

Influence of the Mediterranean Diet on the Risk of Cancers of the Upper Aerodigestive Tract¹

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Abstract

The hypothesis that the Mediterranean diet has a beneficial role on the risk of cancers of the upper aerodigestive tract has been evaluated using data from three case-control studies conducted in Italy between 1992 and 2000. The first study included 598 cases with incident, histologically confirmed cancers of the oral cavity and pharynx and 1491 hospital controls admitted to the same network of hospitals as cases for acute, nonneoplastic diseases. The second one included 304 subjects with squamous cell carcinoma of the esophagus and 743 controls. The third one included 460 laryngeal cancer cases and 1088 controls. A score summarizing eight of the major characteristics of the Mediterranean diet was used. Odds ratios and corresponding 95% confidence intervals (CIs) for increasing levels of this score were estimated using unconditional regression models, adjusted for age, sex, study center, years of education, tobacco consumption, body mass index, and total energy intake. For all cancers considered, a reduced risk was found for increasing levels of the Mediterranean score: the odds ratios for subjects with six or more Mediterranean characteristics, compared with those with less than three characteristics, were 0.40 (95% CI, 0.26–0.62) for oral and pharyngeal, 0.26 (95% CI, 0.13–0.51) for esophageal, and 0.23 (95% CI, 0.13–0.40) for laryngeal cancer. All of the estimates were consistent in strata of the major identified risk factors for these neoplasms. This study provides evidence that an *a priori* defined nutritional pattern, which includes several aspects of the Mediterranean diet, favorably affects the risk of cancers of the upper aerodigestive tract.

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Introduction

Several epidemiological studies have related various aspects of diet to the risk of various common neoplasms, including those of the upper aerodigestive tract (1, 2). However, most of these studies have addressed the association of individual foods or nutrients, and limited attention has been paid to the analysis of their joint effect by considering defined dietary patterns.

In particular, little is known on the possible influence of the Mediterranean diet on cancer risk. This diet, typical of southern European countries, has different variants, characterized, however, by some common features, including abundant plant foods, fresh and varied fruit as the main and usual dessert, high consumption of cereals, olive oil as the main source of fat, moderate consumption of wine mainly during meals, and relatively low intake of meat and dairy products (3, 4).

Growing evidence indicates that the Mediterranean diet has a beneficial influence on health (4–6). Some studies have reported a reduction of risk for coronary heart diseases (7, 8) and an improvement in survival (9–13), and there are suggestions that such a diet could have some favorable effect on cancer risk as well (10, 14).

We have thus evaluated the hypothesis that the Mediterranean diet has a beneficial effect on the risk of cancers of the upper aerodigestive tract using data from three case-control studies conducted in Italy. A simple and intuitive score, summarizing eight of the major characteristics of this diet as proposed by Trichopoulou *et al.* (9), was used to define a dietary pattern reflecting the Mediterranean diet. Such a score has been shown to be a favorable indicator of survival in elderly subjects.

Materials and Methods

The present analysis is based on data from three case-control studies of the upper aerodigestive tract cancers conducted in Italy, whose details have already been given (15–17). Briefly, the first study was conducted between 1992 and 1997 in the provinces of Pordenone, Rome, and Latina and included 598 patients (512 men and 86 women) under 77 years (median age, 57 years) with incident, histologically confirmed cancers of oral cavity and pharynx and 1491 hospital controls (1008 men and 483 women) under 78 years (median age, 57 years; Ref. 15). The second one, conducted in the same period in the provinces of Milan, Pordenone and Padua, included 304 subjects (275 men and 29 women) with incident, histologically confirmed diagnosis of squamous cell carcinoma of the esophagus under 77 years (median age, 60 years) and 743 hospital controls (593 men and 150 women) under 77 years (median age, 60 years; Ref. 16). The third one was conducted between 1992 and 2000 in the provinces of Pordenone and Padua and the greater Milan area and included 460 patients (415 men and 45 women) with incident, histologically confirmed squamous cell carcinoma of the larynx under 79 years (median age, 61 years) and 1088 hospital controls (863 men and 225 women) under 79 years (median age, 61 years; Ref. 17).

