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). 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) [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 intake folate 
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 
endometrium [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

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


*The 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 participate 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 
one 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 
quantiles 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>
<thead>
<tr>
<th>Cancer site</th>
<th>Quartile of intake</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>χ² trend, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity and pharynx</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.56 (0.43–0.74)</td>
<td>0.59 (0.44–0.77)</td>
<td>0.37 (0.26–0.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Esophagus</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.63 (0.40–0.98)</td>
<td>0.45 (0.28–0.73)</td>
<td>0.26 (0.14–0.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stomach</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>1.26 (0.75–2.13)</td>
<td>1.29 (0.73–2.25)</td>
<td>1.59 (0.84–3.01)</td>
<td>0.1853</td>
</tr>
<tr>
<td>Colorectum</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.93 (0.80–1.08)</td>
<td>0.75 (0.64–0.88)</td>
<td>0.74 (0.61–0.90)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Pancreas</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.79 (0.52–1.21)</td>
<td>0.96 (0.61–1.50)</td>
<td>0.74 (0.43–1.28)</td>
<td>0.4539</td>
</tr>
<tr>
<td>Larynx</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.71 (0.52–0.96)</td>
<td>0.80 (0.58–1.09)</td>
<td>0.55 (0.38–0.80)</td>
<td>0.0090</td>
</tr>
<tr>
<td>Breast</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.99 (0.84–1.16)</td>
<td>0.98 (0.82–1.16)</td>
<td>0.82 (0.65–1.03)</td>
<td>0.0098</td>
</tr>
<tr>
<td>Endometrium</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>1.10 (0.77–1.57)</td>
<td>0.79 (0.53–1.18)</td>
<td>1.06 (0.67–1.67)</td>
<td>0.7593</td>
</tr>
<tr>
<td>Ovary</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.95 (0.74–1.23)</td>
<td>0.85 (0.64–1.11)</td>
<td>0.83 (0.60–1.15)</td>
<td>0.2021</td>
</tr>
<tr>
<td>Prostate</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.98 (0.78–1.24)</td>
<td>0.82 (0.64–1.05)</td>
<td>0.79 (0.59–1.05)</td>
<td>0.0483</td>
</tr>
<tr>
<td>Kidney</td>
<td>No. of cases : controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.94 (0.72–1.22)</td>
<td>0.94 (0.71–1.25)</td>
<td>0.86 (0.61–1.20)</td>
<td>0.4143</td>
</tr>
</tbody>
</table>

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

Mean 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.

Estimated 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.

Reference category.
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 0.88–1.23) 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.

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

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Smoking habit</th>
<th>Alcohol drinking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Nonsmokers</td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td></td>
<td>0.66 (0.56–0.78)</td>
<td>0.62 (0.45–0.86)</td>
<td>0.70 (0.57–0.85)</td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
<td>0.53 (0.39–0.71)</td>
<td>0.96 (0.37–2.50)</td>
<td>0.60 (0.40–0.91)</td>
</tr>
<tr>
<td>Colorectum</td>
<td></td>
<td>0.78 (0.69–0.89)</td>
<td>0.89 (0.78–1.03)</td>
<td>0.84 (0.73–0.96)</td>
</tr>
<tr>
<td>Larynx</td>
<td></td>
<td>0.67 (0.55–0.81)</td>
<td>0.74 (0.39–1.41)</td>
<td>0.75 (0.57–0.99)</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>–</td>
<td>–</td>
<td>0.80 (0.71–0.89)</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>–</td>
<td>–</td>
<td>0.95 (0.72–1.25)</td>
</tr>
</tbody>
</table>


*Estimate 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.

**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.

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

**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 folic acid excess through supplementation may have a promoting effect [46]. Folate deficiency leads to DNA damage and inadequate...
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.

references


