (0.85–0.99) in the entire cohort and 0.90 (0.81–0.99) in smokers. Exclusion of cases diagnosed during the first 2 years of follow-up strengthened these associations, the HR being 0.71 (0.55–0.94) for vegetables (smokers) and 0.86 (0.78–0.95) for fruit (entire cohort). Cancer incidence decreased with higher consumption of apples and pears (entire cohort) as well as root vegetables (smokers). In addition to an overall inverse association with fruit intake, the results of this evaluation add evidence for a significant inverse association of vegetable consumption and lung cancer incidence in smokers.

Key words: cancer; diet; epidemiology; fruit; vegetables; lung cancer; smoking

Lung cancer is the most common carcinoma among men worldwide with respect to both incidence and mortality and represents an increasing problem among women[1,2]; still, survival rates are poor. The primary and most effective measure to decrease incidence rates is to control tobacco smoking.[3] Despite convincing evidence for the deleterious effect of smoking, there is considerable interindividual variability in disease susceptibility, and the reasons for which are poorly understood. It is estimated that only ~15% of lifelong smokers in Western Europe will develop lung cancer by the age of 75.[4] Increasing evidence suggests that endogenous and exogenous factors (*e.g.*, allelic variation in selected genes/pathways and dietary factors, respectively) and their interaction modify the association of smoking and lung cancer risk.[5–7] These factors are also potentially relevant in the etiology of lung cancer in nonsmokers.[8]

In 2003, an expert panel at IARC[9] evaluating the evidence for an effect of fruit and vegetable intake on cancer risk concluded that a high intake of fruits probably and intake of vegetables possibly reduces the risk of lung cancer. This conclusion is also supported by a pooled analysis of cohort studies[10] and a recent meta-analysis of cohort studies.[11] The inverse association was found to be stronger for fruit intake when compared to vegetable intake. Although studies in never-smokers also reported significant inverse associations with lung cancer risk, the association of fruits and especially vegetables was often stronger in current smokers.[9] This could be caused by residual confounding if adjustment for smoking is not complete, an argument, which can never be completely excluded when investigating a disease with a very strong risk factor that is inversely associated with the exposure of interest. Alternatively, in subjects with a high and continuous exposure to carcinogens, such as smokers, the suggested benefit from protective substances (and/or their interaction with genetic variants) might be stronger, thus, increasing the likelihood to detect diet-disease associations in epidemiologic research.

Few evaluations by morphological subgroups gave indication for a somewhat stronger association of fruits and vegetables with small-cell and squamous cell carcinoma than for other types of lung cancer.[9] Since these 2 histological subtypes of lung cancer are more often diagnosed in smokers when compared to nonsmokers, more pronounced inverse associations of fruit and vegetable intake for these subtypes would give support for a specific protective effect of plant food against smoking-related carcinogens.

In a first evaluation of data from the European Prospective Investigation into Cancer and Nutrition (EPIC), we reported an inverse association of fruit intake overall and in current smokers and found some indication for an inverse association between vegetable intake and lung cancer risk in smokers.[12] With emphasis on the effects in smokers, the present analyses were performed after a longer follow-up of the cohort, *i.e.*, with an increased number of cases, and extended to the main subgroups of fruit and vegetables. Moreover, a refined statistical approach was used to account for measurement error in the food-frequency-derived dietary intake data, an aspect, which was highlighted recently as an important source of exposure bias also in cohort studies.[13,14] EPIC is one of few cohort studies that are able to correct for misclassification of dietary exposure data by means of 24-hr diet recall data.[15] This approach is especially important in analyses dealing with food intake data since biomarker analyses only apply with nutrients.

Material and methods

Population

EPIC is a large prospective cohort study conducted in 23 centers in 10 European countries [France, Italy (Florence, Varese, Ragusa, Turin, Naples), Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), The Netherlands (Bilthoven, Utrecht), Great Britain (Cambridge, Oxford), Greece, Germany (Heidelberg, Potsdam), Sweden (Malmö, Umea) and Norway, Denmark (Aarhus, Copenhagen)]. About 521,457 participants mostly aged 25–70 years were recruited for this study. In most centers, the participants were recruited from the general population. However, the French cohort encompasses female members of a health insurance scheme for school and university employees and the Spanish and Italian centers include blood donors. In addition, in Utrecht, participants in a mammographic screening program were recruited for the study, and the cohort in Florence also includes screening program participants. In Oxford, half of the cohort consisted of "health conscious" subjects from England, Wales, Scotland and Northern Ireland. The cohorts of France, Norway, Utrecht and Naples include women only.[16]

For this analysis, we excluded prevalent cancer cases (n = 25,868), subjects with incomplete follow-up information (n = 9,296) or with a ratio for energy intake versus energy expenditure in the top and bottom 1% (n = 9,686). Thus, the analysis was based on 478,590 EPIC participants.

Exposure assessment

Food-related questionnaires and lifestyle and personal questionnaires, as well as anthropometric measurements, were collected from all subjects at the time of enrolment in the cohort. The methods have been reported in full.[16] Habitual dietary consumption was recorded over the past year using dietary assessment instruments that were specifically developed for each participating country. Food frequency questionnaires (FFQ) were used at recruitment of the cohorts in France, Italy, Spain, Great Britain, Greece, The Netherlands, Germany, Denmark, Umea and Norway. In Malmö, a nonquantitative FFQ was combined with a 14-day dietary record on hot meals. In a random sample (8%) of each EPIC cohort, highly standardized 24-hr diet recalls were conducted using the software EPIC-SOFT. Detailed 24-hr recall data were available for 36,994 subjects.[15] Foods from the FFQ items were attributed to the identical food groups as defined in EPIC-SOFT, allowing direct comparison between both instruments. The data from this second dietary measurement were used to account for differences in the dietary questionnaires and to minimize measurement error of the FFQ, a procedure called "calibration" (see below).

We considered total daily intake (g/day) of fruit and vegetables as the main exposure variables. The food group fruit consisted of all fresh and dried fruits, excluding nuts and seeds and olives; the food group vegetables did not include potatoes and legumes. The latter were investigated in separate analyses and showed no association with lung cancer risk. Because of their high carbohydrate content, these foods were mostly used to replace for other carbohydrate-rich food; thus, they were not included in the total vegetable variable. Secondary analyses were conducted for the fruit subgroups hard fruits (apples, pears), citrus fruits and fruits containing stones (pits). Concerning vegetables, the subgroups fruiting vegetables (including tomato, pepper, courgette, pumpkin, eggplant, french bean), leafy vegetables, root vegetables, cabbages and onions and garlic were investigated. In addition, all juices from fruit and vegetables as well as the subgroup citrus fruit juices were considered separately.

Detailed information on lifetime history of consumption of tobacco products was assessed by means of questions on smoking status (current, past or never smoker), type of tobacco (cigarettes, cigars or pipe) used, number of cigarettes currently smoked and age when participants started and, if applicable, quit smoking.

Height and weight were measured in all EPIC centers except for France, Norway and Oxford, for which self-reported height and weight was assessed via questionnaire.[16]

Outcome assessment

Cancer diagnoses were based on population registries in Denmark, Varese, Turin, Florence, Ragusa, the Netherlands, Norway, Spain, Sweden and the United Kingdom. An active follow-up through study subjects as well as next-to-kin information, health insurance records and cancer and pathology registries were used in France, Germany, Naples and Greece. Mortality data were also obtained from either the cancer or mortality registries at the regional or national level. Participants were censored as follows: December 1999 (Turin), June 2000 (Bilthoven); December 2000 (Asturias, Murcia, Cambridge), December 2001 (Florence, Varesa, Ragusa, Granada, Navarra, San Sebastian, Oxford, Malmö, Norway), June 2002 (France), December 2002 (Umea, Aarhus, Copenhagen, Naples) and June 2003 (Utrecht). For Germany and Greece, the end of the follow-up was considered to be the last known contact, the date of diagnosis or the date of death, whichever came first.

Definition of lung cancer cases were based on the 2nd revision of the International Classification of Diseases for Oncology (ICD-O-2) and included all invasive cancers that were coded as C34. Histological information was available for 1,085 of 1,126 lung cancers cases and this information was used to define 3 major subgroups by histological type [adenocarcinomas (ICD-O-2 8140/3, 8230/3, 8250/3, 8251/3, 8260/3, 8310/3, 8480/3, 8490/3, 8481/3, 8550/3; n = 369), squamous cell carcinomas (ICD-O-2 8052/3, 8070/3, 8071/3, 8075/3; n = 235) and small cell carcinomas (ICD-O-2 8041/3, 8042/3, 8043/3, 8044/3, 8045/3, 8246/3; n = 190)].

Statistical analysis

Direct standardization based on the age distribution at entry in the combined EPIC cohort in 5-years intervals was performed; this analysis was restricted to age 50–69 years. Cox proportional hazards regression was used to examine the association of fruit and vegetable intake with lung cancer. Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment, exit time was age when participants were diagnosed with cancer, died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. The analyses were stratified by sex to control for differences between men and women in smoking and dietary behavior and by centers to account for center effects such as follow-up procedures and questionnaire design. We further stratified by age at recruitment (in 1-year categories) because our Cox regression models assume that the hazard function does not change during follow-up. However, this is probably not true because of calendar effects.

