NUTRITION AND CANCER, *46*(1), 30–37

The Protective Effect of the Mediterranean Diet on Lung Cancer

Cristina Fortes, Francesco Forastiere, Sara Farchi, Sandra Mallone, Tiziana Trequattrinni, Fabrizio Anatra, Giovanni Schmid, and Carlo A. Perucci

Abstract: *There has been growing interest over recent years in the potential preventive role of the Mediterranean diet in the development of cardiovascular disease and cancer. The present study was designed to evaluate the relationship between the components of the Mediterranean diet and lung cancer. A hospital-based, case-control study of lung cancer was conducted on subjects aged 35+ yr living in the Lazio region and admitted to one of the main hospitals in Rome in the period from 1993 to 1996. Cases (*n *= 342) were patients with newly diagnosed primary lung cancer. Controls (*n *= 292) were recruited from departments of general surgery, orthopedics, ENT, and general medicine and were frequency matched by sex and age (±5 yr) to the cases. Exposure characteristics were obtained by interviewing study subjects. A self-administered food-frequency questionnaire was used. After careful control for several smoking variables, we found a protective effect for high consumption of carrots (odds ratio [OR] = 0.67, 95% confidence interval [CI] = 0.42–1.05), tomatoes (OR = 0.59, 95% CI = 0.34–1.03), white meat (OR = 0.66, 95% CI = 0.42–1.02), exclusive use of olive oil (OR = 0.67, 95% CI = 0.45–0.99), and regular consumption of sage (OR = 0.43, 95% CI = 0.29–0.65). In a multivariate model, considering all food items simultaneously, the protective effect of exclusive olive oil use and sage remained statistically significant. Our results indicate that some food items typical of the Mediterranean diet are associated with decreased lung cancer risk.*

Introduction

Cancer of the lung is the most common type of cancer in the world (1). There is general agreement that the incidence of lung cancer is determined mainly by active cigarette smoking (2) followed by occupational exposures (3). Epidemiological research has provided increasing evidence that dietary habits may play an important role in lung cancer etiology (4–8). In particular, increased vegetable and fruit intakes are associated with reduced risk (5), whereas alcohol (4), salted meat (6), fat (7), and cholesterol intakes (8) are associated with increased risk of lung cancer.

There has been growing interest in recent years in the role of free radicals in the development of cardiovascular disease and cancer. The free radical theory attributes a pivotal role to oxidative damage and to antioxidative capacities of dietary compounds. The Mediterranean diet contains a great variety of natural antioxidants, such as carotenoids, vitamins C and E, phenols, and flavonoids. Markedly lower lung cancer mortality was observed in southern Italy in comparison with the northern part of the country, even after allowing for cigarette consumption, such as to suggest a protective effect of diet (9). In the south of Italy there is a higher consumption of fresh vegetables and monounsaturated fatty acids (mainly olive oil) in comparison with the north of the country (10). It has also been suggested that immigrants from the south to the north have a lower risk of lung cancer (11). There is no analytical epidemiological study that has evaluated the association between the components of the Mediterranean diet and lung cancer.

This study was specifically designed to assess the relationship between dietary components of the Mediterranean diet and lung cancer.

Methods

A hospital-based, case-control study of lung cancer was conducted in one of the main hospitals of the metropolitan area of Rome (Forlanini-S. Camillo Hospital). The study was part of the International Agency for Research on Cancer (IARC) initiative to investigate the role of environmental tobacco smoke on lung cancer (12).

Eligible cases were Caucasian adults between the ages of 35 and 90 yr living in the Lazio region (which includes the city of Rome) and admitted to the hospital in the period from November 1993 to June 1996 for a suspected lung cancer to be further evaluated through diagnostic bronchoscopy. Selection was confined to Caucasian subjects because of the limited numbers of other racial and ethnic groups. Eligible cases were asked for their consent to be interviewed before the diagnostic bronchoscopy.

Controls were selected among patients admitted to the same hospital during the study period from the following

C. Fortes is affiliated with the Clinical Epidemiology Department, Istituto Dermopatico dell'Immacolata, IDI-IRCCSS, Rome, Italy. F. Forastiere and C. A. Perucci are affiliated with the Department of Epidemiology, Rome E Health Authority, Rome, Italy. S. Farchi and S. Mallone are affiliated with the Agency for Public Health, Rome, Italy. T. Trequattrinni, F. Anatra, and G. Schmid are affiliated with the Forlanini Hospital, Rome, Italy.

hospital wards: general surgery, orthopedics, ENT, and general medicine. Subjects admitted to the hospital because of conditions that are somehow related to either smoking or dietary habits, such as most cancers, respiratory diseases, diabetes, cardiovascular, and digestive and renal diseases, were not included in the controls series. A balance between different diagnoses was kept when sampling controls to minimize potential bias if one disease revealed to be related to dietary habits. The control subjects had to be frequency matched to the cases by gender (1:1 for males and 1:2 for females) and age (in 5-yr strata).

