

Dietary Antioxidants and the Risk of Lung Cancer

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The relation between the intake of retinoids, carotenoids, vitamin E, vitamin C, and selenium and the subsequent risk of lung cancer was studied among 4,538 initially cancer-free Finnish men aged 20–69 years. During a follow-up of 20 years beginning in 1966–1972, 117 lung cancer cases were diagnosed. Inverse gradients were observed between the intake of carotenoids, vitamin E, and vitamin C and the incidence of lung cancer among nonsmokers, for whom the age-adjusted relative risks of lung cancer in the lowest tertile of intake compared with that in the highest tertile were 2.5 (p value for trend = 0.04), 3.1 ($p = 0.12$), and 3.1 ($p < 0.01$) for the three intakes, respectively. Adjustment for various potential confounding factors did not materially alter the results, and the associations did not seem to be due to preclinical cancer. In the total cohort, there was an inverse association between intake of margarine and fruits and risk of lung cancer. The relative risk of lung cancer for the lowest compared with the highest tertile of margarine intake was 4.0 ($p < 0.001$), and that for fruits was 1.8 ($p = 0.01$). These associations persisted after adjustment for the micronutrient intakes and were stronger among nonsmokers. The results suggest that carotenoids, vitamin E, and vitamin C may be protective against lung cancer among nonsmokers. Food sources rich in these micronutrients may also have other constituents with independent protective effects against lung cancer. *Am J Epidemiol* 1991;134:471–9.

diet; longitudinal studies; lung neoplasms; selenium; vitamin A; vitamin C; vitamin E

It has been hypothesized that vitamin A has anticancer effects by controlling cellular differentiation and growth and that its precursor beta-carotene, vitamin C, vitamin E, and selenium have anticancer effects because of their antioxidant and other prop-

erties (1, 2). Some, but not all, epidemiologic studies on the association between these micronutrients and the occurrence of lung cancer are in line with these hypotheses (2–7).

The most reliable evidence of an association between these micronutrients and cancer comes from cohort studies. In addition, these have given conflicting results. Most cohort studies on the intake of carotene or of foodstuffs rich in carotene as well as follow-up studies based on circulating beta-carotene levels support the hypothesis that carotene protects against lung cancer (7). In contrast, most studies based either on dietary intakes or on serum retinol levels have reported no protective effect for retinol (4).

There is relatively little information from cohort studies on the association between lung cancer and vitamins C and E and selenium. The findings concerning the relation between vitamin C and lung cancer are in-

Received for publication October 15, 1990, and in final form April 3, 1991.

Abbreviation: CI, confidence interval.

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Supported in part by Public Health Service contract N01-CN-45165 from the Division of Cancer Prevention and Control, National Cancer Institute of the United States.

consistent. An inverse association between the occurrence of lung cancer and the intake of either vitamin C or fruits rich in vitamin C has been reported in some, but not all, studies (5). The results of cohort studies on vitamin E and lung cancer risk are also somewhat discrepant. A significant protective effect of vitamin E against lung cancer was found in one of the serum studies, but other studies have shown only weak or no associations (6). Similarly, studies based on prediagnostic serum selenium samples have reported a significant inverse association, a nonsignificant inverse association, or a nonsignificant positive association (4).

Some of the studies concerning intakes of various micronutrients and lung cancer are based on food frequency questionnaires which only partially cover the total diet of the subjects. For examination of the relative importances of micronutrients and their main food sources, however, comprehensive dietary intake data are needed. Using dietary intake data based on dietary history interviews, we studied the simultaneous relation between dietary intakes of major carotenoids, retinoids, vitamin C, vitamin E, and selenium, and that of the major food sources of these micronutrients and the subsequent development of lung cancer in a cohort of Finnish men followed up for 20 years.

MATERIALS AND METHODS

During 1966–1972, the Mobile Health Clinic of the Social Insurance Institution carried out multiphasic screening examinations in several regions of Finland (8). Altogether, 62,440 men and women aged 15 years or older were invited to take part in the study; the participation rate was 82.5 percent. As part of the main study, dietary histories were obtained from a random subsample of 10,054 participants (9, 10). This study covers the 4,538 men aged 20–69 years from whom dietary histories were obtained and who had never had cancer.

