FRUITS AND VEGETABLES AND LUNG CANCER: FINDINGS FROM THE EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION

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Intake of fruits and vegetables is thought to protect against the development of lung cancer. However, some recent cohort and case-control studies have shown no protective effect. We have assessed the relation between fruit and vegetable intake and lung cancer incidence in the large prospective investigation on diet and cancer, the European Prospective Investigation Into Cancer and Nutrition (EPIC). We studied data from 478,021 individuals that took part in the EPIC study, who were recruited from 10 European countries and who completed a dietary questionnaire during 1992–1998. Follow-up was to December 1998 or 1999, but for some centres with active follow-up to June 2002. During

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follow-up, 1,074 participants were reported to have developed lung cancer, of whom 860 were eligible for our analysis. We used the Cox proportional hazard model to determine the effect of fruit and vegetable intake on the incidence of lung cancer. We paid particular attention to adjustment for smoking. Relative risk estimates were obtained using fruit and vegetable intake categorised by sex-specific, cohort-wide quintiles. After adjustment for age, smoking, height, weight and gender, there was a significant inverse association between fruit consumption and lung cancer risk: the hazard ratio for the highest quintile of consumption relative to the lowest being 0.60 (95% Confidence Interval 0.46–0.78), *p* for trend 0.0099. The association was strongest in the Northern Europe centres, and among current smokers at baseline, and was strengthened when the 293 lung cancers diagnosed in the first 2 years of follow-up were excluded from the analysis. There was no association between vegetable consumption or vegetable subtypes and lung cancer risk. The findings from this analysis can be regarded as re-enforcing recommendations with regard to enhanced fruit consumption for populations. However, the effect is likely to be small compared to smoking cessation.

Key words: *cancer; diet; epidemiology; fruits; vegetables; lung cancer; smoking*

In the 1997 report of the World Cancer Research Fund,[1] it was concluded that there was convincing evidence that vegetables and fruits decrease the risk of lung cancer, with the evidence being most abundant and consistent for green vegetables and carrots, as well as for both vegetables and fruits generally. Apart from vegetables and fruits, several micronutrients, vitamins and minerals commonly found in plants have been considered in relation to lung cancer risk. In some studies, the protective effect from vegetables was attributed to beta-carotene. However, a protective effect of beta-carotene for lung cancer is now considered unlikely because of negative results of trials with beta-carotene supplementation.[2]

Many of the early data available, and considered by the WCRF in their review,[1] did not specifically consider food groups but instead converted data derived from estimates of consumption of different food items to estimated consumption of nutrients and micronutrients, which was the principal focus of many of these investigations. Although it was appreciated that many of these micronutrient-based analyses were in fact producing estimates of fruit and or vegetable consumption, *e.g.*, of nonanimal sources of vitamin A,[3] an early focus of interest for lung cancer and diet,[4] these early studies cannot in practice be used to determine the likely effect of fruit and vegetable consumption on lung cancer risk. Therefore, much of the literature on lung cancer and diet is largely noncontributory to the subject of the present report.

Since the WCRF (1997) report,[1] however, there have been reports on cohort studies in which the effects of estimated fruit and vegetable consumption on lung cancer risk or lung cancer mortality were considered. In a report on 2 U.S. cohorts, an effect of fruit and vegetable intake was found in women but not in men,[5] in an European multi-country cohort, fruit intake was inversely related to lung cancer mortality in male smokers,[6] and in a study in the Netherlands, inverse associations were found for both fruits and vegetables.[7] Inverse associations with lung cancer risk were also found for fruits in cohort studies in China[8] and Japan.[9] However, in a mortality study in the United States, no associations were found for either fruit or vegetable intake.[10] In case-control studies, inverse associations for fruit and for vegetable consumption were found in Sweden[11] and Singapore,[12] but only for vegetables in Taiwan.[13] However, case-control studies in nonsmokers have reported conflicting results. A multicentre study in Europe found a significant effect of increasing vegetable consumption in reducing lung cancer risk,[14] a study in Germany found inverse associations for fruits and for vegetables,[15] but a multicentre study in Canada found no effect of either fruit or vegetable consumption.[16] Part of the difficulty in all studies except in nonsmokers could be in adequately controlling for potential confounding from tobacco use, while the discrepancies could also be explained by the impact of measurement error and by effects of recall bias in the case-control studies. Therefore in the first major analysis of EPIC data in relation to lung cancer risk here reported, considerable attention has been paid to controlling for current and past tobacco use, as well as duration of smoking.[17] A preliminary report on these findings has already been presented.[18] However, the present report represents a considerable expansion of the data base from that reported previously,[18] incorporating data from 4 additional centres (Malmö, Sweden, Greece and 2 in Norway) and updated information from the remaining centres.