In all, 679 patients (74.1% of 918 originally identified as suspected lung cancer cases) and 443 controls (64.0% of the subjects approached) were interviewed by two trained assistants using structured questionnaires regarding demographic data, smoking habits, occupational exposure to carcinogens, environmental tobacco smoke, and diet. A few weeks after the enrollment and the interview of the suspected lung cancer cases, all the relevant findings from bronchoscopy, thoracic surgery, pathology, and other medical records from the hospital were examined to confirm the suspected lung cancer diagnosis. Histological or cytological evidence of a primary lung cancer was searched. A diagnosis of lung cancer was not confirmed for 247 subjects, who had different respiratory diseases mainly associated with smoking, and they were then excluded from the study. A nonsmoker was defined as any subject who had smoked fewer than 400 cigarettes in her or his lifetime. An ex-smoker was defined as a smoker who had given up the habit at least 1 yr before the interview. This definition has been used in the multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe conducted by the IARC, to which this study contributed (12). Subjects were classified as having been exposed to known (list A) or suspected (list B) occupational lung carcinogens (13) on the basis of their positive response to a checklist of specific exposures/occupations.

The Italian version of the European Prospective Investigation into Cancer and Nutrition (EPIC) food-frequency questionnaire (a self-administered questionnaire designed and used in the ongoing European Study) was used to assess dietary habits. In the EPIC questionnaire subjects are asked to describe their frequencies of using foods in reference to the preceding year (before cancer diagnosis and changes in diet, if any, due to illness) (14,15). Diet questionnaires, which refer to a single year, tend to be representative of dietary intake over many years (16).

An additional food-frequency questionnaire was used only to assess the use of fresh herbs that are not present in the EPIC questionnaire but are part of the Mediterranean diet. All cases and controls were asked to indicate average frequency consumption in the year before the onset of the present disease. The frequency intakes of all food groups were defined on a six-point scale as follows: never, less than monthly, less than weekly, one or two times per week, four to five times per week, and daily.

Food items were subdivided into related groups and subgroups based on type of nutrient they contain, such as carrots for β-carotene, tomatoes for lycopene, leafy green vegetables for lutein, and cruciferous vegetables for phenols. For each individual food or food group, the six-point categorical scale was combined to form three categories representing low, medium, and high consumption. Combination of categories was based on the overall distribution among controls. Therefore, for some items such as beverage consumption, olive oil, and the use of fresh herbs, only two categories were used.

Unconditional logistic regression was the method chosen for the statistical analysis. Using the low consumption group as a baseline, odds ratios (ORs) and 95% confidence interval (CI) for the intermediate and high consumption groups were calculated. The dietary categories were also included as ordinal variables in the logistic regression to test for trend (Wald test).

We considered the following variables to be included in the regression model as potential confounders: gender, age (10-yr groups), the interaction between gender and age, a design variable indicating residence in Rome or in the northern part of the region vs. other areas of Lazio, years of school attendance (as a variable with three categories), and exposure to occupations known to present an excess risk for lung cancer (exposure to list A and list B occupations vs. never exposed). Because cigarette smoking is the leading cause of lung cancer, a proper control for this factor is necessary to avoid residual confounding. We adopted the approach recently suggested by Leffondrè et al. (17), considering in the logistic regression three smoking variables simultaneously: an indicator for smoking (no, yes), cumulative cigarettes/day-years, and time since cessation of smoking. Cigarettes/day-years among both current and ex-smokers were centered on the overall mean, whereas the variable was set to 0 for never-smokers. Time since cessation was divided into four categories; current smokers and ex-smokers who had quit in the last 5 yr were considered the reference category. We have estimated cumulative cigarettes/day-years for 4 ever-smoker subjects, for which it was missing, with the control means. We evaluated effect modification by gender for each of the smoking variables. A statistical interaction (P = 0.042) was seen only for ever-smoking, and we then included the gender–ever-smoking interaction term in the final model. After proper control for smoking, education and occupational exposures did not contribute to the overall fit and were therefore removed from the final model.

Additional analyses were performed to test the robustness of the results using a restricted data set of cases and controls that answered all the dietary questions. We performed a multivariate analysis with several dietary variables considered simultaneously; finally, we evaluated the associations after cases were divided according to histological type.

