Dietary Flavonoids and the Risk of Lung Cancer and Other Malignant Neoplasms

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Flavonoids are effective antioxidants and, in theory, may provide protection against cancer, although direct human evidence of this is scarce. The relation between the intake of antioxidant flavonoids and subsequent risk of cancer was studied among 9,959 Finnish men and women aged 15–99 years and initially cancer free. Food consumption was estimated by the dietary history method, covering the total habitual diet during the previous year. During a follow-up in 1967–1991, 997 cancer cases and 151 lung cancer cases were diagnosed. An inverse association was observed between the intake of flavonoids and incidence of all sites of cancer combined. The sex- and age-adjusted relative risk of all sites of cancer combined between the highest and lowest quartiles of flavonoid intake was 0.80 (95% confidence interval 0.67–0.96). This association was mainly a result of lung cancer, which presented a corresponding relative risk of 0.54 (95% confidence interval 0.34–0.87). The association between flavonoid intake and lung cancer incidence was not due to the intake of antioxidant vitamins or other potential confounding factors, as adjustment for factors such as smoking and intakes of energy, vitamin E, vitamin C, and beta-carotene did not materially alter the results. The association was strongest in persons under 50 years of age and in nonsmokers with relative risks of 0.33 (95% confidence interval 0.15–0.77) and 0.13 (95% confidence interval 0.03–0.58), respectively. Of the major dietary flavonoid sources, the consumption of apples showed an inverse association with lung cancer incidence, with a relative risk of 0.42 (95% confidence interval 0.23–0.76) after adjustment for the intake of other fruits and vegetables. The results are in line with the hypothesis that flavonoid intake in some circumstances may be involved in the cancer process, resulting in lowered risks. *Am J Epidemiol* 1997;146:223–30.

diet; flavones; longitudinal studies; lung; neoplasms

It is a well-established fact that consumption of fruits and vegetables is associated with a lowered risk of lung cancer and some other epithelial cancers. It has been suggested that this is due to the antioxidants beta-carotene or vitamin C, which occur in large concentrations in these foods (1). Two large intervention trials, however, unexpectedly presented an elevated risk of lung cancer among individuals using beta-carotene supplements (2, 3), and a third trial found no association between beta-carotene supplementation and lung cancer incidence (4). These findings actualize the question of whether some other substances that are present in fruits and vegetables provide the protection. One such group could be the flavonoids. These products

of plant metabolism with variable phenolic structures (5) are effective antioxidants and, thus, potential protectors against cancer (6).

Although some flavonoids have been reported to be mutagenic in vitro, results from both in vivo and in vitro studies support the hypothesis of an anticarcinogenic effect of these compounds (6). However, evidence of this in humans is scarce. One ecologic study found no association between flavonoid intake and cancer mortality (7), whereas a Dutch cohort study on elderly men found a weak inverse association between flavonoid intake from fruit and vegetable sources and cancers of the alimentary and respiratory tracts combined (8). The Dutch study, however, was based on a relatively small cohort that was followed up for only a few years. The present study, based on the Finnish Mobile Clinic Health Examination Survey, was composed of about 10,000 men and women over a 20-year follow-up and 1,000 incident cancer cases. On the basis of this material, we studied the dietary intake of flavonoids for its association with overall and site-specific cancer risk.

MATERIALS AND METHODS

During 1966–1972, the Finnish Mobile Clinic Health Examination Survey performed multiphasic screening examinations in several regions of Finland (9). A total of 62,440 men and women aged 15 years or older were invited to participate 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. The present study covers the 9,959 men and women from this subsample who had not had cancer before the screening.

All participants completed a premailed questionnaire checked at the baseline examination. The questionnaire yielded information on residence, occupation, smoking, disease symptoms, and use of medicines. Body height and weight were measured at the baseline examination, and the body mass index (weight (kg)/height (m)^2) was calculated. A 100- × 100-mm photofluorogram of the heart and lungs was taken in the anteroposterior and lateral planes. One radiologist interpreted the films and classified the findings according to a qualitative coding scheme (10).

