Association between Mediterranean diet and head and neck cancer: results of a large case–control study in Italy

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The Mediterranean diet (MD) is a known protective factor for head and neck cancer (HNC); however, there is still a lack of studies investigating this association by HNC subsite. The aim of the present study was therefore to evaluate the association between adherence to MD and HNC overall and by cancer subsite, as well as the effect of the individual food components on HNC risk. A case–control study was carried out at the Gemelli Hospital of Rome (Italy). A total of 500 HNC cases and 433 controls were interviewed. Dietary intake was assessed through a validated food frequency questionnaire that collected information on over 25 food items. Odds ratios (ORs) and 95% confidence intervals (CI) of HNC were calculated using a multiple logistic regression model. We found a reduced risk of both oral cavity and pharynx cancer (OR = 0.61; CI: 0.54–0.70) and larynx cancer (OR = 0.64; CI: 0.56–0.73) with increasing adherence to MD. We also found a high consumption of fruit, vegetables, and legumes to be significantly associated with a lower risk of larynx as well as oral cavity and pharynx cancers. Our study showed that adherence to MD acts protectively against HNC overall and by cancer subsite. ***European Journal of Cancer Prevention*** **26:418–423**

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Introduction

Head and neck cancers (HNC), the majority of which are squamous cell carcinomas, include cancers of the oral cavity, pharynx, and larynx (Curado and Boyle, 2013). HNC is the sixth most common cancer worldwide, with an estimated half million new cases in 2012 (Ferlay *et al.*, 2015). The two main causes of HNC are tobacco smoking and alcohol consumption (Winn *et al.*, 2015), although other factors such as human papillomavirus infection for oropharynx (Lewis *et al.*, 2015) affect the risk. Nevertheless, there is increasing evidence that the risk of HNC can be mediated by specific dietary patterns. Fruits and vegetables have long been studied for their role in HNC prevention because they contain numerous substances with potential anticarcinogenic activity (e.g. folate, carotenoids, vitamins) (Edefonti *et al.*, 2015a, 2015b; Galeone *et al.*, 2015; Leoncini *et al.*, 2015a, 2016). A high consumption of red or processed meat was also associated with a higher risk of HNC (Boeing *et al.*, 2006; Chuang *et al.*, 2012).

The typical Mediterranean diet (MD) is characterized by a high intake of monounsaturated fatty acids from olive oil, vegetables and fruits, plant proteins, whole grains, fish, low-fat dairy, moderate alcohol intake, and low red meat consumption (Bach-Faig *et al.*, 2011). MD is known to reduce the risk of developing many noncommunicable diseases including several types of cancer because of the synergic and interactive combinations of nutrients (Schwingshackl and Hoffmann, 2014, 2015; Sofi *et al.*, 2014). Oleic acid, the main component of olive oil, the main ingredient of MD, accompanied by α-tocopherol and phenol oils, exerts strong antioxidant and anti-inflammatory effects and also has a potential influence on cell proliferation, cell-cycle progression, apoptosis, and arachidonic acid metabolism in cancer cells (Corona *et al.*, 2009). Fruits, vegetables, legumes, and nuts, regular ingredients of MD, are good sources of dietary fiber and antioxidants, which are reported to lower the risk of different cancer types (Koushik *et al.*, 2007).

A recent systematic review and meta-analysis suggests that adherence to the highest category of MD is associated with a significantly lower risk of colorectal cancer, breast cancer, prostate cancer, gastric cancer (GC), liver cancer, and HNC (Schwingshackl and Hoffmann, 2015). The combined estimate for HNC was based on data from four studies, of which one was a cohort study and three were case–control studies (Bosetti *et al.*, 2003; Samoli *et al.*, 2010; Filomeno *et al.*, 2014; Li *et al.*, 2014). Moreover, two out of three case–control studies investigated the association between the MD and the risk of cancers of the upper aerodigestive tract and only one study examined subsites of HNC (Bosetti *et al.*, 2003;

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Samoli *et al.*, 2010). Our study aimed to evaluate the association between adherence to MD and HNC overall and by cancer subsite, as well as the effect of the individual food components on the risk of HNC.

