Introduction

An increasing number of studies are focusing on the potential association between dietary folate intake and risk of various cancers (1), particularly of the colorectum and breast (2, 3). A low folate status can induce misincorporation of uracil into DNA, leading to chromosome breaks in humans and hence increasing cancer risk (4). Alcohol may increase folate requirements in the body and cause relative folate deficiencies (2). Although several findings on the relation between folate intake and ovarian cancer risk are inconsistent (5-9), recent results from two prospective studies, including 266 and 147 incident cases of epithelial ovarian cancer, have suggested an interaction of folate and alcohol in ovarian carcinogenesis [i.e., folate would be inversely related to ovarian cancer risk in alcohol drinkers (5, 6), and alcohol in those with high folate intake (7)]. With the aim to provide further data on the issue, we assessed the relation between dietary folate, alcohol consumption, and ovarian cancer risk in a multicentric case-control study conducted in Italy (10).

Materials and Methods

The study was conducted in four Italian areas between 1992 and 1999 (10). Cases were 1,031 women admitted to the major teaching and general hospitals in the areas under surveillance with incident, histologically confirmed epithelial ovarian cancer. Controls were 2,411 women admitted to the same teaching and general hospitals in the areas under surveillance (11). A separate section investigated alcohol consumption in detail.

Data Analysis. Odds ratios (OR) and 95% confidence intervals (95% CI) were derived using unconditional multiple logistic regression models, including terms for age, study center, year of interview, education, parity, body mass index, alcohol consumption, use of oral contraceptives, physical activity, and energy intake (excluding energy from alcoholic beverages). After adjustment for nonalcohol energy intake, our study had 80% power to detect a 35% reduced risk (i.e., an OR ≤ 0.65) for the highest compared with the lowest quintile of folate intake (x = 0.05).

Results

Table 1 reports the distribution of cases and controls, ORs and 95% CIs of ovarian cancer according to quintiles of folate intake of all women together, by histologic subtype and in separate strata of alcohol consumption, methionine, and vitamin B6 intake. Compared with the lowest quintile of dietary folate, the ORs of ovarian cancer were 1.10, 0.99, 1.02 and 0.98 for subsequent quintiles of intake. When further lifestyle, reproductive, and dietary covariates were controlled for, the ORs were 1.14, 1.12, 1.23, and 1.26. For the highest level of folate, the ORs of serous, mucinous, and other subtypes of ovarian cancer were 1.10, 0.41, and 0.85, respectively. In the stratum of non- and low-alcohol drinkers, the OR for an increase in folate intake equal to an SD was 0.93 (95% CI, 0.76-1.14). In the stratum of moderate/high drinkers, the corresponding OR was 1.02 (95% CI, 0.86-1.23), whereas when we considered folate intake in the stratum of hard drinkers only (5th quintile, i.e., >26 g/d), the OR was 1.14 (95% CI, 0.85-1.54). Ovarian cancer risk for folate intake was somewhat higher in strata of low methionine and vitamin B6 (OR, 1.18 and 1.15, respectively) than in strata of high methionine and vitamin B6 (OR, 0.79 and 0.88, respectively).

Discussion

Strengths of this investigation are its large size, the use of a validated and reproducible food frequency questionnaire...
Table 1. ORs and 95% CIs of ovarian cancer according to dietary folate intake; Italy, 1992-1999