The issue of measurement error in nutritional epidemiology is a major problem in defining links between diet and disease endpoints such as cancer. Attempts have been made to correct for measurement error by means of "validation" studies.[19] Since, however, the errors associated with different record or questionnaire methods used for measuring diet are likely to be substantially correlated, the regression dilution factors estimated from conventional "validation" studies are likely to be substantial underestimates.[20,21] Studies in which biomarkers have been used as the reference method for assessing dietary intake indicate that the real degree of regression dilution is substantially larger than previously estimated, rendering suspect earlier negative findings.[20]

All cohort studies so far conducted on diet and cancer have been carried out in populations in whom dietary habits are relatively homogeneous, so that the extent of measurement error would have obscured any but very large underlying diet-disease associations. One way of reducing measurement error is to study different populations with diverse dietary practices, thus increasing the between person variance in diet and enabling measurement error to be minimised.[20] Such was the approach behind the large prospective collaborative project carried out in 10 different European countries, the European Prospective Investigation into Cancer and nutrition (EPIC).[22] This investigation, of 519,978 individuals, is the largest ever conducted specifically on the relation between diet and cancer. Publications elsewhere have demonstrated the heterogeneity of dietary intakes of foods in this collaborative cohort. There is over a 3-fold range in total fruit and vegetables (excluding potatoes) average population consumption between Malmö in Sweden and Murcia in Southern Spain.[23]

METHODS

EPIC is a multi-centre prospective cohort study designed to investigate the relation between food, nutritional status, various lifestyle and environmental factors and the incidence of different forms of cancer. The total cohort consists of subcohorts recruited in centres in 10 European countries: Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden and the United Kingdom. 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.[24]

Study subjects

The 519,978 eligible study subjects were mostly aged 25–70 years and recruited from the general population residing in a given geographical area, a town or a province. Exceptions were the French cohort based on members of the health insurance for state school employees, the Utrecht cohort based on women attending breast cancer screening and most of the Oxford cohort based on vegetarian volunteers and healthy eaters. Eligible subjects were invited to participate in the study by mail or by personal contact. Those who accepted signed an informed consent form, and diet and lifestyle questionnaires were mailed to them to be filled in. Study subjects were then invited to a centre for blood collection and anthropometric measurements including height and weight, and to deliver the completed diet and lifestyle questionnaires; in Norway, height and weight were self-reported.

Diet and lifestyle questionnaires

Following the results of several methodological studies conducted in the early 1990s, diet was measured by country-specific questionnaires designed to capture local dietary habits and to provide high compliance. Seven countries adopted an extensive self-administered dietary questionnaire, which can provide data on up to 300–350 food items per country. In Greece, Spain and Sicily a dietary questionnaire, very similar in content to the above but administered by direct interview, was used. A food frequency questionnaire and a 7-day record was adopted in England. For calibration, a novel methodological approach was implemented in EPIC aimed at calibrating dietary measurements across countries in order to correct for systematic over- or under-estimation of dietary intakes. For this purpose, a second dietary measurement was taken from an 8% random sample of the cohort by using a computerised 24 hr diet recall method that was developed *ad hoc*.[25] Detailed 24 hr recall consumption data were available in computerised form for 36,900 subjects. The lifestyle questionnaires included questions on education and socio-economic status, occupation, history of previous illness and disorders or surgical operation, lifetime history of consumption of tobacco and alcoholic beverages and physical activity.

A list of the fruit and vegetable items that contributed to the total fruit and total vegetable groups, and of the subgroups used in the analysis, is given in the Appendix.

End-points

The follow-up is based on population cancer registries in 7 of the participating countries (Denmark, Italy, Netherlands, Spain, Sweden, United Kingdom and Norway) and on a combination of methods including health insurance records, cancer and pathology registries, and active follow-up through study subjects and their next-of-kin in 3 countries: France, Germany and Greece. Mortality data are also collected from either the cancer registry or mortality registries at the regional or national level. By the end of June 2002, complete follow-up data, and 16,000 cancer cases, had been reported to IARC to 31 December 1998 or December 1999 for the centres with passive follow-up, and more recently for the centres with active follow-up.

The 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) was used. Cancer of the lung as analysed here included invasive cancers coded to C 34. Histological confirmation of diagnosis was not required; it was assumed that the diagnosis reported by the contributing centre was correct. Associations of lung cancer with dietary factors may differ by histological type. Such potential differences have not been considered in the present analysis but will be reported at a later date.

