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Dietary folates and cancer risk in a network of case–control studies

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Background: Folate deficiency leads to DNA damage and inadequate repair, caused by a decreased synthesis of thymidylate and purines. We analyzed the relationship between dietary folate intake and the risk of several cancers.

Patients and methods: The study is based on a network of case–control studies conducted in Italy and Switzerland in 1991–2009. The odds ratios (ORs) for dietary folate intake were estimated by multiple logistic regression models, adjusted for major identified confounding factors.

Results: For a few cancer sites, we found a significant inverse relation, with ORs for an increment of 100 µg/day of dietary folate of 0.65 for oropharyngeal (1467 cases), 0.58 for esophageal (505 cases), 0.83 for colorectal (2390 cases), 0.72 for pancreatic (326 cases), 0.67 for laryngeal (851 cases) and 0.87 for breast (3034 cases) cancers. The risk estimates were below unity, although not significantly, for cancers of the endometrium (OR = 0.87, 454 cases), ovary (OR = 0.86, 1031 cases), prostate (OR = 0.91, 1468 cases) and kidney (OR = 0.88, 767 cases), and was 1.00 for stomach cancer (230 cases). No material heterogeneity was found in strata of sex, age, smoking and alcohol drinking.

Conclusions: Our data support a real inverse association of dietary folate intake with the risk of several common cancers.

Key words: cancer risk, case–control study, diet, folates

introduction

Folates, the water-soluble vitamin B₉, play a central role as cofactors in nucleotide synthesis and have been involved in both prevention and promotion of cancer [1].

Many epidemiological studies have shown that dietary folate intake is inversely related with cancer at several sites [2]. A meta-analysis of 18 case–control studies of colorectal cancer

found an overall odds ratio (OR) for high versus low intake of folates of 0.85 [95% confidence interval (CI) 0.74–0.99] [3], and a pooled analysis of 13 prospective studies found a relative risk (RR) of colon cancer for highest versus lowest intake of folate of 0.92 (95% CI 0.84–1.00) [4]. As for other cancers of the digestive tract, a meta-analysis found overall RRs for the highest versus the lowest intake of dietary folates of 0.66 (95% CI 0.53–0.83) for esophageal squamous cell carcinoma (based on four case–control studies), 0.50 (95% CI 0.39–0.65) for esophageal adenocarcinoma (three case–control studies) and 0.90 (95% CI 0.72–1.13) for gastric cancer (two cohort and

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nine case-control studies) [5]. For pancreatic cancer, a meta-analysis (based on four cohort and one case-control studies) found a RR of 0.49 (95% CI 0.35–0.67) [5]. This inverse association with pancreatic cancer was recently confirmed in an American case-control study, with an OR for the highest quintile of intake of 0.67 (95% CI 0.48–0.93) [6] compared to the lowest one, but not in a large pooled analysis of 14 prospective studies (RR = 1.06, 95% CI 0.90–1.25, for the highest quintile compared to the lowest one) [7].

Data are scantier for oral and pharyngeal, and laryngeal cancer. A case-control study conducted in Uruguay, considering the risk of 11 types of cancer in relation to dietary folate intake, found an OR for an increment of 100 µg/day of 0.56 (95% CI 0.37–0.83) for oral and pharyngeal and of 0.52 (95% CI 0.35–0.77) for laryngeal cancer [2].

The results are inconsistent for endometrial cancer, with two cohort studies finding no relation [8, 9] and a case-control study finding an inverse relation [10], and for ovarian cancer, with one cohort study finding no relation [11] and two cohort studies finding an inverse association with folate intake only in women in the highest category of alcohol drinking [12, 13].

