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Original Paper

Vegetable and Fruit Intake and the Risk of Lung Cancer in Women in Barcelona, Spain

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A case–control study on women was carried out in Barcelona, Spain, to investigate the relationship of lung cancer with the intake of vegetables, fruits and some foods of animal origin. The study included 103 cases and 206 controls matched by age and residence. Diet intake was assessed by means of a food frequency questionnaire. A reduction in risk, adjusted for smoking habit, was found for the intake of yellow/orange vegetables (mainly carrots) and tomatoes. The odds ratio (OR) and 95% confidence interval (CI) for the highest versus lowest tertile of intake were 0.37 (0.19–0.74) for yellow/orange vegetables and 0.45 (0.22–0.91) for tomatoes; both had a significant inverse trend. A tendency to a reduction in risk of lung cancer with increased intake was observed for all vegetables, leafy green vegetables, dark green vegetables and cruciferous, but these associations did not reach statistical significance. No association with lung cancer was found for the intake of fruits or foods of animal origin rich in retinol. Similar patterns were observed for women who never smoked and when the analysis was restricted to adenocarcinoma. © 1997 Published by Elsevier Science Ltd.

Key words: lung neoplasms, vegetables, fruit, case–control studies

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INTRODUCTION

EPIDEMIOLOGICAL EVIDENCE suggesting that some dietary factors may be associated with a reduction in the risk of lung cancer is accumulating. The results have been remarkably consistent, showing a protective effect related to the intake of vegetables and fruits [1–3]. Both are common sources of many substances with potential protective effect, but their effect in reducing lung cancer risk was initially attributed to β-carotene. Epidemiological studies linking dietary factors with a lower risk of lung cancer, along with experiments with animal models, provided the basis for intervention studies [4–6]. Taken together, they provide strong evidence of no benefit of β-carotene supplements, with possible evidence for harm. In fact, in the Finnish study on male smokers [4], the supplementation of β-carotene was unexpectedly associated with a significant 18% increase in lung cancer incidence. One study in the U.S.A. [6] on smokers, former smokers and workers exposed to asbestos found a 28% increase in the risk of lung cancer in the group treated with a combination of β-carotene and retinol, while in the study on male physicians [5], involving both smokers and non-smokers, no association was found between lung cancer and β-carotene supplementation. However, since both prospective and retrospective observational studies continue to suggest that increased vegetable and fruit intake is associated with reduced risk of lung cancer, the hypothesis that vegetables and fruits may exert a protective effect by a mechanism that does not involve β-carotene should be maintained.

While many studies on lung cancer have been carried out on men, few have focused on women. We present the

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results of a case–control study on women in Barcelona, Spain, regarding the relationship between lung cancer and dietary factors, focusing on several types of vegetables and fruits. Although cigarette smoking is the main determinant of lung cancer, more knowledge of other possible factors may lead to a better understanding of the causes of the disease and to improvement in preventive strategies.

MATERIALS AND METHODS

A hospital-based case–control study was carried out between 1989 and 1992 in Barcelona, Spain. A detailed description of the population, methods and results regarding smoking habit has been reported previously [7]. Briefly, from 114 potential cases (women newly diagnosed with a primary lung neoplasm) identified during the study period, 103 were finally included, among whom 101 had histological confirmation; the mean age was 63 years with a range of 32–88 years. Two controls per case were included, matched by age, residence and hospital; 7 women selected as valid controls refused to participate and were replaced. Women admitted for tobacco-related conditions were excluded from selection as controls. The distribution of controls by primary diagnosis included 36% with trauma and other musculoskeletal conditions, mainly hip and other fractures, 20% with diseases of the digestive tract, mainly surgical conditions such as hernia and acute colecistitis, 14% with tumours (excluding tobacco-related) and 6% with disorders of the genitourinary system; other groups with frequencies below 5% included circulatory system, respiratory system, skin, nervous system and blood and haematopoietic tissues. The information was collected by personal interview during the hospitalisation of the subject, by specially trained interviewers.

Diet was assessed by means of a food frequency questionnaire which ascertained the usual frequency of consumption 1 year before the onset of the illness. The questionnaire included 33 items (foods or groups of foods), selected in order to include all the relevant foods regarding vegetables, fruits, dairy products and other animal products, which are the main sources of retinol, β-carotene and vitamin C in the population under study. For each item, the subject was asked to choose one of the 10 categories of frequency of consumption of a standard serving or standard unit (proposed in the questionnaire), ranging from never (less than once per year) to four or more times per day. For foods with known seasonal variability, the frequency was referred to the period of the year when they are usually consumed. The weekly frequency of consumption was estimated by transforming each category of frequency reported in the questionnaire to times per week, taking into account the seasonal variation of some foods. The daily consumption of each food item was obtained by dividing its weekly frequency by seven, and multiplying it by the weight in grams of the standard unit or serving proposed for this particular food. The daily consumption for a group was obtained by aggregating the consumption of components of this group.