STATISTICAL METHODS

Uncalibrated estimates of diet

Both sex-specific and sex- and country-specific quintiles of fruit and vegetable intake were used in the analysis; there was little difference in the results between the 2 methods and results from sex-specific and EPIC-wide quintiles are included in the results. Data from individuals in the top and bottom 1% of the ratio of energy intake to estimated energy requirement calculated from body weight[27] (ei/er ratio) were excluded to reduce the impact on the analysis of implausible extreme values. The other main exclusion was for those recruited with a previously diagnosed cancer of any site, and those for whom the date of diagnosis of lung cancer was recorded as prior to the date of collection of the baseline data.

The main analyses were performed using Cox regression. Confirmatory analyses were also performed using Poisson regression. The 2 approaches were in close agreement, and the results reported here are from the Cox regression. The analyses were stratified by centre to control for centre effects, such as follow up procedures and questionnaire design, and for sex to control for differences between women and men in smoking behaviour and food intake. In addition, several of the analysis were further subdivided into South (Spain, France, Greece and Italy) and North Europe (Denmark, Germany, Netherlands, Norway, Sweden and the United Kingdom), and stratified by centre within these groupings of countries. Age was used as the primary dependent time variable in all Cox regression models. Analyses were controlled for smoking using the categories defined in Table III. In addition, the main analyses were repeated for current smokers, adjusting for intensity of smoking as a continuous variable for the 305,985 subjects for whom such data were available. The analysis focused on all fruit and all vegetable intake considered separately. These quantitative variables were categorised using as cutpoints the sex specific quintiles defined over the entire cohort. Analyses were run using variables as categorically scored from 1 (reference) to 5 according to which interquintile interval an observation lay. Trend tests were computed using these quintile-based scores.

In preliminary analyses, energy adjustment was undertaken both to simulate an isocaloric experiment and to control partially for error in the estimates of fruit and vegetable intake. However, weight provides a considerably better estimate of age and sex specific energy intake,[20] so for the purpose of making isoenergetic comparisons, weight was included in all models. Estimated total energy intake was initially included to control partially for the error in the estimated intake of fruits and vegetables, since there is high correlation between the errors of estimation of different dietary components. To improve this error correction, estimated energy intake was divided into energy from fat and energy from nonfat sources, since it is largely the nonfat components of the diet that contribute to fruit and vegetable intake.[27] Models were run including nonfat energy and with and without energy from fat, and there was little difference in the results from the weight-adjusted models. Therefore models including nonfat and fat energy were not included in the results presented here. However, to control for body size and obesity, in addition to weight, models were also fitted including height. It was found that a better fit was obtained using weight and height, but no further improvement using weight and BMI, so that the results presented are after adjustment for weight and height.

Calibration

To calibrate, as further adjustment for measurement error, we used the 24 hr means from the EPIC-SOFT calibration study.[26] These were available for energy, alcohol and all the EPIC-SOFT food groups, and their subgroups, including fruits and vegetables, and defined subtypes. The method is to multiply the observed values from the food frequency questionnaires (FFQ) by the ratio of the calibration mean to the FFQ mean for the same individuals, per centre and gender sub-group. Cox regression analyses were then run with the adjusted values for each individual.

RESULTS

In the 1,939,011 person years of follow-up since 1992, 1,074 incident lung cancers had been included in the IARC data base by June 2002, 82% being histologically confirmed. Of these individuals with lung cancer, 279 were excluded from the analysis: 6 with no nondietary information in the data base, 44 with no dietary information, 20 with extreme ranking of the ei/er ratio, 124 with a history of previous cancer of another site, 2 because of missing date of diagnosis of lung cancer, 65 censured because of lack of follow-up information and 18 since the records indicated that the lung cancer was metastatic from another cancer site. This left 860 with satisfactory data used in the analysis. Table I shows the numbers of lung cancers included in the analysis according to country, age and sex and the corresponding numbers of cohort members and crude sex-specific incidence rates. The latter have to be interpreted recognising that older cohort members were recruited in some centres than others, but in general they reflect

TABLE I – DESCRIPTION OF THE EPIC COHORT

	Lung cancer cases			Cohort numbers			Person years		Incidence rate per 100,000 PY	
	Men	Women	All	Men	Women	All	Men	Women	Men	Women
Country										
France		54	54		67,956	67,956		437,767		12.3
Italy	32	31	63	14,029	30,522	44,551	53,347	133,727	60.0	23.2
Spain	53	8	61	15,154	24,849	40,003	91,779	144,512	57.7	5.5
UK	77	57	134	22,292	52,205	74,497	106,890	244,858	72.0	23.3
Netherlands	12	52	64	9,895	27,516	37,411	35,313	125,971	34.0	41.3
Greece	27	2	29	10,393	14,785	25,178	38,010	54,659	71.0	3.7
Germany	70	17	87	21,587	27,924	49,511	91,873	117,567	76.2	14.5
Sweden	102	72	174	22,321	26,298	48,619	170,070	199,117	60.0	36.2
Denmark	93	77	170	26,317	28,762	55,079	86,532	95,772	107.5	80.4
Norway		24	24		35,234	35,234		57,432		41.8
Age band										
<35				8,417	19,495	27,912	42,034	89,712	0.0	0.0
35–44	13	17	30	24,858	66,025	90,883	119,802	295,601	10.9	5.8
45–54	82	127	209	50,232	139,344	189,576	238,052	660,000	34.4	19.2
55–64	267	174	441	47,814	90,275	138,089	221,632	457,455	120.5	38.0
65+	104	76	180	10,667	20,894	31,561	52,297	108,614	198.9	70.0
All	466	394	860	141,988	336,033	478,021	673,817	1611,382	69.2	24.5