Results

Among the 432 cases and 443 controls enrolled in the study, the response rate to the dietary questionnaire was 79.2% and 65.9%, respectively. A total of 342 cases and 292 controls were included. Respondents to the dietary questionnaire were not different from nonrespondents with respect to education, smoking habits, residence, and occupational exposure both in cases and controls. Age did not differ for respondent and nonrespondent cases; however, among controls respondents were slightly younger than nonrespondents. Table 1 shows the main demographic characteristics of cases and controls, the frequency distribution of the histological types of lung cancer, and the diagnosis of the hospital controls. Histological or cytological confirmation was obtained for 87.1% of the cases, whereas 12.9% of patients were diagnosed with clinical, radiological, and endoscopic evidence of lung cancer. Squamous cell carcinoma was the most frequent cancer type (45.3%), followed by adenocarcinoma (19.6%).

Table 2 shows the association of lung cancer with cigarette smoking habits, education, and occupational exposure. Approximately 98% of male cases were ever-smokers (ex-smokers = 47.7%), whereas this proportion was 81.3% among controls (ex-smokers = 41.7%). Among females, the corresponding proportions of ever-smokers were 60 and 43.6% (ex-smokers = 14.8 and 18.2%), respectively. Ever-smoking cases had 1,112 cumulative cigarettes/day-years, whereas the corresponding value among the controls was 712. Compared with never-smokers, male smokers with an average of 1,008 cigarettes/day-years had an increased risk of lung cancer (OR = 14.45). The corresponding OR for female smokers was lower given the interaction term (0.28, 95% CI = 0.08–0.95) we found. The risk of lung cancer decreased with time since cessation among ex-smokers, reaching an OR of 0.59 for those who had quit 15 or more years ago. A marginal positive association was seen for occupational exposure to substances/conditions on list A (13), and there was only a slight tendency for risk to diminish as level of education increased.

Table 3 shows the association between lung cancer and weekly consumption of cereals, vegetables, legumes, fruits, and nuts controlling for age, gender, gender*age, place of residence, and the smoking variables. No association was observed for consumption of cereals (bread, pasta, and rice), green salad, cruciferous vegetables, legumes, fruits such as apples, pears, or bananas, fruits rich in β-carotene (peaches, apricots, melons, and prunes), and nuts. Protective effects were, however, observed for high (weekly or more) consumption of leafy green vegetables (OR = 0.61, 95% CI = 0.37–0.98), high (weekly or more) consumption of fresh tomatoes (OR = 0.59, 95% CI = 0.34–1.03), and for medium

Table 1. Demographic Characteristics of the Subjects, Histological Type of Lung Cancer, and Diagnosis of the Controls[a]

Variable	Cases	%	Controls	%
Males	287	83.9	214	73.3
Age (years)				
35–40	3	0.9	5	1.7
41–50	19	5.6	23	7.9
51–60	89	26.0	85	29.1
61–70	148	43.3	131	44.9
71–80	76	22.2	40	13.7
81–90	7	2.0	8	2.7
Residence				
City of Rome, provinces of Rieti and Viterbo	234	68.4	241	82.5
Province of Rome (excluding the city of Rome), provinces of Latina and Frosinone	108	31.6	51	17.5
Histology				
Squamous cell	155	45.3		
Small cell	37	10.8		
Adenocarcinoma	67	19.6		
Large cell	11	3.2		
Mixed cell	28	8.2		
Cases based on clinical diagnosis only	44	12.9		
Diagnosis of the controls				
Infectious diseases			14	4.8
Benign neoplasms			4	1.4
Endocrine system and disease at the immune system			3	1.0
Diseases of the blood			2	0.7
Nervous system, eye, and ear disease			66	22.6
Circulatory system diseases			18	6.2
Upper respiratory tract diseases			15	5.1
Operable diseases of the digestive system			30	10.3
Genitourinary system diseases			5	1.7
Skin and subcutaneous tissue diseases			4	1.4
Musculoskeletal system and connective tissue diseases			55	18.8
Congenital anomalies			4	1.4
Symptoms, signs, and ill-defined conditions			28	9.6
Injury			40	13.7

a: Totals may vary because of missing values.