To adjust for lifelong tobacco smoking, we included current smoking status and intensity of smoking as one variable [never smokers = reference category); current cigarette smokers (3 categories: 1–14, 15–24 and 25+ cigarettes/day); former smokers who stopped less than 10 years ago, 11–20 years ago, 20+ years ago; other smokers (one category including pipe or cigar smokers and occasional smokers); missing information on smoking] and duration of smoking in 10-year categories ($\leq$10 years = reference category, 11–20 years, 21–30 years, 31–40 years, 41–50 years, >50 years) as a second variable in the statistical models. We separately adjusted for amount of smoking and duration of smoking instead of using pack-years of smoking to be better able to differentiate between, *e.g.*, heavy smokers of a short duration and light smokers for a long duration. Additionally, weight and height at recruitment (continuous variable), red meat (quintiles) and processed meat consumption (quintiles), alcohol consumption (quintiles), energy from fat and nonfat energy intake (quintiles), physical activity at work as an indicator of a possible exposure to carcinogens at work (nonworker, sedentary occupation, standing occupation, manual/heavy work and unknown) and education (no degree or primary school completed, technical or professional school completed, secondary school completed, university degree and not specified or missing) were included in the regression models.

The 24-hr diet recalls (24HR) were used to "calibrate" the FFQ-derived data (further on described as calibrated values) across countries and to correct for systematic over- or underestimation of dietary intakes.[17,18] The 24HR values were regressed on the dietary questionnaire values for the main food groups and the subgroups in a linear "calibration model."[19,20] Zero consumption values in the main dietary questionnaires were excluded in the regression calibration models and a zero was directly imputed as a calibrated value. Weight, height, age at recruitment and center were included as covariates, and data were weighted by day of the week and season of the year on which the 24HRwas collected. Country and sex-specific calibration models were used to obtain individual calibrated values of dietary exposure for all participants. Cox regression models were then applied using the calibrated values for each individual on a continuous scale. The standard error of the deattenuated coefficient was calculated with bootstrap sampling in the calibration and disease models consecutively.[18] We decided to present the results from the categorical model (observed values) next to the results from the continuous models (observed and calibrated values) since food intake data derived from FFQ are not necessarily true continuous variables (intake data were calculated by portion size times frequency of consumption).

Subanalyses were performed by smoking status and histology of lung cancer (adenocarcinoma, squamous cell carcinoma and small cell carcinoma). We tested for interaction by including a cross-product term along with the main effect terms in the Cox regression model. The statistical significance of the cross-product term was evaluated using the likelihood ratio test. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, North Carolina).

Results

Overall 1,126 lung cancer cases (608 in men, 518 in women) occurred in 2,980,546 person-years of observation of the entire study population (Table I). Adenocarcinomas of the lung were more common in women (39.4%) than men (27.1%), whereas squamous cell carcinomas were diagnosed more often in men (27.9%) than women (12.7%); 17.3% (men) and 16.6 % (women) were small-cell lung cancer cases. Median follow-up time was 6.4 (interquartile range 4.9–7.7) years. The single largest contribution of lung cancer cases was from the Danish EPIC cohorts (n = 366).

TABLE I – DESCRIPTION OF THE LUNG CANCER CASES AND COHORT BY COUNTRY IN EPIC

	Cases (*n*)	Person-years	Incidence rate (age-standardized[1])	Vegetable consumption[2] (median, g/day)	Fruit consumption[2] (median, g/day)	Histology of the tumor			
						Small cell carcinoma (*n*)	Squamous cell carcinoma (*n*)	Adeno-carcinoma (*n*)	Others or not specified (*n*)
Men									
Italy	43	75,154	105.8	147.2	296.3	8	9	12	14
Spain	54	103,718	81.3	239.8	272.7	6	15	15	18
United Kingdom	62	121,273	40.7	223.1	163.1	8	29	8	17
The Netherlands	17	50,106	136.5	115.3	124.6	2	5	6	4
Greece	35	38,997	95.6	456.6	475.2	5	3	8	19
Germany	106	125,742	120.6	107.0	98.0	32	20	27	27
Sweden	96	175,681	77.9	82.0	120.4	17	28	30	21
Denmark	195	174,742	120.7	151.1	113.1	28	60	59	48
Total	608	865,412				106	169	165	168
Women									
France	42	569,593	10.0	263.8	234.1	0	0	2	40
Italy	36	188,705	20.0	161.4	306.1	6	6	16	8
Spain	13	163,973	7.3	216.2	278.4	0	1	7	5
United Kingdom	52	284,543	25.0	256.2	216.2	8	7	18	19
The Netherlands	72	182,107	41.2	126.5	186.4	13	13	29	17
Greece	3	55,824	–	416.5	473.3	0	0	2	1
Germany	30	163,355	23.8	116.7	117.3	4	1	13	12
Sweden	71	204,895	50.6	119.2	176.5	8	14	33	16
Denmark	171	194,223	98.5	172.0	167.9	38	24	68	41
Norway	28	108,285	47.0	126.3	129.0	7	0	16	5
Total	518	2,115,504				84	66	204	164

[1]Including participants 50–69 years at baseline.–[2]Based on FFQ data.

TABLE II – HAZARD RATIOS AND 95% CONFIDENCE INTERVALS[1] FOR THE RISK OF LUNG CANCER BY SMOKING DURATION AND SMOKING STATUS (INTENSITY) IN THE EPIC COHORT

Smoking status	Smoking duration (years)					
	0	1–10	11–20	21–30	31–40	40+
Life-long nonsmokers	1 (Ref.)					
Current cigarettes:						
<15/d		3.36 (0.83–13.69)	1.18 (0.29–4.84)	3.38 (2.02–5.65)	5.88 (4.28–8.07)	11.19 (8.48–14.77)
15–24/d		–	5.61 (2.03–15.51)	7.98 (5.19–12.26)	12.49 (9.51–16.40)	19.96 (15.50–25.70)
25+/d		–	–	16.31 (9.67–27.50)	26.00 (19.05–35.47)	31.27 (22.83–42.82)
Ex-smokers:						
since <10 years		1.28 (0.18–9.18)	1.35 (0.49–3.71)	2.81 (1.77–4.46)	5.22 (3.75–7.26)	11.41 (8.23–15.82)
10+ years		1.12 (0.70–1.81)	1.41 (0.94–2.12)	2.24 (1.52–3.32)	5.62 (3.69–8.55)	4.34 (1.55–12.20)
Other smoking	1.14 (0.63–2.04)	–	–	7.23 (3.29–15.89)	6.32 (3.64–10.97)	11.71 (7.91–17.33)
Missing information	0.79 (0.19–3.20)[2]					

HR, Hazard ratios; 95% CI, 95% confidence intervals.
[1]Cox regression models were stratified for age, sex, and centre.–[2]Only one category for participants with missing information on smoking status.

About 65% of incident lung cancer cases occurred in subjects who reported currently smoking (at recruitment), 26% in ex-smokers and 9% in life-long nonsmokers. Hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of smoking with lung cancer risk are given in Table II, stratified by smoking intensity, type and duration. As compared to never smokers, the hazard ratio showed a more than 30-fold increased risk of lung cancer for those participants who smoked the most cigarettes (≥25 cig./day) for the longest time (≥40 years).

Overall, a high variation in fruit and vegetable intake across EPIC cohorts (countries) existed. Median fruit and vegetable consumption was highest in Greece, followed by other southern European countries (Table I). Baseline characteristics of participants with low and high fruit and vegetable consumption are given in Table III. Smokers were more frequently found in the lower quintiles of fruit and vegetable intake. Although this was also observed for women who stopped smoking, the opposite was true in male ex-smokers. High fruit and vegetables consumption was associated with higher daily intake of energy and lower consumption of processed meat. Subjects in the highest categories of vegetable but not fruit intake (men) were on average better educated. More women than men were alcohol abstainers and the average alcohol intake among consumers was also lower in female participants.

Average intake of fruit and vegetables by EPIC-wide quintiles, listed in Tables IV and V, shows numbers of cancer cases by intake quintiles and adjusted hazard ratios for fruit and vegetable intake for the entire cohort and stratified by smoking status. Since results were not significantly different between men and women, no sex-stratified results are presented. The significant inverse association between fruit intake and lung cancer as found in the first EPIC report[12] was confirmed; the hazard ratio in the highest (versus lowest) quintile was 0.75 (95% CI 0.49–0.96) in the entire cohort and 0.72 (0.52–0.99) in the subgroup of smokers. Also in agreement with the first report, in the categorical evaluation vegetable intake was not associated with lung cancer risk. However, when applying the continuous model, the association became significant in current smokers (Table VI). Additional correction for measurement error (calibration) distinctly strengthened this association, the hazard ratio being 0.78 (0.62–0.98) per 100 g/day (Table VI). Results did not significantly differ by country ($p = 0.74$ for interaction; Fig. 1) and further adjustment for fruit intake did not modify the estimates. In comparison to vegetables, the HR was 0.90 (0.81–0.99) per 100 g/day increase in fruit intake in smokers, and 0.92 (0.85–0.99) overall. HR (95% CI) for the calibrated fruit intake by country are shown in Figure 2 ($p = 0.57$ for heterogeneity). The test for heterogeneity between smoking