differences in smoking rates by age and gender in the different countries.

Table IIshows sex specific descriptive measures (means and medians) of fruit and vegetable intake and the quintile specific medians of intake.

Table III shows the distribution of lung cancer cases by smoking category, separately for men and women, and the associated hazards ratios. Particularly in men, but also in women, there are strong associations between smoking and lung cancer in this cohort, with highly significant dose response relationships. In subsequent analyses, the associations with dietary variables were evaluated using these strata for the adjustment of the hazard ratios.

Table IV shows the numbers of cancers by quintile and hazard ratios for total fruit and total vegetable intake separately, stratified by centre and sex. The hazard ratio for lung cancer and total fruit intake for the highest quintile was 0.60 (95% CI 0.46–0.78). The trend across quintiles was significant, $p=0.0099$. Subdividing into South and North Europe shows the most consistent association in North Europe. There were similar inverse associations for fruits, which for South Europe is now also statistically significant. Analyses for men and women separately showed similar inverse associations, nonsignificant in men, but significant in women.

There was no evidence of an inverse association for vegetable intake, either for men or women, or for both together in a gender stratified analysis (Table IV), nor when subdivided into South and North Europe. Of vegetable subtypes, there was a suggestion of an inverse association for leafy vegetables, especially in North Europe, but this was not significant (Table IV). There was no association for cruciferous vegetables (Table IV), nor for root vegetables (including carrots) nor onions and garlic (the findings are not tabulated here).

Repeating the analyses for total fruits, adjusting for vegetable intake, slightly strengthened the inverse association, the hazard ratio for the highest relative to the lowest quintile becoming 0.58 (95% CU 0.44–0.76), p for trend 0.0113; whereas there remained no association for vegetable intake after adjusting for fruit intake (the findings are not tabulated here).

After calibration, there was little change in the associations reported in Table IV (the findings are not tabulated here). Significant inverse associations for total fruit consumption persisted, but there were no associations for total vegetable intake.

Analyses were also performed within strata of current smokers, ex-smokers and lifelong nonsmokers. The findings for total fruit and total vegetable intake are presented in Table V. For smokers and lifelong nonsmokers, the associations were similar to those in Table IV, though for nonsmokers, the trend for total fruit consumption was only statistically significant in North Europe. However there was no association for either total fruit or total vegetable intake among ex-smokers.

The significant inverse association with total fruit consumption among smokers persisted largely unchanged when smoking was adjusted as a continuous variable among the 305,985 study subjects for which such data were available. Thus the hazard ratio for the highest quintile relative to the lowest was 0.60 (95% CI 0.52–0.94). For fruits, the corresponding hazard ratio was 0.53 (0.33–0.85).

The analyses in Table IV were repeated excluding the 296 lung cancers diagnosed in the first 2 years of follow-up, the total of numbers of lung cancer cases thus falling to 564 (the findings are not tabulated here). This resulted in an enhancement of the inverse associations for total fruit and fruit consumption reported in Table IV, the hazard ratios for the highest quintile relative to the lowest becoming 0.50 (0.36–0.70) and 0.50 (0.36–0.70), respectively. However, there was little change in the hazard ratios for total vegetable and leafy vegetable consumption reported in Table IV, the hazard ratios for the highest quintile of consumption relative to the lowest becoming 0.95 (0.69–1.31) and 0.85 (0.60–1.21), respectively.

DISCUSSION

The large size of this European collaborative investigation of the relationship between dietary intake and occurrence of cancer will make it possible to eventually investigate histological and molecular subtypes of common cancers. For this first report on lung cancer, however, we have chosen to analyse all incident lung cancers combined. In a subsequent report, we shall consider the various histological subtypes of lung cancer.

