

Folate intake and risk of oral and pharyngeal cancer

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Background: Diet has been recognised as having a role in the aetiology of oral and pharyngeal cancer, and dietary factors may account for 10–15% of cases in Europe. Folate deficiency has been linked to risk of several cancers, but has not been studied adequately with respect to oral cancer.

Patients and methods: This case–control study, conducted in Italy and French-speaking Switzerland, included 749 patients with incident cancer of the oral cavity and pharynx, and 1772 hospital controls with acute, non-neoplastic conditions. The interviews used a validated food frequency questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using multiple logistic regression.

Results: The ORs were 0.68 (95% CI 0.52–0.88) for the intermediate tertile and 0.53 (95% CI 0.40–0.69) for the highest tertile of dietary folate intake, compared with the lowest tertile. No heterogeneity was found in strata of gender, age, methionine intake or alcohol consumption. The combined OR for low-folate and high-alcohol intake versus high-folate and low-alcohol intake was 22.3 (95% CI 13.1–38).

Conclusions: Our study supports a protective role of folate against oral and pharyngeal carcinogenesis. Compared with low folate intake, a consistent reduction in risk was already observed from intermediate levels of intake, suggesting that cancer risk may be related to relative folate deficiency.

Key words: alcohol, case–control study, diet, folate, oral and pharyngeal cancer

Introduction

The incidence rates of cancers of the mouth and pharynx are high in Southern Europe. These neoplasms are much more common in men than in women [1] in this part of the world in particular, due to the high prevalence of tobacco and alcohol use among men. Oral and pharyngeal cancer is strongly related to smoking and alcohol consumption and, in developed countries, the disease is rare in non-drinkers who do not smoke. Nevertheless, a role of diet has been recognised, and dietary factors may account for 10–15% of cases in Europe [2]. A high intake of fruit and vegetables has been linked with a lower risk of oral and pharyngeal cancer, whereas a poor nutritional status and an unbalanced diet have been related to an elevated risk [3, 4].

Folate deficiency has been linked to risk of cancer at several sites [5–7]. Several case–control and cohort studies have examined the relationship between dietary folate intake, or serum folate, and risk of colorectal, breast and other cancers [8, 9]. Many of them have found inverse associations, particularly for colorectal cancer [8–11]. Only a few studies, however, have considered the possible influence of folate on the risk of oral and pharyngeal cancer. No association was found in three case–

control studies from the USA [12], Central America [13] and South America [14], while an Italian study observed significantly lower serum folate levels in head and neck squamous-cell carcinoma patients than in smoking and non-smoking controls [15].

A combined effect of low folate, low methionine and high alcohol intake has been related to excess risk of colon cancer [11, 16, 17]. Folate is essential in the conversion of methionine to *S*-adenosylmethionine, the principal methyl donor in the body [6]. High alcohol consumption interferes with folate absorption and increases folate excretion by the kidney, and can therefore result in a decreased supply of folate [18, 19]. However, a study from Puerto Rico [13] found neither an association between methionine and risk of oral cancer, nor a systematic pattern of risk with respect to folate intake among non-drinkers and heavy drinkers.

To yield further information on the issue, we analysed data from a case–control study conducted in Italy and French-speaking Switzerland. Most subjects in these populations are regular drinkers, and consumption of fruit and vegetables is relatively high [20, 21]. Thus, these populations are particularly suitable for examining the possible relationship between folate and alcohol intake, and risk of oral and pharyngeal cancer.

Patients and methods

The present analysis is based on data from a case–control study of oral and pharyngeal cancer, conducted from 1992 to 1997, in two areas of Italy (the

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Table 1. Relationship between dietary folate and methionine intake, alcohol consumption and risk of oral and pharyngeal cancer among 749 cases and 1772 controls in Italy and Switzerland (1992–1997)

	Mean	SD	Approximated tertile ^a of intake			χ^2 trend	Continuous OR ^c
			1 (low)	2 (intermediate)	3 (high)		
Folate intake ($\mu\text{g}/\text{day}$)							
Cases:controls	281.3	89.7	302:537	249:594	198:641	21.50	
OR (95% CI) ^b			1	0.68 (0.52–0.88)	0.53 (0.40–0.69)	$P < 0.001$	0.67 (0.56–0.80)
Methionine intake (mg/day)							
Cases:controls	2189.2	706.5	222:617	249:594	278:561	0.96	
OR (95% CI) ^b			1	1.13 (0.87–1.48)	1.14 (0.87–1.50)	$P = 0.33$	1.08 (0.88–1.32)
Alcohol drinking (drinks/day)							
Cases:controls	3.3	4.0	96:830	156:605	495:335	227.10	
OR (95% CI) ^b			1	2.20 (1.60–3.03)	11.36 (8.12–15.89)	$P < 0.001$	2.19 (1.96–2.45)

^aFolate and methionine intake were energy adjusted using the residual method.