TABLE III – BASELINE CHARACTERISTICS OF EPIC STUDY PARTICIPANTS BY VEGETABLE AND FRUIT CONSUMPTION

	Vegetable consumption[1]		Fruit consumption[1]	
	Lowest quintile	Highest quintile	Lowest quintile	Highest quintile
Men				
Age (years; mean ± SD)	51.2 ± 10.0	52.6 ± 11.3	51.4 ± 9.97	52.1 ± 10.3
Height (cm; mean ± SD)	175.5 ± 7.1	172.4 ± 7.6	175.9 ± 7.1	172.1 ± 7.5
Weight (kg; mean ± SD)	80.8 ± 12.1	80.8 ± 12.2	81.1 ± 12.2	80.7 ± 11.9
BMI (kg/m^2; mean ± SD)	26.2 ± 3.6	27.1 ± 3.9	26.2 ± 3.7	27.3 ± 3.8
Energy intake[1](kcal/d; mean ± SD)	2246 ± 636	2577 ± 703	2275 ± 641	2637 ± 701
Red meat intake[1](g/d; mean ± SD)	50.8 ± 36.7	61.0 ± 45.6	61.7 ± 44.0	59.6 ± 40.9
Processed meat intake[1](g/d; mean ± SD)	50.1 ± 40.1	22.8 ± 32.8	48.7 ± 40.2	27.4 ± 33.9
Education				
Primary school completed (%)	32.3	28.4	29.1	29.1
University degree (%)	21.8	24.4	26.1	21.4
Heavy manual work (%)	4.7	3.5	4.7	5.0
Smoking status				
Never (%)	30.9	30.4	26.7	29.9
Former, < 10 years (%)	11.9	15.5	12.3	15.4
Former, ≥ 10 years (%)	19.3	20.3	18.9	20.7
Current, 1–14 cig./day (%)	10.0	8.7	10.3	9.3
Current, 15–29 cig./day (%)	12.3	8.3	14.3	8.3
Current, 30+ cig./day (%)	5.6	8.7	7.3	6.9
Other smoking (%)	10.8	8.2	10.3	9.6
Alcohol abstainers (%)	6.5	8.5	5.3	9.4
Alcohol intake[1] (g/d; mean ± SD)	20.9 ± 25.7	22.4 ± 24.9	27.0 ± 29.1	20.9 ± 22.9
Women				
Age (years; mean ± SD)	50.3 ± 9.5	51.1 ± 10.5	48.8 ± 9.6	51.8 ± 10.0
Height (cm; mean ± SD)	162.9 ± 6.7	161.1 ± 6.8	163.3 ± 6.6	160.7 ± 7.0
Weight (kg; mean ± SD)	66.3 ± 11.9	65.3 ± 11.8	65.6 ± 12.0	66.3 ± 11.8
BMI (kg/m^2; mean ± SD)	25.0 ± 4.4	25.2 ± 4.8	24.6 ± 4.4	25.7 ± 4.7
Energy intake[1] (kcal/d; mean ± SD)	1688 ± 473	2147 ± 569	1736 ± 500	2139 ± 566
Red meat intake[1] (g/d; mean ± SD)	32.8 ± 25.7	41.7 ± 36.1	37.3 ± 31.1	41.1 ± 31.9
Processed meat intake[1](g/d; mean ± SD)	31.8 ± 25.3	20.4 ± 23.6	32.1 ± 26.5	20.5 ± 22.9
Education				
Primary school completed (%)	29.9	19.2	24.1	24.0
University degree (%)	15.4	27.7	19.5	21.6
Heavy manual work (%)	1.7	0.4	1.0	0.9
Smoking status				
Never (%)	43.8	51.8	37.9	54.7
Former years (%)				
<10	14.9	7.4	15.8	8.2
≥10	10.5	4.2	13.7	4.2
Current cig./day (%)				
1–14	2.2	1.2	3.3	1.1
15–29	8.9	7.8	9.3	7.7
30+	12.0	12.8	11.9	12.0
Other smoking (%)	7.9	14.9	8.1	12.1
Alcohol abstainers (%)	18.5	16.0	14.5	22.9
Alcohol intake[1] (g/d; mean ± SD)	8.2 ± 11.9	9.7 ± 12.0	11.5 ± 15.1	8.3 ± 10.5

[1]Derived from FFQ data.

groups was statistically significant ($p < 0.001$) for both fruit and vegetables. Stratification of current smokers by smoking intensity showed no distinct differences for the associations with vegetables; however, we found an indication of a stronger (not significant) inverse association of fruit intake and lung cancer risk in smokers of <15 cig./day as compared to subjects who smoked >15 cig./day and >25 cig./day (data not shown). Repeating the analyses in a subgroup of smokers for which we had continuous data for the daily amount of cigarettes smoked did slightly modify these associations. For this subgroup, the inverse association with vegetable intake became statistically significant even in the categorical model with a HR of 0.63 (0.41–0.97; Q5 *vs.* Q1) while the association between fruit intake and lung cancer risk was slightly attenuated.

After exclusion of lung cancer cases diagnosed in the first 2 years of follow-up, the inverse associations between fruit and vegetable intake and lung cancer risk were strengthened in current smokers and in the total study group (Table VI). This is also true for the results of the categorical analyses; the HR (95% CI) for total fruit intake in quintiles 2–5 were 0.96 (0.80–1.16), 0.79 (0.64–0.98), 0.86 (0.68–1.09) and 0.67 (0.50–0.89). In current smokers, the results for the observed intake of total vegetables in quintiles 2–5 were 1.03 (0.82–1.29), 0.83 (0.64–1.08), 0.96 (0.71–1.30) and 0.75 (0.49–1.13) after exclusion of cases that occurred within the first 2 years of follow-up.

Concerning fruit subgroups, consumption of hard fruits (apples, pears) was significantly inversely associated with lung cancer risk, overall and in smokers (Table VI). Indications for an inverse association were also found for citrus fruits, citrus fruit juices, all juices and stone fruits in the categorical models (Table V) but statistical significance was not reached in the continuous models (Table VI). Consumption of root vegetables was inversely related to lung cancer risk, being statistically significant in smokers in the continuous model (Table VI). Cabbage consumption and consumption of onions and garlic was not related to lung cancer (data not shown). Positive associations between leafy vegetables (in never-smokers) and fruiting vegetables (in former-smokers) and lung cancer risk were found in the continuous models but were not apparent in the categorical models.

Results for the association between vegetable ($p = 0.12$ for interaction) and fruit consumption ($p < 0.001$ for interaction) and lung cancer risk differed by histological subtypes. The hazard

TABLE IV – MEAN VEGETABLE AND FRUIT INTAKE AS ASSESSED BY 24-HR DIET RECALLS, BY QUINTILES OF THE FOOD FREQUENCY QUESTIONNAIRE DATA

		Quintiles of intake (g/day; FFQ)				
		1	2	3	4	5
Total vegetables	Range[1]	0–97.3	97.3–146.0	146.0–207.9	207.9–306.8	306.8–2979.3
	Mean[2]	109.1	138.9	166.3	199.0	247.9
Fruiting vegetables	Range	0–21.0	21.0–38.9	38.9–61.5	61.5–100.5	100.5–1496.1
	Mean	41.6	51.1	67.7	85.5	124.7
Leafy vegetables	Range	0–1.5	1.5–8.6	8.6–21.1	21.1–50.0	50.0–1074.3
	Mean	7.3	11.0	17.6	26.9	47.4
Root vegetables	Range	0–4.8	4.8–12.3	12.3–24.4	24.4–44.0	44.0–973.9
	Mean	10.3	12.1	15.7	22.3	34.6
Cabbages	Range	0–2.7	2.7–10.5	10.5–21.5	21.5–41.9	41.9–1246.6
	Mean	10.6	14.7	18.3	21.8	27.8
Total fruits	Range	0–89.7	89.7–154.7	154.7–238.3	238.3–356.8	356.8–4645.6
	Mean	85.4	150.9	205.6	260.8	345.7
Hard fruits[3]	Range	0–11.8	11.8–36.3	36.3–65.0	65.0–115.0	115.0–2269.4
	Mean	43.0	49.3	72.5	93.5	164.9
Citrus fruits	Range	0–5.9	5.9–16.6	16.6–41.7	41.7–82.9	82.9–2487.2
	Mean	24.6	18.6	31.7	53.6	87.2
Stone fruits	Range	0–1.1	1.1–6.3	6.3–19.1	19.1–53.4	53.4–854.9
	Mean	28.8	8.3	18.2	32.2	56.7
Total juices	Range	0	0–8.6	8.6–42.9	42.9–116.1	116.1–4000.0
	Mean	21.5	21.4	37.5	79.9	182.2
Citrus fruit juices	Range	0	0–3.5	3.5–14.3	14.3–54.8	54.8–2632.0
	Mean	12.9	14.7	23.5	34.0	106.6

FFQ, Food frequency questionnaire.
[1]Ranges are based on FFQ.–[2]Mean values are based on 24-hr diet recalls.–[3]Apples, pears.

ratios of the sum of fruit and vegetables and juices (per 100 g, calibrated values) were 0.87 (0.76–0.997), 0.98 (0.87–1.09) and 0.93 (0.85–1.02) for small-cell carcinoma, squamous cell carcinoma and adenocarcinoma, respectively. Considering fruit and vegetable intake separately, the point estimates were lowest but not statistically significant for small-cell carcinoma as compared to the 2 other subtypes. A detailed description of the association of fruit and vegetable intake with histological subtypes of lung cancer will be provided in a separate report.

Discussion

In addition to the inverse association of fruit intake and lung cancer risk, the updated results from this large prospective cohort study demonstrate that lung cancer incidence in smokers was significantly lower in individuals with high compared to those with low vegetable intake. These relationships became more pronounced after correction for measurement error (calibration) and after exclusion of cases diagnosed within the first 2 years of follow-up.