Material and methods

Participants and study design

Patients with tumors of the oral cavity, oropharynx, hypopharynx, and larynx were enrolled at the Fondazione Policlinico Universitario "A. Gemelli" (Rome, Italy) from 2002 to 2014. Details on the codes of diagnosis used to select patients have been described previously (Leoncini *et al.*, 2015b). The controls included patients who were admitted to the same hospital as the cases, in the same period, for a condition unrelated to cancer. Patients and hospital controls were interviewed by trained interviewers or medical doctors using a structured questionnaire on demographics, medical history, family history of HNC, alcohol and tobacco consumption, and other relevant lifestyle factors. All patients and control participants were enrolled after they provided informed consent according to the rules of the Ethical Committee of the University. The overall participation rate was 98% for both cases and controls.

Dietary intake and Mediterranean diet score

Information on diet was obtained using a validated food frequency questionnaire including 27 items of foods and beverages. HNC patients were asked to focus on 1 year before the interview when answering the questions. To calculate the total energy intake, we used the Italian food composition database, supplemented with other published data [Salvini *et al.*, 1996; Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione (INRAN), 2010; Gnagnarella *et al.*, 2015]. A Mediterranean diet score (MDS) was used to evaluate the level of adherence to the traditional Mediterranean dietary pattern (Sofi *et al.*, 2014). Briefly, the MDS is based on nine components of the MD, some potentially beneficial components and other potentially detrimental components: fruit, vegetables, legumes, cereals, fish, meat and meat products, dairy products, alcohol, and olive oil. For each component, an individual is assigned a value of 0, 1, or 2 on the basis of their level of consumption. The MDS is also generated by the sum of points assigned to each of the individual components, with the highest score corresponding to the closest adherence to the dietary pattern. As our questionnaire did not contain dietary intake for cereals, dairy products, and olive oil, in our study the MDS was based on six of the nine components of the MD. The following dietary components each contributed with maximum points to the sum score: high consumption of fruits, high consumption of vegetables, high consumption of legumes, high consumption of fish, low consumption of meat and meat products, and moderate alcohol consumption (1–2 alcoholic unit/day). Thus, the MDS ranges from 0 (minimal adherence) to 12 (maximal adherence).

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (CI) of HNC were calculated according to the six dietary components included in the MDS and the MDS in the strata of selected covariates. We used an unconditional logistic regression model adjusted by age, sex, tobacco smoking (never, exsmoker, and current smoker), alcohol drinking (<1, 1–2, >2 drinks/day), and total energy intake (Breslow and Day, 1980). The definition of smoking status was as follows: the participants who were smoking at the time of the study or who had smoked 1 year before diagnosis for cases and 1 year before the interview for controls were defined as current smokers; the participants who had quit smoking more than 1 year before diagnosis for cases and 1 year before the interview for controls were defined as exsmokers; and the participants who had never smoked were defined as nonsmokers. Statistical analyses were carried out separately for oral and pharyngeal cancer, laryngeal cancer, and overall HNC, and were carried out using Stata software (Stata Statistical Software: Release 13; StataCorp LP, College Station, Texas, USA).

Results

Our study included 500 cases of HNC and 433 controls. Demographic characteristics as well as smoking and drinking habits of both cases and controls are reported in Table 1. Eighty percent of the participants were men among the cases and 59% were men among the controls. Cases were significantly older than controls and more likely to be heavy smokers and heavy drinkers.

Table 2 reports the distribution of age and selected risk factors in cases and control participants according to MDS. Among the controls, no differences among the three MDS categories were observed in age. The proportion of heavy smokers was higher among individuals with a higher MDS than among individuals with a lower score, whereas the reverse was true for heavy drinkers. Among the cases, the mean age was higher among patients with higher adherence to the MD. The proportion of both heavy smokers and heavy drinkers was higher among patients with a lower MDS.

Table 3 reports the ORs of HNC according to the MDS and the six items included in the MDS. Adherence to MD is associated with a reduction in the risk of both oral cavity and pharynx cancer (OR: 0.61, 95% CI: 0.54–0.70), and larynx cancer (OR: 0.64, 95% CI: 0.56–0.73). A high consumption of fruit (OR of cancer of the oral cavity and pharynx: 0.09, 95% CI: 0.04–0.25; OR of larynx cancer: 0.10, 95% CI: 0.03–0.30), vegetables (OR of cancer of the oral cavity and pharynx: 0.06, 95% CI: 0.02–0.20; OR of larynx cancer: 0.06, 95% CI: 0.02–0.19), and legumes (OR of cancer of the oral cavity and pharynx: 0.05, 95% CI:

