Adherence to the Mediterranean diet and nasopharyngeal cancer risk in Italy

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Abstract

Purpose: Few studies investigated the role of diet on nasopharyngeal cancer (NPC) risk in non-endemic areas. The aim of this study was to assess the association between adherence to the traditional Mediterranean diet and NPC risk in a southern European low-risk population.

Methods: We conducted a hospital-based case-control study in Italy including 198 histologically confirmed NPC cases and 594 matched controls. Dietary habits were collected by means of a validated food-frequency questionnaire, including 83 foods, food groups, or beverages. Adherence to the traditional Mediterranean diet was assessed through a Mediterranean Diet Score (MDS), based on the nine dietary components characterizing this dietary profile, i.e., high intake of vegetables, fruits and nuts, cereals, legumes, and fish; low intake of dairy products and meat; high monounsaturated to saturated fatty acid ratio; and moderate alcohol intake. We estimated odds ratios (ORs) of NPC, and the corresponding 95% confidence intervals (CIs), for increasing categories of the MDS (i.e., increasing adherence) using multiple logistic regression models, adjusted for major confounding factors.

Results: As compared to MDS≤4, the ORs of NPC were 0.83 (95% CI: 0.54-1.25) for MDS of 5 and 0.66 (95% CI: 0.44-0.99) for MDS≥6, with a significant trend of decreasing risk (p 0.043). The corresponding population attributable fraction was 22%, indicating that 22% of NPC cases in this population would be avoided by shifting all subjects to a score ≥6.

Conclusions: Our study supports a favorable role of the Mediterranean diet on NPC risk.

Key words: case–control study, Mediterranean diet, nasopharyngeal cancer, risk factor, prevention

Introduction

Nasopharyngeal carcinoma (NPC) represents the vast majority of nasopharyngeal tumors. It is a rare disease in most part of the world, including North America and Europe, where incidence rates are generally less than 1 case per 100,000 person-years for both sexes [1]. Conversely, rates are substantially higher in a few well-selected populations, including natives of southern China (e.g., Hong-Kong), Southeast Asia, the Arctic, and the Middle East/North Africa [1]. The histological distribution of NPC and corresponding risk factors vary along with incidence rates. The undifferentiated carcinoma comprises over 95% of NPC in high-incidence areas and is consistently associated to Epstein-Barr virus (EBV) infection [2]. Conversely, keratinizing squamous cell carcinoma is predominant in low-incidence regions, and may have a distinct etiology, sharing some of the well-known lifestyle risk factors for head and neck cancers, including alcohol and tobacco [3,4].

Dietary factors may play a role on the risk of NPC [5]. However, so far, epidemiological knowledge comes mainly from high-risk regions and, aside from the causal association with salt-preserved fish and pickled vegetable consumption [6-9], evidence for other dietary factors is still weak. Increased risks of NPC were observed in association with other preserved food items in studies on endemic populations [8,10], where preserved foods are a dietary staple, but also in a study from the US, only among non-keratinizing and undifferentiated tumors [11]. Few studies, particularly from high-incidence areas, evaluated the association with vegetables and fruit consumption, and, overall, suggested an inverse relation with NPC risk [12-14].

High consumption of vegetables, fruit, and olive oil, moderate consumption fish and wine, and low meat consumption are key features of the traditional Mediterranean diet [15]. Adherence to this dietary pattern has been favorably related to all-cause mortality [16,17], cerebrovascular [18] and cardiovascular diseases [17,19], as well as to incidence of overall cancer [15] and of cancer at selected sites, including upper aerodigestive tract [20], pancreas [21], stomach [22], and breast [23]. The only study assessing the relation between adherence to the Mediterranean diet and NPC risk was carried

out in a high-incidence Chinese population and found no association [24]. However, concerns have been raised about using *a priori* scores for quantification of adherence to the Mediterranean dietary pattern in a non-Mediterranean population [25].

We evaluated whether close adherence to the traditional Mediterranean diet may decrease NPC risk in a multicentric case-control study from Italy, a low-incidence Mediterranean country. This study provides the opportunity to understand how dietary risk factors and potential preventive measures for NPC differ between endemic and non-endemic NPC areas.

