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Short Communication

Dietary intakes of carotenoids and other nutrients in the risk of nasopharyngeal carcinoma: a case–control study in Italy

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BACKGROUND: Dietary habits have been related to the risk of nasopharyngeal carcinoma (NPC), but information on a wide range of macro- and micronutrients is still lacking, particularly for low-incidence countries.

METHODS: We conducted a hospital-based case–control study in Italy on 198, histologically confirmed, NPC cases of Caucasian ethnicity of 18–76 years of age. Controls were 594 Caucasian cancer-free patients admitted to general hospitals for acute conditions. Nutrients intake was assessed through a validated food-frequency questionnaire. Adjusted odds ratios (ORs) and the corresponding confidence intervals (CIs) were estimated through logistic regression.

RESULTS: Dietary intake of carotenoids were inversely related to NPC risk, notably carotene (OR for highest *vs* lowest quartile = 0.46; 95% CI: 0.26–0.79), α-carotene (OR = 0.57; 95% CI: 0.33–0.97), and β-carotene (OR = 0.42; 95% CI: 0.24–0.75). Increased NPC risk was observed for elevate cholesterol intake (OR = 1.85; 95% CI: 1.12–3.05).

CONCLUSION: Study findings suggest a protective effect of carotenoids against NPC in a low-risk population, adding further support to a possible beneficial role of a diet rich in fruits and vegetables in cancers of the head and neck.

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Incidence rates of nasopharyngeal carcinoma (NPC) show wide geographic variations, being 40-fold more frequent in endemic areas than in Europe and North America (Chang and Adami, 2006). This remarkable heterogeneity may be partly explained by differences in the age at first infection with the Epstein–Barr virus (EBV) (Chang and Adami, 2006), the main cause of undifferentiated NPC. However, the ubiquity of EBV suggests that other risk factors may have a role in NPC aetiology. Notably, well-established risk factors for other head and neck carcinomas (i.e., tobacco smoking and alcohol drinking) appear to have a stronger causal role in NPC in low-incidence compared with high-incidence populations including the Italian one (Polesel *et al*, 2011).

So far, the relationship between NPC risk and diet was investigated in NPC high-risk areas (World Cancer Research Fund/American Institute for Cancer Research, 2007) and in the United States (Farrow *et al*, 1998, Kasum *et al*, 2002). However, only three studies considered specific food constituents (Lee *et al*, 1994, Farrow *et al*, 1998, Kasum *et al*, 2002), reporting inverse associations for fibre, vitamin C, vitamin E, and β-carotene. These findings matched the World Cancer Research Fund/American Institute for Cancer Research (2007) revision, which concluded that the evidence, although sparse, was generally consistent in showing a negative association with non-starchy vegetables and fresh fruits.

This study investigated the relation between NPC and a wide range of macro- and micronutrients in Italy, a southern European country where NPC is rare.

MATERIALS AND METHODS

Between 1992 and 2008, we conducted a case–control study on NPC within an established network of collaborating centres, including Aviano (Pordenone) and Milan in northern Italy, and Naples and Catania in southern Italy (Polesel *et al*, 2011). Study subjects were 198 Caucasian cases, aged 18–76 years (median age: 52 years), admitted for incident and histologically confirmed NPC to major general hospitals in the study areas. They included 137 (68.5%) undifferentiated NPCs (Shanmugaratnam and Sobin, 1991), 23 (11.5%) keratinising squamous cell carcinomas (here referred to as differentiated NPCs), and 40 (20%) not otherwise specified NPCs. EBV status was available for 61 NPC cases based on the detection of EBV nuclear antigen in tissue samples. All 57 undifferentiated NPCs and two out of four differentiated NPCs were EBV-positive.

Three controls were frequency-matched to each case, according to sex, age, and place of residence. The control group included 594

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Caucasian patients (aged 19–76 years; median age: 52 years) admitted for a wide spectrum of acute conditions to the same hospitals as cases. Controls were admitted for traumatic orthopaedic disorders (34%), other orthopaedic disorders (32%), acute surgical conditions (22%), and miscellaneous other illnesses (12%). Otherwise, controls admitted for malignant neoplasms, conditions related to tobacco smoking or alcohol consumption, or any other disorder associated to long-term modification of diet were not eligible for this study. All study participants signed an informed consent, according to the recommendations of the Internal Review Boards of each study hospital.