In recent publications, reviewing the scientific evidence and using meta-analytic approaches,[9–11] it has been concluded that fruit and vegetable consumption is inversely associated with lung cancer incidence. The association seems to be stronger for fruit intake as compared to vegetable intake, and the strength of the association is smaller in cohort studies than in case-control studies. With respect to the findings in prospective studies, both the meta-analysis of Riboli and Norat[11] (HR 0.92, 95% CI 0.84–1.07) and the pooled analysis of cohort studies[10] (HR 0.88, 95% CI 0.78–1.00) reported risk estimates for the association of vegetable intake (per 100 g/day) that were not or borderline statistically significant. In the pooling project, smoking status was not a significant modifier of the association of fruit intake with lung cancer risk; however, vegetable intake was inversely associated with lung cancer among current smokers but not among never or past smokers.[10] These results fit well with our findings in EPIC although there are also some differences. In EPIC, heterogeneity between smoking strata was statistically significant for both fruit and vegetable intake. In addition, risk estimates for vegetable intake and lung cancer risk in never and past smokers were above unity (not significant), thus explaining the missing effect for vegetables in the entire EPIC cohort. At least some differences in risk estimates between both cohort analyses (pooling project, EPIC) may be explainable by the deviating prevalence of smoking and the proportion of histological subtypes of lung cancer in the cohorts. The prospective studies considered differed between reviews/meta-analyses. The pooling project[10] included data from 8 prospective cohort studies from northern America and Europe.[21–27] Riboli and Norat[11] considered some of these and included other cohort studies.[28–34] In the IARC-coordinated review,[9] another 5 more recent publications from prospective studies were considered.[12,35–38] Since then, only few additional reports from 2 Japanese cohort studies[39,40] and from the Danish EPIC cohort[41] were published.

In case-control studies dealing with non-smokers only, an inverse association between plant food consumption and lung cancer risk was repeatedly reported either for fruits or for vegetables or both[42–46] though others could not confirm these findings.[47,48] As in ours, most cohort studies have limited statistical power to disentangle differential effects by smoking status because of low numbers of cases in never smokers (and probably also in past smokers). For example, a stratified analysis of data from the Netherlands Cohort Study[22] reported risk estimates for vegetable consumption in never smokers above unity (not significant), similar to the findings in EPIC. Expert committees concluded on the basis of the available evidence that there is no clear indication that the effect of fruit is limited to (ex-)smokers.[9] Also, in this analysis, including 98 never smokers in EPIC, the calibrated risk estimate per 100 g total daily fruit consumption is below unity (not significant; Table VI). With respect to vegetable intake, however, the result in EPIC strengthens the finding in the pooling project that a significant inverse association is only seen in the group of smokers.

When we used restricted cubic spline models, the test for nonlinearity was not significant, indicating that a linear model sufficiently describes the inverse association between fruit and vegetable consumption and lung cancer risk (Fig. 3). However, this might not be true for some subgroups of fruits and vegetables. When comparing results obtained by means of the linear model and showing a positive association for vegetable subgroups in never or past smokers (Table VI) with the results from the categorical model (Table V), an increase in risk could not be confirmed by the latter. Food-frequency derived consumption data are not

TABLE V – HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR THE RISK OF LUNG CANCER BY QUINTILES OF FRUIT AND VEGETABLE INTAKE (OBSERVED)

	All participants			Current smokers			Former smokers			Never smokers		
	N	HR	95% CI	N	HR	95% CI	N	HR	95% CI	N	HR	95% CI
Total vegetables												
Q1	342	1		255	1		65	1		22	1	
Q2	250	0.96	0.81 – 1.14	187	1.08	0.89 – 1.32	52	0.81	0.55 – 1.17	9	0.39	0.18 – 0.86
Q3	224	1.01	0.84 – 1.21	129	0.92	0.73 – 1.15	73	1.25	0.87 – 1.78	20	0.82	0.43 – 1.57
Q4	167	0.98	0.80 – 1.21	101	1.03	0.79 – 1.33	41	0.76	0.49 – 1.17	24	0.98	0.50 – 1.90
Q5	143	1.06	0.83 – 1.36	59	0.78	0.54 – 1.13	60	1.33	0.85 – 2.08	23	0.97	0.46 – 2.04
Fruiting vegetables												
Q1	301	1		216	1		61	1		23	1	
Q2	254	0.83	0.69 – 0.98	180	0.86	0.70 – 1.06	57	0.73	0.50 – 1.06	15	0.62	0.31 – 1.21
Q3	228	1.01	0.84 – 1.22	149	1.07	0.86 – 1.34	61	0.93	0.64 – 1.35	16	0.66	0.34 – 1.30
Q4	192	1.18	0.97 – 1.45	105	1.17	0.90 – 1.52	63	1.23	0.83 – 1.82	23	0.92	0.49 – 1.72
Q5	151	1.10	0.86 – 1.41	81	0.98	0.70 – 1.37	49	1.22	0.77 – 1.93	21	0.94	0.47 – 1.88
Leafy vegetables												
Q1	411	1		305	1		86	1		16	1	
Q2	255	0.89	0.74 – 1.06	165	0.86	0.69 – 1.07	69	0.86	0.61 – 1.23	19	1.25	0.58 – 2.71
Q3	193	0.97	0.77 – 1.21	106	0.94	0.70 – 1.26	60	0.99	0.65 – 1.52	17	1.11	0.45 – 2.76
Q4	169	1.00	0.77 – 1.30	101	1.05	0.75 – 1.46	50	0.98	0.60 – 1.60	18	0.99	0.38 – 2.57
Q5	108	0.83	0.60 – 1.15	54	0.80	0.52 – 1.24	26	0.68	0.35 – 1.30	28	1.05	0.38 – 2.93
Root vegetables												
Q1	321	1		243	1		59	1		17	1	
Q2	274	0.97	0.82 – 1.15	195	0.95	0.78 – 1.16	60	0.97	0.66 – 1.41	19	1.35	0.68 – 2.67
Q3	212	0.94	0.78 – 1.13	132	0.91	0.72 – 1.14	63	0.99	0.68 – 1.44	16	1.01	0.49 – 2.08
Q4	152	0.83	0.68 – 1.03	90	0.85	0.65 – 1.11	44	0.76	0.50 – 1.16	17	1.02	0.50 – 2.09
Q5	167	0.94	0.76 – 1.16	71	0.76	0.56 – 1.02	65	1.06	0.70 – 1.58	29	1.66	0.85 – 3.25
Cabbages												
Q1	253	1		182	1		48	1		23	1	
Q2	293	0.93	0.77 – 1.12	198	0.83	0.66 – 1.04	73	1.32	0.87 – 2.01	19	0.89	0.46 – 1.70
Q3	219	0.84	0.68 – 1.03	144	0.83	0.66 – 1.04	54	1.09	0.69 – 1.71	20	0.98	0.50 – 1.92
Q4	203	1.06	0.86 – 1.31	133	1.05	0.81 – 1.36	47	1.05	0.66 – 1.68	21	1.18	0.61 – 2.28
Q5	158	1.03	0.80 – 1.34	74	0.91	0.65 – 1.28	69	1.37	0.82 – 2.30	15	1.00	0.44 – 2.25
Total fruits												
Q1	382	1		308	1		62	1		12	1	
Q2	262	0.98	0.83 – 1.16	170	0.93	0.76 – 1.13	75	1.21	0.85 – 1.70	16	0.91	0.43 – 1.94
Q3	184	0.84	0.70 – 1.02	99	0.74	0.58 – 0.94	64	1.09	0.75 – 1.57	20	0.92	0.44 – 1.92
Q4	171	0.94	0.77 – 1.15	85	0.82	0.63 – 1.07	47	0.98	0.65 – 1.48	36	1.45	0.73 – 2.92
Q5	127	0.75	0.59 – 0.96	69	0.72	0.52 – 0.99	43	0.93	0.59 – 1.48	14	0.59	0.25 – 1.38
Hard fruits												
Q1	270	1		220	1		39	1		11	1	
Q2	288	1.07	0.90 – 1.27	196	0.99	0.81 – 1.22	67	1.43	0.95 – 2.16	25	1.97	0.95 – 4.11
Q3	194	0.92	0.76 – 1.12	103	0.73	0.57 – 0.94	65	1.50	0.99 – 2.27	24	1.69	0.81 – 3.54
Q4	183	0.85	0.69 – 1.03	110	0.83	0.65 – 1.06	52	1.03	0.66 – 1.59	20	1.23	0.56 – 2.70
Q5	191	0.85	0.69 – 1.05	102	0.80	0.62 – 1.04	68	1.19	0.77 – 1.83	18	0.95	0.41 – 2.22
Citrus fruits												
Q1	327	1		245	1		61	1		21	1	
Q2	269	0.92	0.78 – 1.08	177	0.84	0.69 – 1.03	80	1.36	0.96 – 1.91	11	0.57	0.27 – 1.22
Q3	175	0.82	0.67 – 0.996	106	0.80	0.62 – 1.02	52	1.05	0.71 – 1.55	16	0.59	0.30 – 1.17
Q4	192	0.86	0.71 – 1.04	119	0.86	0.68 – 1.09	49	0.87	0.59 – 1.30	23	0.80	0.43 – 1.50
Q5	163	0.87	0.70 – 1.07	84	0.76	0.57 – 1.01	49	0.97	0.64 – 1.47	27	1.06	0.56 – 2.00
Stone fruits												
Q1	252	1		198	1		44	1		10	1	
Q2	312	0.95	0.79 – 1.14	204	0.76	0.62 – 0.95	87	1.80	1.22 – 2.66	18	2.32	0.96 – 5.60
Q3	232	0.89	0.73 – 1.08	136	0.65	0.51 – 0.83	76	1.84	1.22 – 2.77	19	1.99	0.85 – 4.63
Q4	148	0.92	0.73 – 1.16	84	0.75	0.56 – 1.01	48	1.69	1.06 – 2.70	16	1.32	0.57 – 3.05
Q5	117	0.89	0.68 – 1.15	62	0.68	0.49 – 0.96	26	1.23	0.68 – 2.20	28	1.89	0.87 – 4.13
Total juices												
Q1	283	1		179	1		76	1		28	1	
Q2	331	0.89	0.73 – 1.08	230	0.84	0.66 – 1.08	78	0.97	0.66 – 1.43	21	1.12	0.58 – 2.15
Q3	166	0.79	0.63 – 0.98	118	0.87	0.66 – 1.14	33	0.67	0.42 – 1.05	14	0.69	0.35 – 1.38
Q4	169	0.74	0.59 – 0.91	96	0.63	0.48 – 0.84	54	0.95	0.64 – 1.41	16	0.83	0.42 – 1.61
Q5	177	0.89	0.72 – 1.10	108	0.89	0.68 – 1.17	50	0.86	0.57 – 1.29	19	0.94	0.49 – 1.80
Citrus fruit juices												
Q1	232	1		162	1		57	1		13	1	
Q2	236	0.82	0.66 – 1.02	173	0.81	0.62 – 1.05	46	0.75	0.47 – 1.21	15	1.66	0.71 – 3.90
Q3	172	0.94	0.74 – 1.20	130	1.00	0.76 – 1.33	31	0.70	0.41 – 1.17	11	1.63	0.65 – 4.12
Q4	144	0.78	0.61 – 0.99	86	0.66	0.49 – 0.89	45	0.98	0.62 – 1.56	11	1.29	0.53 – 3.16
Q5	154	0.82	0.65 – 1.03	102	0.78	0.59 – 1.02	38	0.82	0.52 – 1.30	13	1.43	0.61 – 3.33
Vegetables and fruits												
Q1	402	1		319	1		66	1		17	1	
Q2	237	0.83	0.70 – 0.98	156	0.81	0.66 – 0.99	67	1.02	0.71 – 1.45	12	0.51	0.24 – 1.10
Q3	207	0.91	0.76 – 1.10	131	0.94	0.75 – 1.18	55	0.91	0.62 – 1.34	20	0.71	0.36 – 1.42
Q4	147	0.84	0.67 – 1.04	64	0.66	0.49 – 0.89	54	1.06	0.70 – 1.60	27	0.88	0.44 – 1.76
Q5	133	0.88	0.68 – 1.14	61	0.68	0.47 – 0.99	49	1.20	0.75 – 1.94	22	0.80	0.37 – 1.74

