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**Null Results in Brief**

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

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**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 network of hospitals for acute, nonmalignant, and nongynecologic conditions, unrelated to hormonal diseases or to long-term modifications of diet.

A standard questionnaire was given by centrally trained interviewers during hospital stay, including detailed information on personal characteristics, lifestyle habits, a problem-oriented medical history, history of cancer in relatives, menstrual and reproductive factors, and use of oral contraceptives and hormone therapy. A food frequency questionnaire was developed to assess the usual diet during the 2 years preceding diagnosis (for cases) or hospital admission (for controls). The food frequency questionnaire included 78 foods, food groups, or dishes divided into six sections: first courses, second courses, side dishes, fruits, desserts, and beverages. For a few seasonal vegetables and fruits, duration of consumption and vitamin B6 intake. Compared with the lowest quintile of 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 intake (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...
(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, and the specific interest of the Italian population that has relatively high levels of alcohol (mostly wine) consumption, and smoking habit.

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 frequent 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

We thank M.P. Bonifacino for editorial assistance.

### References


### 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</td>
<td>84.296</td>
<td>95.258</td>
<td>90.215</td>
<td>84.212</td>
<td>89.207</td>
</tr>
<tr>
<td>Cases/controls</td>
<td>94.264</td>
<td>101.272</td>
<td>95.220</td>
<td>123.228</td>
<td>119.221</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.96 (0.63-1.46)</td>
<td>0.99 (0.63-1.54)</td>
<td>1.38 (0.87-2.19)</td>
<td>1.33 (0.77-2.28)</td>
<td>1.27 (0.77-2.02)</td>
</tr>
<tr>
<td>Median value</td>
<td>65.216</td>
<td>108.219</td>
<td>114.246</td>
<td>95.255</td>
<td>117.270</td>
</tr>
<tr>
<td>OR (95% CI)</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>0.49 (0.21-1.06)</td>
</tr>
<tr>
<td>Vitamin B6 intake†</td>
<td>127.350</td>
<td>129.287</td>
<td>115.234</td>
<td>96.200</td>
<td>71.134</td>
</tr>
<tr>
<td>Cases/controls</td>
<td>1.18 (0.81-1.73)</td>
<td>1.16 (0.76-1.78)</td>
<td>1.22 (0.75-1.99)</td>
<td>1.22 (0.64-2.32)</td>
<td>1.43 (0.51-4.51)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.07 (0.62-1.87)</td>
<td>0.84 (0.48-1.46)</td>
<td>0.88 (0.50-1.56)</td>
<td>0.77 (0.41-1.44)</td>
<td>1.31 (0.25-2.63)</td>
</tr>
<tr>
<td>Median value</td>
<td>32.130</td>
<td>80.204</td>
<td>94.232</td>
<td>122.283</td>
<td>165.537</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.88 (0.57-1.34)</td>
<td>0.89 (0.56-1.41)</td>
<td>0.81 (0.49-1.34)</td>
<td>0.73 (0.40-1.32)</td>
<td>0.97 (0.32-0.93)</td>
</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.

### Table 1. ORs and 95% CIs of ovarian cancer according to dietary folate intake; Italy, 1992-1999
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