0.01–0.25; OR of larynx cancer: 0.02, 95% CI: 0.01–0.11) was significantly associated with a lower risk of larynx as well as oral cavity and pharynx cancers. Decreased meat consumption was associated with a decreased risk of larynx cancer (OR: 0.53, 95% CI: 0.29–0.98), but not with a decreased risk of cancer of the oral cavity and pharynx (OR: 0.81, 95% CI: 0.43–1.54). In comparison with heavy drinkers, the OR for oral cavity and pharynx cancer was 0.12 (95% CI: 0.06–0.25) for nondrinkers or light drinkers and 0.19 (95% CI: 0.11–0.33) for moderate drinkers, and that for larynx cancer was 0.18 (95% CI: 0.09–0.37) for nondrinkers or light drinkers and 0.33 (95% CI: 0.20–0.55) for moderate drinkers.

Table 1 Characteristics of the 500 head and neck cancer cases and 433 controls

	n (%)	
Characteristics	Cases ($n=500$)	Controls ($n=433$)
Sex		
Male	402 (80.4)	254 (58.7)
Female	98 (19.6)	179 (41.3)
Age (years)		
< 60	169 (33.9)	205 (47.5)
60–64	91 (18.3)	50 (11.6)
65–69	94 (18.9)	50 (11.6)
70–74	68 (13.7)	51 (11.8)
≥ 70	76 (15.3)	76 (17.6)
Missing	2 (0.4)	1 (0.2)
Cigarette smoking status		
Never	75 (15.1)	237 (54.7)
Former	196 (39.4)	103 (23.8)
Current	226 (45.5)	93 (21.5)
Missing	3 (0.6)	0 (0.0)
Years of smoking		
Never	75 (15.8)	237 (55.8)
≤ 10	12 (2.5)	44 (10.4)
11–20	52 (11.0)	52 (12.2)
21–30	105 (22.2)	34 (8.0)
31–40	104 (21.9)	28 (6.6)
> 40	126 (26.6)	30 (7.1)
Missing	26 (5.2)	8 (1.8)
Number of cigarettes per day		
Nonsmoker	75 (15.2)	237 (55.6)
≤ 10	59 (12.0)	71 (16.7)
11–20	190 (38.6)	77 (18.1)
21–30	72 (14.6)	22 (5.2)
31–40	61 (12.4)	13 (3.1)
> 40	35 (7.1)	6 (1.4)
Missing	8 (1.6)	7 (1.6)
Alcohol drinking status		
Never	110 (22.0)	195 (45.0)
Former	22 (4.4)	8 (1.8)
Current	367 (73.5)	230 (53.1)
Missing	1 (0.2)	0 (0.0)
Drinks per day		
Never	110 (22.0)	195 (45.0)
< 1	35 (7.0)	70 (16.2)
1–2	158 (31.7)	130 (30.0)
> 2	196 (39.3)	38 (8.8)
Missing	1 (0.2)	0 (0.0)

The percentages of valid cases for each variable are computed based on just the total number of non-missing cases.

Table 4 reports the ORs of HNC according to the MDS in strata of selected covariates. For both cancers, the protective effect of MD on HNC did not differ by sex; however, it mostly increased with age. When stratifying by tobacco smoking, the protective effect was more pronounced among current smokers than among never smokers. For oral and pharyngeal cancer, the ORs for a 1-point increment in the score were 0.47 (95% CI: 0.26–0.87) among never smokers, 0.33 (95% CI: 0.18–0.60) among former smokers, and 0.13 (95% CI: 0.06–0.28) among current smokers ($P_{\text{heterogeneity}}=0.035$). For larynx cancer, the ORs for a 1-point increment in the score were 0.84 (95% CI: 0.35–2.05) among never smokers, 0.33 (95% CI: 0.19–0.57) among former smokers, and 0.25 (95% CI: 0.14–0.44) among current smokers ($P_{\text{heterogeneity}}=0.078$). Appreciable heterogeneity was also detected across strata of smoking intensity for both cancer of the oral cavity and pharynx and cancer of the larynx ($P_{\text{heterogeneity}}=0.103$ and 0.062, respectively), with a stronger inverse association for heavy smokers. There was no difference in the effect of adherence to the MD pattern on the risk of both oral and pharyngeal and laryngeal cancers when different strata of alcohol consumption were considered. However, appreciable heterogeneity was observed across strata of alcohol consumption for laryngeal cancer ($P_{\text{heterogeneity}}=0.096$), with a stronger inverse association for heavy drinkers.