TABLE V – HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR THE RISK OF LUNG CANCER BY QUINTILES OF FRUIT AND VEGETABLE INTAKE (OBSERVED) (CONTINUED)

	All participants			Current smokers			Former smokers			Never smokers		
	N	HR	95% CI	N	HR	95% CI	N	HR	95% CI	N	HR	95% CI
Vegetables and fruits And juices												
Q1	412	1		326	1		72	1		14	1	
Q2	242	0.90	0.77 – 1.07	163	0.91	0.75 – 1.11	61	0.87	0.61 – 1.24	16	0.91	0.44 – 1.89
Q3	200	0.96	0.80 – 1.15	112	0.87	0.69 – 1.10	63	1.08	0.75 – 1.55	23	1.10	0.54 – 2.22
Q4	136	0.78	0.63 – 0.97	63	0.64	0.47 – 0.86	45	0.88	0.58 – 1.33	27	1.24	0.61 – 2.54
Q5	136	0.92	0.72 – 1.18	67	0.78	0.56 – 1.09	50	1.19	0.76 – 1.87	18	0.88	0.39 – 2.00

All results are adjusted for tobacco smoking (status and duration), education (5 categories), physical activity at work (5 categories), intake of red meat, intake of processed meat, height, weight, nonfat energy intake, energy intake from fat, ethanol intake at baseline. HR, Hazard ratios; 95% CI, 95% confidence intervals.

TABLE VI – OBSERVED AND CALIBRATED* HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR THE RISK OF LUNG CANCER BY VEGETABLE AND FRUIT CONSUMPTION

Variable	Increment	Model	Hazard ratios			
			All participants	Current smokers	Former smokers	Never smokers
Total vegetables	Per 100 g	Calibrated[1]	1.003 (0.846–1.189)	0.780 (0.620–0.980)	1.297 (0.955–1.761)	1.423 (0.847–2.391)
		Observed	1.011 (0.952–1.074)	0.913 (0.836–0.997)	1.090 (0.988–1.203)	1.104 (0.940–1.297)
w/o first 2 years		Calibrated	0.943 (0.773–1.150)	0.716 (0.548–0.937)	1.183 (0.823–1.700)	1.565 (0.867–2.824)
		Observed	0.980 (0.910–1.055)	0.871 (0.783–0.969)	1.062 (0.937–1.203)	1.131 (0.927–1.380)
Fruiting vegetables	Per 10 g	Calibrated	1.020 (0.988–1.053)	0.990 (0.949–1.033)	1.065 (1.005–1.128)	1.035 (0.928–1.153)
		Observed	1.012 (0.999–1.025)	0.999 (0.981–1.018)	1.028 (1.006–1.051)	1.010 (0.973–1.049)
Leafy vegetables	Per 10 g	Calibrated	1.023 (0.938–1.116)	0.949 (0.837–1.076)	1.015 (0.867–1.189)	1.230 (0.997–1.517)
		Observed	1.000 (0.975–1.026)	0.974 (0.938–1.012)	0.996 (0.951–1.043)	1.058 (1.002–1.117)
Root vegetables	Per 10 g	Calibrated	0.967 (0.915–1.023)	0.926 (0.855–1.003)	0.981 (0.887–1.085)	1.091 (0.962–1.238)
		Observed	0.989 (0.967–1.012)	0.961 (0.928–0.995)	1.006 (0.970–1.044)	1.026 (0.979–1.075)
Cabbages	Per 10 g	Calibrated	1.033 (0.944–1.130)	0.999 (0.888–1.123)	1.035 (0.882–1.214)	1.209 (0.887–1.647)
		Observed	1.003 (0.978–1.027)	0.998 (0.961–1.037)	1.000 (0.964–1.038)	1.002 (0.923–1.089)
Total fruits	Per 100 g	Calibrated	0.917 (0.847–0.994)	0.895 (0.807–0.993)	0.929 (0.799–1.079)	0.966 (0.736–1.269)
		Observed	0.950 (0.907–0.995)	0.939 (0.884–0.998)	0.953 (0.874–1.039)	0.961 (0.837–1.103)
w/o first 2 years		Calibrated	0.859 (0.780–0.947)	0.831 (0.733–0.942)	0.906 (0.755–1.088)	0.920 (0.663–1.278)
		Observed	0.906 (0.856–0.959)	0.887 (0.822–0.957)	0.922 (0.829–1.072)	0.949 (0.808–1.114)
Hard fruits	Per 100 g	Calibrated	0.861 (0.751–0.987)	0.845 (0.708–1.009)	0.965 (0.762–1.222)	0.607 (0.348–1.060)
		Observed	0.895 (0.819–0.978)	0.878 (0.779–0.990)	0.993 (0.858–1.150)	0.708 (0.509–0.983)
Citrus fruits	Per 10 g	Calibrated	0.987 (0.967–1.008)	0.988 (0.963–1.014)	0.973 (0.933–1.016)	1.015 (0.938–1.098)
		Observed	0.991 (0.978–1.003)	0.994 (0.979–1.010)	0.972 (0.945–0.999)	1.009 (0.969–1.050)
Stone fruits	Per 10 g	Calibrated	0.981 (0.937–1.027)	0.983 (0.927–1.043)	0.917 (0.833–1.011)	1.029 (0.908–1.168)
		Observed	1.001 (0.979–1.023)	1.004 (0.976–1.034)	0.959 (0.909–1.011)	1.004 (0.954–1.056)
Total juices	Per 100 g	Calibrated	0.974 (0.885–1.071)	0.956 (0.850–1.076)	1.054 (0.876–1.268)	0.804 (0.490–1.318)
		Observed	0.989 (0.927–1.054)	0.984 (0.908–1.066)	1.034 (0.915–1.169)	0.865 (0.651–1.150)
Citrus fruit juices	Per 100 g	Calibrated	1.000 (0.871–1.148)	0.979 (0.831–1.152)	1.024 (0.754–1.391)	1.117 (0.608–2.053)
		Observed	1.021 (0.928–1.123)	1.006 (0.897–1.129)	1.055 (0.868–1.282)	0.961 (0.626–1.477)
Vegetables and fruits	Per 100 g	Calibrated	0.946 (0.888–1.007)	0.885 (0.815–0.962)	1.015 (0.905–1.138)	1.043 (0.849–1.281)
		Observed	0.973 (0.942–1.006)	0.939 (0.897–0.982)	1.004 (0.948–1.065)	1.011 (0.918–1.112)
w/o first 2 years		Calibrated	0.895 (0.830–0.965)	0.832 (0.754–0.919)	0.967 (0.841–1.112)	1.053 (0.830–1.335)
		Observed	0.939 (0.902–0.978)	0.897 (0.848–0.948)	0.978 (0.909–1.051)	1.006 (0.899–1.125)
Vegetables and fruits and juices	Per 100 g	Calibrated	0.947 (0.898–0.999)	0.900 (0.840–0.964)	1.019 (0.923–1.125)	0.997 (0.825–1.205)
		Observed	0.973 (0.946–1.002)	0.946 (0.910–0.984)	1.007 (0.955–1.061)	0.989 (0.904–1.082)

All results are adjusted for tobacco smoking (status and duration), education (5 categories), physical activity at work (5 categories), intake of red meat, intake of processed meat, height, weight, nonfat energy intake, energy intake from fat, ethanol intake at baseline. Values inside parentheses indicate 95% confidence intervals (95% CI).

[1]Calibrated by means of the "calibration" procedure (see Methods section).

strictly continuous since they are calculated as the product of given categories of standard portion size and frequency of consumption. In addition, the subgroup "unclassified" (mostly used for food items not fully described during the interviews), which was considered in the food groups total fruits and total vegetables, contains different information across countries. Also, depending on the dietary habits in the country or center, there are some examples where the information in subgroups is incomplete or absent (*e.g.*, leafy vegetables in Norway; cabbages in Umea, Sweden).