Trained interviewers administered a structured questionnaire to cases and controls during their hospital stay, thus keeping refusal below 3%. The questionnaire collected information on socio-demographic factors, lifestyle habits, smoking and drinking habits, a problem-oriented medical history, and family history of cancer. Usual diet during the two years before interview was investigated through a food-frequency questionnaire specifically targeting the Italian population, including 78 foods or recipes. Subjects were asked to indicate the average weekly consumption of several dietary items. Serving size was defined either in 'natural' units (e.g., one teaspoon of sugar, one egg, one medium apple) or as an average serving in the Italian diet (e.g., 80 g serving of pasta, 150 g of red meat, 100 g of salad). The questionnaire was successfully tested for reproducibility (Franceschi *et al*, 1993) and validity (Decarli *et al*, 1996) on a sample of the healthy general population in the study areas. Nutrient supplementation was not assessed in the present study, but it was generally uncommon in the Italian population (Skeie *et al*, 2009).

Energy and specific nutrient intakes were estimated using an Italian food composition database (Gnagnarella *et al*, 2004). To evaluate the role of the nutrients independently of total energy intake, energy-adjusted nutrients were derived by residual method (Willett and Stampfer, 1998). The energy-adjusted nutrients were categorised into approximate quartiles according to the distribution among controls; the corresponding odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression models (Breslow and Day, 1980), adjusting for centre, sex, age, education, place of living, year of interview, non-alcohol energy, and possible confounders (i.e., tobacco smoking and alcohol drinking; Table 1). Results were presented only for major macronutrients, according to animal or vegetal source, and for the most common micronutrients. The test for linear trend was based on the likelihood-ratio test between the models with and without linear terms for each variable of interest (Breslow and Day, 1980).

Table 1 Distribution of 198 cases of nasopharyngeal cancer and 594 controls, according to socio-demographic characteristics and selected variables

	Cases *N* (%)	Controls *N* (%)	
Centre[a]			
Aviano	150 (75.8)	450 (75.8)	
Milan	48 (24.2)	144 (24.2)	
Sex[a]			
Men	157 (79.3)	471 (79.3)	
Women	41 (20.7)	123 (20.7)	
Age (years)[a]			
<44	52 (26.3)	159 (26.7)	
45–54	64 (32.3)	186 (31.3)	
55–64	47 (23.7)	144 (24.2)	
⩾65	35 (17.7)	105 (17.7)	
Place 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)	
χ^2			1.65; $P=0.44$
Smoking habits[b]			
Never	60 (30.6)	196 (33.0)	
Former	60 (30.6)	181 (30.5)	
Current (cigarettes per day)			
<15	21 (10.7)	78 (13.1)	
⩾15	55 (28.1)	139 (23.4)	
χ^2			5.97; $P=0.05$
Alcohol drinking (drinks per week)			
<14	72 (36.4)	235 (40.3)	
14–20	39 (19.7)	149 (25.1)	
⩾21	87 (43.9)	210 (35.4)	
χ^2			5.12; $P=0.07$
Total energy (kCal per day)			
<2070	36 (18.2)	162 (27.3)	
2070 to <2506	43 (21.7)	154 (25.9)	
2506 to <3030	53 (26.7)	146 (24.6)	
⩾3030	66 (33.3)	132 (22.2)	
χ^2			15.41; $P<0.01$

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

RESULTS

NPC risk was positively associated with intake of cholesterol (OR for highest *vs* lowest quartile = 1.85; 95% CI: 1.12–3.05; *P*-trend = 0.01) and saturated fatty acids (OR = 1.75; 95% CI: 1.04–2.95), although the trend in risk for the latter was of borderline significance (*P*-trend = 0.07) (Table 2). The association with animal fat intake was of borderline statistical significance (OR = 1.58; 95% CI: 0.96–2.61; *P*-trend = 0.07). No association emerged for other macronutrients.

