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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 hospital in each area during a 7-year period, with 2,411 women admitted to the same network of hospitals for acute, nonmalignant, and nongynecologic conditions serving as 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 was elicited.

Energy and nutrient intakes, including folate, methionine, and vitamin B6, were computed from the food frequency questionnaire using an Italian food composition database (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 (z = 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...
(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 drinking (22.0% of controls had an intake of >25 g/d). We thank M.P. Bonifacino for editorial assistance.

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 of dietary folate with ovarian cancer risk, nor a relevant interaction of folate with alcohol drinking was observed (17), are reassuring for the control group that we included 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.

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### References