Still, there is not really a precise answer to the question how a potentially protective effect of fruit and vegetables on lung cancer risk could be mediated at the cellular or molecular level. A wealth of experimental evidence for possible cancer-preventive biological mechanisms of a series of plant-food derived compounds, including vitamin C, carotenoids, isothiocyanates, flavonoids and other polyphenolics, has been published.[49–51] Since randomized controlled trials with high doses of some micronutrients (retinol, β-carotene, tocopherols) to prevent lung cancer have not demonstrated a chemopreventive effect, current strategies for chemoprevention of lung cancer aim at factors other than plant-food derived compounds.[52,53] In epidemiological (observational) studies, food subgroups, which are considered as main sources of a specific compound or group of compounds, are analyzed to obtain hints on the responsible bioactive compounds. Following this strategy, we observed a significant inverse association for apples and pears (hard fruit) and lung cancer risk, again confirming results from the pooling project.[10] Hard fruit is the major fruit subgroup in terms of quantity (Table IV) and is often more regularly consumed than others. Apples contain substantial amounts of vitamin C and are one of the major sources of quercetin and phloretin in the diet.

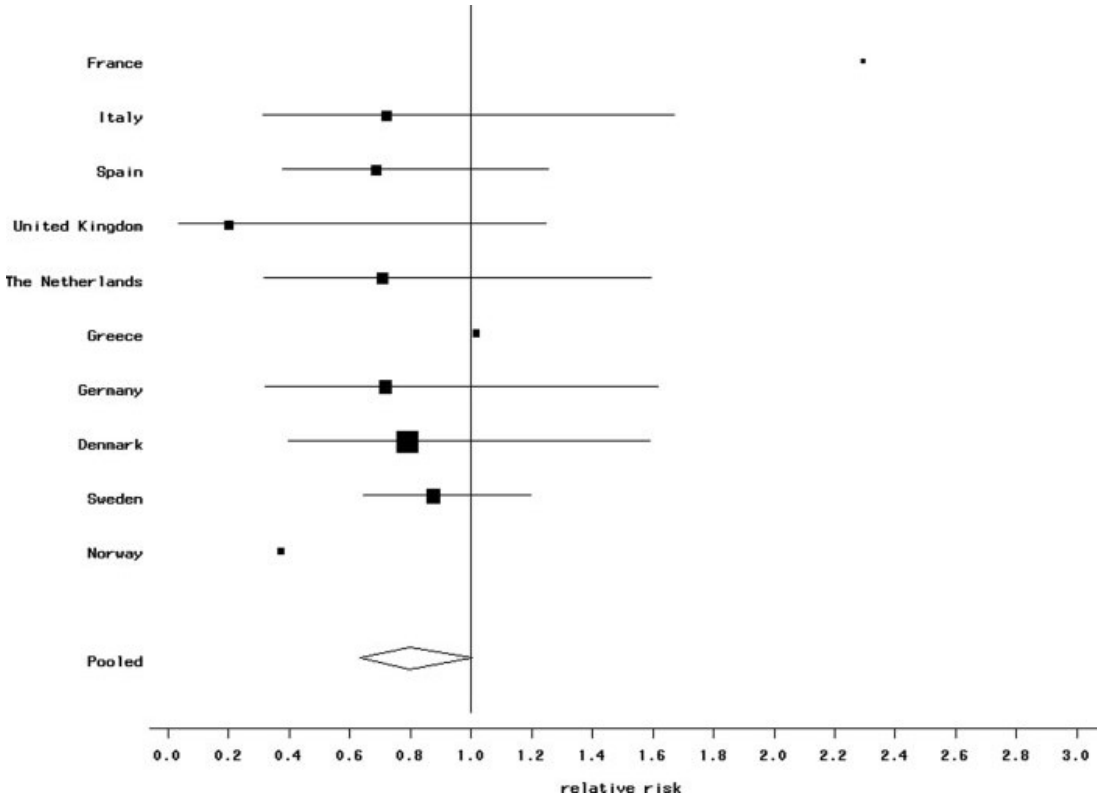

Figure 1 – Vegetable intake (calibrated values) and relative risk (hazard ratio, 95% confidence interval) of lung cancer in smokers, by country [the size of the square is proportional to the number of cases by country].

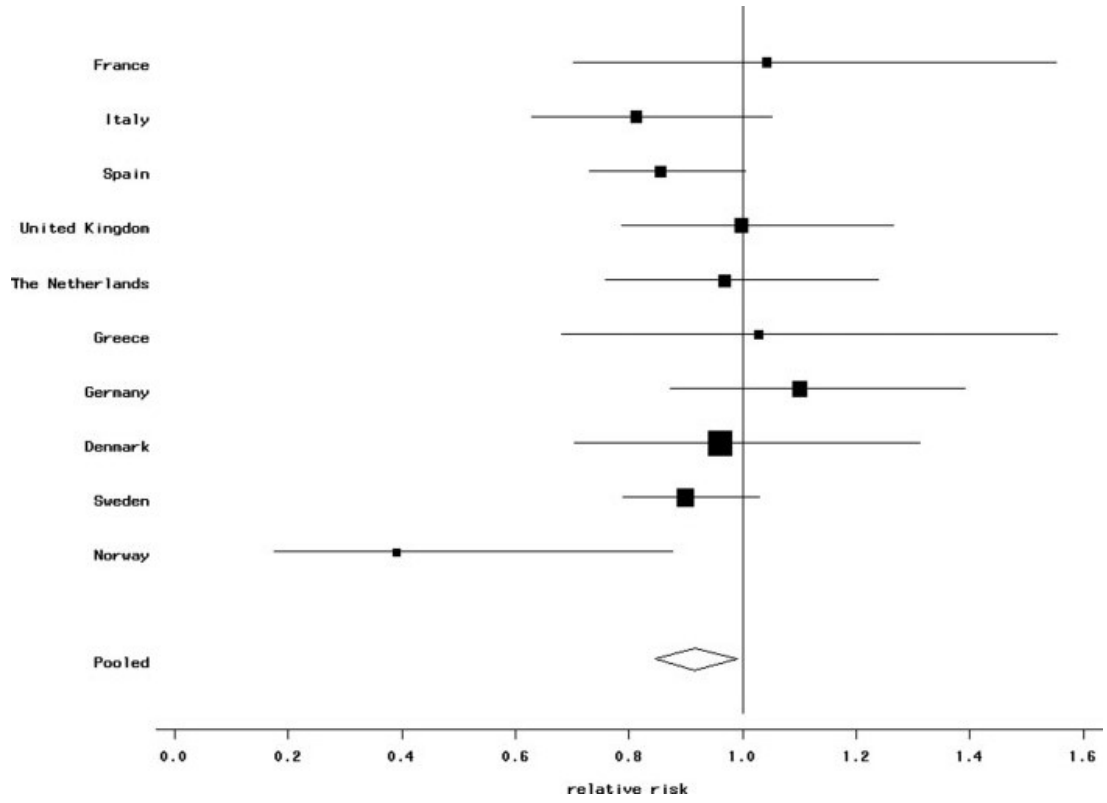

Figure 2 – Fruit intake (calibrated values) and relative risk (hazard ratio, 95% confidence interval) of lung cancer by country [the size of the square is proportional to the number of cases by country].

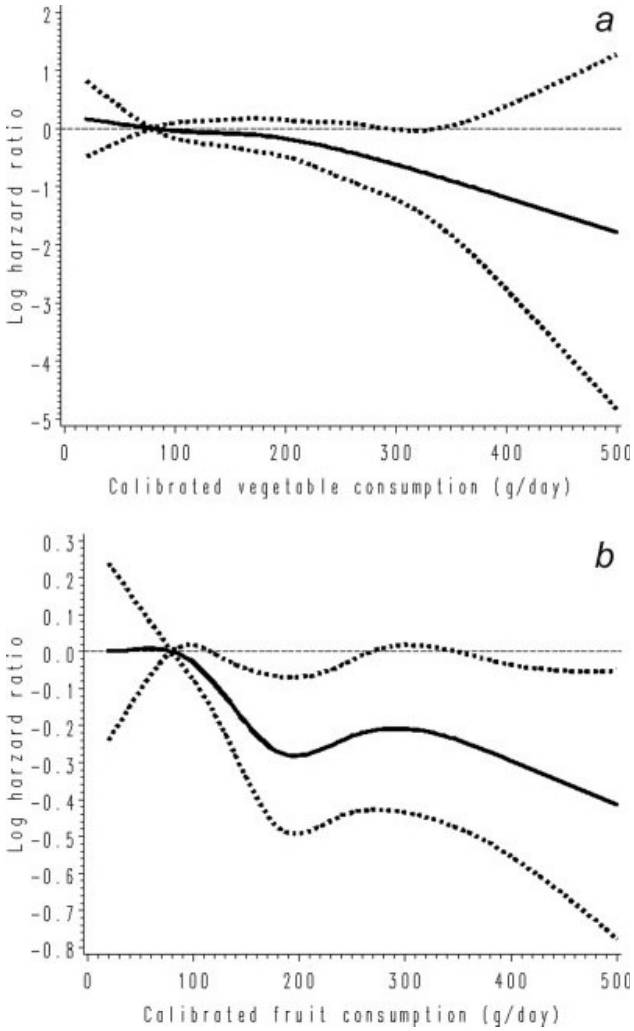

FIGURE 3 – Restricted cubic spline models describing the relative risk (hazard ratio) of lung cancer (*a*) by total vegetable intake (calibrated) in smokers only as well as (*b*) by total fruit intake (calibrated) in the entire cohort (tests for nonlinearity were not significant; dotted lines represent 95% confidence interval).