Table 2. Association Between Lung Cancer and Cigarette Smoking, Occupational Exposure, and Education[a]

Variable	Cases	%	Controls	%	OR[b]	95% CI
Smoking habits						
Never smokers among males	5	1.7	40	18.7	1.00	
Ever smokers among males	282	98.3	174	81.3	14.45	5.34–39.08
Never smokers among females	22	40.0	44	56.4		
Ever smokers among females	33	60.0	34	43.6	0.28[c]	0.08–0.95
Cigarettes/day-years (per 800)[d]	1.39		0.89		2.10[e]	1.54–2.86
Time since cessation among ex-smokers						
Current and ex-smokers who stopped <6 yr previously	253	74.0	206	70.6	1.00	
6–10 yr	31	9.1	21	7.2	0.82	0.43–1.57
11–15 yr	24	7.0	17	5.8	0.78	0.38–1.62
>15 yr	34	9.9	48	16.4	0.59	0.33–1.06
Occupational exposure[f]						
No	226	66.1	213	72.9	1.00	
List A	37	10.8	14	4.8	1.37	0.66–2.82
List B	79	23.1	65	6.4	0.83	0.53–1.31
Education (yr)						
<8	213	62.3	157	53.8	1.00	
8–13	115	33.6	125	42.8	0.73	0.49–1.07
>13	13	3.8	9	3.1	1.52	0.57–4.08

a: Abbreviations are as follows: OR, odds ratio; CI, confidence interval.
b: ORs are adjusted for sex, age, and residence.
c: Interaction term gender–ever smoking.
d: For ever smokers, cigarettes/day-years was mean centered (cigarettes/day-years minus mean cigarettes/day-years). For never smokers, cigarettes/day-years was 0. The unit of measurement was 800, e.g., 20 cigarettes/day for 40 yr.
e: OR represents the increase in risk for each 800 cigarettes/day-years increase.
f: List A includes occupations known to present an excess risk for lung cancer, and list B includes suspected occupations (6).

(less than weekly; OR = 0.59, 95% CI = 0.39–0.90) and high levels of consumption of carrots (weekly or more; OR = 0.67, 95% CI = 0.42–1.05). Protective effects were also observed for consumption of fruits rich in vitamin C, although these were associated with wide CIs.

With the exception of white meat, no effect was found in the association between lung cancer and weekly consumption of meat (red, liver, and offal) and fish (Table 4). A protective effect was observed for medium (weekly; OR = 0.50, 95% CI = 0.31–0.82) and high levels of consumption of white meat (more than weekly; OR = 0.66, 95% CI = 0.42–1.03). A protective effect was also observed for medium (less than monthly; OR = 0.56, 95% CI = 0.34–0.92) and high levels of consumption of eggs (monthly or more; OR = 0.63, 95% CI = 0.39–1.02) and for medium (daily; OR = 0.73, 95% CI = 0.47–1.13) and high levels (more than daily; OR = 0.54, 95% CI = 0.29–1.02) of consumption of milk and yogurt, although these were associated with wide CIs.

Consumption of aperitifs, liqueurs, spirits, beer, and wine was not associated with an increase in risk for lung cancer (Table 5). There did not appear to be any protective effect or increased risk for tea or coffee consumption. A protective effect for lung cancer was found among those who used olive oil exclusively versus others who used other vegetable oils (OR = 0.67, 95% CI = 0.45–0.99) and among those who had a regular intake of fresh herbs, especially parsley (OR = 0.31, 95% CI = 0.11–0.84) and sage (OR = 0.43, 95% CI = 0.29–0.65; Table 5). Protective effects were also observed for rosemary and basil, although these were associated with wide CIs.

To confirm the findings, the analyses were restricted to the 175 cases and 154 controls for whom we had complete dietary data. The protective effect of fresh tomatoes (OR = 0.39, 95% CI = 0.16–0.95), medium consumption of carrots (OR = 0.41, 95% CI = 0.23–0.74), white meat (OR = 0.56, 95% CI = 0.30–1.06), olive oil (OR = 0.63, 95% CI = 0.37–1.07), and sage (OR = 0.46, 95% CI = 0.26–0.83) remained, whereas the effect of the other dietary variables was weaker and/or not significant: leafy green vegetables (OR = 0.77, 95% CI = 0.40–1.50), eggs (OR = 0.61, 95% CI = 0.30–1.26), milk and yogurt (OR = 1.17, 95% CI = 0.49–2.84), and parsley (OR = 0.39, 95% CI = 0.10–1.58). No changes in the risk estimates were observed when we controlled for dietary changes in the last year (data not shown).

Further analysis concentrated on whether some of the observed protective effects may be explained by other dietary confounders. We performed a multivariate analysis that considered the dietary variables consistently found in the univariate models (fresh tomatoes, carrots, white meat, olive oil, and sage). Considering all these food items simultaneously, only the exclusive use of olive oil (OR = 0.65, 95% CI = 0.42–0.99) and sage (OR = 0.42, 95% CI = 0.28–0.66) had statistically significant protective effects.