We found that total fruit consumption was inversely associated with lung cancer risk but that there was no association for total vegetable consumption. An inverse association for both factors was marked in analyses unadjusted for smoking but was substantially attenuated when such adjustment was introduced. For current smokers, after adjustment for smoking intensity and duration, the inverse association for total fruit consumption was statistically significant and persisted largely unchanged when smoking was adjusted as a continuous variable among the study subjects for which such data were available. Therefore, it seems unlikely that the inverse association with total fruits is due to residual confounding with smoking. The number of cases of lung cancer in nonsmokers, especially in men, was very small, but nonsignificant inverse associations were also noted for total fruits but not total

TABLE II – SEX-SPECIFIC ESTIMATED INTAKE OF TOTAL FRUITS AND OF TOTAL VEGETABLES, IN G. PER DAY, AND MEDIAN INTAKE BY QUINTILE

	Mean (s.d.)/median	Quintile median				
		1	2	3	4	5
Women						
Total fruits	257.3 (191.3)/ 218.2	68.6	142.4	218.2	308.6	490.4
Total vegetables	219.1 (142.9)/ 185.4	78.1	130.7	185.4	260.1	402.5
Men						
Total fruits	227.0 (208.4)/ 165.9	41.2	102.3	165.9	265.4	486.4
Total vegetables	194.1 (150.7)/ 152.4	56.9	106.0	152.4	222.0	385.9

TABLE III – DISTRIBUTION OF FREQUENCY AND INTENSITY OF SMOKING FOR LUNG CANCER CASES BY GENDER, AND HAZARD RATIOS FOR EACH STRATUM STRATIFIED BY CENTRE

Smoking variable	Males		Females	
	Number of lung cancers	Hazard ratio (95% CI)	Number of lung cancers	Hazard ratio (95% CI)
Non-smokers	13	1.00	61	1.00
Current smokers				
< 15 cigarettes/day	63	9.95 (5.23–18.95)	74	3.52 (2.23–5.57)
15–24 cigarettes/day	123	22.52 (12.08–41.97)	103	9.59 (6.24–14.76)
25 + cigarettes/day	78	40.67 (21.21–77.95)	42	18.30 (10.83–30.93)
Duration of smoking				
0–10 years	5	1.02 (0.36–2.85)	12	1.32 (0.58–3.00)
11–20 years	22	2.25 (1.15–4.04)	12	0.71 (0.31–1.63)
21–30 years	48	2.18 (1.28–3.70)	36	1.73 (1.01–2.96)
31–40 years	113	1.84 (1.18–2.86)	85	2.16 (1.35–3.44)
40 or more years	196	1.36 (0.90–2.05)	88	1.63 (1.02–2.61)
Other type of smoking	52	6.61 (3.50–12.46)	35	1.93 (1.19–3.13)
Ex-smokers, quit smoking				
0–10 years ago	73	6.01 (3.03–11.92)	44	2.63 (1.48–4.66)
11–20 years ago	32	2.36 (1.1–5.08)	13	1.11 (0.52–2.38)
> 20 years ago	27	1.27 (0.55–2.94)	18	1.30 (0.58–2.91)
Missing information on smoking	2	4.89 (1.08–22.11)	2	0.70 (0.10–5.07)

TABLE IV – NUMBERS OF LUNG CANCERS AND HAZARD RATIOS BY QUINTILE OF SEX SPECIFIC FRUIT AND VEGETABLE INTAKE; COX REGRESSION ADJUSTED FOR SMOKING, WEIGHT, HEIGHT AND STRATIFIED BY SEX AND CENTRE OR SEX AND CENTRE STRATA FOR SOUTH (SPAIN, FRANCE, GREECE, ITALY) AND NORTH EUROPE (DENMARK, GERMANY, NETHERLANDS, NORWAY, SWEDEN, UNITED KINGDOM) SEPARATELY