The comparisons of the daily intake of foods or groups of foods were carried out by comparing the means of intake of cases and controls using the non-paired *t*-test, after the logarithmic transformation of variables. Estimations of odds ratios (OR) and confidence intervals (CI) were carried out by means of conditional logistic regression for matched case–control studies [8]. The results are presented by tertiles of consumption based on the distribution of controls, taking the lowest tertile as the reference category. A chi-squared test for linear trend in increasing or decreasing risk with increasing intake was obtained by fitting a model with a single term for the variable coded as 1, 2 or 3 according to the subject's tertile of intake [8]. The categorical analysis was also carried out with tertiles based on the overall distribution of cases and controls, and the test for trend was carried out using the median of each tertile instead of an indicator variable; these results did not appreciably differ from results of above-mentioned analysis and are not presented. In order to control the potential confounding effect of cigarette smoking, the smoking status (never, former and current smokers), and total pack-years smoked by ever smokers were included in the model. Statistical significance was always set at 0.05 and confidence intervals were set at 95%.

Table 1. Daily intake (grams) of selected foods and groups of foods among women

	Cases (n = 103)		Controls (n = 206)		
Foods and groups of foods*	Mean (SD)		Mean (SD)		P value†
Animal origin					
Liver	3.09	(5.10)	2.90	(5.64)	0.55
Non-dairy products	107.60	(50.17)	118.39	(74.22)	0.34
Dairy products	366.40	(226.54)	408.14	(257.72)	0.23
Vegetables					
Leafy green	82.29	(57.42)	90.43	(56.95)	0.049
Dark green	155.26	(85.24)	176.66	(106.20)	0.10
Yellow/orange	13.85	(14.70)	19.86	(20.07)	0.043
Tomatoes	62.81	(63.85)	66.59	(48.80)	0.27
Cruciferous	13.74	(18.03)	19.06	(31.06)	0.16
Vegetables (overall)	328.05	(150.38)	349.00	(168.31)	0.29
Fruits					
Citrus fruits	59.93	(47.00)	57.16	(46.19)	0.45
Other fresh fruits	130.26	(99.35)	126.66	(83.10)	0.96
Fresh fruits (overall)	190.19	(128.41)	183.81	(113.56)	0.82

*See Appendix for the composition of groups.

†For non-paired *t*-test, after $\log_e$ transformation of the variables.

RESULTS

Table 1 shows the daily consumption of some foods and groups of foods. Cases consumed less vegetables than controls for all single foods or groups studied, the difference being significant for the leafy green and yellow/orange vegetables. The cases consumed less dairy and non-dairy animal products and more fruits than controls, but the differences were non-significant.

A tendency to reduction in risk with increasing intake of all groups of vegetables was observed (Table 2). A high consumption of yellow/orange vegetables and tomatoes (highest versus lowest tertile) appeared to be significantly associated with a reduction in risk of lung cancer, showing a significant linear trend as well. Apart from statistical significance, the pattern of reduction in risk with increased intake of vegetables was consistent for all kinds and groups of vegetables. No association was observed with animal products or fruits, although some tendency to increased risk was apparent for the high consumption of liver and with increased intake of fruits. However, none of the ORs nor the linear trend were statistically significant for fruits or animal products.

Given the small number of ever smokers and cases with squamous, small cell or other types, we carried out separate analyses only for adenocarcinoma and never smokers (Table 3). Regarding vegetables, the results were very similar to those found for the whole group for non-smoking women and for adenocarcinoma, although for the latter subgroup there was a significant reduced risk with increased intake of dark green vegetables and the association with tomatoes was lower. In these analyses the tertile cut-off points were re-established on the basis of the vegetable consumption of non-smoker controls or controls matched to cases of adenocarcinoma type.

DISCUSSION

Our results agree with the previous evidence regarding the protective effect of high intake of vegetables in relation to lung cancer in women. Although statistical significance was reached only for yellow/orange vegetables and tomatoes, all other groups (dark green, leafy green and cruciferous), as well as all vegetables combined showed a tendency to decreased risk with increased intake. No such effect was observed for fresh fruits; in fact there appeared to be a positive, although non-significant association, with fresh fruits, including citrus and non-citrus. Regarding foods of animal origin which are common sources of retinol, there was not a clear pattern: while liver seemed to be positively associated with lung cancer, an inverse association with dairy and non-dairy products was suggested, neither of them being statistically significant.