For breast cancer the evidence is inconsistent. A meta-analysis, considering the relation of breast cancer risk with an increments of 200 µg/day of dietary folates, found a null relation in 8 prospective studies (RR = 0.97, 95% CI 0.88–1.07), and an inverse association in 13 case-control studies (OR = 0.80, 95% CI 0.72–0.89). In a meta-analysis of 6 prospective and 2 case-control studies of prostate cancer the RR was 1.11 (95% CI 0.96–1.28) for an increase of plasmatic concentration of 10 nmol/l) [15].

As the evidence is inconsistent for a few cancer sites, we have analyzed the relation between dietary intake of folates and the risk of cancers at selected sites using data from a network of case-control studies, conducted in Italy and Switzerland. This large dataset allowed adjustment for a large number of covariates. Previous analyses of subsets of this dataset showed significant inverse associations between dietary folate intake and cancers of oral cavity and pharynx [16], esophagus [17], colorectum [18], pancreas [19] and prostate [20], and no relation with cancers of the stomach [21], breast [22] and ovary [23].

materials and methods

Between 1991 and 2009, we conducted an integrated series of case-control studies on several neoplasms in various areas of northern (the greater Milan area; the provinces of Pordenone, Padua, Udine, Gorizia and Forlì; the urban area of Genoa), central (the provinces of Rome and Latina), and southern (the urban area of Naples) Italy. We also conducted companion studies on cancers of the oral cavity and pharynx, esophagus, colorectum, larynx, breast and endometrium in the Canton of Vaud, Switzerland. The present analysis includes a total of 1467 cases of cancer of the oral cavity and pharynx [16, 24–26], 505 cases of cancer of the esophagus [17, 27–29], 230 of cancer of the stomach [30], 2390 of cancer of the colorectum [18, 31, 32], 851 of cancer of the larynx [33], 326 of cancer of the pancreas [34], 454 of cancer of the endometrium [35], 3034 of cancer of the breast [22, 36, 37], 1031 of cancer of the ovary [23, 38], 1468 of cancer of the prostate [20, 39], 767 of cancer of the kidney [40] and a total of 22 828 controls (Table 1).

Table 1. Number of cases of selected cancer sites and controls, by sex and median age

Cancer site	Cases (men/ women)	Median age (years)	Controls ^a (men/ women)	Median age (years)
Oral cavity and pharynx	1190/277	58	2553/1208	58
Esophagus	438/67	60	919/340	60
Stomach	143/87	63	286/261	63
Colorectum	1401/989	62	2586/2357	58
Colon	835/628	62	2586/2357	58
Rectum	566/361	63	2586/2357	58
Pancreas	174/152	63	348/304	63
Larynx	770/81	62	1564/406	61
Breast	–/3034	55	–/3392	56
Endometrium	–/454	62	–/1366	61
Ovary	–/1031	56	–/2411	57
Prostate	1468/–	66	1451/–	63
Kidney	494/273	62	988/546	61

Italy and Switzerland, 1991–2009.

^aThe sum is higher than the total as some controls are common to more cancer sites.

All studies included incident cases identified in the major teaching and general hospitals of the study areas. Controls were subjects admitted to the same network of hospitals as cases for a wide spectrum of acute, non-neoplastic conditions, unrelated to known risk factors for the corresponding cancer site. Overall, 26% of controls were admitted for traumatic conditions, 15% for nontraumatic orthopedic conditions, 27% for acute surgical conditions and 32% for miscellaneous other illnesses.

Refusal to participation of subjects approached was <5% in Italy, and was ~15% in Switzerland. The study protocols were revised and approved by the ethical committees of the hospitals involved, according to the regulations at the time of each study conduction, and all participants gave informed consent.