Materials and Methods

A case-control study was carried out between 1992 and 2008 in the provinces of Milan and Pordenone (Northern Italy), and Napes and Catania (Southern Italy) [26]. Cases were 198 patients (157 men and 41 women; median age 52 years; range 18-76 years), admitted to major teaching and general hospital in the study areas, with an incident histologically confirmed diagnosis of NPC, and without previous history of cancer at other sites. Among these, 137 (69.2%) were undifferentiated NPC, 23 (11.6%) were keratinizing squamous cell carcinomas (hereafter referred to as differentiated NCP), and for 38 (19.2%) the information was missing. EBV status was defined on the basis of the detection of EBV nuclear antigen in tissue samples, and was available for 61 patients only. All 57 undifferentiated NCP having information on EBV infection, and 2 out of 4 differentiated NPC were EBV positive. Controls were 594 patients (471 men and 123 women; median age 52 years; range 19-76 years) admitted to the same hospitals as cases for a wide spectrum of acute, non-neoplastic diseases, unrelated to known risk factors for NPC, including tobacco smoking and alcohol drinking, as well as long term dietary modifications. Controls were frequency-matched to cases according to sex, age (±2 years), period of interview (±2 years), and study area in a proportion of 3:1. Thirty-four percent of the controls were admitted for traumas, 32% for other orthopedic disorders, 22% for acute surgical conditions, and 12% for various other conditions. Less than 3% of both cases and controls originally approached did not agree to participate. The study protocol was approved by the ethical committees of the hospitals

involved, according to the regulations at the time of study conduction, and all participants provided a written informed consent to participate.

Cases and controls were interviewed during their hospital stay by centrally trained interviewers, using a structured questionnaire. This included information on socio-demographic characteristics, anthropometric variables, lifestyle factors, including tobacco smoking, a problem-oriented personal medical history, family history of cancer, and, for women, menstrual and reproductive history. Information on diet was based on a reproducible and valid food frequency questionnaire (FFQ), including 83 foods, food groups, and the most common Italian recipes, as well as various types of alcoholic beverages [27-29]. Intakes reported at least once a month but less than once a week were coded as 0.5 per week. Dietary supplements were not considered, given their unfrequent consumption in this population. Italian food composition tables [30] were used to calculate the intake of total energy and various nutrients.

Mediterranean Diet

Adherence to the Mediterranean diet was investigated using an *a priori* score, developed by Trichopoulou and colleagues [16], including nine dietary components. For each study participant, a value of 0 or 1 was assigned to each component of the score as follows: for components typical of the traditional Mediterranean diet (i.e., vegetables, legumes, fruits and nuts, cereals, fish and seafood, high monounsaturated/saturated fatty acids), participants with an intake above or equal to the sex-specific median were assigned a value of 1, and 0 otherwise; for components less frequently consumed in the traditional Mediterranean diet (i.e. dairy products and meats), participants with a consumption below the sex-specific median were assigned a value of 1, and 0 otherwise. A value of 1 was also given to men consuming 10 g to less than 50 g of ethanol/day and to women consuming 5 g to less than 25 g of ethanol/day; otherwise, a value of 0 was assigned. The Mediterranean Diet Score (MDS) was calculated adding up the values for each of the nine components. Thus, the score ranged between 0 (representing minimal adherence) and 9 (maximal adherence).

Statistical analysis

We estimated odds ratios (ORs) of NPC and corresponding 95% confidence intervals (CIs) for the MDS score in categories (0-4, 5, ≥6, i.e., approximate tertiles), as well as for 1 point increment, through unconditional logistic regression models, adjusting for sex, age, and place of residence (model 1), and further for education, tobacco smoking, and total energy intake (model 2). We also estimated the ORs for MDS categories by NCP histological types and across strata of sex, age, and tobacco smoking. Polytomous logistic regression model was used to test for heterogeneity between the two histological categories. Heterogeneity across strata was tested through likelihood ratio tests. We calculated the population attributable fraction (PAF) to estimate the proportion of NPC cases that might have been avoided by shifting all subjects to the lowest risk category (i.e., score ≥6), according to the method of Bruzzi et al. [31]. Variance calculation and 95% CI for the PAF were obtained as described by Benichou and Gail [32,33].