Total number lung cancers = 860	Quintile					
	1	2	3	4	5	*p* for trend
Total Fruits						
Numbers lung cancers	245	184	168	157	106	
Hazard ratios (95% CI)						
Sex and centre strata	1.00	0.86 (0.70–1.05)	0.78 (0.63–0.97)	0.78 (0.63–0.98)	0.60 (0.46–0.78)	0.0099
Sex and centre strata, South Europe	1.00	1.16 (0.66–2.05)	0.71 (0.40–1.24)	1.07 (0.65–1.75)	0.57 (0.34–0.97)	0.2154
Sex and centre strata, North Europe	1.00	0.82 (0.66–1.02)	0.81 (0.65–1.02)	0.68 (0.53–0.89)	0.68 (0.49–0.94)	0.0529
Fruits						
Numbers lung cancers	235	205	161	159	100	
Hazard ratios (95% CI)						
Sex and centre strata	1.00	0.88 (0.72–1.08)	0.75 (0.61–0.93)	0.77 (0.62–0.96)	0.56 (0.43–0.73)	0.0099
Sex and centre strata, South Europe	1.00	0.99 (0.56–1.78)	0.80 (0.47–1.38)	0.93 (0.56–1.52)	0.53 (0.31–0.89)	0.0434
Sex and centre strata, North Europe	1.00	0.87 (0.71–1.08)	0.74 (0.58–0.94)	0.72 (0.56–0.93)	0.62 (0.44–0.88)	0.0196
Total vegetables						
Numbers lung cancers	220	180	175	149	136	
Hazard ratios (95% CI)						
Sex and centre strata	1.00	0.99 (0.81–1.23)	1.08 (0.87–1.34)	0.98 (0.77–1.23)	1.00 (0.76–1.30)	0.8528
Sex and centre strata, South Europe	1.00	1.20 (0.67–2.16)	1.32 (0.76–2.31)	1.34 (0.78–2.30)	1.32 (0.75–2.32)	0.1699
Sex and centre strata, North Europe	1.00	0.97 (0.78–1.22)	1.05 (0.83–1.33)	0.91 (0.70–1.19)	0.94 (0.68–1.29)	0.3458
Leafy vegetables						
Numbers lung cancers	249	176	163	148	124	
Hazard ratios (95% CI)						
Sex and centre strata	1.00	0.92 (0.74–1.13)	0.89 (0.71–1.11)	0.92 (0.72–1.16)	0.89 (0.66–1.19)	0.2961
Sex and centre strata, South Europe	1.00	2.01 (0.69–5.86)	1.74 (0.64–4.76)	1.90 (0.72–5.00)	1.85 (0.72–4.77)	0.4822
Sex and centre strata, North Europe	1.00	0.89 (0.72–1.10)	0.87 (0.69–1.10)	0.89 (0.68–1.17)	0.77 (0.49–1.22)	0.0531
Cruciferous vegetables						
Numbers lung cancers:	195	173	164	152	176	
Hazard ratios (95% CI)						
Sex and centre strata	1.00	1.13 (0.89–1.43)	1.21 (0.94–1.55)	1.11 (0.87–1.43)	1.21 (0.92–1.60)	0.2526
Sex and centre strata, South Europe	1.00	1.14 (0.74–1.75)	1.68 (1.07–2.63)	1.04 (0.61–1.75)	1.81 (1.09–3.03)	0.2328
Sex and centre strata, North Europe	1.00	1.06 (0.79–1.42)	1.04 (0.77–1.41)	1.05 (0.78–1.42)	1.01 (0.73–1.42)	0.6911

vegetables in this sub-group, which were significant for the North European countries. However, there were no associations among former cigarette smokers. Former cigarette smokers as a group had a higher consumption of total fruits and total vegetables than current smokers (the findings are not tabulated here). The lack of an inverse association with total fruit consumption in this sub-

TABLE V – NUMBERS OF LUNG CANCERS AND HAZARD RATIOS BY QUINTILE OF SEX SPECIFIC FRUIT AND VEGETABLE INTAKE; COX REGRESSION ADJUSTED FOR SMOKING, WEIGHT, HEIGHT AND STRATIFIED BY SEX AND CENTRE, OR SEX AND CENTRE STRATA FOR SOUTH (SPAIN, FRANCE, GREECE, ITALY) AND NORTH EUROPE (DENMARK, GERMANY, NETHERLANDS, NORWAY, SWEDEN, UNITED KINGDOM) SEPARATELY, FOR SMOKERS, EX-SMOKERS AND LIFE-LONG NON-SMOKERS