Discussion

We report that higher adherence to MD protects against the development of HNC. In particular, we found that (i) high consumption of fruit, vegetables, and legumes is associated with a decreased risk of oral and pharyngeal,

Table 2 Distribution of age and selected risk factors by categories of the Mediterranean diet score among cases and controls

	Cases			Controls		
MDS[a]	0–4	5–7	> 7	0–4	5–7	> 7
Number of participants [*n* (%)]	275 (55)	203 (40.6)	22 (4.4)	140 (32.3)	252 (58.2)	41 (9.5)
Age (years)	62.5 (11.1)	63.3 (11.5)	68.8 (10.8)	56.2 (16.2)	60.2 (15.8)	59.1 (16.5)
Current cigarette smokers	53.1	38.4	13.6	22.1	20.2	26.8
Heavy smokers[b]	40.6	27.0	19.0	9.6	7.2	25.0
Heavy drinkers[c]	60.0	15.3	0.0	15.7	5.2	7.3

Values are expressed as mean (SD) or percentage.
MDS, Mediterranean diet score.
[a]The MDS, which ranges from 0 (minimal adherence) to 12 (maximal adherence), was categorized into three groups: 0–4, 5–7, and 8–12 points.
[b]Heavy smokers were defined as those smoking more than 20 cigarettes/day.
[c]Heavy drinkers were defined as those consuming more than 2 drinks/day.

Table 3 Odds ratios and 95% confidence intervals for oral and pharyngeal, laryngeal, and HNC overall cancers according to six dietary components included in the Mediterranean diet score

Dietary components[a]	Participants *n* (%)	OR[b] (95% CI) Oral cavity and pharynx	OR[b] (95% CI) Larynx	OR[b] (95% CI) Total
Fruit score				
0	60 (8.3)	1.00	1.00	1.00
1	518 (71.9)	0.68 (0.44–1.06)	1.23 (0.78–1.95)	0.94 (0.65–1.37)
2	142 (19.7)	0.09 (0.04–0.25)	0.10 (0.03–0.30)	0.10 (0.04–0.22)
Vegetables score				
0	43 (6.0)	1.00	1.00	1.00
1	412 (57.5)	0.23 (0.08–0.71)	0.18 (0.06–0.58)	0.21 (0.09–0.49)
2	261 (36.5)	0.06 (0.02–0.20)	0.06 (0.02–0.19)	0.06 (0.03–0.15)
Legumes score				
0	55 (19.7)	1.00	1.00	1.00
1	109 (39.1)	0.32 (0.13–0.80)	0.37 (0.13–1.03)	0.43 (0.19–0.96)
2	115 (41.2)	0.05 (0.01–0.25)	0.02 (0.01–0.11)	0.06 (0.01–0.23)
Fish score[c]				
0	29 (10.0)	1.00	1.00	1.00
1	132 (45.7)	0.59 (0.33–1.04)	1.11 (0.59–2.10)	0.82 (0.50–1.36)
2	128 (44.3)	0.46 (0.17–1.23)	0.61 (0.21–1.82)	0.52 (0.22–1.23)
Meat score				
0	84 (12.7)	1.00	1.00	1.00
1	26 (3.9)	1.67 (0.60–4.67)	1.17 (0.39–3.52)	1.35 (0.55–3.33)
2	552 (83.4)	0.81 (0.43–1.54)	0.53 (0.29–0.98)	0.65 (0.39–1.10)
Alcohol score				
0	239 (32.7)	1.00	1.00	1.00
1	339 (46.4)	0.12 (0.06–0.25)	0.18 (0.09–0.37)	0.16 (0.09–0.29)
2	153 (20.9)	0.19 (0.11–0.33)	0.33 (0.20–0.55)	0.29 (0.19–0.45)
MDS (as continuous)		0.61 (0.54–0.70)	0.64 (0.56–0.73)	0.64 (0.58–0.71)

CI, confidence interval; HNC, head and neck cancer; OR, odds ratio.
[a]For fruit, vegetables, legumes, and fish, 2 points were assigned to the highest category of consumption, 1 point for the middle category, and 0 point for the lowest category. Conversely, for meat 2 points were assigned for the lowest category, 1 point for the middle category, and 0 point for the highest category of consumption. For alcohol (1 alcohol unit = 12 g of alcohol), 2 points were assigned to the middle category (1–2 alcohol units/day), 1 point to the lowest category (< 1 alcohol unit/day), and 0 point to the highest category of consumption (>2 alcohol units/day).
[b]Estimates from logistic regression adjusted for age, sex, tobacco smoking, alcohol drinking, and total energy intake.
[c]More than 5% of data were missing.