Table 1 ORs and 95% CIs for cancers of the upper aerodigestive tract, according to eight items included in the Mediterranean diet score, Italy, 1992–2000

	Median intake (portions/week)		Cancer, OR ^a (95% CI)		
	Men	Women	Oral/pharyngeal	Esophageal	Laryngeal
Monounsaturated/saturated fat ratio	1.4	1.3	0.72 (0.56–0.93)	0.73 (0.51–1.01)	0.97 (0.73–1.28)
Alcohol	28	7.0	4.26 (3.11–5.83)	6.04 (3.79–9.62)	2.77 (2.01–3.83)
Legumes	1	1.0	1.09 (0.87–1.38)	1.03 (0.74–1.42)	0.75 (0.58–0.98)
Cereals	30.3	24.1	0.77 (0.59–1.00)	0.96 (0.667–1.38)	0.92 (0.68–1.24)
Fruit	11.7	12.9	1.06 (0.83–1.35)	0.95 (0.68–1.31)	0.82 (0.62–1.07)
Vegetables	9.8	10.1	0.79 (0.62–1.01)	0.72 (0.51–1.01)	0.51 (0.39–0.67)
Meat and meat products	7	6.0	1.42 (1.11–1.81)	1.50 (1.06–2.13)	1.53 (1.15–2.04)
Milk and dairy products	9.6	11.3	1.09 (0.86–1.40)	1.24 (0.87–1.75)	1.07 (0.81–1.42)

^a Estimates from unconditional logistic regression adjusted for age, sex, study center, education, tobacco smoking, BMI, and total energy intake. Estimates for non or heavy drinkers *versus* moderate drinkers (for alcohol) and for subjects with intake over the median of other items *versus* those with intake below the median (for other food items).

In all studies, controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute, non neoplastic conditions, not related to smoking, alcohol consumption, or long-term modifications of diet. In the oral and pharyngeal and esophageal cancer studies, controls were frequency matched with cases by 5-year age groups, sex, and study center, with a control-to-case ratio of ~2 for males and ~5 for females. Overall, 28% of the controls were admitted for traumas, 35% for nontraumatic orthopedic disorders, 16% for acute surgical conditions, and 21% for miscellaneous other illnesses, including eye, ear, nose, throat, skin, or dental disorders. In all studies, response rate was >95% for both cases and controls.

The interview-administered questionnaire included information on sociodemographic characteristics, anthropometric measures, lifestyle habits, including tobacco smoking and alcohol drinking, and personal and family medical history.

The subjects' usual diet during the 2 years before cancer diagnosis or hospital admission (for controls) was investigated through a validated food frequency questionnaire (18, 19), including 78 foods and beverages, as well as a range of recipes, *i.e.*, the most common ones in the Italian diet, grouped into seven sections: (a) bread and cereal dishes (first courses); (b) meat and other main dishes (second courses); (c) vegetables (side dishes); (d) fruit; (e) sweets, desserts and soft drinks; (f) milk and hot beverages; and (g) alcoholic beverages. Subjects were asked to indicate the average weekly frequency of consumption of each dietary item; occasional intakes (lower than once a week but at least once a month) were coded as 0.5/week. An Italian food composition database, integrated with other sources when needed, was used to estimate total energy intake (20).

A Mediterranean diet score was defined *a priori* on the basis of eight characteristics of the traditional Mediterranean diet, as suggested by Trichopoulos *et al.* (9): high monounsaturated/saturated fat ratio; moderate alcohol intake; high consumption of cereals; high consumption of legumes; high consumption of fruit; high consumption of vegetables; low consumption of meat and meat products; and low consumption of milk and dairy products. The cutpoints for the items considered were set to the median values among controls specific for sex. For each subject, a point was attributed in the presence of each characteristic, and none in the absence. For alcohol, a value of 1 was attributed to moderate drinkers, *i.e.* subjects with consumption below the median, and of 0 to those with consumption above the median, as well as to non drinkers. A Mediterranean diet score was then calculated by summing up the points for each of the eight items. Thus, a subject whose diet had all the characteristics of the Mediterranean diet had a score

of 8, whereas a subject who had a diet with none of these characteristics had a score of 0.

ORs³ and the corresponding 95% CIs were estimated using unconditional multiple logistic regression models (21), including terms for age (5-year groups), sex, study center, years of education (<7, 7–11, ≥12), tobacco consumption (never, ex-smoker, current smoker of <15, 15–24, ≥25 cigarettes/day), BMI (quintiles), and total energy intake (quintiles). Tests for trend were based on the likelihood ratio test between models with and without a linear term for the diet score.