Many observational studies have reported results on the association between lung cancer and consumption of vegetables and fruits. Taken together, eight cohort studies [9–16] and 21 case–control studies [17–37] suggest that there is an inverse association between the risk of lung cancer and vegetable and fruit intake. Among eight prospective studies, six [9–11, 13, 14, 16] reported an inverse association with some groups of vegetables, but only one [16] observed a significant trend; two studies [12, 15] reported no association or inconsistent results. Regarding fruits, two prospective studies [12, 13] observed a significant inverse association with fruits, the latter restricted to non-smokers; one study [9] did not study fruits, three [10, 15, 16] reported inverse but non-significant association, while two [11, 14] reported a positive, although non-significant association. A significant decreased risk of lung cancer with increased intake of some vegetables was found in 14 case–control studies [17–20, 22, 26, 27, 31–37], while in another five [21, 23–25, 30] the inverse association did not reach statistical significance and two [28, 29] showed no association. Sixteen case–control studies reported results on the relationship between lung cancer and some kind of fruits: nine studies found an inverse relationship, statistically significant in six [24, 25, 29, 32, 33, 37] and non-significant in three [19, 31, 35]; four studies found no association or inconsistent results [22, 26, 27, 30], and three reported a positive non-significant association [23, 28, 34].

The effect of vegetables in reducing lung cancer risk has been mainly attributed to β-carotene; the high provitamin A activity, as well as the anti-oxidant effect, have been proposed as potential mechanisms of action of β-carotene on carcinogenesis. However, there are many substances in veg-

Table 2. Risk of lung cancer in women, by level of food intake in tertiles. ORs and 95% CI by conditional logistic regression, adjusted for smoking status and total pack-years smoked

	Level of intake (tertiles)			
Foods and groups of foods*	Low	Medium	High	*P* for trend
Animal origin				
Liver	1	0.80 (0.45–1.40)	1.57 (0.82–3.02)	0.32
Non-dairy products	1	1.03 (0.57–1.85)	0.72 (0.38–1.35)	0.32
Dairy products	1	0.81 (0.45–1.46)	0.77 (0.42–1.40)	0.39
Vegetables				
Leafy green	1	1.12 (0.60–2.09)	0.61 (0.30–1.22)	0.19
Dark green	1	0.73 (0.40–1.34)	0.58 (0.29–1.15)	0.11
Yellow/orange	1	0.83 (0.46–1.49)	0.37 (0.19–0.74)	0.007
Tomatoes	1	0.77 (0.43–1.38)	0.45 (0.22–0.91)	0.026
Cruciferous	1	0.93 (0.52–1.66)	0.54 (0.26–1.13)	0.13
Vegetables (overall)	1	0.84 (0.45–1.56)	0.65 (0.32–1.31)	0.23
Fruits				
Citrus fruits	1	1.31 (0.67–2.56)	1.43 (0.66–3.13)	0.37
Other fresh fruits	1	1.45 (0.73–2.87)	1.41 (0.65–3.07)	0.41
Fresh fruits (overall)	1	1.32 (0.68–2.54)	1.20 (0.56–2.56)	0.66

*See Appendix for the composition of groups.

Table 3. Risk of lung cancer in women, by level of intake of vegetables, according to the histological type (adenocarcinoma) and smoking status (never smokers)

	Level of intake (tertiles)			
Vegetables and groups of vegetables*	Low	Medium	High	*P* for trend
Adenocarcinoma†				
Leafy green	1	0.92 (0.39–2.20)	0.59 (0.24–1.45)	0.26
Dark green	1	0.50 (0.21–1.18)	0.35 (0.13–0.94)	0.03
Yellow/orange	1	1.35 (0.59–3.11)	0.24 (0.08–0.71)	0.02
Tomatoes	1	0.85 (0.42–1.76)	0.37 (0.14–1.00)	0.06
Cruciferous	1	0.64 (0.29–1.42)	1.01 (0.40–2.54)	0.85
Vegetables (overall)	1	0.69 (0.30–1.61)	0.62 (0.24–1.60)	0.30
Never smokers‡				
Leafy green	1	1.05 (0.54–2.03)	0.72 (0.35–1.50)	0.41
Dark green	1	0.48 (0.24–0.94)	0.57 (0.29–1.13)	0.08
Yellow/orange	1	0.87 (0.46–1.65)	0.35 (0.16–0.74)	0.009
Tomatoes	1	0.66 (0.36–1.21)	0.38 (0.17–0.83)	0.015
Cruciferous	1	0.88 (0.47–1.64)	0.59 (0.28–1.26)	0.19
Vegetables (overall)	1	0.62 (0.30–1.27)	0.77 (0.38–1.56)	0.45

*See Appendix for the composition of groups.