During their hospital stay, cases and controls were asked by centrally trained interviewers to fill a standard questionnaire, which included personal and sociodemographic characteristics, anthropometric measures and lifestyle habits (including tobacco smoking, alcohol consumption and physical activity). A reproducible [41] and valid [42] food-frequency questionnaire (FFQ) was used to assess the patients' usual diet in the 2 years preceding diagnosis (for cases) or hospital admission (for controls). The FFQ included the average weekly consumption of 78 food items or food groups and beverages. Intakes lower than once per week, but at least once per month, were coded as 0.5 per week. Energy and nutrient intake, including folates, were computed using an Italian food composition database [43].

statistical analysis

ORs and the corresponding 95% CI of various cancers according to quartiles of intake of dietary folates, based on the distribution of controls, were estimated using unconditional or conditional multiple logistic regression models [44], depending on whether cases and controls for the considered anatomical sites were matched or not. All models included terms for sex (when appropriate), quinquennia of age, study center, year of interview, education, alcohol drinking, tobacco smoking, body mass index, total energy intake and physical activity at work. Stratifications for sex, age,

tobacco smoking and alcohol drinking were performed for cancer sites showing significant association with the disease.

results

Table 2 shows the distribution of cancer cases and controls according to quartile of dietary folate intake and the corresponding ORs. The ORs for the highest quartile of intake compared to the lowest one were significantly below unity for cancers of oral cavity and pharynx (OR = 0.37), esophagus (OR = 0.26), colorectum (OR = 0.74) and larynx (OR = 0.55), with a significant trend in risk. The OR was of borderline significance for breast (OR = 0.82) and prostate cancer (OR = 0.79), with a significant trend in risk no relationship was

found for cancer of the stomach (OR = 1.59), pancreas (OR = 0.74), endometrium (OR = 1.06), ovary (OR = 0.83) and kidney (OR = 0.86).

The relation between an increment of 100 µg/day of folate with diet and risk of cancer at investigated sites is reported in Figure 1. There was a significant inverse association for cancers of the oral cavity and pharynx (OR = 0.65), esophagus (OR = 0.58), colorectum (OR = 0.83), pancreas (OR = 0.72), larynx (OR = 0.67) and breast (OR = 0.87). The risk estimates were below unity, although not significantly, for cancers of the endometrium (OR = 0.87), ovary (OR = 0.86), prostate (OR = 0.91) and kidney (OR = 0.88). The OR was 1.00 for stomach cancer. Further adjustment for vegetable intake generally weakened the inverse association, and the ORs for an

Table 2. Distribution of cases of selected cancer sites and controls, and corresponding odds ratio (OR) and 95% confidence interval (CI), according to quartiles of dietary folate intake

Cancer site	Quartile of intake ^a				χ^2 trend, <i>P</i>
	1st	2nd	3rd	4th	
Oral cavity and pharynx					
No. of cases : controls	394 : 940	313 : 940	365 : 941	395 : 940	
OR ^b (95% CI)	1 ^c	0.56 (0.43–0.74)	0.59 (0.44–0.77)	0.37 (0.26–0.51)	<0.0001
Esophagus					
No. of cases : controls	144 : 314	110 : 316	122 : 317	128 : 315	
OR ^b (95% CI)	1 ^c	0.63 (0.40–0.98)	0.45 (0.28–0.73)	0.26 (0.14–0.48)	<0.0001
Stomach					
No. of cases : controls	38 : 136	55 : 138	61 : 137	76 : 136	
OR ^b (95% CI)	1 ^c	1.26 (0.75–2.13)	1.29 (0.73–2.25)	1.59 (0.84–3.01)	0.1853
Colorectum					
No. of cases : controls	587 : 1235	607 : 1236	555 : 1236	641 : 1236	
OR ^b (95% CI)	1 ^c	0.93 (0.80–1.08)	0.75 (0.64–0.88)	0.74 (0.61–0.90)	0.0004
Pancreas					
No. of cases : controls	74 : 163	73 : 163	92 : 163	87 : 163	
OR ^b (95% CI)	1 ^c	0.79 (0.52–1.21)	0.96 (0.61–1.50)	0.74 (0.43–1.28)	0.4539
Larynx					
No. of cases : controls	215 : 493	182 : 491	225 : 493	229 : 492	
OR ^b (95% CI)	1 ^c	0.71 (0.52–0.96)	0.80 (0.58–1.09)	0.55 (0.38–0.80)	0.0090
Breast					
No. of cases : controls	644 : 848	757 : 848	836 : 848	797 : 848	
OR ^b (95% CI)	1 ^b	0.99 (0.84–1.16)	0.98 (0.82–1.16)	0.82 (0.65–1.03)	0.0098
Endometrium					
No. of cases : controls	98 : 227	124 : 227	99 : 227	133 : 227	
OR ^b (95% CI)	1 ^c	1.10 (0.77–1.57)	0.79 (0.53–1.18)	1.06 (0.67–1.67)	0.7593
Ovary					
No. of cases : controls	208 : 602	267 : 603	263 : 603	293 : 603	
OR ^b (95% CI)	1 ^c	0.95 (0.74–1.23)	0.85 (0.64–1.11)	0.83 (0.60–1.15)	0.2021
Prostate					
No. of cases : controls	297 : 363	346 : 362	304 : 364	347 : 362	
OR ^b (95% CI)	1 ^c	0.98 (0.78–1.24)	0.82 (0.64–1.05)	0.79 (0.59–1.05)	0.0483
Kidney					
No. of cases : controls	194 : 383	190 : 384	196 : 384	187 : 383	
OR ^b (95% CI)	1 ^c	0.94 (0.72–1.22)	0.94 (0.71–1.25)	0.86 (0.61–1.20)	0.4143