However, we could not clearly confirm the inverse association of citrus fruit consumption or juices as seen in other prospective studies,[10] in EPIC, risk estimates for lung cancer decreased with increasing consumption of these food subgroups but hardly reached statistical significance. In the pooling project, statistical analyses of food-derived intake of vitamins C, E, A, folate and carotenoids showed an inverse association between β-cyptoxanthin and vitamin C and lung cancer risk; the vitamin C effect was not independent of β-cryptoxanthin, a compound mainly provided by citrus fruits and citrus juices.[54,55] In the near future, technical developments will enable the analysis of a wide spectrum of nutritional biomarkers, including nonnutritive compounds from plant food, in epidemiological studies. This will also allow analyses for joint effects of various food components on cancer development.[50]

Among vegetable subgroups, consumption of root vegetables (carrots as the major food) was inversely associated with lung cancer risk in smokers. Similar associations have been reported in studies on diet and lung cancer and, together with the results on β-carotene for which carrots are a good source, led to the implementation of intervention studies with β-carotene.[7] We found no clear indication for a reduced risk of lung cancer in subjects with high intake of leafy vegetables (nonsignificant risk reduction in smokers), cabbages and onion and garlic in our data. However, there is recent evidence for differential effects by gene variants. The most prominent example is the interaction between isothiocyanate derived from brassicaceae (cruciferous vegetables, cabbages) consumption and variants of glutathion-S-transferases (M1, T1).[6,56,57] In addition to the rapidly increasing knowledge of genotypic characteristics describing lung cancer susceptibility,[58] gene-diet interactions shall be thoroughly investigated in the future. Hopefully, the emerging evidence will allow identification of specific population groups described by genotype and phenotype (*e.g.* smokers) that can benefit most from identified dietary strategies.

When studying the association of plant food consumption with lung cancer risk, most complete adjustment for smoking is crucial since smoking as a confounder is associated with both lung cancer risk and intake of plant food. Although we put much emphasis on avoiding residual confounding by smoking through refined adjustment for duration and amount of smoking, this source of bias can never be completely excluded. As expected, adjustment for smoking had the strongest effect on the risk estimates. Without adjustment for smoking (but adjusted for all other variables as indicated in Table V), the hazard ratios (95% CI) for lung cancer risk by quintiles 2–5 of total fruit intake were 0.73 (0.62–0.85), 0.56 (0.46–0.67), 0.56 (0.46–0.69) and 0.44 (0.34–0.56). For total vegetable intake, the results by quintiles 2–5 were 0.78 (0.66–0.93), 0.76 (0.63–0.90), 0.67 (0.54–0.82) and 0.71 (0.55–0.90) (for comparison with the results of the fully adjusted model, see Table V). We used several approaches to test for residual confounding by smoking. First, we rerun the analysis in a subgroup of the cohort for which continuous data on the amount of cigarettes smoked were available and the inverse association with vegetable intake was found to be even stronger than seen in the whole cohort. Second, we used a modified model for smoking adjustment as developed by a data-driven approach applied in the EPIC data set[59] and found hardly any deviation from the results reported here. In addition, we examined associations by tumor cell types since these are differently affected by smoking.[60,61] In our data set, 12% of adenocarcinoma cases were never smokers as compared to 2 and 1% in squamous and small cell carcinoma, respectively. A statistically significant inverse association was found only for fruit and vegetable consumption and small-cell carcinoma, and there was no indication for an association between vegetable intake and squamous cell carcinoma (data not shown). This gives support to a differential effect of vegetables in squamous and small cell types of lung cancer and does not argue in favor of residual confounding by smoking since this source of bias might have affected both subtypes similarly. Further limitations of the present evaluation refer to a still relatively short follow-up period and a limited power for the analysis of subgroups, *i.e.*, histological subtypes and groups of past or never smokers, due to low numbers of cases. With the exclusion of the first 2 years of observation, the risk estimates became more distinct both for fruits and vegetables. Assuming that dietary and smoking behavior may have changed close to diagnosis, the HR obtained after exclusion should reflect the true underlying association more correctly.

A major strength of the present evaluation is the substantial limitation of measurement error by means of the calibration procedure, using the results from the standardized 24-hr diet recalls. This novel methodological approach implemented in EPIC aims at correcting for systematic over- and underestimation of dietary intakes.[17,20] However, the calibrated hazard ratios may still be affected to some extent by measurement error since the error structure in the reference method is not entirely independent of that in the FFQ.[62,63] This also implies that the true risk estimates might be even more pronounced.

For comparison of the results presented here with the results included in the earlier report from EPIC published in 2004,[12] the different approaches for calibration of FFQ data have to be considered. A not yet optimized calibration procedure was applied when the analysis for the fist paper was carried out. Thus, comparability

of calibrated results between both papers is limited. As compared to the first publication,[12] the effect of fruit intake (not calibrated, by quintiles) is attenuated in the present results (Table V). Since the statistical models for the categorical variables are nearly identical in both evaluations, this effect should largely result from the inclusion of more cases that occurred during a longer period of follow-up.

Besides its large size, a methodological strength of the EPIC project as a whole is the inclusion of participants from 10 European countries with distinctly diverging dietary habits. In the 24-hr diet recall, we observed a more than 5-fold variation in medians across countries (Table II); a detailed description of fruit and vegetable intake patterns across EPIC centers is given elsewhere.[64] A high between-person variation in diet decreases the impact of measurement error and enables the detection of only modest diet disease relationships. Overall, major successful attempts have been made to limit measurement error in food intake data and thus in risk estimates in EPIC.

In conclusion, by means of EPIC data, we could largely reproduce the findings from the pooling project and thus strengthened the scientific evidence on the role of fruit and vegetable consumption in primary lung cancer prevention. Besides an overall inverse effect of fruit consumption, in current smokers, a significant inverse association was also found for vegetable consumption; however, an association between vegetable intake and lung cancer risk in never and past smokers seems less likely. Despite these findings, by far the most effective measure for preventing lung cancer in smokers remains the cessation of smoking.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. Lyon: IARC Press, 2004.
2. Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. Int J Cancer 2005;117:294–9.
3. Boyle P, Dresler C. Preventing the lung cancer epidemic. Ann Oncol 2005;16:1565–6.
4. Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 2000;321:323–9.
5. Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. Cancer Epidemiol Biomarkers Prev 2000;9:3–28.
6. Brennan P, Hsu CC, Moullan N, Szeszenia-Dabrowska N, Lissowska J, Zaridze D, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, et al. Effect of cruciferous vegetables on lung cancer in patients stratified by genetic status: a mendelian randomisation approach. Lancet 2005;366:1558–60.
7. World Cancer Research Fund in association with the American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: a Global Perspective. Washington, DC: American Institute for Cancer Research, 1997.
8. Brennan P, Fortes C, Butler J, Agudo A, Benhamou S, Darby S, Gerken M, Jokel KH, Kreuzer M, Mallone S, Nyberg F, Pohlabeln H, et al. A multicenter case-control study of diet and lung cancer among non-smokers. Cancer Causes Control 2000;11:49–58.
9. Vainio H, Bianchini F, eds. IARC Handbooks of Cancer Prevention, Vol. 8: Fruit and vegetables. Lyon: IARC Press, 2003.
10. Smith-Warner SA, Spiegelman D, Yaun SS, Albanes D, Beeson WL, van den Brandt PA, Feskanich D, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, et al. Fruits, vegetables and lung cancer: A pooled analysis of cohort studies. Int J Cancer 2003; 107:1001–11.
11. Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am J Clin Nutr 2003;78(3, Suppl): 559S–569S.
12. Miller AB, Altenburg HP, Bueno-de-Mesquita B, Boshuizen HC, Agudo A, Berrino F, Gram IT, Janson L, Linseisen J, Overvad K, Rasmuson T, Vineis P, et al. Fruits and vegetables and lung cancer: findings from the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2004;108:269–76.
13. Kristal AR, Peters U, Potter JD. Is it time to abandon the food frequency questionnaire? Cancer Epidemiol Biomarkers Prev 2005;14:2826–8.
14. Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N. Are imprecise methods obscuring a relation between fat and breast cancer? Lancet 2003;362:212–14.
15. Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G, Kroke A, Trichopoulos D, Trichopoulou A, Lauria C, Bellegotti M, Ocke MC, et al. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. Public. Health. Nutr 2002;5:1125–45.
16. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondiere UR, Hemon B, Casagrande C, Vignat J, Overvad K, Tjonneland A, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–24.
17. Ferrari P, Kaaks R, Fahey MT, Slimani N, Day NE, Pera G, Boshuizen HC, Roddam A, Boeing H, Nagel G, Thiebaut A, Orfanos P, et al. Within- and between-cohort variation in measured macronutrient intakes, taking account of measurement errors, in the European Prospective Investigation into Cancer and Nutrition study. Am J Epidemiol 2004;160:814–22.
18. Rosner B, Gore R. Measurement error correction in nutritional epidemiology based on individual foods, with application to the relation of diet to breast cancer. Am J Epidemiol 2001;154:827–35.
19. Rosner B, Willett WC, Spiegelman D. Correction of logistic-regression relative risk estimates and confidence-intervals for systematic within-person measurement error. Stat Med 1989;8:1051–69.
20. Kaaks R, Riboli E, Van Staveren W. Calibration of dietary-intake measurements in prospective cohort studies. Am J Epidemiol 1995;142:548–56.
21. Feskanich D, Ziegler RG, Michaud DS, Giovannucci EL, Speizer FE, Willett WC, Colditz GA. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. J Natl Cancer Inst 2000;92:1812–23.
22. Voorrips LE, Goldbohm RA, Verhoeven DT, van Poppel GA, Sturmans F, Hermus RJ, van den Brandt PA. Vegetable and fruit consumption and lung cancer risk in the Netherlands Cohort Study on diet and cancer. Cancer Causes Control 2000;11:101–15.
23. Steinmetz KA, Potter JD, Folsom AR. Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. Cancer Res 1993;53:536–43.
24. Fraser GE, Beeson WL, Phillips RL. Diet and lung cancer in California Seventh-day Adventists. Am J Epidemiol 1991;133:683–93.
25. Albanes D, Heinonen OP, Taylor PR, Virtamo J, Edwards BK, Rautalahti M, Hartman AM, Palmgren J, Freedman LS, Haapakoski J, Barrett MJ, Pietinen P, et al. α-Tocopherol and -carotene supplements and lung cancer incidence in the α-tocopherol, β-carotene cancer prevention study: effects of base-line characteristics and study compliance. J Natl Cancer Inst 1996;88:1560–70.
26. Bandera EV, Freudenheim JL, Marshall JR, Zielezny M, Priore RL, Brasure J, Baptiste M, Graham S. Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States). Cancer Causes Control 1997;8:828–40.
27. Rohan TE, Jain M, Howe GR, Miller AB. A cohort study of dietary carotenoids and lung cancer risk in women (Canada). Cancer Causes Control 2002;13:231–7.
28. Jansen MCJF, Bueno-de-Mesquita HB, Räsänen L, Fidanza F, Nissinen AM, Menotti A, Kok FJ, Kromhout D. Cohort analysis of fruit and vegetable consumption and lung cancer mortality in European men. Int J Cancer 2001;92:913–18.
29. Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, β-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. Br J Cancer 1992;66:673–9.
30. Kromhout D. Essential micronutrients in relation to carcinogenesis. Am J Clin Nutr 1987;45(5, Suppl):1361–7.
31. Ocke MC, Bueno-de-Mesquita HB, Feskens EJ, van Staveren WA, Kromhout D. Repeated measurements of vegetables, fruits, β-carotene, and vitamins C and E in relation to lung cancer. The Zutphen Study. Am J Epidemiol 1997;145:358–65.
32. Kvale G, Bjelke E, Gart JJ. Dietary habits and lung cancer risk. Int. J Cancer 1983;31:397–405.
33. Wang LD, Hammond EC. Lung cancer, fruit, green salad and vitamin pills. Chin Med J (Engl) 1985;98:206–10.
34. Chow WH, Schuman LM, McLaughlin JK, Bjelke E, Gridley G, Wacholder S, Chien HT, Blot WJ. A cohort study of tobacco use, diet, occupation, and lung cancer mortality. Cancer Causes Control 1992;3:247–54.
35. Breslow RA, Graubard BI, Sinha R, Subar AF. Diet and lung cancer mortality: a 1987 National Health Interview Survey cohort study. Cancer Causes Control 2000;11:419–31.