†Adenocarcinoma: 53 cases and their 106 matched controls; ORs and 95% CI by conditional logistic regression, adjusted for the smoking status (ever versus never smokers) and total pack-years smoked.

‡Never smokers: 80 cases and 150 controls (70 sets with 1 case and 2 controls and 10 sets with 1 case and 1 control; 20 controls who never smoked were excluded from this analysis because they were matched to cases who were never smokers). ORs (crude) and 95% CI by conditional logistic regression.

etables, including other carotenoids, for which protective mechanisms have been postulated [38]. Yellow/orange vegetables are by far the most important sources of carotenoids with provitamin A activity, including β- as well as α-carotene. Dark green vegetables are the main sources of lutein and zeoxanthin (xantophyll carotenoids) without provitamin A activity, and some of them contain folate as well, while leafy green vegetables have moderate amounts of xantophyll carotenoids. Lycopene is found in tomatoes but it is scarce in other common vegetables, and cruciferous contain dithioltiones, glucosinolates, isothiocyanate and indoles. Among studies reporting a significant inverse association of vegetables and lung cancer, many groups or individual foods have been found to be associated: green leafy [16, 31, 33], carrots and/or yellow/orange vegetables [18–20, 22, 26, 32], dark green vegetables [19, 26, 31], cruciferous [22, 26, 33] and tomatoes [26]; most of them also reported association with total amount of vegetables.

In our study, cases ate more citrus fruits and other fresh fruits than controls, although differences were non-significant. The high and rather homogeneous fruit consumption in our population should be taken into account: 42% of controls consumed citrus fruits once per day, and 30% two or more times per day, with similar proportions for cases. There were no subjects in the category of non-consumers of fresh fruits, either among cases or controls.

The results of our study are remarkably consistent with previous studies [16, 26, 27] showing a significant protective effect of vegetables for lung cancer in women, and a non-significant relation or no association with fruits. The study in Hawaii [26], in addition to vegetables as a group, found an inverse significant association with carrots, dark green vegetables, cruciferous and tomatoes. Tomatoes have been recently reported as a protective factor for digestive tract cancers [39]. It is worth noting the consistent effect of vegetables taken as an overall group in many studies, including the present study. Moreover, some authors explicitly compared the effect of foods and nutrients in the same study. A cohort study on non-smoking women [16] found an inverse significant association of lung cancer with all vegetables and green leafy vegetables, while the inverse associations with the nutrients vitamin C and β-carotene were non-significant. A case–control study on Caucasian men [19] reported that the inverse associations with lung cancer risk were more pronounced for intakes of vegetables, dark green and dark yellow/orange vegetables than for carotenoids. Finally, a recent publication [40] re-analysed data from a previous case–control study [26] using newly available food composition data for α-carotene, β-carotene and lutein. The protective effect reported for vegetable consumption was stronger than the effects of the three carotenoids, suggesting that other components of vegetables may contribute to cancer inhibition.

The findings regarding protective dietary factors for lung cancer have been considered more convincing for males than females, but this probably reflects the greater number of studies and larger sample sizes of males. Many early studies found protective effects primarily in former or current smokers, with more pronounced reduction in risk in heavy and long-term smokers. However, the protective effects from vegetables have been shown in studies including only women or with separate results for women [16, 20, 26, 27, 32, 34, 35, 37] and for non-smokers [17, 26, 27, 32, 34, 37]. Another consistent finding from previous studies is that the protective effect is not restricted to squamous or small cell lung cancer types, although the association with these types seems stronger than with adenocarcinoma. As can be shown in Table 3 in our study, the results for women who never smoked or for adenocarcinoma were quite similar to those found in the whole group.

Some methodological issues must be taken into account. Our study is a hospital-based study. Some exclusion diagnoses were applied to controls, but these were mainly tobacco-related conditions, the primary objective of our study. However, a closer examination of individual diagnosis did not show diagnosis known or suspected of being associated with the intake of fruits or vegetables. Nine controls were hospitalised for causes suspected of association with dietary factors other than vegetables and fruits. The analysis excluding these controls did not change the patterns of risk (results not shown). Among previous case–control studies reviewed, nine [17, 18, 20, 23, 25, 29, 30, 33, 36] were hospital based.