Subjects were classified according to smoking status as those who had never smoked, exsmokers, cigar or pipe smokers only, smokers of less than 15 cigarettes a day, and smokers of more than or equal to 15 cigarettes a day. Never smokers and exsmokers were also combined to form a class of nonsmokers, whereas all others were classified as current smokers. The participants were classified by history of chronic cough and use of cough medicine: both cough and use of cough medicine, either cough or medicine, and no cough or medicine. The subjects were hierarchically grouped on the basis of chest radiographs as follows: no lung abnormality, scar, calcification or some finding suggestive of tuberculosis, emphysema (if no scar), and other abnormality (if neither scar nor emphysema).

Food consumption was estimated at the baseline examination by the dietary history interview method, covering the total habitual diet of the subjects during the previous year (11). Structured interviews were conducted guided by a preformed questionnaire listing more than 100 food items and mixed food dishes. Several of the questions were open ended and intended to be specified by the respondent. Food amounts were given per day, week, month, or year according to the choice of the respondent. Food models were used to help the subjects to estimate portion sizes. The total intake of five major flavonoids including quercetin, kaempferol, myricetin, luteolin, and apigenin was estimated, using concentrations derived from analyses completed recently in the Netherlands (12, 13). The reported values for 28 vegetables and nine fruits covered those vegetables and fruits found in the present population with an average consumption exceeding 1 g per day. For berries commonly used in Finland but not reported in the Dutch analyses (lingonberries, blueberries, black currants, raspberries, and gooseberries), flavonoid contents were completed with the values shown in other previous studies (14, 15). Since consumption of berries and berry products was mainly recorded as average figures, the calculations of flavonoids from these foods were less accurate than from other fruits and vegetables. All food composition values for flavonoids were given as aglycons.

The contents of vitamin C in food items were derived from Finnish food composition tables (16). The amounts of beta-carotene and various tocopherols and tocotrienols in the diet were based on analyses of Finnish foods (17, 18). The vitamin E activities of the various tocopherols and tocotrienols, in alpha-tocopherol equivalents, were estimated using the factors of McLaughlin and Weihrauch (19). The vitamin intakes represent the amounts in raw foodstuffs, while the estimation of fatty acids has been presented elsewhere (20). Energy intake was calculated on the basis of the amounts of protein, fat, and available carbohydrate consumed.

The mean flavonoid intake was 4.0 (standard deviation = 2.7) mg/day and ranged from 0 to 41.4 mg/day. Quercetin was the most important contributor to the estimated amount of flavonoids; on average, about 95 percent of the total flavonoid intake was quercetin. Apples and onions were the major sources of flavonoids, together providing 64 percent of the total flavonoid intake. Other notable sources were other fruits, berries, sweetened juices and jams (mainly from berries), and vegetables. The 4- to 8-month repeatability of the daily consumption of flavonoids was 0.49, and the 4- to 7-year repeatability was 0.35. Of flavonoid sources, fruits and vegetables showed short-term reliabilities of 0.64 and 0.63 and long-term reliabilities of 0.39 and 0.47, respectively. The corresponding values for berries and sweetened juices and jams were 0.36 and 0.35 (short-term reliability) and 0.10 and 0.25 (long-term reliability), respectively (11).

Information regarding cancer incidence during the follow-up was obtained by linking the nationwide Finnish Cancer Registry (21) to the dietary data. The primary site of the cancer was coded according to the *International Classification of Diseases*, Seventh Revision (22). A total of 997 new cancer cases were noted, of which 151 lung cancer cases occurred during a follow-up of 194,822 person-years in 1967–1991.

The sex- and age-adjusted mean levels of several potential confounding factors among cancer patients

and persons free from cancer were estimated, based on the linear model (23). The Cox proportional hazards model was used to estimate the association between flavonoids and their major sources and the risk of cancer at several different sites (24). Adjustment for potential confounding factors was done by including these in the models. Relative risks were estimated for quartiles of intake, using the lowest quartile as the reference category. Repeatability was estimated as the reliability coefficient (25).

RESULTS

Those persons who developed lung cancer during the 24-year-long follow-up period were older, were more often males and smokers, had more often lung symptoms, and were leaner than those not developing the disease (table 1). Their intakes of flavonoids and energy were significantly lower, and they appeared to consume fewer vegetables and fruits and more saturated fatty acids. The flavonoid intake was inversely associated with age and smoking and positively associated with the intake of antioxidant vitamins, fiber, fatty acids, and energy (table 2).