NPC risk was negatively associated to carotenoids intake (Table 3), notably carotene (OR = 0.46; 95% CI: 0.26–0.79; *P*-trend < 0.01), α-carotene (OR = 0.57; 95% CI: 0.33–0.97), and β-carotene (OR = 0.42; 95% CI: 0.24–0.75). Vitamin C intake was also negatively associated with NPC risk (OR = 0.62; 95% CI: 0.37–1.04; *P*-trend = 0.06), though of borderline significance. Likewise, the results suggested a direct association between elevated phosphorus intake and NPC risk (OR = 1.80; 95% CI: 1.06–3.05). Other water-soluble vitamins, minerals, fat-soluble vitamins, and glutathione were not significantly related to NPC risk (Table 3).

Dietary findings were similar when analyses were stratified by alcohol drinking and cigarette smoking (data not shown), as well as when undifferentiated NPCs were assessed separately (ORs for highest *vs* lowest quartile were 2.14 for cholesterol, 0.61 for vitamin C, 0.48 for carotene, 0.73 for α-carotene, and 0.44 for β-carotene).

DISCUSSION

This study investigated the association between macro- and micronutrients, and the risk of NPC in a southern European population. High intake of cholesterol was associated to increased NPC risk and so was intake of animal fats and saturated fatty acids (borderline statistical significance). Conversely, intake of carotenoids, particularly α-carotene and β-carotene, were negatively associated to NPC risk. Our study findings are consistent with previous work on the topic, showing a negative association between NPC risk and orange/yellow/red pigmented

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Table 2 Energy-adjusted OR for NPC and corresponding 95% CI,[a] according to intake of selected macronutrients, fatty acids, and cholesterol

Nutrient	Quartile, OR (95% CI)				χ^2-trend	Continuous OR (95% CI)[c]
	I[b]	II	III	IV		
Macronutrients						
Animal proteins	1	1.20 (0.70–2.04)	1.36 (0.81–2.29)	1.54 (0.93–2.54)	$P=0.08$	1.28 (1.01–1.61)
Vegetal proteins	1	1.01 (0.62–1.64)	0.94 (0.57–1.56)	0.80 (0.48–1.33)	$P=0.39$	0.77 (0.56–1.06)
Animal fats	1	1.03 (0.60–1.75)	1.02 (0.59–1.76)	1.58 (0.96–2.61)	$P=0.07$	1.43 (1.12–1.83)
Vegetal fats	1	1.17 (0.70–1.95)	1..27 (0.77–2.10)	0.82 (0.50–1.36)	$P=0.54$	0.82 (0.66–1.04)
Sugars	1	1.20 (0.73–1.98)	0.92 (0.55–1.54)	1.09 (0.67–1.78)	$P=0.99$	1.00 (0.81–1.25)
Starch	1	1.56 (0.94–2.57)	1.34 (0.81–2.22)	1.13 (0.67–1.89)	$P=0.74$	0.88 (0.66–1.17)
Fatty acids and cholesterol						
Saturated fatty acids	1	1.55 (0.91–2.65)	1.35 (0.78–2.32)	1.75 (1.04–2.95)	$P=0.07$	1.44 (1.08–1.92)
Monounsaturated fatty acids	1	1.04 (0.61–1.77)	1.07 (0.63–1.82)	0.98 (0.59–1.60)	$P=0.93$	0.91 (0.71–1.16)
Polyunsaturated fatty acids	1	0.94 (0.56–1.58)	1.21 (0.71–2.04)	1.11 (0.66–1.87)	$P=0.54$	0.96 (0.77–1.20)
Cholesterol[d]	1	1.11 (0.65–1.89)	1.13 (0.65–1.94)	1.85 (1.12–3.05)	$P=0.01$	1.40 (1.08–1.81)

Abbreviations: CI = confidence interval; NPC = nasopharyngeal carcinoma; OR = odds ratio. [a]Estimated by unconditional logistic regression model, adjusted for centre, sex, age, place of living, year of interview, education, tobacco smoking, alcohol drinking, and non-alcohol energy. Adjustment for energy was made according to residual model. [b]Reference category. [c]The OR was estimated for an increase equals to 1 s.d. among controls [d]Estimated from food of animal or mixed origin.