^bEstimates from unconditional logistic regression models adjusted for sex, age, study centre, education, body mass index, alcohol consumption, smoking habit and non-alcohol energy intake. The reference category was the first (lowest) tertile of intake.

^cThe measurement unit was set at 1 SD of the distribution of controls.

OR, odds ratio; CI, confidence interval; SD, standard deviation.

provinces of Pordenone in north-eastern Italy, and Rome and Latina in central Italy) and in the Swiss Canton of Vaud [22].

The study included 749 incident, histologically confirmed cases with cancer of the oral cavity and pharynx (634 men and 115 women), admitted to the major teaching and general hospitals in the areas under surveillance. Cancers of the lip, salivary glands and nasopharynx were not included. Cases ranged between 22 and 77 years of age (median 57 years). Controls comprised a total of 1252 men and 520 women, aged 20–78 years (median 57 years), admitted to the same network of hospitals for acute, non-neoplastic conditions not associated with smoking, alcohol or long-term dietary change. Patients were admitted for acute surgical conditions (29%), for non-alcohol-related traumas (mostly fractures and sprains) (23%), for other orthopaedic disorders (25%), and for other miscellaneous illnesses such as eye, ear, nose and throat, or skin diseases (23%). Less than 5% of cases and controls approached during their hospital stay refused to participate.

Data were collected by trained interviewers, using a structured questionnaire, including information on sociodemographic characteristics such as education and occupation, lifetime smoking and alcohol-drinking habits, physical activity, a problem-oriented personal medical history and family history of cancers.

An interviewer-administered food frequency questionnaire (FFQ) was developed to assess the usual diet during the 2 years preceding the diagnosis (for cases) or hospital admission (for controls), in order to estimate intake of total energy as well as that of selected nutrients. The questionnaire included 78 foods, food groups or dishes, divided into six sections: (i) bread, cereals, first courses; (ii) second courses (i.e. meat, fish and other main dishes); (iii) side dishes (i.e. vegetables); (iv) fruits; (v) sweets, desserts and soft drinks; and (vi) milk, hot beverages and sweeteners. For a few vegetables and fruits, seasonal consumption and the corresponding duration were elicited. At the end of each section, one or two open questions were used to include foods that were not included in the questionnaire, but that were eaten at least once per week. There were a few differences in the dietary items listed in the Italian and Swiss versions of the questionnaire, to account for different eating and drinking patterns. Dietary supplementation was not considered, given the low frequency of use by these populations. Information from the FFQ was managed using a specifically developed SAS programme to avoid any disproportion. Such data were, whenever possible, corrected, or otherwise treated as missing values. If information on a dietary item was missing, we substituted it with the median

value of consumption of the item, according to the relevant study centre. To compute energy and nutrient intake, including folate, *ad hoc*-developed food composition databases were used and integrated with other sources when necessary [23]. The FFQ was satisfactorily reproducible [24] and valid [25].

Odds ratios (OR) of oral and pharyngeal cancer and their corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression models [26], including terms for age, gender, study centre, education, body mass index, alcohol drinking and smoking habit. To adjust for non-alcohol energy intake, folate intake residuals were computed [27]. Thus, folate cut-off points do not express absolute frequencies of intake, and consequently do not provide information on levels of consumption. However, when the tertiles were computed with respect to the absolute intake of folate, the cut-off points were 235.9 $\mu\text{g}/\text{day}$ and 300.7 $\mu\text{g}/\text{day}$. Tertiles of folate, methionine and alcohol intake were based on the combined distribution of cases and controls. The significance of the linear trends in risk was assessed by comparing the differences between the deviances of the models, without and with a term for folate intake, to the χ^2 distribution with 1 degree of freedom [26]. To test for interactions, the differences in $-2 \times \log(\text{likelihood})$ of the models with and without interaction terms were compared with the χ^2 distribution with the same number of degrees of freedom as the interaction terms. When the variables were entered in the regression models, the measurement unit was set at 1 standard deviation (SD) of the distribution of controls.