The sex- and age-adjusted relative risk of all sites of cancer combined between persons in the highest and lowest quartiles of flavonoid intake was 0.80 (95 percent confidence interval 0.67–0.96) (table 3). The rates for men and women were 0.75 (95 percent con-

TABLE 1. Mean levels of selected variables adjusted for age and sex of cancer patients and cancer-free persons, Finnish Mobile Clinic Health Survey, 1967–1991

	Sex (% males)*	Age (years)†	Serum cholesterol (mg/dl)	Body mass index (kg/m²)	Smoking (%)	Chest radiographic examination, scar, or calcification (%)	Chronic cough or use of cough medicine (%)
Lung cancer patients (n = 151)	95.6	53.5	252	22.5	71.0	17.0	40.4
Other cancer patients (n = 846)	48.6	51.5	242	24.7	44.6	5.9	20.5
Cancer-free persons (n = 8,962)	52.5	37.7	250	24.8	39.3	6.3	18.1
p value for heterogeneity	<0.001	<0.001	<0.001	<0.001	0.21	<0.001	<0.001

	Dietary Intake/day								
	Vegetables (g)	Fruits (g)	Berries (g)	Sweetened juices and jams (g)	Apple (g)	Onion (g)	Flavonoids (mg)	B-Carotene (mg)	Vitamin E (mg)
Lung cancer patients (n = 151)	328	95	15.6	32.5	31.2	3.65	3.51	1.84	7.22
Other cancer patients (n = 846)	334	117	14.9	36.4	44.2	3.64	3.97	1.98	7.50
Cancer-free persons (n = 8,962)	337	120	16.2	38.2	45.2	3.86	4.15	2.10	7.61
p value for heterogeneity	0.64	0.02	0.26	0.21	0.02	0.16	<0.01	0.16	0.25

	Dietary Intake/day							
	Vitamin C (mg)	Fiber (g)	Saturated fatty acids (g)	Mono-unsaturated fatty acids (g)	Poly-unsaturated fatty acids (g)	Poly-unsaturated: saturated ratio (%)	Cholesterol (mg)	Energy (kcal)
Lung cancer patients (n = 151)	76.3	27.9	66.3	37.1	7.50	11.8	474	2,595
Other cancer patients (n = 846)	80.1	28.6	60.0	34.3	7.57	13.6	504	2,527
Cancer-free persons (n = 8,962)	81.8	29.3	61.6	35.3	7.67	13.4	489	2,601
p value for heterogeneity	0.13	0.13	0.01	0.04	0.76	0.04	0.08	0.05

* Adjusted for age.
† Adjusted for sex.

TABLE 2. Mean level of selected variables adjusted for sex and age in quartiles* of flavonoid intake, Finnish Mobile Clinic Health Survey, 1967–1991

	Sex (% males)†	Age (years)‡	Serum cholesterol (mg/dl)	Body mass index (kg/m²)	Smoking (%)	Chest radiographic examination, scar, or calcification (%)	Chronic cough or use of cough medicine (%)
Flavonoid quartile							
1 (lowest)	53.0	45.2	247	24.7	39.3	6.4	20.1
2	52.4	39.1	249	24.8	37.0	7.0	18.9
3	52.1	36.6	250	24.8	32.0	5.4	16.8
4 (highest)	53.9	36.0	250	24.8	33.2	7.0	19.0
p value for trend	0.04	<0.001	0.26	0.26	<0.001	0.64	0.05

	Dietary intake/day									
	β-Carotene (mg)	Vitamin E (mg)	Vitamin C (mg)	Fiber (g)	Saturated fatty acids (g)	Mono-unsaturated fatty acids (g)	Poly-unsaturated fatty acids (g)	Poly-unsaturated: saturated ratio (%)	Cholesterol (mg)	Energy (kcal)
Flavonoid quartile										
1 (lowest)	1.33	6.29	54.0	24.4	57.1	31.5	6.53	12.5	416	2,277
2	1.78	7.03	70.3	27.4	59.8	33.7	7.19	13.0	457	2,481
3	2.26	7.77	86.1	30.0	61.9	35.4	7.72	13.5	497	2,632
4 (highest)	2.89	9.12	112.4	34.4	66.8	39.8	9.07	14.6	572	2,948
p value for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