Table 3 Energy-adjusted OR for NPC and corresponding 95% CI,[a] according to intake of selected minerals, vitamins, carotenoids, and glutathione

Nutrient	Quartile, OR (95% CI)				χ^2-trend	Continuous OR (95% CI)[c]
	I[b]	II	III	IV		
Minerals						
Calcium	1	1.49 (0.87–2.54)	1.94 (1.13–3.33)	1.64 (0.95–2.81)	$P=0.06$	1.27 (1.04–1.55)
Sodium	1	0.98 (0.60–1.60)	1.02 (0.61–1.69)	1.33 (0.80–2.19)	$P=0.29$	1.13 (0.86–1.49)
Potassium	1	0.88 (0.54–1.43)	0.84 (0.50–1.40)	0.79 (0.48–1.29)	$P=0.34$	0.95 (0.73–1.25)
Phosphorus	1	2.08 (1.22–3.54)	1.24 (1.72–2.16)	1.80 (1.06–3.05)	$P=0.17$	1.37 (1.02–1.83)
Iron	1	0.91 (0.56–1.49)	0.79 (0.46–1.37)	0.71 (0.39–1.30)	$P=0.24$	0.91 (0.68–1.22)
Zinc	1	0.98 (0.59–1.63)	0.92 (0.55–1.53)	1.14 (0.70–1.84)	$P=0.66$	1.13 (0.82–1.57)
Water-soluble vitamins						
Thiamine	1	0.94 (0.57–1.55)	0.80 (0.48–1.33)	1.08 (0.66–1.76)	$P=0.91$	1.09 (0.81–1.46)
Riboflavin	1	1.32 (0.79–2.19)	0.88 (0.52–1.50)	1.34 (0.80–2.23)	$P=0.55$	1.17 (0.93–1.48)
Vitamin C	1	1.04 (0.64–1.70)	0.89 (0.54–1.46)	0.62 (0.37–1.04)	$P=0.06$	0.88 (0.72–1.07)
Vitamin B6	1	0.79 (0.47–1.31)	0.90 (0.55–1.48)	0.90 (0.56–1.46)	$P=0.79$	0.94 (0.71–1.24)
Folate	1	0.81 (0.50–1.31)	0.87 (0.53–1.43)	0.68 (0.41–1.12)	$P=0.18$	0.89 (0.71–1.13)
Niacin	1	0.92 (0.56–1.53)	0.97 (0.58–1.61)	1.02 (0.62–1.68)	$P=0.89$	0.94 (0.74–1.20)
Fat-soluble vitamins, carotenoids, and glutathione						
Retinol	1	1.14 (0.68–1.92)	0.87 (0.52–1.48)	1.02 (0.62–1.67)	$P=0.82$	1.01 (0.85–1.21)
Carotene	1	1.02 (0.63–1.63)	0.70 (0.42–1.15)	0.46 (0.26–0.79)	$P<0.01$	0.73 (0.59–0.91)
α-carotene	1	1.26 (0.77–2.06)	0.87 (0.52–1.44)	0.57 (0.33–0.97)	$P=0.02$	0.74 (0.60–0.90)
β-carotene	1	1.03 (0.64–1.64)	0.67 (0.41–1.11)	0.42 (0.24–0.75)	$P<0.01$	0.74 (0.60–0.92)
β-criptoxanthin	1	1.36 (0.83–2.25)	1.24 (0.74–2.08)	1.09 (0.65–1.82)	$P=0.85$	0.92 (0.75–1.12)
Luthein/Zeaxanthin	1	0.82 (0.50–1.35)	0.79 (0.48–1.32)	0.69 (0.40–1.19)	$P=0.19$	0.89 (0.72–1.10)
Lycopene	1	1.40 (0.85–2.30)	1.28 (0.78–2.12)	1.05 (0.63–1.74)	$P=0.93$	0.97 (0.80–1.18)
Vitamin D	1	1.31 (0.78–2.22)	0.98 (0.58–1.67)	1.62 (0.99–2.66)	$P=0.12$	1.15 (0.96–1.38)
Vitamin E	1	0.80 (0.49–1.31)	0.86 (0.53–1.40)	0.69 (0.42–1.14)	$P=0.19$	0.80 (0.62–1.03)
Glutathione	1	0.74 (0.46–1.21)	0.62 (0.37–1.03)	0.73 (0.44–1.22)	$P=0.16$	0.84 (0.67–1.05)
Reduced glutathione	1	0.74 (0.46–1.20)	0.60 (0.36–1.00)	0.72 (0.44–1.19)	$P=0.13$	0.84 (0.67–1.05)

