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Micronutrients and ovarian cancer: an Italian case–control study

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Background

The role of dietary factors on ovarian carcinogenesis was originally suggested on the basis of descriptive epidemiology and correlational studies. Few studies have considered micronutrients and ovarian cancer risk (La Vecchia *et al.*, 1987). Most studies, however, were relatively small in size, not always specifically focused on diet or based on validated food frequency questionnaires that allowed for total energy or other relevant diet-related factors.

The present paper provides further insight on the relation between intakes of several micronutrients, vitamins, and minerals and ovarian cancer using data from a large case–control study conducted in Italy and based on a validated food frequency questionnaire.

Materials and Methods

A case–control study on ovarian cancer was conducted between January 1992 and September 1999 in five Italian areas (Bosetti *et al.*, 2001).

Cases were 1031 patients with a first histologically confirmed epithelial ovarian carcinoma diagnosed 1 year prior to interview, identified in major teaching and general hospitals. Controls were 2411 patients admitted for acute, non-neoplastic diseases to the same network of hospitals. Controls were comparable to cases with reference to age (quinquennia) and study center.

The interviewer-administered food frequency questionnaire assessed the usual diet (including 78 foods, groups or recipes) over the 2 years preceding diagnosis or hospital admission (controls).

To compute micronutrient and energy intake, an Italian food composition database was used (Salvini *et al.*, 1998). Reproducibility and validity of the food frequency questionnaire were satisfactory (Franceschi *et al.*, 1995; Decarli *et al.*, 1996).

Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were obtained by means of unconditional multiple logistic regression models that included eight adjustment terms plus energy according to the residual model. Tests for trend were done between the models with and without a linear term for each nutrient's quintile.

Results

Table 1 gives the distribution of ovarian cancer cases and control subjects according to selected variables. Cases tended to be significantly more educated than controls, to have a lower parity, and to report a family history of ovarian and/or breast cancer more frequently.

Table 2 gives the ORs of ovarian cancer according to subsequent quintiles of intake of various micronutrients compared to the lowest one, together with the tests for linear trend in risk. An inverse association was observed for calcium intake (OR=0.7 for highest versus lowest quintile of intake; 95% CI, 0.6–1.0) and a borderline direct association for zinc

Table 1. Distribution of 1031 cases of epithelial ovarian cancer and 2411 controls, according to age and selected variables. Italy, 1992–1999

	Cases		Controls	
	n	(%)	*n*	(%)
Age (years)				
<45	183	(17.8)	443	(18.4)
45–54	287	(27.8)	615	(25.5)
55–64	325	(31.5)	724	(30.0)
≥ 65	236	(22.9)	629	(26.1)
Education[a] (years)				
<7	577	(56.0)	1442	(59.8)
7–11	227	(22.0)	620	(25.7)
≥ 12	227	(22.0)	349	(14.5)
Parity[a]				
Nulliparous	184	(17.9)	381	(15.8)
1–2	572	(55.5)	1268	(52.6)
3	229	(22.1)	639	(26.5)
≥ 4	46	(4.5)	123	(5.1)
Family history of ovarian and/or breast cancer[a]				
No	902	(87.5)	2291	(95.0)
Yes	129	(12.5)	120	(5.0)

[a]Significant difference between cases and controls adjusted for age and residence ($P<0.01$).
[b]The sum does not add up to the total because of a few missing values.

(OR=1.4; 95% CI, 1.0–1.8). There was a significant inverse association for vitamin E (OR=0.6; 95% CI, 0.5–0.8), beta-carotene (OR=0.8; 95% CI, 0.6–1.0) and lutein/zeaxanthin (OR=0.6; 95% CI, 0.5–0.8). Most inverse associations were linear across quintiles, with significant trends in risk.

Discussion

Our data support the hypothesis that calcium and selected antioxidant micronutrients are inversely associated with epithelial ovarian cancer.

Vitamin E was mainly derived here from olive oil used in vegetable seasoning. Carotenoids and a fraction of vitamin E are derived from fruits and various vegetables. Calcium has been inversely related to the cancer-promoting effect of high dietary fat intake.