Smokers only	Quintile					*p* for trend
	1	2	3	4	5	
Total Fruits						
Numbers lung cancers (n = 532)	196	103	102	79	52	
Hazard ratios (95% CI):						
Sex and centre strata	1.00	0.70 (0.54–0.90)	0.84 (0.65–1.09)	0.71 (0.53–0.95)	0.51 (0.35–0.73)	0.0555
Sex and centre strata, South Europe	1.00	1.00 (0.47–2.12)	0.88 (0.45–1.74)	0.85 (0.45–1.59)	0.42 (0.21–0.84)	0.0123
Sex and centre strata, North Europe	1.00	0.69 (0.51–0.88)	0.82 (0.61–1.08)	0.66 (0.46–0.93)	0.63 (0.39–1.01)	0.1332
Total vegetables						
Numbers lung cancers (n = 532)	162	128	102	80	60	
Hazard ratios (95% CI):						
Sex and centre strata	1.00	1.07 (0.83–1.37)	1.02 (0.78–1.34)	0.96 (0.71–1.30)	0.80 (0.55–1.17)	0.0362
Sex and centre strata, South Europe	1.00	2.06 (0.96–4.40)	1.32 (0.60–2.94)	1.60 (0.75–3.43)	1.20 (0.54–2.69)	0.8082
Sex and centre strata, North Europe	1.00	0.98 (0.75–1.28)	1.01 (0.76–1.35)	0.88 (0.62–1.25)	0.75 (0.46–1.21)	0.0199
Ex-Smokers only	**Quintile**					***p* for trend**
	1	2	3	4	5	
Total Fruits						
Numbers lung cancers (n = 236)	35	62	51	44	44	
Hazard ratios (95% CI):						
Sex and centre strata	1.00	1.39 (0.90–2.16)	0.88 (0.55–1.38)	0.90 (0.56–1.44)	1.07 (0.65–1.76)	0.7582
Sex and centre strata, South Europe	1.00	1.13 (0.28–4.50)	0.25 (0.05–1.20)	0.68 (0.20–2.33)	0.74 (0.23–2.41)	0.6044
Sex and centre strata, North Europe	1.00	1.45 (0.91–2.31)	1.01 (0.62–1.63)	0.89 (0.53–1.49)	1.09 (0.61–1.93)	0.6970
Total vegetables						
Numbers lung cancers (n = 236)	40	41	52	47	56	
Hazard ratios (95% CI):						
Sex and centre strata	1.00	0.92 (0.58–1.46)	1.21 (0.77–1.90)	1.09 (0.68–1.77)	1.29 (0.78–2.14)	0.1058
Sex and centre strata, South Europe	1.00	0.24 (0.03–2.24)	1.91 (0.56–6.48)	1.62 (0.47–5.56)	1.48 (0.42–5.22)	0.4299
Sex and centre strata, North Europe	1.00	0.96 (0.59–1.55)	1.06 (0.65–1.73)	0.97 (0.57–1.64)	1.22 (0.70–2.13)	0.1196
Life-long Nonsmokers only	**Quintile**					***p* for trend**
	1	2	3	4	5	
Total Fruits						
Numbers lung cancers (n = 88)	13	19	14	32	10	
Hazard ratios (95% CI):						
Sex and centre strata	1.00	1.02 (0.48–2.16)	0.64 (0.29–1.42)	1.19 (0.59–2.39)	0.33 (0.13–0.83)	0.2429
Sex and centre strata, South Europe	1.00	2.97 (0.61–14.48)	1.24 (0.23–6.75)	3.47 (0.78–15.48)	0.91 (0.18–4.71)	0.8613
Sex and centre strata, North Europe	1.00	0.64 (0.26–1.59)	0.53 (0.21–1.34)	0.61 (0.24–1.55)	0.19 (0.04–0.81)	0.0339
Total vegetables						
Numbers lung cancers (n = 88)	18	10	20	21	19	
Hazard ratios (95% CI):						
Sex and centre strata	1.00	0.56 (0.24–1.28)	1.14 (0.56–2.33)	0.98 (0.47–2.04)	0.99 (0.45–2.21)	0.6741
Sex and centre strata, South Europe	1.00	0.33 (0.08–1.45)	0.84 (0.27–2.60)	0.83 (0.28–2.47)	1.07 (0.35–3.26)	0.4646
Sex and centre strata, North Europe	1.00	0.72 (0.26–1.98)	1.38 (0.55–3.48)	1.08 (0.39–2.99)	0.56 (0.14–2.29)	0.4920

group, therefore, could be due to the fact that they were health conscious and that they chose to consume a more healthy diet as well as to terminate their smoking.

It is of interest that an analysis of the effect of diet at baseline in the U.S. Carotene and Retinol Efficacy Trial (CARET) found a protective effect of fruits and some vegetable sub-groups in the placebo but not the intervention arm of the trial.[28] Thus for total fruits, the relative risk of lung cancer incidence for the highest quintile relative to the lowest in the placebo arm was 0.56 (0.39–0.81) but 0.79 (0.57–1.11) in the intervention arm (the trend for the former but not the latter association was statistically significant). Although there were no significant associations in either arm for total vegetable consumption, in the placebo arm the relative risk for the highest compared to the lowest quintile for cruciferous vegetable intake was 0.68 (0.45, 1.04) and for "other" vegetables 0.56 (0.37, 0.85), both with significant trends, but there was no inverse association for such consumption in the intervention arm. It would seem, therefore, that a dietary supplement of beta-carotene somehow counteracts the inhibitory effect not only of some vegetable subtypes but also of fruits.

The lack of a protective effect of vegetable consumption or of various vegetable subgroups in the present study is in conflict not only with the CARET trial results but also with some other previous investigations. In particular, a prospective study in Shanghai showed a clear protective effect of isothiocyanates, mainly contained in cruciferous vegetables.[29] Individuals with detectable isothiocyanates in the urine were at decreased risk of lung cancer [smoking-adjusted relative risk for lung cancer 0.65 (95% CI 0.43–0.97)]. This protective effect was seen primarily among individuals with homozygous deletion of GSTM1 [0.36 (0.20–0.63)] and particularly with deletion of both GSTM1 and GSTT1 [0.28 (0.13–0.57)].