Abbreviations: CI = confidence interval; NPC = nasopharyngeal carcinoma; OR = odds ratio. [a]Estimated by unconditional logistic regression model, adjusted for centre, sex, age, place of living, year of interview, education, tobacco smoking, alcohol drinking, and non-alcohol energy. Adjustment for energy was made according to residual model. [b]Reference category. [c]The OR was estimated for an increase equals to 1 s.d. among controls.

vegetables (i.e., carotenoid-rich foods) (Armstrong *et al*, 1998; Yaun *et al*, 2000; Kasum *et al*, 2002).

An inverse association between carotenoids intake and cancer risk was consistently reported for other epithelial cancers of the aero-digestive tract, such as mouth, pharynx, larynx, oesophagus, and lung (World Cancer Research Fund/American Institute for Cancer Research, 2007). Carotenoids are well-known antioxidants with anti-mutagenic and immune-regulatory actions (Krinsky, 1991; Chew and Park, 2004).

Elevated dietary cholesterol has been associated to excess risk of several cancers (Hu *et al*, 2011). Mechanisms have been proposed to explain the possible role of cholesterol in cancer development, including cellular inflammation due to alterations in lipid and apolipoprotein levels (Ferretti *et al*, 2006), and increased levels of proinflammatory cytokines (Haddy *et al*, 2003). However, the present results should be interpreted with caution, as no information on different serum lipoproteins were available for our study, and elevated cholesterol intake could be an indicator

that a diet rich in meat, eggs, and dairy products may have unfavourable effects.

The lack of information on EBV status in the majority of NPC cases was a weakness of the present study. In the subset of cases with available EBV information, all undifferentiated NPCs were EBV-positive, suggesting that EBV should not be considered a confounder. In addition, when we assessed EBV-related undifferentiated NPCs separately, similar associations emerged with intake of carotenoids and cholesterol, as in the overall analyses.

The ability of food-frequency questionnaires to estimate circulating nutrient levels is an additional concern in a dietary study. However, the results from the EPIC study suggested that intakes of specific food items as measured by questionnaires are good predictors of plasma concentrations of some nutrients, carotenoids in particular (Al-Delaimy *et al*, 2005).

Other potential limitations of this study include the relatively small sample size, and possible information and selection biases. Because of the rarity of NPC in Italy, yielding an adequate sample size in a reasonable length of time was a challenge. *Vis-a-vis* interview of cases and controls by the same trained interviewers, under similar conditions in a hospital setting, minimised information bias. Careful attention was also paid to exclude from the control group subjects admitted for any condition that might have induced modification of the usual diet. In addition, the almost complete case ascertainment in the catchment areas, the nearly complete participation of identified cases and controls, and the use of a validated and reproducible questionnaire (Franceschi *et al*, 1993; Decarli *et al*, 1996) contributed to strengthen our findings.

In conclusion, our investigation revealed a protective effect of carotenoids against NPC in low-incidence populations, supporting the beneficial role of a diet rich in fruits and vegetables in head and neck cancers. Similar results on β-carotene were reported in Singapore Chinese (Lee *et al*, 1994), suggesting that our findings could be extended to populations at high risk for NPC.

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Conflict of interest

The authors declare no conflict of interest.

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