All the analyses were performed using the SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 gives the distribution of NPC cases and controls according to selected sociodemographic characteristics. Cases were more educated, and more frequently tobacco smokers and alcohol drinkers than controls.

Table 2 shows the ORs and corresponding 95% CIs of NPC according to categories of MDS. Compared to a MDS of 0-4, the OR of NPC was 0.83 (95% CI: 0.54-1.25) for a MDS of 5, and 0.66 (95% CI: 0.44-0.99) for a MDS≥6 (p for trend 0.043). No difference emerged between model 1 and model 2, which allowed for tobacco smoking, education and total energy intake. The corresponding PAF was 22% (95% CI: 0.5-43%), indicating that 22% of NPC cases in this population would be avoided by shifting all subjects to the highest category of adherence (i.e., score ≥6). A 11% decrease

in risk was associated to a 1 point increment in the MDS (OR=0.89, 95% CI, 0.80-0.98) (data not shown in Table).

No significant heterogeneity was observed by NCP histological types and across the strata considered (Table 3).

Discussion

The present study from a Mediterranean low-risk area for NPC found that adherence to the traditional Mediterranean diet is significantly inversely related to NPC risk, as seen for many other cancer sites [34]. Subjects with a MDS of 6 or more have an almost 35% decreased risk in comparison to subjects with a score of 4 or less. In this population, about 22% of cases would be avoided by shifting all subjects to the highest MDS.

To our knowledge, only another study investigated the role of Mediterranean diet on NPC risk [24]. This case-control study was carried out in the province of Guangdong, China, a region with dramatically elevated rates of NPC, and included 600 NPC cases and 600 matched controls. Dietary habits of the study participants were collected by means of a semiquantitative 78-item FFQ, with satisfactory reproducibility and reasonable validity. To quantify adherence to the Mediterranean diet, authors calculated a modified version the original MDS by Trichopoulou et al [16], i.e., the alternate Mediterranean diet (aMED) index [35], by excluding potato products from the vegetables group, separating fruit and nuts into 2 groups, eliminating the dairy group, including whole-grain products only, including only red and processed meats in the meat group, and assigning 1 point for the alcohol component to individuals with an intake between 5 and 15 g/day. They found an OR of 0.85 (95% CI, 0.59-1.22) for aMED≥6 versus aMED≤2, after accounting for several covariates. In the same publication, significant inverse relations were reported with closer adherence to selected other *a priori* dietary scores, including the Healthy Eating Index-2005 (HEI-2005), the alternate Healthy Eating Index (aHEI), and the Diet Quality Index-International. The use of scores assessing adherence to the Mediterranean dietary pattern with components derived from study-specific cut-off, as for MDS or

aMED, may, however, be problematic in non-Mediterranean populations, since the intake of several components is likely lower (or higher) than in a typical Mediterranean population. Thus, the score may be less able to discriminate between beneficial or harmful levels of intakes [36]. The traditional Mediterranean diet is intimately linked to the lifestyles of people from areas bordering the Mediterranean Sea, and is characterized by consumption of selected dietary products, some of which relatively uncommon outside the Mediterranean area (e.g., olive oil and wine). In the Mediterranean region, the major source of monounsaturated fatty acid (MUFA) is olive oil and the high ratio of MUFA to saturated fatty acid reflects high consumption of olive oil and low consumption of animal products [37,38]. Outside the Mediterranean region, olive oil is rarely consumed, and MUFA intake mainly originates from higher meat consumption rather than from vegetable oils. Further, the alcohol component of the score considers only the amount of alcohol consumed, but the pattern of alcohol drinking is peculiar in Mediterranean countries, with regular (rather than binge) drinking, mainly at meals and with wine being the most common type of alcoholic beverage [39]. In our study, 67% of alcohol consumers drunk alcohol exclusively during meals, and approximately 75% drunk wine daily, while only 10% drunk beer and 11% drunk spirits on a daily basis. High alcohol consumption is a recognized risk factor for NPC [3,4]. Our MDS was favorably influenced by moderate, but unfavorably by high alcohol consumption. Thus, our findings may be related by the typical drinking pattern of Mediterranean populations [40]. In addition, red wine contains a complex mixture of potentially preventive bioactive compounds (predominantly phenolic) and in particular flavonols which may be beneficial for health [41]. In contrast, the Chinese population consumes a wide range of alcoholic beverages, with beer and industry- and hand-made spirits being the most popular ones [42,43]. In a national survey from China, only 1.2% of drinking men and 13.2% of drinking women indicated wine as the preferred alcoholic beverage [43]. Moreover, the different types of vegetables and fruit may have a significant impact on phytochemical intake, and hence on disease risk. In the population analyzed in the paper by Wang et al [44,24], dark green leafy vegetables made up about 60% of the total vegetable intake for men and women, and about one third of the total fruit