Food consumption was estimated at the baseline examination by the dietary history method covering the total habitual diet of

the subjects during the previous year (9, 11). The amounts of retinoids, carotenoids, and various tocopherol and tocotrienol compounds and the content of selenium in the diet, were based on analyses of Finnish foods (12–15). The vitamin E activities of different tocopherols and tocotrienols in alpha-tocopherol equivalents were estimated by using the factors in the paper by McLaughlin and Weinrauch (16). The intake of preformed vitamin A and the vitamin A activity of different provitamin A carotenoids were calculated in retinol equivalents according to the Food and Nutrition Board (17). The vitamin C content and that of other nutrients in food items were derived from several sources, mainly from international food composition tables. Energy intake was calculated on the basis of the amounts of protein, fat, and available carbohydrate consumed. The nutrient intakes represent amounts in raw foodstuffs. Because few men (1.4 percent) used vitamin supplements, this association with lung cancer could not be studied.

In this cohort, vegetables provided on average 70 percent and dairy products 26 percent of dietary carotenoids (i.e., provitamin A carotenoids). Dairy products and liver supplied the largest proportions of retinoids (i.e., preformed vitamin A), with average proportions of 53 and 35 percent, respectively. On average, 33 percent of vitamin C was derived from potatoes, 36 percent from fruits and berries, 18 percent from vegetables, and 12 percent from dairy products. Cereals provided 32 percent of the dietary vitamin E, dairy products provided 20 percent, and margarine provided 13 percent. On average, 85 percent of the selenium was supplied by animal products (i.e., meat products, fish, eggs, and dairy products), and 12 percent by cereals.

The short- and long-term repeatabilities of the daily consumption of the pertinent foodstuffs and micronutrients were estimated by repeating the dietary interviews 4–8 months and 4–7 years after the initial interviews. Overall, the short-term repeatability was high, with the intraclass correlation coefficient (r) ranging from 0.47 to 0.83

for the food groups and, with one exception, from 0.53 to 0.78 for the nutrients. The repeatability of retinoid intake was low ($r = 0.16$), mainly as a result of the low repeatability of liver intake. The coefficient of long-term repeatability, with one exception, ranged from 0.28 to 0.55 for the food groups and from 0.29 to 0.58 for the nutrients. Although the short-term repeatability of margarine intake was high ($r = 0.83$), the long-term repeatability was very low ($r = 0.10$), mainly because of a rapid increase in margarine use in Finland during the follow-up.

All participants completed a preailed questionnaire checked at the baseline examination. The questionnaire yielded information about residence, social class, occupation, use of drugs (e.g., vitamin supplements), and smoking. The classification of social class was made on the basis of occupational esteem (18). Subjects were classified according to smoking status as never smokers, ex-smokers, and current smokers. The two first classes were also combined to form a class of nonsmokers. Body height and weight were measured at the baseline examination, and the body mass index (weight (kg)/height (m²)) was calculated.

Information concerning subsequent cancer incidence, available through the nationwide Finnish Cancer Registry (19), was linked to the dietary data in order to study the association between the intake of various micronutrients and the incidence of lung cancer. During the 20-year follow-up period 1967–1986, 117 lung cancer cases (*International Classification of Diseases, Seventh Revision*, codes 162–163) (20) were diagnosed, including 18 small cell carcinomas, 41 squamous cell carcinomas, 11 adenocarcinomas, and 47 other carcinomas.

The age-adjusted mean levels of several descriptive and potential confounding factors among cancer cases and noncases were estimated using the general linear model (21). The Cox proportional hazards model was used to estimate the association between the dietary factors and risk of lung cancer adjusting for age and other possible confounding factors (22). Relative risks were

computed for tertiles of intake by using the lowest tertile as the reference category. Statistical significances were tested by using the likelihood ratio test based on Cox models. The repeatability of the reported intake of micronutrients and foods was estimated with the intraclass correlation coefficient (23).

RESULTS

The baseline characteristics of lung cancer cases and noncases are presented in table 1. Men who subsequently developed lung cancer were older, thinner, more often current smokers, and from lower social classes than the other men.