Italy and Switzerland, 1991–2009.

^aMean values of upper cut-point were (µg/day): 208.77 for the first quartile, 257.25 for the second quartile and 312.47 for the third quartile.

^bEstimated from multiple logistic regression models adjusted for sex (when appropriate), age, study center, year of interview, education, alcohol drinking, tobacco smoking, body mass index, total energy intake and physical activity at work.

^cReference category.

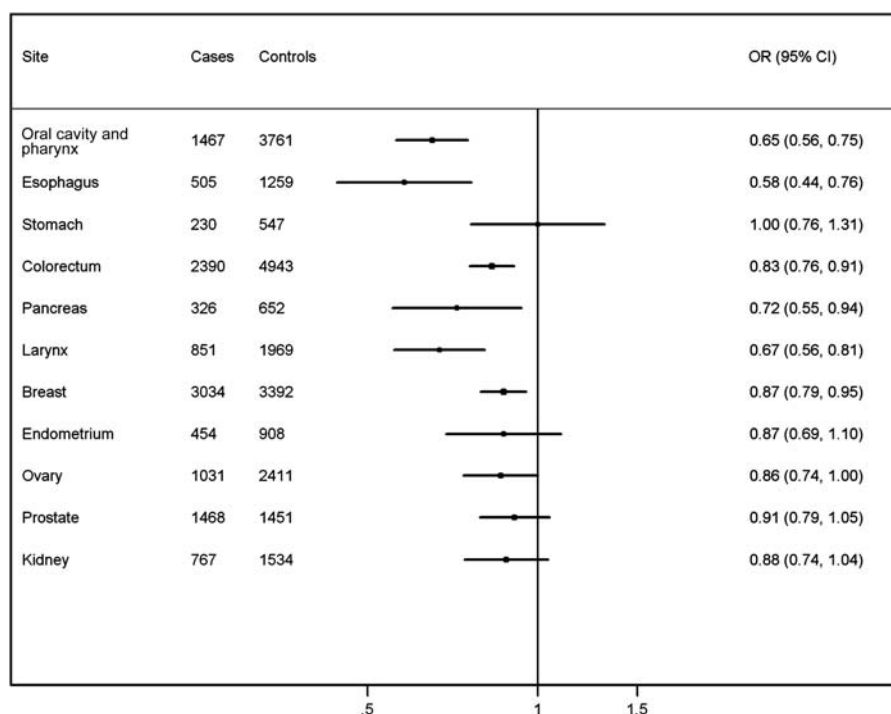


Figure 1 Dietary folate intake and risk of selected cancers. Black squares indicate the odds ratio (OR) and the horizontal lines represent 95% confidence interval (CI) for an increment of dietary folate intake of 100 µg/day.