Table 4 Odds ratios and 95% confidence intervals for oral and pharyngeal, laryngeal, and head and neck overall cancers according to the Mediterranean diet score in the strata of selected covariates

	Oral cavity and pharynx		Larynx		HNC	
	OR[a] (95% CI)	*P* for heterogeneity	OR[a] (95% CI)	*P* for heterogeneity	OR[a] (95% CI)	*P* for heterogeneity
Sex						
Male	0.27 (0.18–0.43)	0.794	0.33 (0.22–0.48)	0.610	0.35 (0.25–0.49)	0.714
Female	0.30 (0.16–0.57)		0.26 (0.12–0.60)		0.31 (0.18–0.54)	
Age (years)						
< 60	0.43 (0.26–0.72)	0.033	0.51 (0.29–0.88)	0.211	0.49 (0.32–0.76)	0.074
60–64	0.05 (0.01–0.28)		0.25 (0.10–0.61)		0.18 (0.07–0.45)	
65–69	0.44 (0.16–1.21)		0.27 (0.01–0.74)		0.37 (0.16–0.84)	
70–74	0.19 (0.06–0.59)		0.20 (0.07–0.55)		0.24 (0.11–0.56)	
≥ 75	0.09 (0.03–0.33)		0.16 (0.06–0.44)		0.15 (0.07–0.36)	
Cigarette smoking status						
Never	0.47 (0.26–0.87)	0.035	0.84 (0.35–2.05)	0.078	0.55 (0.32–0.93)	0.043
Former	0.33 (0.18–0.60)		0.33 (0.19–0.57)		0.36 (0.22–0.57)	
Current	0.13 (0.06–0.28)		0.25 (0.14–0.44)		0.21 (0.12–0.36)	
Number of cigarettes per day						
Nonsmoker	0.47 (0.26–0.87)	0.103	0.84 (0.35–2.05)	0.062	0.55 (0.32–0.93)	0.035
1–20	0.26 (0.15–0.46)		0.38 (0.23–0.60)		0.28 (0.20–0.39)	
> 20	0.15 (0.06–0.37)		0.22 (0.11–0.43)		0.20 (0.11–0.38)	
Alcohol drinking status						
Never	0.39 (0.21–0.75)	0.192	0.32 (0.16–0.63)	0.875	0.36 (0.22–0.60)	0.567
Former	nc		nc			
Current	0.23 (0.14–0.36)		0.30 (0.20–0.46)		0.30 (0.20–0.43)	
Drinks per day						
< 1	0.21 (0.05–0.82)	0.675	0.86 (0.24–3.12)	0.096	0.44 (0.16–1.21)	0.382
1–2	0.37 (0.17–0.78)		0.42 (0.22–0.78)		0.43 (0.25–0.75)	
>2	0.23 (0.08–0.70)		0.14 (0.04–0.43)		0.20 (0.08–0.53)	

CI, confidence interval; HNC, head and neck cancer; OR, odds ratio.
[a]Estimates from logistic regression adjusted for age, sex, tobacco smoking, alcohol drinking, and total energy intake.
nc, not computable.

and laryngeal cancer; (ii) low meat consumption is associated with a decreased risk of laryngeal cancer; and (iii) moderate alcohol consumption is associated with a decreased risk of both oral and pharyngeal, and laryngeal cancers compared with high alcohol consumption. The association between adherence to the Mediterranean dietary pattern and the risk of HNC appeared to be stronger for smokers.