The analysis was repeated after considering two histological subgroups: squamous cell cancer and adenocarcinoma. Too few subjects had small cell and mixed cell carcinoma of the lung to permit a separate analysis. There appeared strong protective effects against squamous cell cancer for middle (OR = 0.43, 95% CI = 0.22–0.89) and high con-

Table 3. Association Between Lung Cancer and Weekly Consumption of Cereals, Vegetables, Legumes, Fruits, and Nuts[a]

Foods	Cases	Controls	OR[b]	95% CI	*P*
Bread					
Low (up to daily)	102	80	1.00		
Medium (1–2 times/day)	112	110	0.76	0.49–1.18	
High (more than 2 times/day)	70	56	0.93	0.55–1.57	0.992
Pasta and rice					
Low (less than daily)	127	115	1.00		
Medium (daily)	178	125	1.09	0.73–1.59	
High (more than daily)	15	15	1.00	0.41–2.40	0.798
Green salad					
Low (up to weekly)	89	60	1.00		
Medium (2–4 times/wk)	151	116	1.17	0.74–1.84	
High (>4 times/wk)	72	86	0.85	0.52–1.41	0.549
Cruciferous vegetables					
Low (never)	44	51	1.00		
Medium (less than weekly)	163	112	1.81	1.08–3.05	
High (weekly or more)	84	88	1.41	0.81–2.48	0.335
Leafy green vegetables					
Low (monthly or less)	92	53	1.00		
Medium (up to weekly)	121	94	0.79	0.49–1.28	
High (more than weekly)	106	119	0.61	0.37–0.98	0.037
Tomatoes					
Low (monthly or less)	60	29	1.00		
Medium (up to weekly)	112	97	0.61	0.34–1.09	
High (more than weekly)	159	156	0.59	0.34–1.03	0.122
Carrots					
Low (never)	161	91	1.00		
Medium (less than weekly)	101	108	0.59	0.39–0.90	
High (weekly or more)	75	89	0.67	0.42–1.05	0.066
Legumes					
Low (never)	65	54	1.00		
Medium (less than weekly)	132	115	1.08	0.67–1.75	
High (weekly or more)	131	112	1.12	0.69–1.82	0.524
Fruits (apples, pears, and bananas)					
Low (up to weekly)	81	78	1.00		
Medium (2–4 times/wk)	86	86	1.21	0.74–1.97	
High (>4 times/wk)	170	122	1.31	0.85–2.03	0.133
Fruits rich in vitamin C (oranges and tangerines)					
Low (up to weekly)	39	22	1.00		
Medium (2–4 times/wk)	95	88	0.62	0.31–1.23	
High (>4 times/wk)	182	161	0.66	0.35–1.27	0.325
Fruits rich in b-carotene (peach, apricots, melon, and prunes)					
Low (less than weekly)	48	47	1.00		
Medium (weekly)	126	98	1.20	0.69–2.09	
High (more than once/wk)	164	137	1.33	0.78–2.25	0.361
Nuts					
Low (never)	92	69	1.00		
Medium (less than weekly)	180	165	1.00	0.65–1.52	
High (weekly or more)	60	52	1.15	0.66–2.02	0.524

a: Totals may vary because of missing values.
b: Adjusted for sex, age, smoking habit, interaction sex*smoking, and residence.

sumption of fresh tomatoes (OR = 0.52, 95% CI = 0.27–1.00), middle (OR = 0.56, 95% CI = 0.33–0.97) and high consumption of carrots (OR = 0.63, 95% CI = 0.35–1.13), middle (OR = 0.44, 95% CI = 0.24–0.82) and high consumption of white meat (OR = 0.63, 95% CI = 0.36–1.09), the use of sage (OR = 0.29, 95% CI = 0.17–0.51), the use of parsley (OR = 0.25, 95% CI = 0.08–0.80), and the exclusive use of olive oil (OR = 0.57, 95% CI = 0.33–0.97). A protective effect was also seen for adenocarcinoma for middle (OR = 0.39, 95% CI = 0.18–0.86) and high consumption of white meat (OR = 0.49, 95% CI = 0.24–0.98) and for the use of sage (OR = 0.54, 95% CI = 0.28–1.05).

Discussion

The results of the present study suggest that consumption of carrots, tomatoes, white meat, regular use of sage and the exclusive use of olive oil are associated with a decreased lung cancer risk, after careful control of smoking habit.