increment of 100 µg/day of folate with diet were 0.69 (95% CI 0.59–0.81) for oral and pharyngeal, 0.78 (95% CI 0.57–1.06) for esophageal, 1.39 (95% CI 0.98–1.97) for stomach, 1.04 (95% CI 0.94–1.16) for colorectal, 0.72 (95% CI 0.53–0.98) for pancreatic, 0.81 (95% CI 0.66–1.00) for laryngeal, 0.96 (95% CI 0.86–1.08) for breast, 0.76 (95% CI 0.56–1.03) for endometrial, 1.11 (95% CI 0.92–1.35) for ovarian, 1.05 (95% CI 0.88–1.23) for prostatic and 1.07 (95% CI 0.87–1.31) for kidney cancer.

A stratified analysis by sex, age, tobacco smoking and alcohol drinking for cancer sites showing an inverse relation with dietary folate intake is shown in Table 3. There was no material heterogeneity across strata of the selected covariates, except for a slightly stronger inverse relation of folates with breast cancer risk in women <60 years compared with older ones.

discussion

We found an inverse association of dietary folate intake with oral and pharyngeal, esophageal, colorectal, pancreatic, laryngeal and breast cancers. The risk estimates were below unity, although not significantly, for cancers of the endometrium, ovary, prostate and kidney. No relation was found with stomach cancer.

The role of folates in the carcinogenic process is complex, and probably includes both positive and negative aspects depending on the dose [45]. It has been shown that folate deficiency has an inhibitory effect on the progression of colorectal adenomas and neoplasia, while folic acid excess through supplementation may have a promoting effect [46]. Folate deficiency leads to DNA damage and inadequate

Table 3. Odds ratio (OR)^a and 95% confidence interval (CI) for an increment of dietary folate intake of 100 µg/day in strata of selected covariates

Cancer site	Sex		Age (years)		Smoking habit		Alcohol drinking	
	Men	Women	<60	≥60	Nonsmokers	Current smokers	Nondrinkers	Current drinkers
Oral cavity and pharynx	0.66 (0.56–0.78)	0.62 (0.45–0.86)	0.70 (0.57–0.85)	0.60 (0.49–0.75)	0.63 (0.51–0.78)	0.65 (0.52–0.81)	0.65 (0.47–0.90)	0.63 (0.54–0.75)
Esophagus	0.53 (0.39–0.71)	0.96 (0.37–2.50)	0.60 (0.40–0.91)	0.51 (0.34–0.75)	0.73 (0.51–1.06)	0.38 (0.24–0.60)	0.62 (0.25–1.53)	0.52 (0.38–0.70)
Colorectum	0.78 (0.69–0.89)	0.89 (0.78–1.03)	0.84 (0.73–0.96)	0.83 (0.73–0.94)	0.82 (0.73–0.91)	0.86 (0.73–1.03)	0.73 (0.61–0.88)	0.86 (0.78–0.96)
Larynx	0.67 (0.55–0.81)	0.74 (0.39–1.41)	0.75 (0.57–0.99)	0.60 (0.46–0.77)	0.74 (0.58–0.95)	0.54 (0.40–0.72)	1.05 (0.63–1.73)	0.64 (0.52–0.78)
Breast	–	–	0.80 (0.71–0.89)	1.01 (0.86–1.18)	0.86 (0.78–0.96)	0.89 (0.74–1.08)	0.85 (0.74–0.98)	0.87 (0.77–0.98)
Prostate	–	–	0.95 (0.72–1.25)	0.89 (0.75–1.06)	0.94 (0.80–1.11)	0.84 (0.62–1.13)	0.71 (0.46–1.11)	0.93 (0.80–1.09)

Italy and Switzerland, 1991–2009.