consumption came from pome fruit. Conversely, in Mediterranean countries, fruiting vegetables (artichoke, cucumber, eggplant, pepper, pumpkin, tomato) are by far the most consumed vegetables, accounting for almost half of total vegetable intake in Italy [45], and consumption of summer fruit, such as pomegranates, figs, grapes and "orange fruit" (e.g., apricots, peaches, nectarines, cantaloupe melons) is relatively popular [25]. Thus, considering the different eating and lifestyle habits, and NPC rates in the Italian and Chinese population, and given the different FFQs and scores used (MDS vs aMED) in the two studies, divergence of results for Mediterranean diet and NPC are not surprising.

Our results on the Mediterranean dietary pattern are consistent with those on nutrients, food groups and *a posteriori* dietary patterns from our [46,26,14,47] and other studies in low-incidence areas [11,48], which pointed to a reduced risk of NPC for high consumption of non-preserved vegetables and fresh fruit, and their related nutrients. In particular, we recently reported a significant inverse association with the intake of vegetables, in particular yellow- or red-pigmented ones, and a nonsignificant inverse one with fruit intake [14]. Among nutrients and other food components, we found reduced risks of NPC for increased intakes of carotenoids, vitamin C [26], and fiber [46]. In the Iowa Women's Health Study, a cohort of 34,651 postmenopausal women with 18 cases of NPC, strong inverse associations emerged with intake of yellow-orange vegetables and fibers [48]. In addition, a population-based case-control study in the USA including 133 NPC cases showed non-significant inverse associations for consumption of total fresh fruit, citrus fruit, dark green vegetables and yellow vegetables, as well as for beta carotene and vitamin C. Of note, in the analyses according to histological NPC type, the risk of differentiated squamous cell carcinoma was significantly decreased for vitamin C intake above the lowest quartile [11].

We have no information on EBV status for most cancer cases. However, among cases with available information on EBV status, all undifferentiated NPCs were EBV-positive, suggesting that EBV infection was the cause of the majority of cases of that histological type is this population as well. We observed a consistent inverse association with MDS when considering undifferentiated NPCs alone.

The small sample size reflects the low rates of NPC in Italy. Information from a population inherently at low risk may help identifying additional correlates, which would otherwise be overwhelmed in a high-risk population by the action of other causal pathways such as those involving EBV infection and genetic susceptibility. Potential weaknesses of our study include selection and information bias. However, subjects admitted to hospitals for conditions related to diet modifications, tobacco smoking and alcohol abuse were not eligible as controls, case ascertainment in the catchment areas was almost complete, and participation of cases and controls was >95%. Information bias was minimized by the direct interview of cases and control by the same trained interviewers in similar hospital conditions. The use of a satisfactorily reliable and valid FFQ [28,29,49], and the availability of a number of confounding factors for adjustment purpose contributed to strengthen our findings. Still, residual confounding is a possible limitation. However, the estimates from the fully adjusted model were closed to those adjusted for sex, age and place of residence only, indicating that residual confounding is unlikely to have a major impact on the key results of our study.

In conclusion, our study, one of the few conducted in a non-endemic area for NPC, supports a favorable role of the Mediterranean dietary pattern on this cancer site.

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Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

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Table 1. Distribution of 198 cases of nasopharyngeal carcinoma and 594 controls according to sociodemographic characteristics. Italy 1992–2008.