Studies on the effect of dietary factors must rely on a reasonably valid diet assessment. Food frequency questionnaires are reasonably valid to assess the intake of specific nutrients or groups of foods, and are primarily used to categorise people by relative rather than absolute intake. We used a questionnaire very similar to a food frequency questionnaire validated in Spain; the results from the validation study showed that it provided a reliable scale for categorising individuals by level of past nutrient intake [41].

One limitation of food frequency questionnaires is that they usually focus on some groups or specific nutrients, and they do not allow for adjustment of total energy intake or macronutrients. It would be desirable to adjust for dietary fat and cholesterol, since both have been proposed as potential risk factors for lung cancer [3]. Although we did not collect all the relevant sources of fat intake, the dairy products and other animal products rich in retinol may be considered as quite good indicators of the consumption of saturated fat. Adjusting for these two variables did not change the ORs for any of the vegetable groups, nor the respective tests for trend (results not shown). These results are in agreement with previous observations showing that, regarding the relationship of lung cancer risk with vegetables and dietary fat intake, both associations seem to be independent and neither is completely explained by the other [3].

Tobacco smoking is the main determinant of the risk of lung cancer, so adequate control of confounding by smoking is crucial in the assessment of the effect of dietary factors. It has been reported that the consumption of vegetables and fruits is higher in women who never smoked than in current smokers, and, among smokers, the intake of these foods is inversely related to the intensity of the smoking habit [42, 43]. In our study [7], 22.3% of cases and 11.2% of controls had smoked sometime during their lives, resulting in an OR of 3.1 (95% CI 1.4–6.8); most of them were current smokers with an OR of 3.6 (95% CI 1.6–8.3), and a few of them were former smokers, with an OR of 1.6 but with a wide interval because of small numbers. Cigarette smoking was associated with an increase in risk of 62% for each 10 pack-years (OR 1.62, 95% CI 1.2–2.2). We included in each model one indicator variable for smoking status (never, former or current smoker), as well as the number of pack-years for ever smokers. However, we had previously shown that the smoking habit in our study was measured with quite high reliability [7], so errors in measurement of the confounder probably did not bias the effect estimates for dietary factors. Moreover, a high proportion of our cases and controls were never smokers, among which no confounding effect by active smoking habit should exist, and results for vegetables in this subgroup (Table 3) were quite similar to those smoking adjusted.

In conclusion, our study adds to the evidence of the protective effect of vegetables for lung cancer risk in women. We found that this protection was significant for the high intake of carrots and tomatoes, and that this effect seems to apply to smokers and non-smokers and to all histological types. Given the results of recent intervention trials, β-carotene seems not to be associated with lung cancer risk, but the role of other carotenoids cannot be discarded. Many other phytochemicals could be involved in lung carcinogenesis. Despite our lack of understanding of underlying mechanisms, it seems reasonable to assert that a diet rich in vegetables may be helpful to reduce the risk of lung cancer, keeping in mind that quitting smoking must remain the primary goal for lung cancer prevention.

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APPENDIX

Composition of groups of foods

Dairy products: Milk (whole), milk (skimmed), cheese, butter, margarine, yoghurt, cream, custard.

Non-dairy products (animal origin): Liver, offal, fish (fresh and frozen), fish (canned), chicken, eggs.

Vegetables (overall): Spinach, chard, lettuce, tomatoes, potatoes, cruciferous,* carrots, peas, green beans, peppers (red/green),† legumes.

Leafy green vegetables: Spinach, chard, lettuce.

Dark green vegetables: Spinach, chard, lettuce, cruciferous, green beans, peppers (green).

Yellow/orange vegetables: Carrots, peppers (red).

Fresh fruits (overall): Citrus,‡ apple/pear, melon, peach, apricot, banana, plum.

Other fresh fruits: Fresh fruits excluding citrus.

*Cruciferous. They were collected as a single item in the questionnaire, but it referred to the overall group; examples mentioned were cabbage, broccoli and cauliflower.

†Peppers (red/green). In the questionnaire only one generic item ('peppers') was collected, without distinction of both types. It was assumed that the quantity of each type was the same; a half of the total amount estimated for peppers was attributed to green peppers when computing dark green vegetables, and the other half was attributed to red peppers when computing yellow/orange vegetables.

‡Citrus fruits. They were collected as a single item in the questionnaire, but it referred to the whole group; examples mentioned were orange, lemon and tangerine.