The mean daily intake of energy and different food items at the baseline among subsequent lung cancer cases and noncases, adjusted for age, is shown in table 2. Among the cases, the intake of energy was higher, but the intakes of vegetables, fruits and berries, and margarine were lower. In addition, the mean daily intakes of various carotenoids were lower, but the intake of retinoids was higher among the cases than among the controls (table 3). There was a significant inverse gradient between the age-adjusted daily intake of fruits and margarine and the incidence of lung cancer; the relative risks between the lowest and highest tertiles of intake of these foods were 1.8 (p value for trend = 0.01) and 4.0 ($p < 0.001$), respectively. Adjustment for smoking did not materially alter the results. The micronutrients presented only nonsignificant associations with lung cancer risk.

The possible modifying effects of age, smoking, social class, and energy or fat intake on the relation between micronutrient intake and occurrence of lung cancer were also studied. The strongest interaction was observed with respect to smoking. The age-adjusted relative risk of lung cancer between tertiles of intake of carotenoids, vitamin E, and vitamin C showed an inverse association among nonsmokers, but not among smokers (table 4). Adjustment for several potential confounding factors (geographic area, social class, body mass index, height, and energy

TABLE 1. Selected characteristics* of the lung cancer cases and noncases: the cancer incidence follow-up of the Finnish Mobile Clinic Health Survey, 1967-1986

Characteristic	Cancer cases (n = 117)			Noncases (n = 4,421)		
	No.	Mean (%)	Standard deviation	No.	Mean (%)	Standard deviation
Age (years)		54.1	9.2		40.4	13.0
Height (cm)		173.3	5.7		172.7	6.7
Weight (kg)		72.2	11.2		75.0	11.1
Body mass index (kg/m ²)		24.0	3.1		25.1	3.3
Smoking						
Never	6	7.1		1,112	25.1	
Former	18	8.2		985	22.5	
Current	93	84.7		2,324	52.4	
Social class†						
I (highest)	4	3.4		174	3.9	
II (median)	47	43.7		2,272	51.3	
III (lowest)	47	42.7		1,355	30.6	
IV (farmers)	19	10.2		619	14.2	

* The means of all the characteristics except age and smoking have been adjusted for both age and smoking. Age has been adjusted for smoking, and smoking has been adjusted for age.

† One noncase with missing data was excluded.

TABLE 2. Age-adjusted mean (\pm standard deviation) daily intake of energy and various foods for cases and noncases: the cancer incidence follow-up of the Finnish Mobile Clinic Health Survey, 1967-1986

Foods (g/day)	Cases (n = 117)	Noncases (n = 4,421)
Energy (kcal/day)	3,093 \pm 1,016	3,000 \pm 925
Cereals	334 \pm 152	335 \pm 147
Potatoes	282 \pm 149	275 \pm 141
Vegetables	94 \pm 71	103 \pm 73
Green	47 \pm 36	48 \pm 36
Yellow or red	32 \pm 36	36 \pm 40
Fruits and berries	120 \pm 94	144 \pm 117
Fruits	71 \pm 68	92 \pm 96
Berries	14 \pm 17	14 \pm 19
Margarine	5 \pm 8	8 \pm 14
Dairy products	1,165 \pm 574	1,082 \pm 487
Milk	912 \pm 559	848 \pm 471
Butter	62 \pm 31	54 \pm 31
Meat and meat products	189 \pm 123	176 \pm 112
Liver	4 \pm 8	4 \pm 6
Fish	43 \pm 52	39 \pm 49
Eggs	36 \pm 27	37 \pm 32

and fat intakes) did not materially change the results. When the cancer cases diagnosed during the first 2 years of follow-up were excluded from the analyses, the results were not notably altered. The relative risk of cancer among nonsmokers in the lowest tertile of intake compared with that in the highest

was 2.0 (95 percent confidence interval (CI) 0.5-7.7) for carotenoids, 2.6 (95 percent CI 0.7-9.1) for vitamin E, and 2.7 (95 percent CI 0.7-10.0) for vitamin C.