36. Holick CN, Michaud DS, Stolzenberg-Solomon R, Mayne ST, Pietinen P, Taylor PR, Virtamo J, Albanes D. Dietary carotenoids, serum β-carotene, and retinol and risk of lung cancer in the α-tocopherol, β-carotene cohort study. Am J Epidemiol 2002;156:536–47.
37. Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. Br J Cancer 2003;88:689–94.
38. Neuhouser ML, Patterson RE, Thornquist MD, Omenn GS, King IB, Goodman GE. Fruits and vegetables are associated with lower lung cancer risk only in the placebo arm of the β-carotene and retinol efficacy trial (CARET). Cancer Epidemiol Biomarkers Prev 2003;12:350–8.
39. Wakai K, Ando M, Ozasa K, Ito Y, Suzuki K, Nishino Y, Kuriyama S, Seki N, Kondo T, Watanabe Y, Ohno Y, Tamakoshi A, for JACC Study Group. Updated information on risk factors for lung cancer: findings from the JACC Study. J Epidemiol 2005;15(Suppl 2):S134–S139.
40. Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. Cancer Causes Control 2004;15:349–57.
41. Skuladottir H, Tjonneland A, Overvad K, Stripp C, Christensen J, Raaschou-Nielsen O, Olsen JH. Does insufficient adjustment for smoking explain the preventive effects of fruit and vegetables on lung cancer? Lung Cancer 2004;45:1–10.
42. Brennan P, Fortes C, Butler J, Agudo A, Benhamou S, Darby S, Gerken M, Jokel KH, Kreuzer M, Mallone S, Nyberg F, Pohlabeln H, et al. A multicenter case-control study of diet and lung cancer among non-smokers. Cancer Causes Control 2000;11:49–58.
43. Seow A, Poh WT, Teh M, Philip Eng P, Wang Y-T, Tan W-C, Chia K-S, Yu MC, Lee H-P. Diet, reproductive factors and lung cancer risk among Chinese women in Singapore: evidence for a protective effect of soy in nonsmokers. Int J Cancer 2002;97:365–71.
44. Kreuzer M, Heinrich J, Kreienbrock L, Rosario AS, Gerken M, Wichmann HE. Risk factors for lung cancer among nonsmoking women. Int J Cancer 2002;100:706–13.
45. Nyberg F, Agrenius V, Svartengren K, Svensson C, Pershagen G. Dietary factors and risk of lung cancer in never-smokers. Int J Cancer 1998;78:430–36.
46. Ko YC, Lee CH, Chen MJ, Huang CC, Chang WY, Lin HJ, Wang HZ, Chang PY. Risk factors for primary lung cancer among non-smoking women in Taiwan. Int J Epidemiol 1997;26:24–31.
47. Hu J, Mao Y, Dryer D, White K, The Canadian Cancer Registries Epidemiology Research Group. Risk factors for lung cancer among Canadian women who have never smoked. Cancer Detect Prev 2002;26:129–38.
48. Kubik AK, Zatloukal P, Tomasek L, Pauk N, Havel L, Krepela E, Petruzelka L. Dietary habits and lung cancer risk among non-smoking women. Eur J Cancer Prev 2004;13:471–80.
49. Howells LM, Manson MM. Prospects for plant-derived chemopreventive agents exhibiting multiple mechanisms of action. Curr Med Chem Anticancer Agents 2005;5:201–13.
50. Manson MM, Farmer PB, Gescher A, Steward WP. Innovative agents in cancer prevention. Recent Results Cancer Res 2005;166:257–75.
51. Surh YJ. Cancer chemoprevention with dietary phytochemicals. Nat Rev Cancer 2003;3:768–80.
52. Hirsch FR, Lippman SM. Advances in the biology of lung cancer chemoprevention. J Clin Oncol 2005;23:3186–97.
53. van Zandwijk N. Chemoprevention in lung carcinogenesis—an overview. Eur J Cancer 2005;41:1990–2002.
54. Männistö S, Smith-Warner SA, Spiegelman D, Albanes D, Anderson K, van den Brandt PA, Cerhan JR, Colditz G, Feskanich D, Freudenheim JL, Giovannucci E, Goldbohm RA, et al. Dietary carotenoids and risk of lung cancer in a pooled analysis of seven cohort studies. Cancer Epidemiol Biomarkers Prev 2004;13:40–8.
55. Cho E, Hunter DJ, Spiegelman D, Albanes D, Beeson WL, van den Brandt PA, Colditz GA, Feskanich D, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, et al. Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: a pooled analysis of 8 prospective studies. Int J Cancer 2006;118:970–8.
56. Bianchini F, Vainio H. Isothiocyanates in cancer prevention. Drug Metab Rev 2004;36:655–67.
57. Zhao B, Seow A, Lee EJ, Poh WT, Teh M, Eng P, Wang YT, Tan WC, Yu MC, Lee HP. Dietary isothiocyanates, glutathione S-transferase-M1, -T1 polymorphisms and lung cancer risk among Chinese women in Singapore. Cancer Epidemiol Biomarkers Prev 2001;10:1063–7.
58. Wu X, Zhao H, Suk R, Christiani DC. Genetic susceptibility to tobacco-related cancer. Oncogene 2004;23:6500–23.
59. Boshuizen HC, Bueno-de-Mesquita HB, Altenburg HP, Agudo A, Le Marchand L, Berrino F, Janzon L, Rasmuson T, Vineis P, Lukanova A, Linseisen J, Riboli E, Miller A, for EPIC Working Group on Lung Cancer. Adjustment for smoking in lung cancer analyses in the EPIC cohort. IARC Sci Publ 2002;156:59–61.
60. Lubin JH, Blot WJ. Assessment of lung cancer risk factors by histologic category. J Natl Cancer Inst 1984;73:383–9.
61. De Stefani E, Boffetta P, Ronco AL, Brennan P, Correa P, Deneo-Pellegrini H, Gutierrez LP, Mendilaharsu M. Squamous and small cell carcinomas of the lung: similarities and differences concerning the role of tobacco smoking. Lung Cancer 2005;47:1–8.
62. Day NE, McKeown N, Wong MY, Welch A, Bingham S. Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. Int J Epidemiol 2001;30:309–17.
63. Kipnis V, Midthune D, Freedman LS, Bingham S, Schatzkin A, Subar A, Carroll R. Empirical evidence of correlated biases in dietary assessment instruments and its implications. Am J Epidemiol 2001;153:394–403.
64. Agudo A, Slimani N, Ocke MC, Naska A, Miller AB, Kroke A, Bamia C, Karalis D, Vineis P, Palli D, Bueno-de-Mesquita HB, Peeters PH, et al. Consumption of vegetables, fruit and other plant foods in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts from 10 European countries. Public Health Nutr 2002;5:1179–96.