* Quartiles are <2.1, 2.1–3.2, 3.3–4.8, and >4.8 mg/in men and <2.4, 2.4–3.6, 3.7–5.5, and >5.5 mg in women.
† Adjusted for age.
‡ Adjusted for sex.

fidence interval 0.59–0.97) and 0.85 (95 percent confidence interval 0.65–1.11), respectively. A strong inverse association was present between flavonoid intake and the incidence of lung cancer, and the sex- and age-adjusted relative risk was 0.54 (95 percent confidence interval 0.34–0.87). Further adjustment for geographic area, occupation, smoking, body mass index, and intakes of energy, vitamin C, vitamin E, beta-carotene, fiber, poly- and monounsaturated fatty acids, saturated fatty acids, and cholesterol did not notably alter the association. When also chronic cough or the use of cough medicine and chest radiographic findings was adjusted, the relative risk was 0.44 (95 percent confidence interval 0.24–0.81). Exclusion of the lung cancer cases occurring during the first 2 years of follow-up also did not alter the results, as the relative risk was 0.53 (95 percent confidence interval 0.29–0.98). The other cancer sites showed nonsignificant associations.

Study of the association in subgroups of the population revealed a stronger association between flavonoid intake and lung cancer in younger rather than older persons (table 4). The association was also stronger among nonsmokers than among current smokers and during the first 15 years of follow-up than for later periods.

Of the major dietary sources of flavonoid intake, apples showed a significant inverse association with lung cancer incidence (table 5). The relative risk of lung cancer between the highest and lowest quartiles of the intake was 0.42 (95 percent confidence interval 0.23–0.76). Adjustment for the intakes of vegetables and fruits other than apples did not notably alter the results, giving a relative risk of 0.48 (95 percent confidence interval 0.27–0.85). Intakes of other foods containing flavonoids were not significantly associated with lung cancer incidence.

DISCUSSION

The results of the present study suggest the presence of an inverse association between flavonoid intake and subsequent lung cancer incidence, which is not due to consumption of antioxidant vitamin C or E or beta-carotene. The suggested beneficial effect of flavonoids was mainly ascribed to quercetin, which provided over 95 percent of the total flavonoid intake in the present population. This finding is in line with the suggested anticarcinogenic effect of flavonoid compounds from both experimental and in vitro studies (26). The main risk factor in lung cancer, cigarette smoke, is one of the most important external sources that increase the

TABLE 3. Relative risk of different sites of cancer among quartiles of flavonoid intake, Finnish Mobile Clinic Health Survey, 1967–1991