Results

Table 1 shows the median weekly consumption of the eight dietary components included in the Mediterranean score among male and female controls and the OR for each of these items for cancers of the upper aerodigestive tract, comparing subjects over the median value of each item, to those below the median. The risk for cancers of the upper aerodigestive tract increased for no or high consumption of alcohol (OR = 4.26 for oral and pharyngeal, 6.04 for esophageal, and 2.77 for laryngeal cancer) and high meat and meat products intake (OR = 1.42, 1.50, and 1.53). A reduced risk, although estimates were not always significant, was found for high intake of monounsaturated/saturated fat ratio (OR = 0.72 for oral and pharyngeal, 0.73 for esophageal, and 0.97 for laryngeal cancer) and vegetables (OR = 0.79, 0.72, and 0.51 for the 3 cancers, respectively). No associations were observed for the other dietary items considered.

The ORs of cancers of the upper aerodigestive tract according to the Mediterranean diet score are given in Table 2. A reduced risk of the three cancers considered was found for increasing levels of the Mediterranean score: the ORs for subjects with six or more Mediterranean characteristics, compared with those with less than three characteristics were 0.40 (95% CI, 0.26–0.62) for oral and pharyngeal, 0.26 (95% CI, 0.13–0.51) for esophageal, and 0.23 (95% CI, 0.13–0.40) for laryngeal cancer. The trends in risk were significant for all cancers considered. The continuous ORs for a unit increment of the Mediterranean score were 0.77 (95% CI, 0.71–0.83) for oral and pharyngeal, 0.72 (95% CI, 0.65–0.81) for esophageal, and 0.71 (95% CI, 0.65–0.78) for laryngeal cancer.

The association between the Mediterranean diet score and cancers of the oral cavity and pharynx, esophagus, and larynx

³ The abbreviations used are: OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table 2 ORs^a and 95% CIs for cancers of the upper aerodigestive tract, according to the Mediterranean diet score, Italy, 1992–2000

Cancer	Mediterranean diet score (no. of characteristics) ^b					Continuous OR	χ^2 trend
	<3	3	4	5	≥6		
Oral/pharyngeal							
Cases/controls	214/241	148/363	120/376	73/308	41/201		
OR (95% CI)	1 ^c	0.52 (0.38–0.71)	0.41 (0.30–0.57)	0.35 (0.24–0.50)	0.40 (0.26–0.62)	0.77 (0.71–0.83)	35.56 ^d
Esophageal							
Cases/controls	102/147	90/176	66/174	31/159	14/83		
OR (95% CI)	1 ^c	0.82 (0.55–1.23)	0.63 (0.41–0.95)	0.27 (0.16–0.45)	0.26 (0.13–0.51)	0.72 (0.65–0.81)	33.50 ^d
Laryngeal							
Cases/controls	183/225	109/245	98/279	48/214	19/124		
OR (95% CI)	1 ^c	0.54 (0.39–0.77)	0.47 (0.33–0.66)	0.31 (0.20–0.47)	0.23 (0.13–0.40)	0.71 (0.65–0.78)	46.39 ^d

^a Estimates from unconditional logistic regression adjusted for age, sex, study center, education, tobacco smoking, BMI, and total energy intake.

^b The sum does not add up to the total because of some missing values.

^c Reference category.

^d $P < 0.001$.

Table 3 ORs and 95% CIs for cancers of the upper aerodigestive tract according to the Mediterranean diet score in strata of selected covariates, Italy, 1992–2000

Strata	Cancer, continuous OR ^a (95% CI)		
	Oral/pharyngeal	Esophageal	Laryngeal
Age (yr)			
<60	0.77 (0.69–0.85)	0.69 (0.59–0.82)	0.72 (0.62–0.83)
≥60	0.77 (0.68–0.87)	0.73 (0.63–0.85)	0.70 (0.62–0.79)
Sex			
Male	0.79 (0.73–0.87)	0.71 (0.64–0.80)	0.71 (0.65–0.78)
Female	0.68 (0.56–0.82)	0.82 (0.55–1.23)	0.83 (0.56–1.22)
Tobacco smoking			
Nonsmokers ^b	0.74 (0.61–0.89)	0.75 (0.60–0.93)	0.76 (0.61–0.95)
Smokers ^c	0.79 (0.72–0.86)	0.72 (0.63–0.82)	0.68 (0.62–0.76)
Alcohol drinking (drinks/week)			
<28	0.81 (0.71–0.94)	0.82 (0.65–1.04)	0.80 (0.67–0.95)
≥28	0.86 (0.77–0.96)	0.81 (0.70–0.93)	0.76 (0.67–0.85)

^a Estimates from unconditional logistic regression adjusted for age, sex, study center, education, tobacco smoking, BMI, and total energy intake.