Few other interactions were observed. There was an interaction between vitamin C intake and age in that the relative risk of lung cancer between the lowest and highest tertiles of intake was 1.8 (95 percent CI 0.9-3.7) among men under age 50 years and 1.0 among the older men. There was also a suggestive nonsignificant interaction between intakes of energy and micronutrients. The relative risk of lung cancer between low and high intakes of various micronutrients ranged from 1.6 to 2.4 in the lowest tertile and from 0.5 to 0.7 in the highest tertile of energy intake.

Because several of the studied micronutrients had common dietary sources and correlated intakes, with the correlation coefficients ranging from 0.14 to 0.58, the association between each micronutrient and lung cancer was also examined after adjustment for intakes of the other micronutrients. This additional adjustment did not change the results appreciably, suggesting independent effects of carotenoids, vitamin E, and vitamin C on lung cancer risk among nonsmokers. The age-adjusted relative risk of

TABLE 3. Age-adjusted mean (\pm standard deviation) daily intake of different micronutrients for cases and noncases: the cancer incidence follow-up of the Finnish Mobile Clinic Health Survey, 1967-1986

Nutrient	Cases (n = 117)	Noncases (n = 4,421)
Total vitamin A (μ g) (RE)*	1,826 \pm 1,515	1,687 \pm 955
Retinoids (μ g) (RE)	1,571 \pm 1,463	1,395 \pm 845
Carotenoids (μ g) (RE)	255 \pm 257	292 \pm 301
Beta-carotene (μ g)	1,481 \pm 1,488	1,691 \pm 1,737
Alpha-carotene (μ g)	51 \pm 96	68 \pm 116
Gamma-carotene (μ g)	39 \pm 48	40 \pm 50
Lycopene (μ g)	684 \pm 850	718 \pm 895
Lutein and zeaxanthine (μ g)	1,111 \pm 484	1,160 \pm 460
Vitamin E (mg)	8.5 \pm 3.5	8.5 \pm 3.8
Alpha-tocopherol (mg)	7.1 \pm 2.9	7.2 \pm 3.2
Beta-tocopherol (mg)	0.7 \pm 0.3	0.7 \pm 0.4
Gamma-tocopherol (mg)	2.2 \pm 2.7	2.8 \pm 4.2
Delta-tocopherol (mg)	0.4 \pm 0.7	0.6 \pm 1.3
Vitamin C (mg)	81 \pm 36	83 \pm 36
Selenium (μ g)	29 \pm 19	28 \pm 17

* RE, retinol equivalents.

TABLE 4. Age-adjusted relative risk* of lung cancer between tertiles of intake of various micronutrients by smoking status: the cancer incidence follow-up of the Finnish Mobile Clinic Health Survey, 1967-1986

Smoking status and tertile	Micronutrient				
	Retinoids (RE)†	Carotenoids (RE)	Vitamin E	Vitamin C	Selenium
Nonsmokers (n = 2,121)					
Highest	1.0	1.0	1.0	1.0	1.0
Middle	1.40	3.60	1.90	2.36	1.13
Lowest	1.47	2.50	3.06	3.11	1.03
p value (trend)	0.72	0.04	0.12	<0.01	0.63
Smokers (n = 2,417)					
Highest	1.0	1.0	1.0	1.0	1.0
Middle	0.95	0.99	0.78	0.93	0.64
Lowest	0.73	1.08	0.80	0.81	0.83
p value (trend)	0.08	0.91	0.58	0.36	0.63

* Based on the Cox model including age and an interaction term between smoking status and the micronutrient.

† Retinol equivalents.

lung cancer for men with low (tertile) intakes of all three micronutrients compared with men with no intake in the lowest tertile was 3.7 (95 percent CI 0.9-16.7) among nonsmokers and 0.7 among current smokers.

An inverse association was observed between margarine intake and the incidence of lung cancer among both smokers and nonsmokers (table 5). A similar association was also observed between lung cancer and intakes of foods from plant sources rich in micronutrients, especially fruits and berries and potatoes, among nonsmokers, but not among smokers. The overall association between intake of vegetables and cancer risk

was not significant, but a relatively strong relation was observed with regard to intake of yellow and red vegetables, with a relative risk of 2.6 (95 percent CI 0.8-8.3) between the lowest and highest tertiles of intake among nonsmokers. The corresponding risks for green and other vegetables were 1.9 (95 percent CI 0.7-5.6) and 0.9 (95 percent CI 0.3-2.4), respectively. No similar associations were observed for foods from animal sources rich in these micronutrients (dairy products, meat products, fish, and eggs). The results were not changed after adjustment for various confounding factors (age, social class, geographic area, energy and fat in-