Site of cancer	Flavonoid quartile*	No. of cases	Adjustment A†		Adjustment B‡	
			Relative risk	95% confidence interval	Relative risk	95% confidence interval
All sites	1 (lowest)	325	1		1	
	2	249	0.90	0.77–1.07	0.93	0.79–1.11
	3	232	0.95	0.81–1.14	1.03	0.85–1.24
	4 (highest)	191	0.80	0.67–0.96	0.87	0.70–1.09
Lung	1 (lowest)	63	1		1	
	2	42	0.77	0.52–1.14	0.76	0.50–1.16
	3	21	0.46	0.28–0.76	0.50	0.29–0.85
	4 (highest)	25	0.54	0.34–0.87	0.53	0.29–0.97
Stomach	1 (lowest)	21	1		1	
	2	16	0.95	0.49–1.82	1.03	0.53–2.02
	3	14	0.98	0.49–1.94	1.16	0.55–2.43
	4 (highest)	13	0.91	0.45–1.85	1.15	0.48–2.78
Colorectum	1 (lowest)	30	1		1	
	2	14	0.57	0.30–1.08	0.64	0.33–1.23
	3	16	0.76	0.41–1.40	0.86	0.44–1.69
	4 (highest)	12	0.58	0.30–1.15	0.74	0.32–1.68
Pancreas	1 (lowest)	10	1		1	
	2	9	1.10	0.45–2.73	1.40	0.54–3.61
	3	5	0.72	0.24–2.14	1.16	0.35–3.84
	4 (highest)	5	0.72	0.24–2.14	1.46	0.37–5.71
Prostate	1 (lowest)	18	1		1	
	2	20	1.35	0.71–2.55	1.62	0.82–3.18
	3	12	1.05	0.50–2.19	1.23	0.56–2.69
	4 (highest)	12	1.03	0.49–2.15	1.39	0.56–3.46
Urinary organs	1 (lowest)	17	1		1	
	2	19	1.34	0.69–2.59	1.50	0.76–2.98
	3	11	0.90	0.42–1.95	1.19	0.52–2.71
	4 (highest)	7	0.58	0.24–1.41	0.84	0.29–2.45
Nervous system	1 (lowest)	9	1		1	
	2	8	0.85	0.33–2.23	0.85	0.31–2.28
	3	9	0.99	0.39–2.53	0.87	0.31–2.47
	4 (highest)	4	0.44	0.13–1.45	0.32	0.08–1.37
Leukemia/lymphoma	1 (lowest)	20	1		1	
	2	13	0.75	0.37–1.51	0.77	0.37–1.60
	3	8	0.51	0.22–1.17	0.56	0.23–1.36
	4 (highest)	12	0.78	0.38–1.61	0.90	0.36–2.25
Skin (basal carcinoma)	1 (lowest)	44	1		1	
	2	33	0.90	0.57–1.41	0.96	0.60–1.52
	3	46	1.43	0.94–2.18	1.50	0.95–2.37
	4 (highest)	27	0.86	0.53–1.39	0.91	0.51–1.64
Breast	1 (lowest)	26	1		1	
	2	17	0.74	0.41–1.36	0.66	0.35–1.25
	3	23	1.00	0.56–1.76	0.90	0.48–1.66
	4 (highest)	21	0.94	0.52–1.68	0.72	0.36–1.48

* Quartiles are <2.1, 2.1–3.2, 3.3–4.8, and >4.8 mg in men and <2.4, 2.4–3.6, 3.7–5.5, and >5.5 mg in women.
† Adjustment A, adjusted for age and sex.
‡ Adjustment B, adjusted for sex, age, geographic area, occupation, body mass index, smoking, and intakes of energy, vitamin C, vitamin E, β-carotene, fiber, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and cholesterol.

oxidative load of tissues (27). Since oxidative stress is thought to be involved in various stages of cancer development (28) and as flavonoids are effective antioxidants, our suggestion of a protective effect against

TABLE 4. Relative risk* of lung cancer and all sites of cancer combined between highest and lowest quartiles of flavonoid intake in categories of different variables, Finnish Mobile Clinic Health Survey, 1967–1991

Variable	Category	Lung cancer			All sites of cancer		
		No. of cases	Relative risk	95% confidence interval	No. of cases	Relative risk	95% confidence interval
Sex	Men	143	0.56	0.31–1.03	547	0.81	0.61–1.02
	Women	8	—†	—	449	0.96	0.71–1.29
Age	<50 years	56	0.33	0.15–0.77	387	0.66	0.48–0.91
	≥50 years	95	0.74	0.36–1.51	609	0.91	0.70–1.19
Smoking	No	33	0.13	0.03–0.58	637	0.87	0.67–1.13
	Current	118	0.66	0.35–1.26	359	0.85	0.61–1.17
Follow-up	≤15 years	116	0.45	0.22–0.89	604	0.86	0.65–1.14
	>15 years	35	1.04	0.28–3.83	392	0.89	0.62–1.29

* Adjusted for sex, age, geographic area, occupation, body mass index, smoking, and intakes of energy, vitamin C, vitamin E, β-carotene, fiber, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and cholesterol.
† —, not possible to estimate.