^aEstimate from multiple logistic regression models adjusted for sex (when appropriate), age, study center, year of interview, education, alcohol drinking, tobacco smoking, body mass index, total energy intake and physical activity at work.

repair, caused by a decreased synthesis of thymidylate and purines [47], and genomic hypomethylation leading to colonic neoplasia [48]. However, at supplementation doses, folates may negatively influence epigenetic gene regulation leading to cancer promotion [49], and two randomized clinical trials of folic acid suggested a potential nonsignificant increased risk of colon and prostate cancers [50], and a potential increased risk of colorectal adenomas [51]. In our study, we have no information on dietary supplementation, which, however, is uncommon in Italy [20]; thus, our results are related to dietary folates only.

In the Italian diet, folates derive approximately for 21% from vegetables, for 25% from cereals and for the other 50% from all other foods [52]. Thus, it is not easy to disentangle the effect of folates from that of specific foods or other related nutrients or food components [52], and folates cannot be considered a general marker for a more favorable dietary pattern or healthier lifestyle. Moreover, most inverse relations were weakened but tended to persist after adjustment for vegetable intake, further suggesting that folates cannot be merely considered an indirect indicator of vegetable intake (one of the major sources of folates in the Italian diet), but they may have a real protective role on several cancers.

The inverse relation between folate intake and the risk of several cancer sites was further supported by the observation that the decreased risk was similar across strata of major covariates. If not due to the multiple comparison and hence the play of chance, the slightly weaker effect of folates on breast cancer in older women may be related to metabolic differences in the elderly.

Alcohol intake inhibits folate-mediated methionine synthesis and may interrupt methylation processes mediated by methionine (the substrate for biologic methylation), inducing DNA hypomethylation in the intestinal mucosa [53]. Folate intake has been reported to reduce the risk of ovarian cancer in alcohol drinkers [11, 12]. However, in our dataset, we found no appreciable modulation of alcohol intake on the relation between folates and the risk of ovarian and the other cancers considered [23].

Our data are in broad agreement with those of the literature. We confirmed the protective effect of dietary folate on the risk of colorectal [3, 4], esophageal [5], oral and pharyngeal [2] and laryngeal and the absence of consistent relation with stomach cancer [5] found in other studies. However, we did not confirm the inverse association of dietary folate intake with kidney cancer found in a case-control study from Uruguay [2]. For pancreatic cancer, we found an inverse association only when the OR was calculated in continuous. This borderline inverse association is in agreement with overall evidence based on a pooled analysis of prospective studies finding no relation [7], and on a meta-analysis [5] and a subsequent case-control study [6] finding overall protection.

All studies included in the present analysis are hospital based. However, selection bias should be limited as participation of cases and controls was similar, and cases and controls were identified in the major teaching and general hospitals of the areas under surveillance. Moreover, we excluded from the control group patients admitted to hospital

for chronic conditions or digestive tract diseases, which could have affected dietary habits. In a reproducibility study, a satisfactory comparability of dietary information was found between subjects interviewed at home and in the hospital [54]. The similar interview setting for cases and controls provides reassurance against potential information bias [54], and there is also no reason to suspect different selective recall of food intake on the basis of the disease status. The FFQ was satisfactorily valid and reproducible [41, 42]. An indirect support for a real inverse association between folate intake and cancer at several sites comes from the consistent relation across strata of age, sex, alcohol intake and tobacco smoking, and from the absence of association for a few cancer sites, which exclude a systematic bias due to study design. A major strength of our study was the possibility to allow for several confounding factors. However, residual confounding remains possible, also given to the influence of other cofactors and intake of other foods on folate absorption in the jejunum.

In conclusion, our data support a real inverse association of folate dietary intake with the risk of several common cancers.

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disclosure

The authors have declared no conflicts of interest.

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