Table 4. Association Between Lung Cancer and Weekly Consumption of Meat, Fish, Eggs, Cheese, and Milk and Yogurt

Foods	Cases	Controls	OR[b]	95% CI	*P*
Red meat					
Low (up to weekly)	69	51	1.00		
Medium (2–4 times/wk)	191	174	0.80	0.50–1.27	
High (>4 times/wk)	59	47	1.00	0.55–1.83	0.702
White meat (chicken, turkey, and rabbit)					
Low (less than weekly)	106	59	1.00		
Medium (weekly)	82	89	0.50	0.31–0.82	
High (more than weekly)	134	131	0.66	0.42–1.02	0.205
Liver and offals					
Low (never)	115	99	1.00		
Medium (less than monthly)	145	125	0.86	0.58–1.29	
High (monthly or more)	72	60	0.82	0.50–1.34	0.450
Fish					
Low (less than weekly)	77	60	1.00		
Medium (weekly)	166	145	0.90	0.57–1.41	
High (more than weekly)	67	72	0.86	0.50–1.46	0.481
Fish rich in omega-3 fatty acids (sardines, anchovies, tuna, and salmon)					
Low (less than weekly)	184	143	1.00		
Medium (weekly)	72	63	1.03	0.65–1.61	
High (more than weekly)	70	80	0.78	0.50–1.21	0.206
Eggs					
Low (never)	84	48	1.00		
Medium (less than monthly)	102	104	0.56	0.34–0.92	
High (monthly or more)	145	133	0.63	0.39–1.02	0.169
Cured ham and salami					
Low (never)	64	48	1.00		
Medium (less than monthly)	104	87	0.95	0.56–1.61	
High (monthly or more)	124	113	0.90	0.54–1.49	0.574
Cheese					
Low (less than weekly)	106	72	1.00		
Medium (weekly)	38	43	0.63	0.35–1.13	
High (more than weekly)	175	165	0.77	0.51–1.15	0.234
Milk and yogurt					
Low (less than daily)	159	110	1.00		
Medium (daily)	82	84	0.73	0.47–1.13	
High (more than daily)	30	36	0.54	0.29–1.02	0.015

a: Totals may vary because of missing values.
b: Adjusted for sex, age, smoking habit, interaction sex*smoking, and residence.

The relation between the intake of carotenoid-rich fruits and vegetables and lung cancer has been shown in many studies (5,18,19). The protective effect of tomatoes and carrots for lung cancer found in this study is consistent with the findings of other investigations (18,19). The study of Agudo et al. (18) showed a reduction in lung cancer risk as a result of both the high consumption of tomatoes among women (OR = 0.45; 95% CI = 0.22–0.91) and the intake of yellow/orange vegetables (mainly carrots) (OR = 0.37; 95% CI = 0.19–0.74). Darby and colleagues (19) also showed both a protective effect for carrots (OR = 0.36, 95% CI = 0.24–0.53) and tomato sauce (OR = 0.59, 95% CI = 0.47–0.75). It has been suggest that tomato consumption protects DNA from oxidative damage (20) and has chemopreventive properties for lung adenocarcinoma (21).

Several epidemiological studies suggest that the consumption of meat, eggs and whole milk increase lung cancer risk (7,22,23). In this study, we found no excess risk associated with red meat, preserved meat, egg and milk consumption. On the contrary, we found a protective effect for poultry that could be explained by either the high content of oleic acid in its composition or simply because it is an indicator of a specific protective dietary profile.

We found a protective effect for the exclusive consumption of olive oil versus the consumption of other vegetables oils. This finding, unique for lung cancer, is consistent with other previous studies that examined the role of olive oil and cancer in other sites (24,25). In contrast to seed oils, olive oil consists primarily of oleic acid, a monounsaturated fatty acid that is more resistant to oxidation than polyunsaturated fatty acids. The resistance of olive oils to oxidation can probably be attributed to the presence of antioxidants in its composition (polyphenols and vitamin E) (26). Phenolic components are potent scavengers of superoxide radicals and inhibitors of neutrophils respiratory burst. Polyphenols has been suggested to prevent interaction of benzo-a-pyrene with DNA, because their strong antagonistic activity inhibits polycycling aromatic hydrocarbons (27). Vitamin E is a potent antioxidant and is thought to inhibit the formation of nitrosamines (28).