It is not known which specific micronutrients might be responsible for a protective effect of fruits, although it is possible that different anti-oxidants including vitamins play a role.[30] Flavonoids are a particularly relevant group of phenolics that occur in fruits, vegetables and some beverages. Their dietary intake in humans ranges between 23 mg and 1 g/day per person.[31] Urinary excretion of these substances has been reported,[32] and isoflavonoids and lignans have been shown to inhibit the mutagenicity of various aromatic and heterocyclic amines.[33]

The consumption of phenolics has been shown to decrease the level of DNA adducts in experimental studies in humans and animals. Moderate wine consumption (a source of phenolics) inhibited peroxide-induced micronucleated cells,[34] while the con-

sumption of flavonoids inhibited DNA damage related to lipid peroxidation.[35]

It is possible that the very strong effect of smoking as a risk factor for lung cancer has overwhelmed real, but much weaker, inverse associations for vegetable consumption than for fruits. Although there has to be measurement error associated with the estimates of effects of active smoking, this is likely to be much less than the measurement error associated with estimates of dietary intake, even though we had no estimate of the effect of environmental tobacco smoke exposure. It is relevant that the probable measurement error associated with estimated intake of units of fruits is less than estimated consumption of a variety of vegetables, or even vegetable subclasses. Indeed, our analysis suggests that much of the effect of fruit consumption is derived from the grouping fruits, probably because this grouping includes about 90% of the total fruit intake in the EPIC cohort.[23] Possibly relevant is that in Europe fruits are consumed largely in the raw state, but in nonMediterranean countries, vegetables are almost invariably cooked. It is also of interest that we were able to demonstrate stronger effects of fruits in Northern than Southern European countries, probably because there is a more uniform and higher consumption of fruits in the South. The strong inverse association of fibre intake with colorectal cancer in EPIC[36] was demonstrated under circumstances where there was not such a strong confounder of dietary intake to be considered as in the analyses reported here. It has always been clear that even if there is a protective effect associated with fruit and or vegetable consumption with lung cancer, such an effect is substantially less than the benefit to be obtained from stopping smoking. If anything, such a cautionary message has been reinforced by the findings reported here.

In interpreting the present findings, it must be borne in mind that the duration of follow-up in EPIC is still short, and that, in this rather healthy population (there are more nonsmokers than would be expected from truly random samples of the base population in each country), lung cancers are accumulating more slowly than for other common cancer sites. Furthermore, the diet collected at baseline may be only a poor reflection of that etiologically relevant, a supposition supported by the stronger inverse associations found for fruit intake when cases diagnosed in the first 2 years of follow-up were excluded. It may be expected therefore that additional analyses of the association of fruit and vegetable consumption with lung cancer will be more informative after a few more years of follow-up. For the time being, however, the findings from this analysis can be regarded as re-enforcing, rather than negating, the recommendations of the World Cancer Research Fund[1] on appropriate dietary modifications for populations, particularly with regard to enhanced fruit consumption.

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APPENDIX: – COMPOSITION OF FRUIT AND VEGETABLE GROUPS AND SUBGROUPS USED IN THE ANALYSIS

Total fruits Fruit subgroups[a]	Sum of all 4 fruit subgroups Food items included
Fruits	All fresh and dried fruit items, including citrus fruits
Nuts and seeds	all nuts and seeds, nut spread
Mixed fruits	Mixed nuts and raisins, fruit cocktail, fruit salad
Olives	Olives only

Total vegetables Vegetable subgroup	Sum of all 10 vegetable subgroups Food items included
Leafy vegetables	Spinach, lettuce (all variants), (swiss) chard, chicory, wine leaf, beet leaves, turnip tops, borage, seaweed, thistle, watercress
Fruiting vegetables	Avocado, pepper (sweet, chilli), courgette, tomato, pumpkin, eggplant, artichoke, cucumber/gherkin, french bean, sugar pea, caper, okra
Root vegetables	Beetroot, swede, carrot, turnip, parsnip, celeriac, radish, salsify
Cruciferous vegetables	Cabbage (white, red, curly, chinese, sauerkraut, savoy), cauliflower, brussels sprouts, broccoli
Mushrooms	All types of mushrooms
Grain and pod vegetables	(Sweet) corn, broad bean, pea
Onion, garlic	Onion, garlic, shalott
Stalk vegetables, sprouts	Blanched celery, leek, fennel, asparagus, sprouts (alfalfa, mungbean, bamboo, other beans)
Mixed salad/vegetables	(used in Italy, Germany, Sweden, Denmark only)
Unclassified	(used in Spain, Naples, France only) unspecified (green) vegetables

[a]*Fruit juices and soups are not included.*