<table>
<thead>
<tr>
<th>Quintile of folate intake*</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women Cases/controls</td>
<td>159:480</td>
<td>209:491</td>
<td>209:466</td>
<td>218:483</td>
<td>236:491</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.00 (0.82-1.24)</td>
<td>1.00 (0.72-1.35)</td>
<td>1.00 (0.73-1.43)</td>
<td>0.98 (0.67-1.44)</td>
<td>0.99 (0.87-1.13)</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>1.14 (0.83-1.56)</td>
<td>1.12 (0.80-1.57)</td>
<td>1.23 (0.85-1.80)</td>
<td>1.26 (0.80-1.97)</td>
<td>1.11 (0.90-1.49)</td>
</tr>
<tr>
<td>Serous (493 cases)</td>
<td>1.11 (0.77-1.62)</td>
<td>1.05 (0.68-1.65)</td>
<td>1.15 (0.74-1.81)</td>
<td>1.15 (0.66-1.84)</td>
<td>1.07 (0.79-1.44)</td>
</tr>
<tr>
<td>Mucinous (81 cases)</td>
<td>1.04 (0.28-1.46)</td>
<td>0.48 (0.20-1.16)</td>
<td>0.59 (0.24-1.44)</td>
<td>0.41 (0.14-1.18)</td>
<td>2.08 (0.21-1.18)</td>
</tr>
<tr>
<td>Other (176 cases)</td>
<td>0.39 (0.32-1.08)</td>
<td>0.73 (0.40-1.32)</td>
<td>0.84 (0.45-1.53)</td>
<td>0.85 (0.42-1.74)</td>
<td>0.01 (0.92)</td>
</tr>
<tr>
<td>Alcohol drinking ≤1 g/d</td>
<td>1.03 (0.79-1.36)</td>
<td>1.00 (0.75-1.36)</td>
<td>1.02 (0.76-1.41)</td>
<td>0.98 (0.69-1.40)</td>
<td>1.14 (0.90-1.43)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.16 (0.77-1.75)</td>
<td>1.05 (0.68-1.65)</td>
<td>1.15 (0.74-1.81)</td>
<td>1.15 (0.66-1.84)</td>
<td>1.07 (0.79-1.44)</td>
</tr>
<tr>
<td>Methionine intake &lt;Median value</td>
<td>1.29 (0.82-2.02)</td>
<td>0.94 (0.59-1.50)</td>
<td>0.72 (0.43-1.20)</td>
<td>0.71 (0.40-1.26)</td>
<td>4.59 (1.03-20.17)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.08 (0.57-2.02)</td>
<td>1.13 (0.66-1.62)</td>
<td>1.20 (0.79-2.01)</td>
<td>1.19 (0.70-2.02)</td>
<td>0.10 (0.57-0.75)</td>
</tr>
<tr>
<td>Vitamin B6 intake &lt;Median value</td>
<td>1.22 (0.68-2.17)</td>
<td>0.94 (0.59-1.50)</td>
<td>0.72 (0.43-1.20)</td>
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</tr>
</tbody>
</table>

*Cut points for quintiles of folate intake among controls were 186, 231, 268, and 316 μg/d. The lowest quintile was taken as reference category.

†For an increase in folate intake equal to an SD, calculated among controls (83.47 μg/d).

‡Estimates from unconditional logistic regression models adjusted for age, study center, year of interview, education, parity, body mass index, alcohol consumption, oral contraceptives use, physical activity, and nonalcohol energy intake.

§Including all the adjustments above, plus further terms for menopausal status, family history of breast and/or ovarian cancer, age at menarche, first birth and menopause, hormone replacement therapy use, diabetes, fruit and vegetable consumption, and smoking habit.

∥Energy-adjusted intake.

(12-14), the low percentage of refusals of the subjects contacted, and the specific interest of the Italian population that has relatively high levels of alcohol (mostly wine) consumption (15). Our results do not indicate a major role of folate in ovarian cancer risk, nor a relevant interaction of folate with alcohol or with methionine or vitamin B6. These findings are in broad agreement with the available evidence from various studies, which in turn indicated inverse (5), absent (9), and direct (7, 8) relation of folate with ovarian cancer risk.

Our findings were confirmed after inclusion in the regression models of several lifestyle, reproductive, and dietary covariates, and at various levels of alcohol drinking. With reference to histologic subtypes of ovarian cancer (16), no association emerged for serous, endometrioid, and clear-cell tumors. However, the inverse relation of dietary folate with mucinous ovarian cancers was consistent with previous findings from the Swedish Mammography Cohort (5), but still uncertain because of the small number of mucinous cases in both studies.

Among possible explanations of the inconsistent findings of the studies, there are potential bias of epidemiologic studies. Case-control studies are generally more liable to bias than prospective ones. However, findings from a companion case-control study of breast cancer, where an inverse association with folate intake (stronger in high alcohol drinkers) was observed (17), are reassuring for the control group that we investigated, because the breast and ovarian studies were conducted on similar populations and shared a number of control subjects too.

In addition, differences in folate intake and alcohol consumption between various populations should be taken into account. In fact, the estimated median intake of folate widely differed between our study (248 μg/d) and the Swedish (178 μg/d) and the Iowa studies (331 μg/d; refs. 5–7). Further, the pattern of alcohol drinking in our investigation was peculiar for this population because we observed a large proportion of nondrinkers (40.6% of controls) as well as of hard drinkers (22.0% of controls had an intake of >25 g/d).

Notwithstanding these considerations, our findings from one of the largest data sets of ovarian cancer collected to date, as well as the overall epidemiologic evidence, do not support a role of folate and alcohol in ovarian carcinogenesis (18).

Acknowledgments
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References
Dietary Folate, Alcohol Consumption, and Risk of Ovarian Cancer in an Italian Case-Control Study

Claudio Pelucchi, Monia Mereghetti, Renato Talamini, et al.


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