Table 5. Association Between Lung Cancer and Beverages, Olive Oil, and Fresh Herbs[a]

Foods Beverages	Cases	Control	OR[b]	95% CI	*P*
Aperitifs					
Low (never)	185	154	1.00		
Medium (less than weekly)	120	107	0.96	0.65–1.43	
High (weekly or more)	21	16	0.83	0.38–1.79	0.652
Liqueurs and spirits					
Low (never)	174	141	1.00		
Medium (less than weekly)	110	104	0.76	0.50–1.14	
High (weekly or more)	40	35	0.74	0.41–1.33	0.090
Beer					
Low (never)	144	107	1.00		
Medium (less than weekly)	143	142	0.78	0.53–1.15	
High (weekly or more)	39	33	0.67	0.36–1.23	0.107
Wine					
Low (never)	99	94	1.00		
Medium (up to daily)	129	114	1.00	0.65–1.53	
High (more than daily)	97	70	0.87	0.53–1.43	0.826
Coffee					
Low (less than daily)	98	95	1.00		
Medium (1–2 per day)	100	78	1.08	0.68–1.71	
High (more than twice/day)	112	75	0.87	0.53–1.41	0.373
Tea					
Low (never)	166	115	1.00		
Medium (less than weekly)	66	76	0.68	0.43–1.08	
High (weekly or more)	50	35	1.15	0.66–2.00	0.880
Exclusive use of olive oil					
No	187	143	1.00		
Yes	85	99	0.67	0.45–0.99	
Garlic					
No	14	14	1.00		
Yes	312	271	0.87	0.36–2.06	
Parsley					
No	20	6	1.00		
Yes	322	286	0.31	0.11–0.84	
Rosemary					
No	48	27	1.00		
Yes	278	258	0.66	0.37–1.15	
Basil					
No	28	17	1.00		
Yes	298	268	0.63	0.31–1.30	
Sage					
No	117	57	1.00		
Yes	209	228	0.43	0.29–0.65	

a: Totals may vary because of missing values.
b: Adjusted for sex, age, smoking habit, interaction sex*smoking, and residence.

In this study the regular use of sage was also associated with a protective effect for lung cancer. Since prehistoric times spices have used frequently not only for their flavor, but also because of their power of preserving food. It has been shown that solvent extracts of rosemary, sage, and basil are effective antioxidants (29).

This study has strengths and some limitations. We were able to consider several potential food items since we used a complete and well-validated food frequency dietary questionnaire (EPIC). However, the influence of current diet on recall of past diet might lead to bias when the eating habits of cases (but not controls) has changed as a result of diagnosis or treatment. The use of incident cases has decreased the possibility of this sort of bias, and the results were similar when we controlled for changes in diet made in the last year. It is clear that dietary profiles are associated with many factors, such as socioeconomic status and cigarette smoking. However we considered in detail these variables. We had a low response rate, especially among the controls. If participation of the controls were an indicator of health consciousness, the observed protective effect of some food items would be overestimated. However, when we compared participants and refusals among the controls with regards to smoking status no difference emerged, an indication that such a bias is likely to be minimal. Moreover, to overcome the possible bias associated with missing values we restricted the analysis to subjects with complete dietary data. Another limitation of the study is that the additional food-frequency questionnaire on consumption of herbs was not validated directly. It was however similar in design to the EPIC questionnaire that we used to assess the other components of diet, which was thoroughly validated.

In conclusion, our results support evidence linking some foods rich in antioxidants to decreased lung cancer risk, and suggest that the exclusive use of olive oil and fresh herbs in particular sage may be indicators of the protective effect of the Mediterranean diet.

Acknowledgments and Notes

For their collaboration in data collection, we thank Olga Catena, Loretta Scannavini, Vincenzo Goffredo and Giovanna Piras. We thank Margaret Becker Huber for the english revision and Patrizia Compagnucci for editing the manuscript. Address correspondence to Francesco Forastiere, Department of Epidemiology, Rome E Health Authority, Via di Santa Costanza, 53, 00198 Rome, Italy. Phone: 0039 06 83060484. FAX: 0039 06 83060463. E-mail: epiamb1@asplazio.it.

Submitted 8 October 2002; accepted in final form 31 March 2003.