TABLE 5. Age-adjusted relative risk of lung cancer between tertiles of intake of different foods in strata of smoking status*: the cancer incidence follow-up of the Finnish Mobile Clinic Health Survey, 1967-1986

Foods	Nonsmokers (tertile) (n = 2,121)				Smokers (tertile) (n = 2,417)			
	Highest	Middle	Lowest	p value for trend	Highest	Middle	Lowest	p value for trend
Cereals	1.0	2.25	2.50	0.51	1.0	1.04	1.25	0.41
Potatoes	1.0	1.17	2.08	0.06	1.0	0.89	0.81	0.38
Vegetables	1.0	0.91	1.44	0.12	1.0	1.13	0.98	0.81
Fruits and berries	1.0	2.92	7.69	<0.001	1.0	0.82	0.98	0.89
Margarine	1.0	8.75	12.50	0.03	1.0	1.88	2.50	0.03
Dairy products	1.0	0.27	0.46	0.35	1.0	0.77	0.88	0.24
Meat products	1.0	0.72	0.88	0.74	1.0	0.71	0.75	0.47
Fish	1.0	0.64	0.50	0.75	1.0	1.01	0.50	0.86
Eggs	1.0	0.52	1.37	0.57	1.0	0.81	0.95	0.85

* Cox model including age and an interaction term between the foods and smoking status.

takes, body mass index, and height) or for all foodstuffs other than the one under consideration.

To shed more light upon the nature of the observed associations between food intake and risk of lung cancer, we included the micronutrients and the foodstuffs that were their richest sources in the regression model simultaneously. The relative risk of lung cancer between the lowest and highest tertiles of intake of fruits and berries was 8.1 (95 percent CI 1.8-37.2) among nonsmokers and 1.1 (95 percent CI 0.6-2.1) among smokers, and the corresponding risks for margarine were 16.2 (95 percent CI 2.1-126.8) and 3.1 (95 percent CI 1.5-6.1), respectively.

DISCUSSION

In agreement with several previous studies (7), this study demonstrated an inverse association between lung cancer incidence and intakes of carotenoids and of red, yellow, and green vegetables. This association was apparent among nonsmokers, but not among smokers. Some previous studies have reported a similar association only among persons with low exposure to cigarette smoke, i.e., nonsmokers, ex-smokers, and light smokers (24-28). These findings support the hypothesis that the amount of carotene in common diets is not sufficient to provide a defense strong enough to protect against heavy exposure to cigarette smoke.

It should be noted that the intake of carotenoid sources was much lower in Finland than in other countries during the 1960s and 1970s (29) and that the intake among smokers in this study was especially low. On the other hand, an inverse association between intake of foodstuffs rich in carotenoids and risk of lung cancer has also been reported among current smokers, including heavy smokers (30-32). The possible modifying effect of smoking on the association between carotene intake and lung cancer risk may thus vary, depending on other, still unknown conditions.

The intake of preformed vitamin A was not related to lung cancer risk in this study. This finding is consistent with most, but not all, previous studies (4). Furthermore, with some exceptions (33), little association has been reported between the intake of vitamin A supplement and cancer risk (26, 28, 34). The lack of association in this study may, however, also arise from the fact that intake of retinoids may be inaccurate because of unreliable information about intake of liver, the richest source of retinoids.

We observed an inverse gradient among nonsmokers between the occurrence of lung cancer and the intake of vitamin C as well as with the intake of fruits, potatoes, and vegetables; together these accounted for over 80 percent of the entire vitamin C intake of the study population. Several prior studies have reported similar results, but divergent results have also been published (5). In in-

ternational comparisons, the intake of vitamin C was rather low in Finland (29), and our results therefore support the hypothesis that vitamin C may have a protective effect in populations with a relatively low intake of this vitamin (24).