TABLE 5. Relative risk* of lung cancer and all sites of cancer combined between highest and lowest quartiles of flavonoid sources, Finnish Mobile Clinic Health Survey, 1967–1991

Source	Relative risk	95% confidence interval
Lung		
Apple	0.42	0.23–0.76
Other fruits	0.66	0.35–1.26
Berries	1.80	1.11–2.93
Sweetened juices and jams	0.79	0.47–1.33
Onion	0.75	0.45–1.25
Other vegetables	0.75	0.41–1.37
All sites		
Apple	0.87	0.72–1.04
Other fruits	0.90	0.71–1.14
Berries	1.24	1.02–1.51
Sweetened juices and jams	1.13	0.93–1.38
Onion	1.02	0.84–1.25
Other vegetables	0.93	0.74–1.17

* Adjusted for sex, age, geographic area, occupation, smoking, body mass index, and intakes of energy, vitamin C, vitamin E, β-carotene, fiber, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and cholesterol.

lung cancer is plausible. The evidence from human studies, however, is scarce (8), and applicability of the findings of animal experiments and in vitro studies to humans is uncertain, as the metabolism and even the absorption of flavonoids in humans remain poorly known (29).

We also found a significant inverse association between the intake of apples, the main source of flavonoids in the present study population, and lung cancer incidence. Other main sources of flavonoids in the present study population included other fruits, veg-

etables, berries, juices, and jams. The decreased cancer risk of those consuming greater amounts of vegetables and fruits has mostly been ascribed to higher intakes of antioxidant vitamins from these foods (1, 30). In the population of the present study, an inverse association between the intake of antioxidant vitamins and lung cancer was demonstrated previously (31). As apples are a relatively poor source of vitamin C and beta-carotene, adjustment for these antioxidant vitamins did not notably alter the association. Other substances in apples, such as flavonoids, are thus likely to provide the protection.

Besides apples, onions were main sources of flavonoids in the present population. Onions, together with garlic, scallions, leeks, and chives, belong to the allium vegetable family, which contains different organosulfur compounds with antimutagenic and anticarcinogenic effects (32, 33). There is relatively consistent evidence from observational epidemiologic studies suggesting an inverse association between the intake of allium vegetables and the occurrence of gastrointestinal cancer (33). In the few studies reported on lung cancer, no significant association has been found (34, 35). In line with these results, ours did not provide a significant association between lung cancer risk and the consumption of onions, the most important allium vegetable consumed by the present population during the time for the baseline examination. Thus, it is improbable that the association observed between flavonoid intake and lung cancer risk was due to other anticarcinogenic effects of allium vegetables.

Although our findings support the hypothesis that flavonoids may provide protection against lung cancer, it remains possible that the associations observed

were caused by differences in factors not controlled in the analyses. As suggested, apples and other foodstuffs rich in flavonoids may contain other biologically active, but still unknown compounds, which provide the protection (36). It is also possible that a lifestyle associated with a high intake of foodstuffs rich in flavonoids may reduce the risk of lung cancer. Finally, although the intakes of antioxidant vitamins and their main sources were adjusted in the analyses, it is possible that the relatively low reliability of the intake estimates of the micronutrients (11) did not allow for a sufficient adjustment to eliminate the association due to them.

Persons with a high intake of berries showed an elevated risk of lung cancer. This unexpected finding may be due to the flavonoid composition of berries. In addition to quercetin, several berries used in Finland contain considerable amounts of other flavonoids such as myricetin (13, 15, 37). It has been shown in in vitro studies that myricetin manifests prooxidant properties and catalyzes oxygen radical production (38, 39). The intake estimates of flavonoids from berries were less valid than those from other foods. In addition, the poor long-term maintenance of berry consumption (11) indicated the presence of a possible misclassification of intake during the follow-up. It is also possible that the positive association observed is merely due to the multiple comparisons undertaken.

The strength of association between flavonoid intake and lung cancer incidence appeared to vary between subpopulations. A stronger association present in younger than older persons may be due to a selection among elderly persons that may hide the association. Furthermore, the association was closer among nonsmokers than current smokers. The intake of flavonoids in the present population was exceptionally low, therefore making it tempting to speculate that the antioxidative potential available was not sufficient to protect smokers against their amount of oxidative stress.

Preclinical cancer may have affected dietary intake and consequently flavonoid intake at the baseline. Exclusion of cancer cases at the baseline and those occurring during the first years of follow-up would diminish this type of bias. The results were not notably altered by exclusion of these cancers; furthermore, the follow-up here was sufficiently long to demonstrate the temporal order. In the Dutch study, the follow-up times were much shorter, leaving this question open (8).