References

1. World Cancer Research Fund and American Institute for Cancer Research: Food, nutrition and the prevention of cancer. *Patterns Cancer* **1.1.2,** 35–52, 1997.
2. International Agency for Research on Cancer: *Tobacco Smoking. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*, Lyon, France: IARC, 1986.
3. Pohlaben H, Boffetta P, Ahrens W, Merletti F, Agudo A, et al.: Occupational risks for lung cancer: results from a multicenter case-control study in nonsmokers. *Epidemiology* **11,** 532–538, 2000.
4. Bandera VE, Freudenheim JL, Graham S, Marshall JR, Haughey BP, et al.: Alcohol consumption and lung cancer in white males. *Cancer Causes Control* **3,** 361–369, 1992.
5. Block G, Patterson B, and Subar A: Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. *Nutr Cancer* **18,** 1–29, 1992.
6. De Stefani E, Deneo-Pellegrini H, Carzoglio JC, Ronco A, and Mendilaharsu M: Dietary nitrosodimethylamine and the risk of lung cancer: a case-control study from Uruguay. *Cancer Epidemiol Biomarkers and Prev* **5,** 679–682, 1996.
7. Goodman MT, Hankin JH, Wilkens LR, and Kolonel NL: High–fat foods and the risk of lung cancer. *Epidemiology* **3,** 288–299, 1992.
8. Wu Y, Zheng W, Sellers T, Kushi L, Bostick RM, et al.: Dietary cholesterol, fat, and lung cancer incidence among older women: the IOWA women's health study (United States). *Cancer Cause Control* **5,** 395–400, 1994.
9. Taioli E, Nicolosi A, and Wynder EL: Possible role of diet as a host factor in the aetiology of tobacco-induced lung cancer: an ecological study in southern and northern Italy. *Int J Epidemiol* **20,** 611–614, 1991.
10. Saba A, Turrini A, Misura G, and Cialfa E: Indagine nazionale sui consumi alimentare delle famiglie 1980–84. *Società Ital Sci Aliment* **4,** 53–65, 1990.
11. Buiatti E, Kriebel D, Geddes M, Santucci M, and Pucci N: A case-control study of lung cancer in Florence, Italy. Occupational risk factor. *J Epidemiol Community Health* **39,** 244–250, 1985.
12. Boffetta P, Agudo A, Ahrens W, Benhamou E, Benhamou S, et al.: Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. *JNCI* **90,** 1440–1450, 1998.
13. Ahrens W and Merletti F: A standard tool for the analysis of occupational lung cancer in epidemiological studies. *Int J Occup Environ Health* **4,** 236–240, 1998.
14. Riboli E: Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC) (review). *Ann Oncol* **3,** 783–791, 1992.
15. Pisani P, Faggiano F, Krough V, et al.: Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC centres. *Int J Epidemiol* **26,** 152–160, 1997.
16. Willet W: *Nutritional Epidemiology*, 2nd ed, Oxford: Oxford University Press, 1998.
17. Leffrondré K, Abrahamowicz M, Siemiatycki J, and Rachet B: Modelling smoking history: a comparison of different approaches. *Am J Epidemiol* **156,** 813–823, 2002.
18. Agudo A, Esteve MG, Pallares C, Pallares C, Martinez-Ballarin I, et al.: Vegetable and fruit intake and the risk of lung cancer in women in Barcelona, Spain. *Eur J Cancer* **33,** 1256–1261, 1997.
19. Darby S, Whitley E, Doll R, and Silcocks P: Diet, smoking and lung cancer: a case-control study of 1000 cases and 1500 controls in south-west England. *Br J Cancer* **84,** 728–735, 2001.
20. Rehman A, Bourne LC, Halliwell B, and Rice-Evans CA: Tomato consumption modulates oxidative DNA damage in humans. *Biochem Biophys Res Commun* **7,** 828–831, 1999.
21. Kim DJ, Takasuka N, Kim JM, Sekine K, Ota T, et al.: Chemoprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU and DMH. *Cancer Lett* **120,** 15–22, 1997.
22. Jain M, Burch JD, Howe GR, Risch HA, and Miller AB: Dietary factors and risk of lung cancer: results from a case-control study, Toronto, 1981–1985. *Int J Cancer* **45,** 287–293, 1990.
23. Yi-xiong Lei, Wen-chao Cai, Yong-zhong Chen, and Ying-Xiu Du: Some lifestyle factors in human cancer: a case-control study of 792 lung cancer cases. *Lung Cancer* **14,** S121–S136.
24. Trichopoulou A, Katsouyanni K, Stuver S, Tzala L, Gnardellis C, et al.: Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. *JNCI* **87,** 110–116, 1995.
25. Bosetti C, La Vecchia C, Talamini R, Simonato L, Zambon P, et al.: Food groups and risk of squamous cell esophageal cancer in Northern Italy. *Int J Cancer* **87,** 289–294, 2000.
26. Papadopoulos G and Boskou D: Antioxidants effects of natural phenols on olive oil. *J Am Oil Chem Soc* 669–671, 1991.
27. Ferro-Luzzi A and Sette S: The Mediterranean diet: an attempt to define its present and past composition. *Eur J Clin Nutr* **43,** 13–29, 1989.
28. Byers T and Perry G: Dietary carotenes, vitamin C, and vitamin E as protective antioxidants in human cancer. *Annu Rev Nutr* **12,** 139–159, 1992.
29. Namiki M: Antioxidants/antimutagens in food. *Crit Rev Food Sci Nutr* **29,** 273–300, 1990.