	Cases		Controls	
	n	(%)	n	(%)
Sex[a]				
Men	157	(79.3)	471	(79.3)
Women	41	(20.7)	123	(20.7)
Age (years)[a]				
<45	52	(26.3)	159	(26.8)
45-54	64	(32.3)	186	(31.3)
55-64	47	(23.7)	144	(24.2)
≥65	35	(17.7)	105	(17.7)
Study centre[a]				
Aviano	150	(75.8)	450	(75.8)
Milan	48	(24.2)	144	(24.2)
Area of residence[a]				
North-East	90	(45.5)	270	(45.5)
North-West	48	(24.2)	144	(24.2)
Centre, South, Islands	60	(30.3)	180	(30.3)
Education (years)[b]				
<7	67	(33.8)	221	(37.3)
7-11	73	(36.9)	222	(37.5)
≥12	58	(29.3)	149	(25.2)
Tobacco smoking[b]				
Never	60	(30.8)	196	(33.1)
Former	60	(30.8)	181	(30.5)
Current				
<15 cigarettes/day	21	(10.8)	82	(13.8)
≥15 cigarettes/day	54	(27.7)	134	(22.6)
Alcohol drinking (drinks/week)[b]				
<14	82	(41.8)	262	(44.3)
14-27	46	(23.5)	159	(26.9)
≥28	68	(34.7)	171	(28.9)

[a]Matching variables. [b]The sum does not add to the total because of missing values.

Table 2. Distribution of 198 cases of nasopharyngeal carcinoma and 594 controls, odds ratios (OR) and 95% confidence intervals (CI) for categories of the Mediterranean diet score. Italy, 1992–2008.

	Ca	**%**	**Co**	**%**	**OR[a]**	**95% CI**	**OR[b]**	**95% CI**
Mediterranean diet score[c]								
0-4	100	51.0	264	44.6	1.00	-	1.00	-
5	45	23.0	136	23.0	0.87	0.58-1.31	0.83	0.54-1.25
≥6	51	26.0	192	32.4	0.69	0.47-1.02	0.66	0.44-0.99
χ^2trend (*p-value*)					4.9	*(0.027)*	4.1	*(0.043)*

Abbreviations: Ca, cases; Co, controls.

[a] Estimates from unconditional multiple logistic regression model adjusted for sex, age, and place of residence.

[b] Further adjusted for education, tobacco smoking, and total energy intake.

[c] The sum does not add up to the total because of 4 missing values on one score's component (i.e., the alcohol component).

Table 3. Odds ratios (OR)[a] and 95% confidence intervals (CI) of nasopharyngeal carcinoma for categories of the Mediterranean diet score by histological types and in strata of selected covariates[b]. Italy, 1992–2008.

	Mediterranean diet score			
	0-4	**5**	**≥6**	*p for heterogeneity*
Histological type				
Undifferentiated	70:264 1 [c]	34:136 0.89 (0.55-1.42)	32:192 0.57 (0.35-0.92)	*0.239*
Other	30:264 1 [c]	11:136 0.68 (0.32-1.43)	19:192 0.95 (0.50-1.79)	
Sex				
Men	78:206 1 [c]	35:110 0.79 (0.50-1.27)	42:153 0.70 (0.44-1.09)	*0.559*
Women	22:58 1 [c]	10:26 1.01 (0.40-2.53)	9:39 0.55 (0.22-1.36)	
Age (years)				
<55	58:159 1 [c]	30:79 1.00 (0.59-1.69)	27:106 0.68 (0.40-1.15)	*0.051*
≥55	42:105 1 [c]	15:57 0.59 (0.29-1.20)	24:86 0.66 (0.35-1.22)	
Smoking				
Never smokers	30:87 1 [c]	12:42 0.74 (0.33-1.62)	18:67 0.85 (0.42-1.70)	*0.782*
Ever smokers	70:177 1 [c]	33:94 0.84 (0.51-1.38)	33:125 0.60 (0.37-0.99)	

[a] Estimates from unconditional multiple logistic regression models adjusted for sex (when appropriate), age (when appropriate), place of residence, education, tobacco smoking (when appropriate), and total energy intake.
[b] The sum does not add up to the total because of some missing values.
[c] Reference category.