In this study, we found a strong inverse association between margarine intake and risk of lung cancer among both smokers and nonsmokers. A significant correlation between margarine intake and serum alpha-tocopherol level has previously been reported in this study cohort (35), raising the possibility that the protective effect of margarine might derive from vitamin E. However, an inverse association between serum vitamin E (36) and dietary vitamin E and risk of lung cancer was observed only among nonsmokers in this study population. Only some of the previous studies on the association between dietary or serum vitamin E and risk of lung cancer have found an inverse association (6), suggesting that vitamin E may exert its protective effect against cancer only in certain circumstances. The strong association between the intake of margarine and reduced risk of cancer might also be due to factors other than vitamin E. In particular, people consuming margarine at the time of the study baseline may have been more health conscious than others, and they may therefore have been exposed to fewer lung cancer risk factors. The fact that the long-term repeatability of margarine intake was low in this cohort supports this hypothesis rather than a direct association between some substances of margarine and lung cancer risk. Diets low in margarine may also contain high levels of butter and other fats, which may possibly increase lung cancer risk (37). However, in this study the association between margarine intake and lung cancer occurrence was not due to an interaction with or confounding by ingestion of animal fat.

The independent associations observed between the intakes of carotenoids, vitamin C, and vitamin E and incidence of lung cancer among nonsmokers persisted after adjustment for several confounders, including intake of different nutritional factors

such as fats and energy. It is nevertheless possible that the associations observed were caused by differences in factors not controlled for in the analyses. One such factor is alcohol consumption. Our results suggest that vitamin C cannot fully account for the anticancer effect observed for its main food sources (e.g., fruits and berries and potatoes). Similarly, the diminished risk of lung cancer among margarine users did not appear to be entirely due to vitamin E intake.

There are several possible explanations for our observation that the known micronutrients in vegetables, fruits, and margarine failed to account fully for the observed strong associations between the consumption of these foodstuffs and cancer risk. Fruits and vegetables contain nonnutritive substances such as terpenes, flavones, and phenols, which may be anticarcinogenic (38). It is also possible that other healthful behaviors associated with high intake of these foodstuffs may reduce risk of lung cancer. An alternative explanation is that the nonsmoking lung cancer cases with low intake of several micronutrients suffered from some kind of poor diet specifically predisposing them to cancer. Finally, it is possible that because of low reliability of the intake estimates of the micronutrients, the adjustment was not effective enough to eliminate the association due to the micronutrients.

We failed to see an inverse association between selenium intake and lung cancer risk in this study, although a strong inverse association has been demonstrated between serum selenium level and lung cancer risk in this cohort of men, which had an unusually low serum selenium level (39). The lack of association may be due to the fact that reported dietary intake reflects selenium status less well than serum level does (2), especially in Finland where considerable changes in the dietary intake of selenium have recently occurred (40).

The findings of this longitudinal study are based on dietary histories collected up to 20 years prior to the diagnosis of cancer, thereby avoiding the potential influence of disease on either actual or reported intake.

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The results did not notably change when the cancer cases occurring during the first years of follow-up were excluded, and it was thus improbable that the observed associations were influenced by the effect of preclinical cancer on dietary recall. However, several points should be made concerning the measurement, analysis, and interpretation of the dietary data presented here. First, the dietary history method has its limitations, and the consequential misclassification of subjects tends to diminish observable associations between dietary exposure and outcome (41). The strength of the associations between micronutrient intake and risk of lung cancer may also be underestimated in this study because dietary habits such as consumption of margarine have changed considerably in Finland during the 20-year follow-up period (42). For example, the consumption of margarine has increased greatly during this period. The problem is compounded by the fact that the micronutrient content of food may have changed over time; most importantly, the selenium content of food has increased gradually during the follow-up period (40, 43). Furthermore, in this study micronutrient intake was calculated solely from food sources, ignoring the contribution of vitamin supplements. Although supplement use was uncommon at the time of the baseline examination, it has increased during the follow-up period (44).

In summary, we found an inverse relation between the dietary intake of carotenoids, vitamin C, and vitamin E and the incidence of lung cancer among nonsmokers. We also found that the intake of foodstuffs rich in vitamins C and E was associated with a reduced risk of lung cancer, but that this could not be fully attributed to the protective effect of the micronutrients. Future studies should focus on the effects of different dietary patterns and modifying factors on the possible association between micronutrients and lung cancer.

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