Results

Table 1 shows the distribution of cases and controls, and the ORs of oral and pharyngeal cancer for approximate tertiles of folate, methionine and alcohol intake. Mean values (and standard deviations) of intake among controls and a test for trend are also shown. The risk of oral and pharyngeal cancer was nearly halved (OR = 0.53, 95% CI 0.40–0.69) for subjects in the highest tertile of intake of folate compared with those in the lowest tertile, with a significant inverse trend in risk ($P < 0.001$). No association was observed for methionine intake, while for alcohol consumption the OR was 11.4 (95% CI 8.1–15.9) in the highest tertile of consumption (≥ 38 drinks/week) compared with the lowest one

Table 2. Relationship between dietary folate intake and risk of oral and pharyngeal cancer among 749 cases and 1772 controls in strata of selected covariates (Italy and Switzerland, 1992–1997)

Stratum	Tertile ^a of folate intake, OR ^b			χ^2 trend	Continuous OR ^c
	1 (low)	2 (intermediate)	3 (high)		
Sex					
Men					
Cases:controls	258:410	218:435	158:407	12.12	
OR (95% CI)	1	0.69 (0.52–0.92)	0.58 (0.42–0.80)	$P < 0.001$	0.72 (0.59–0.88)
Women					
Cases:controls	44:127	31:159	40:234	10.13	
OR (95% CI)	1	0.61 (0.32–1.15)	0.36 (0.19–0.67)	$P < 0.01$	0.53 (0.35–0.81)
Age					
<60 years					
Cases:controls	165:315	148:331	126:375	6.89	
OR (95% CI)	1	0.74 (0.52–1.06)	0.61 (0.42–0.88)	$P < 0.01$	0.67 (0.53–0.85)
≥60 years					
Cases:controls	137:222	101:263	72:266	13.30	
OR (95% CI)	1	0.65 (0.44–0.95)	0.46 (0.30–0.70)	$P < 0.001$	0.68 (0.51–0.89)
Alcohol drinking^d					
Low					
Cases:controls	37:243	29:238	30:349	7.58	
OR (95% CI)	1	0.77 (0.45–1.33)	0.47 (0.28–0.81)	$P < 0.01$	0.67 (0.47–0.94)
Intermediate					
Cases:controls	73:189	48:224	35:192	11.24	
OR (95% CI)	1	0.52 (0.33–0.84)	0.42 (0.25–0.72)	$P < 0.001$	0.50 (0.34–0.73)
High					
Cases:controls	191:105	171:131	133:99	4.44	
OR (95% CI)	1	0.78 (0.52–1.16)	0.63 (0.41–0.97)	$P = 0.03$	0.75 (0.58–0.98)
Drinking pattern^e					
Only at meals					
Cases:controls	102:360	81:410	73:435	6.03	
OR (95% CI)	1	0.71 (0.49–1.02)	0.62 (0.42–0.91)	$P = 0.01$	0.71 (0.54–0.93)
Out of meals/both					
Cases:controls	187:105	158:121	115:112	9.16	
OR (95% CI)	1	0.68 (0.44–1.05)	0.49 (0.31–0.78)	$P < 0.01$	0.68 (0.51–0.91)
Methionine intake^d					
Low					
Cases:controls	115:187	66:168	59:234	14.90	
OR (95% CI)	1	0.65 (0.41–1.03)	0.38 (0.24–0.63)	$P < 0.001$	0.50 (0.35–0.74)
Intermediate					
Cases:controls	106:184	88:247	63:206	4.15	
OR (95% CI)	1	0.63 (0.40–0.97)	0.62 (0.39–1.01)	$P = 0.04$	0.72 (0.53–0.99)
High					
Cases:controls	81:166	95:179	76:201	3.02	
OR (95% CI)	1	0.80 (0.49–1.29)	0.64 (0.39–1.06)	$P = 0.08$	0.73 (0.56–0.95)

^aEnergy adjusted using the residual method.

^bEstimates from unconditional logistic regression models adjusted for sex, age, study centre, education, body mass index, alcohol consumption, smoking habit and non-alcohol energy intake. The reference category was the first (lowest) tertile of intake.

^cThe measurement unit was set at 1 SD of the distribution of controls.

^dIn tertiles. Cut-off points: alcohol, 14.5 and 38 drinks/week; methionine, 1854 and 2417 mg/day.

^eAmong ever-drinkers.

OR, odds ratio; CI, confidence interval; SD, standard deviation.

Table 3. Odds ratios^a and 95% confidence intervals of oral and pharyngeal cancer according to tertiles of intake of folate and alcohol (Italy and Switzerland, 1992–1997)

Alcohol consumption ^b	Tertile of folate intake		
	3 (high)	2 (intermediate)	1 (low)
Low	1 ^c	1.66 (0.94–2.93)	2.30 (1.34–3.96)
Intermediate	2.29 (1.30–4.05)	2.89 (1.68–4.97)	5.65 (3.34–9.56)
High	16.19 (9.53–27.53)	17.08 (10.12–28.84)	22.35 (13.14–38.00)

^aEstimates from unconditional logistic regression models adjusted for sex, age, study centre, education, body mass index, smoking habit and non-alcohol energy intake.

^bIn tertiles. Cut-off points: 14.5 and 38 drinks per week.

^cReference category.

(≤ 14 drinks/week). The continuous OR for an increase of four drinks/week (1 SD) was 2.19 (95% CI 1.96–2.45).

