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

Cristina Bosetti, Silvano Gallus, Antonia Trichopoulou, Renato Talamini, Silvia Franceschi, Eva Negri, and Carlo La Vecchia

Istituto di Ricerche Farmacologiche “Mario Negri,” 20157 Milan, Italy [C. B., S. G., E. N., C. L. V.]; Department of Hygiene and Epidemiology, University of Athens Medical School, GR 11527 Goudi, Athens, Greece [A. T.]; Servizio di Epidemiologia, Centro di Riferimento Oncologico, Aviano (PN), Italy [R. T.]; International Agency for Research on Cancer, Lyon, France [S. F.]; and Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy [C. L. V.]

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 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.

Introduction

Several epidemiological studies have related various aspects of the Mediterranean 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.

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 areas of Pordenone and Padua, included 304 subjects (275 men and 29 women) with incident, histologically confirmed cancers of the 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 province of Milan, included 460 patients (415 men and 45 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 province 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).

Received 2/17/03; revised 6/11/03; accepted 6/26/03.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 This work was conducted with the support of the Italian Association for Cancer Research and the Italian League against Cancer.

2 To whom requests for reprints should be addressed, at Istituto di Ricerche Farmacologiche “Mario Negri,” Via Eritrea 62, 20157 Milan, Italy. Phone: 39-02-39014-526; Fax: 39-02-33200231; E-mail: bosetti@marionegri.it.
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 8, whereas a subject who had a diet with none of these characteristics had a score of 0.

ORs 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

---

**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

<table>
<thead>
<tr>
<th>Item</th>
<th>Median intake (portions/week)</th>
<th>Oral/pharyngeal</th>
<th>Esophageal</th>
<th>Laryngeal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monounsaturated/saturated fat ratio</td>
<td>1.4</td>
<td>0.72 (0.56–0.93)</td>
<td>0.73 (0.51–1.01)</td>
<td>0.97 (0.73–1.28)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>28</td>
<td>4.26 (3.11–5.83)</td>
<td>6.04 (3.79–9.62)</td>
<td>2.77 (2.01–3.83)</td>
</tr>
<tr>
<td>Legumes</td>
<td>1</td>
<td>1.09 (0.87–1.38)</td>
<td>1.03 (0.74–1.42)</td>
<td>0.75 (0.58–0.98)</td>
</tr>
<tr>
<td>Cereals</td>
<td>30.3</td>
<td>0.77 (0.59–1.00)</td>
<td>0.96 (0.66–1.38)</td>
<td>0.92 (0.68–1.24)</td>
</tr>
<tr>
<td>Fruit</td>
<td>11.7</td>
<td>1.06 (0.83–1.35)</td>
<td>0.95 (0.68–1.31)</td>
<td>0.82 (0.62–1.07)</td>
</tr>
<tr>
<td>Vegetables</td>
<td>9.8</td>
<td>0.79 (0.62–1.01)</td>
<td>0.72 (0.51–1.01)</td>
<td>0.51 (0.39–0.67)</td>
</tr>
<tr>
<td>Meat and meat products</td>
<td>7</td>
<td>1.42 (1.11–1.81)</td>
<td>1.50 (1.06–2.13)</td>
<td>1.53 (1.15–2.04)</td>
</tr>
<tr>
<td>Milk and dairy products</td>
<td>9.6</td>
<td>1.09 (0.86–1.40)</td>
<td>1.24 (0.87–1.75)</td>
<td>1.07 (0.81–1.42)</td>
</tr>
</tbody>
</table>

---

The abbreviations used are: OR, odds ratio; CI, confidence interval; BMI, body mass index.
Estimates from unconditional logistic regression adjusted for age, sex, study center, education, tobacco smoking, BMI, and total energy intake.

In nonsmokers (including ex-smokers since 20 years), the estimates were consistent in subjects below and over 60 years in men and women, (Table 3). For all cancers considered, the estimates were confirmed to be a reasonable and reliable estimate of the Mediterranean diet score in strata of selected covariates, Italy, 1992–2000.

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

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Mediterranean diet score (no. of characteristics)</th>
<th>Continuous OR</th>
<th>χ² trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral/pharyngeal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases/controls</td>
<td>212/241</td>
<td>1.22 (0.96–1.55)</td>
<td>0.143</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.96–1.05</td>
<td></td>
</tr>
<tr>
<td>Esophageal</td>
<td>192/225</td>
<td>1.11 (0.93–1.34)</td>
<td>0.189</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.93–1.08</td>
<td></td>
</tr>
<tr>
<td>Laryngeal</td>
<td>163/192</td>
<td>1.02 (0.86–1.21)</td>
<td>0.828</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00</td>
<td>0.86–1.18</td>
<td></td>
</tr>
</tbody>
</table>

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 countries, has also been related 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 in nondrinkers in the higher risk category.

With reference to meat and diary 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).

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

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

Reference category.

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

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

<table>
<thead>
<tr>
<th>Strata</th>
<th>Cancer, continuous ORa (95% CI)</th>
<th>Mediterranean diet score (no. of characteristics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>0.77 (0.69–0.85)</td>
<td>1</td>
</tr>
<tr>
<td>≥60</td>
<td>0.77 (0.68–0.87)</td>
<td>1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.79 (0.73–0.87)</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>0.68 (0.56–0.82)</td>
<td>1</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokersb</td>
<td>0.74 (0.61–0.89)</td>
<td>1</td>
</tr>
<tr>
<td>Smokersc</td>
<td>0.79 (0.72–0.86)</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol drinking (drinks/week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28</td>
<td>0.81 (0.71–0.94)</td>
<td>1</td>
</tr>
<tr>
<td>≥28</td>
<td>0.86 (0.77–0.96)</td>
<td>1</td>
</tr>
</tbody>
</table>

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.

Downloaded from cebp.aacrjournals.org on August 27, 2017. © 2003 American Association for Cancer Research.
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.

Acknowledgments
We thank Maria Paola Bonifacino for editorial assistance.

References

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

Cristina Bosetti, Silvano Gallus, Antonia Trichopoulou, et al.


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/12/10/1091

Cited articles
This article cites 27 articles, 8 of which you can access for free at:
http://cebp.aacrjournals.org/content/12/10/1091.full#ref-list-1

Citing articles
This article has been cited by 9 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/12/10/1091.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.