^b Including never smokers and ex-smokers since ≥20 years.

^c Including current smokers and ex-smokers since <20 years.

has been additionally analyzed in strata of selected covariates, including age, sex, tobacco smoking, and alcohol drinking (Table 3). For all cancers considered, the estimates were consistent in subjects below and over 60 years in men and women, in nonsmokers (including ex-smokers since ≥20 years) and smokers (including ex-smokers since <20 years), and in drinkers of <28 drinks/week and of ≥28 drinks/week.

Discussion

This study provides evidence that an *a priori* defined nutritional pattern, which includes several aspects of the Mediterranean diet, favorably affects the risk of cancers of the upper aerodigestive tract.

Among the components of the Mediterranean diet with a beneficial effect on cancers of the upper aerodigestive cancer are plant foods (6). These imply a high intake of various micronutrients with known antioxidant and anticarcinogenic properties, including carotenoids, vitamins C and E, flavonoids, phytosterols, folates, as well as dietary fibers (5, 22, 23), which have been associated, in variable degrees, to a reduced risk of cancers of the upper aerodigestive tract (1).

Olive oil, largely consumed in the Mediterranean coun-

tries, has also been reported to have a favorable influence on various neoplasms (24). Its protective effect on cancer risk has been explained by its antioxidant properties attributable both to oleic acid itself and to the presence of other nutrients such as vitamin E and polyphenols (25). However, its beneficial influence on cancer risk could also be because olive oil is largely consumed with vegetables and pulses.

Cereals (including bread, pasta, rice, and potatoes) have usually been considered a healthy component of the Mediterranean diet. No consistent protective effect has, however, been reported on cancers of the upper aerodigestive tract (1), probably on account of the fact that this group of foods includes refined carbohydrates, characterized by a high glycemic index and load. These, in turn, appear to increase cancer risk (26).

Elevated alcohol consumption is strongly related to cancers of the upper digestive and respiratory tract (27, 28). Thus, in this population, characterized by particularly high levels of alcohol consumption, heavy alcohol drinkers were included with nondrinkers in the higher risk category.

With reference to meat and dairy products, there are suggestions that foods of animal origin and animal fats could have a detrimental effect on these neoplasms (29). The limited intake of animal foods and fats from animal sources, which characterizes the Mediterranean diet pattern, could also contribute to its favorable effect on cancers of the upper aerodigestive tract.

More than on a single dietary aspect, however, the interest of this study has to be related to the strong inverse relation given by the combination of various food items in a single score, previously related to a favorable health outcome and an improved survival in the elderly (9). Such a score, however, does not necessarily represent the ideal Mediterranean diet. We preferred to use this simple, intuitive *a priori* score to estimate the risk attributable to a specific diet more than define a dietary pattern based, for example, on factor or cluster analysis, even if the latter may well have provided apparently stronger relations (30). We have also avoided using a risk score derived from the combination of partial regression coefficients derived in a logistic model because this approach generates biased estimates of risk reduction and the fitting of the model is hampered by the high correlation among food groups (31).

Among the limitations of our study are the potential biases of hospital-based case-control studies. To reduce any potential information bias, the questionnaire was administered to both cases and controls by the same interviewers, under similar condition, and information on alcohol, tobacco, and diet was satisfactorily reliable and reproducible (32, 33). Subjects with

admission diagnoses related to tobacco smoking, alcohol drinking, and diet modifications were not considered as eligible controls. Among the strengths of the study there are the almost complete participation of cases and controls, the comparable catchment areas of study subjects and the accurate control for tobacco, as well as other potential confounding factors. The inverse relation with the comprehensive score used, moreover, was consistent across strata of the major identified risk factors for the neoplasms considered. Dietary information was collected using a satisfactory reproducible and valid food frequency questionnaire (18, 19), which allowed to adjust for total energy intake. The major strength of the study, however, is the application of an *a priori* and independently developed Mediterranean score to a population with a considerable variability with respect to this score.

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