Several meta-analyses have previously reported MD to markedly reduce the risk of cancer (Sofi *et al.*, 2008, 2010; Schwingshackl and Hoffmann, 2014, 2015). Dietary factors may influence cancer susceptibility through several mechanisms, such as suppression of spontaneous mutations, affecting cell proliferation and the methylation of DNA and induction of apoptosis (Cummings and Bingham, 1998). It has been reported that the phenolic content of olive oil, one of the principal components of MD, can specifically affect cancer-regulated oncogenes (Sotiroudis and Kyrtopoulos, 2008). Furthermore, phenolic compounds present in extra virgin olive oil may exert chemopreventive effects through direct antioxidant effects and actions on cancer cell signaling and cell-cycle progression (Corona *et al.*, 2009). The protective effect of high consumption of fruits and vegetables may be explained through the biological effects of flavonoids, including antioxidant activity, inhibition of inflammation, antimutagenic, and antiproliferative properties as well as involvement in cell signaling, cell-cycle regulation, and angiogenesis (Arts and Hollman, 2005). In addition, MD is characterized by low intake of red meat, reported to significantly influence the risk of several cancer types (Xu *et al.*, 2013; Song *et al.*, 2014; Zhu *et al.*, 2014).

Adherence to MD was reported to be associated with a significantly lower risk of colorectal cancer, breast cancer, prostate cancer, gastric cancer, and liver cancer (Schwingshackl and Hoffmann, 2015). However, there is limited evidence on the role of MD in HNC prevention. Three case–control and one cohort study have so far addressed the impact of MD on the risk of HNC. Bosetti *et al.* (2003) reported that higher adherence to MD significantly decreases the risk of oral and pharyngeal and laryngeal cancer (by 23 and 29%, respectively). Samoli *et al.* (2010) found that adherence to the traditional MD is associated with a reduced risk of cancers of the oral cavity and oropharynx, larynx, and esophagus, collectively called upper aerodigestive tract cancers. More recently, Filomeno *et al.* (2014) reported strong evidence of a beneficial role of the MD in oral and pharyngeal cancer prevention (by 27%). The only cohort study published so far that has prospectively evaluated the association between MD pattern and the risk of HNC reported a significant reduction in the risk of HNC associated with a high score of MD adherence (Li *et al.*, 2014). Adherence to the MD has been associated not only with a decreased risk of HNC but also with a reduction in the overall risk of HNC mortality by 60% (Schwingshackl and Hoffmann, 2015).

With reference to the effect of the specific components of the MD, our findings are consistent with the evidence from a review on diet and oral and pharyngeal cancer and from a large case–control study on diet and upper aerodigestive tract, where a high intake of fruit and vegetables has been linked to a lower risk of HNC, whereas a high intake of red meat and alcohol has been related to an increased risk (Lagiou *et al.*, 2009; Lucenteforte *et al.*, 2009). Several epidemiological studies have also examined the association between consumption of fish and the risk of HNC, with conflicting results (Wiseman, 2008; Lucenteforte *et al.*, 2009).

Further, we investigated the association between MD and HNC, specifically comparing results obtained in nonsmokers and smokers, as well as in nondrinkers and drinkers (Toporcov *et al.*, 2012). A strong protective effect was observed in heavy tobacco consumers. Similarly, in a large European study, the association between adherence to the Mediterranean dietary pattern and the risk of cancer appeared to be stronger for smokers and smoking-related cancers (Couto *et al.*, 2011). Although residual confounding may be considered a candidate among potential explanations (Stram *et al.*, 2002), this reinforces the hypothesis that the protective effect of the MD on the risk of HNC is real because of its antioxidant properties (Couto *et al.*, 2011).

Our analysis had several strengths. The large number of cases enabled us to examine associations within subgroups of the study population with adequate statistical power. The response rate was high, for both cases and controls, thereby minimizing any potential selection bias. We could also adequately adjust for the potential confounding effects of demographic information and other risk factors, such as tobacco smoking and alcohol drinking.

The limitations of our study include potential biases of hospital-based case–control studies and especially recall bias. Disease may have affected food habits; participants could not recall their diet accurately before the cancer really started. However, we investigated dietary habits 1 year before cancer diagnosis to minimize bias. It is also possible that the dietary habits of hospital controls may have differed from those of the general population. Moreover, we used a food frequency questionnaire to ascertain adherence to a MD and the major limitation of the food frequency method is that it may have considerable measurement errors (Thiebaut *et al.*, 2007). Finally, information was not available for three out of nine components of the traditional MD: cereals, dairy products, and olive oil.

In conclusion, in the present case–control study, high adherence to MD protects against the development of

HNC, and more so among smokers than among never smokers.

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Conflicts of interest

There are no conflicts of interest.

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