Table 2 considers folate intake in strata of selected covariates. The inverse relation with folate was apparently stronger in the lowest tertile of methionine intake (OR = 0.38; *P*-value for trend < 0.001), but the test for heterogeneity was non-significant. No heterogeneity was observed across strata of gender, age, alcohol consumption and drinking pattern.

Table 3 considers the combined effect of folate and alcohol intake, taking as reference category subjects with low alcohol and high folate intake, i.e. those at lower risk of cancer. ORs increased with increasing alcohol and decreasing folate intake. Thus, the highest OR was 22.3 (95% CI 13.1–38.0) for low folate and high alcohol intake. High compared with low alcohol consumption increased the risk of cancer 16-fold in those with high folate intake, and ~ 10 -fold in those with intermediate or low folate intake.

Discussion

Folate deficiency may increase the risk of cancer by inducing an imbalance in DNA precursors, leading to modified DNA synthesis and repair. It can also alter normal DNA methylation, which may contribute to loss of normal control of proto-oncogene expression. Folate and methionine are involved in the production of *S*-adenosylmethionine, the primary methyl donor in the body [6]. If methionine levels are low, more folate is used as methyl-tetrahydrofolate to form methionine. This may lower the level of methylene-tetrahydrofolate, which is necessary for DNA synthesis [5, 10].

Coherently, in this study high folate appeared to exert a stronger protection in subjects with low intake of methionine. However, methionine intake was not related to risk of oral and pharyngeal cancer, and the test for heterogeneity was non-significant. Alcohol consumption is a well assessed, strong risk factor for oral cancer. High intakes of alcohol are also responsible for decreased folate absorption in the body, and may increase folate requirements [18]. Thus, the combined role of folate and alcohol on oral and pharyngeal carcinogenesis is of specific interest. In this population, the inverse association between folate and risk of oral and pharyngeal cancer was similar across strata of alcohol intake, and consequently the risk in those with low folate and high alcohol intake was increased > 22 times.

The association between folate and oral cancer may, at least in part, be due to fruit and vegetables, which are the main sources of folate and are inversely related to cancer risk [13, 28, 29]. However, in this study, adjustment for fruit and vegetable consumption only slightly reduced the inverse association between folate and oral cancer risk, which remained significant (OR = 0.66, 95% CI 0.49–0.89). The possibility that other micronutrients, particularly those contained in fruit and vegetables, are responsible for the protective effect observed could not be excluded [29]. For several micronutrients, this was difficult to verify, given the strong correlations with folate intake and the risk of generating over-adjusted models. For example, the correlation coefficients were 0.68 for vitamin C, 0.57 for β -carotene, 0.82 for vitamin B6 and 0.61 for vitamin E, and these micronutrients were also inversely related to oral and pharyngeal cancer [30]. When we added in the regression model a term for vitamin C, the OR for high folate intake became 0.78 (95% CI 0.57–1.08). A similar modifying effect was observed adjusting for β -carotene (OR = 0.70; 95% CI 0.52–0.95), while no differences emerged when we included models terms for vitamins B6 and E.

Aspirin, when taken in therapeutic doses, may exert an anti-folate activity [31]. In this population, aspirin was regularly used by only eight cases (1.1%) and 17 controls (1.0%). Consequently, neither the adjustment for aspirin use nor the exclusion of regular users materially changed the results.

The present findings are consistent with those reported for other neoplasms. In a companion study on colorectal cancer [17], a protective effect of folate was found. Another Italian study found a favourable effect of folate against breast cancer risk in women consuming two or more alcoholic beverages per day [32]. A recent US case-control study found a significant inverse association between folate intake and oesophageal cancer, which shares several risk factors with oral and pharyngeal cancer [33]. On the other hand, the three case-control studies conducted in America that have considered folate and oral cancer risk have not found consistent associations [12–14]. The different results observed in our study may originate from the higher consumption of alcohol in our population, as well as from differences in average intake and main food sources of folate in different populations.

A possible limitation of this study lies in the use of hospital controls, since their dietary habits may be different from those of the general population. However, we attempted to exclude from

the control group those subjects with conditions associated with long-term modifications of diet. On the other hand, however, the use of hospital controls should reduce recall bias and increase the comparability of information obtained by cases and controls [34]. Strengths of the study are the almost complete participation rate, the use of a validated and reproducible FFQ [24, 25] that allowed to control for intake of energy and of other nutrients, and the similar catchment areas of cases and controls.

In conclusion, our study, based on a population with high alcohol intake, supports a protective role of folate in the aetiology of oral and pharyngeal cancer. Given the findings obtained in similar populations for colorectal and breast cancer [17, 32], these data confirm the importance of folate in the process of carcinogenesis. Compared with low folate intake in this population, a significant reduction in risk was found for intermediate levels, suggesting that oral cancer risk may be mainly linked to relative folate deficiencies.

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