The accuracy of the food composition values used to generate the intakes of dietary components and of the instruments used to collect food consumption data is a cause for concern in nutritional epidemiologic research. In the present study, we estimated the flavonoid intakes mainly using values of recent Dutch analyses (13), which thus far offer the most comprehensive food composition data on dietary flavonoids. Because several factors such as variety, growing conditions, and maturation can affect the flavonoid content of plants (37), the food compositions in the Netherlands were possibly not identical to those in Finland. The average intake of flavonoids in the present study population, however, was of a similar order as the intake of the same flavonoids in middle-aged Finnish men, as analyzed from their diets composed according to food consumption figures collected during the 1960s (7), thus suggesting that the Dutch food composition values of flavonoids were applicable to the Finnish foods. Flavonoids are suggested to be heat stable and, accordingly, losses due to cooking and frying are low (12).

In general, the repeatability of the dietary history method during some months was moderate or good, whereas the agreement for the measurements repeated several years apart was lower (11). Similarly the short-term repeatability of the flavonoid intake data was moderate, but the long-term repeatability was poorer, indicating an increased misclassification of the flavonoid intake during the long follow-up period. Accordingly, we found that the association was stronger during the first 15 years of follow-up than during later periods, suggesting that the overall estimates of the strength of association are conservative.

In addition to vegetables and fruits, tea and red wine are major sources of flavonoids (12). Data on tea and red wine were not available in the present study; however, the tea consumption of Finns is low, as coffee was mainly consumed as a refreshment beverage at the time of baseline. The consumption of red wine is also low in Finland, as beer and liquors are preferred. The contribution of tea and red wine to flavonoid intake was thus small in the present population. Accordingly, the total intake of flavonoids in Finland is very low compared with that in several other countries (7).

No significant association was present here between flavonoid intake and any malignancy other than lung cancer. This finding was in agreement with those of other studies (7, 8). Nevertheless, we observed suggestive inverse associations for colorectal cancer and cancer of the nervous system. It cannot be excluded that the lack of significance may have been due to the small number of cancer cases at these sites.

In summary, we found an inverse relation between the dietary intake of flavonoids and the incidence of lung cancer that was most likely attributable to the consumption of apples, the main source of flavonoids

in the present population. Although our finding was independent of the intake of antioxidant vitamins, the potential importance of other biologically active compounds of fruits and vegetables on the relation cannot be excluded. Further prospective studies from populations with variable flavonoid intake should be focused on effect-modifying and confounding factors, such as dietary patterns and lifestyle, until firmer conclusions can be drawn about the role of flavonoids in the etiology of lung cancer.

ACKNOWLEDGMENTS

REFERENCES

1. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. Nutr Cancer 1992;18:1–29.
2. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029–35.
3. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150–5.
4. Hennekens CH, Buring JE, Manson JA, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996;334:1145–9.
5. Kuhnau J. The flavonoids. A class of semi-essential food components: their role in human nutrition. World Rev Nutr Diet 1976;24:117–91.
6. Harborne JB, ed. The flavonoids. Advances in research since 1986. London: Chapman and Hall, 1994.
7. Hertog MGL, Kromhout D, Aravanis C, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. Arch Intern Med 1995;155: 381–6.
8. Hertog MGL, Feskens EJM, Hollman PCH, et al. Dietary flavonoids and cancer risk in the Zutphen elderly study. Nutr Cancer 1994;22:175–84.
9. Knekt P. Serum alpha-tocopherol and the risk of cancer. Helsinki: Social Insurance Institution, Finland, 1988:1–148. (Series ML: 83).
10. Aromaa A. Epidemiology and public health impact of high blood pressure in Finland. (In Finnish with an English summary). Helsinki: Social Insurance Institution, Finland, 1981. (Series AL: 17).
11. Järvinen R, Seppänen R, Knekt P. Short-term and long-term reproducibility of dietary history interview data. Int J Epidemiol 1993;22:520–7.
12. Hertog MGL, Hollman PCH, Katan MB, et al. Intake of potentially anticarcinogenic flavonoids and their determinants in adults in the Netherlands. Nutr Cancer 1993;20:21–9.
13. Hertog MGL. Flavonols and flavones in foods and their relation with cancer and coronary heart disease risk. (Dissertation). The Hague: CIP-data Koninklijke Bibliotheek, 1994.
14. Wildanger W, Herrmann K. Die phenolischen Inhaltstoffe des Obstes. II. Die Flavonole des Obstes. (In German). Z Lebensm Unters Forsch 1973;151:103–8.
15. Starke H, Herrmann K. Die phenolischen Inhaltsstoffe des

16. Obstes. VIII. Veränderungen des Flavonolgehaltes während der Fruchtentwicklung. (In German). Z Lebensm Unters Forsch 1976;161:131–5.
16. Rastas M, Seppänen R, Knuts L-R, et al, eds. Nutrient composition of foods. 3rd ed. Helsinki: Social Insurance Institution, Finland, 1990.
17. Heinonen M. Carotenoids and retinoids in Finnish foods and the average diet. (Dissertation). Helsinki: Department of Food Chemistry and Technology, University of Helsinki, 1990: 1–75. (EKT series 811).
18. Piironen V. Tocopherols and tocotrienols in foods and in the average Finnish diet. (Dissertation). (In Finnish with an English summary). Helsinki: Department of Food Chemistry and Technology, University of Helsinki, 1986:1–173. (EKT series 726).
19. McLaughlin PJ, Weihrauch JL. Vitamin E content of foods. J Am Diet Assoc 1979;75:647–65.
20. Knekt P, Albanes D, Seppänen R, et al. Dietary fat and risk of breast cancer. Am J Clin Nutr 1990;52:903–8.
21. Teppo L, Pukkala E, Hakama M, et al. Way of life and cancer incidence in Finland. A municipality-based ecological analysis. Scand J Soc Med Suppl 1980;19:1–84.
22. World Health Organization. International classification of diseases. Manual of the international statistical classification of diseases, injuries, and causes of death. Seventh Revision. Geneva: World Health Organization, 1955.
23. Cohen J, Cohen P. Applied multiple regression/correlation analysis for the behavioral sciences. New York: Wiley, 1975.
24. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley, 1980.
25. Winer BJ. Statistical principles in experimental design. 2nd ed. Tokyo: McGraw-Hill and Kogakusha, 1971.
26. Middelton E, Kandaswami C. The impact of plant flavonoids on mammalian biology: implications for immunity, inflammation, and cancer. In: Harbone JB, ed. The flavonoids. Advances in research since 1986. London: Chapman and Hall, 1994.
27. Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci U S A 1993;90:7915–22.
28. Cerutti PA. Oxy-radicals and cancer. Lancet 1994;344:862–3.
29. Hollman PCH, de Vries JHM, van Leeuwen SD, et al. Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. Am J Clin Nutr 1995;62: 1276–82.
30. van Poppel G. Carotenoids and cancer: an update with emphasis on human intervention studies. Eur J Cancer 1993;29A: 1335–44.
31. Knekt P, Järvinen R, Seppänen R, et al. Dietary antioxidants and the risk of lung cancer. Am J Epidemiol 1991;134:471–9.
32. Dorant E, van den Brandt PA, Goldbohm RA, et al. Garlic and its significance for the prevention of cancer in humans: a critical view. Br J Cancer 1993;67:424–9.
33. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. J Am Diet Assoc 1996;96:1027–39.
34. Huang C, Zhang X, Qiao Z, et al. A case-control study of dietary factors in patients with lung cancer. Biomed Environ Sci 1992;5:257–65.
35. Dorant E, van den Brandt PA, Goldbohm RA. A prospective cohort study on Allium vegetable consumption, garlic supplement use, and the risk of lung carcinoma in the Netherlands. Cancer Res 1994;54:6148–53.
36. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II. Mechanisms. Cancer Causes Control 1991;2:427–42.
37. Herrmann K. Flavonols and flavones in food plants: a review. J Food Technol 1976;11:433–48.
38. Hodnick WF, Kung FS, Roettger WJ, et al. Inhibition of mitochondrial respiration and production of toxic oxygen radicals by flavonoids. A structure-activity study. Biochem Pharmacol 1986;35:2345–57.
39. Maridonneau-Parini I, Braquet P, Garay RP. Heterogenous effect of flavonoids on K loss and lipid peroxidation induced by oxygen-free radicals in human red cells. Pharmacol Res Commun 1986;18:61–72.