With reference to potential recall and selection bias, awareness of any particular dietary hypothesis in ovarian cancer etiology was very limited since the issue had not received widespread media attention. All diagnoses that might have been associated causally with or have determined special dietary habits of controls were excluded. The comparability of dietary history between cases and controls should have been improved by interviewing subjects in the same hospital setting. Adjustment for total energy intake should have reduced potential bias due to differential over- or underreporting of food intakes.

The major strengths of this study are the large dataset examined, consistency of findings across major categories of controls, reliance on a validated food frequency questionnaire, the nearly complete participation rate of patients, and substantial heterogeneity of the studied populations.

In conclusion, the findings of the present study support the hypothesis that intakes of a few micronutrients are inversely related to epithelial ovarian cancer. Whether this reflects a specific effect of these micronutrients, or the general favourable influence of a diet rich in olive oil and vegetables remains outside the scope of observational epidemiological studies.

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Table 2. Odds ratios (OR)[a] of ovarian cancer and corresponding 95% confidence intervals (CI) according to intake of selected micronutrients and minerals. Italy, 1992–1999

			Quintile, OR (95% CI)					
Micronutrient	Mean[b]	Standard deviation	1 (lowest)[c]	2	3	4	5	χ^2
Calcium (g)	1.0	0.4	1	0.9 (0.7–1.2)	0.8 (0.6–1.1)	0.8 (0.6–1.0)	0.7 (0.6–1.0)	6.31[d]
Potassium (g)	3.6	1.1	1	1.0 (0.7–1.3)	0.8 (0.6–1.1)	1.1 (0.9–1.5)	0.8 (0.6–1.1)	0.82
Phosphorus (g)	1.4	0.4	1	1.1 (0.9–1.5)	1.1 (0.8–1.4)	1.1 (0.8–1.5)	0.8 (0.6–1.1)	1.67
Iron (mg)	12.8	4.0	1	1.0 (0.8–1.3)	1.0 (0.7–1.3)	1.0 (0.7–1.3)	1.0 (0.8–1.3)	0.01
Zinc (mg)	11.9	3.5	1	1.1 (0.8–1.4)	1.0 (0.7–1.3)	1.1 (0.8–1.4)	1.4 (1.0–1.8)	3.69
Thiamin (mg)	0.8	0.3	1	1.1 (0.8–1.4)	1.3 (1.0–1.7)	1.2 (0.9–1.6)	1.1 (0.8–1.5)	1.04
Riboflavin (mg)	1.5	0.5	1	1.2 (0.9–1.6)	1.0 (0.8–1.4)	0.9 (0.7–1.2)	1.0 (0.8–1.4)	0.49
Vitamin C (mg)	146.2	78.6	1	1.0 (0.8–1.3)	1.2 (0.9–1.6)	0.9 (0.7–1.2)	1.1 (0.8–1.4)	0.10
Vitamin B6 (mg)	1.8	0.5	1	0.9 (0.6–1.1)	0.9 (0.7–1.2)	1.1 (0.8–1.4)	1.1 (0.8–1.4)	1.79
Folic acid (mcg)	256.0	83.5	1	1.0 (0.7–1.3)	1.1 (0.8–1.4)	1.0 (0.7–1.3)	1.0 (0.7–1.3)	0.07
Niacin (mg)	16.4	4.9	1	1.1 (0.9–1.5)	1.2 (0.9–1.5)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	1.89
Retinol (mg)	0.7	0.9	1	0.9 (0.6–1.1)	0.9 (0.6–1.2)	0.8 (0.6–1.0)	1.1 (0.8–1.4)	0.15
Carotene (mg)	4.3	2.2	1	1.0 (0.8–1.3)	0.9 (0.7–1.1)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	4.43[d]
α-carotene (mg)	0.8	0.7	1	0.9 (0.7–1.1)	0.8 (0.6–1.0)	0.7 (0.5–0.9)	0.9 (0.7–1.2)	2.62
β-carotene (mg)	4.9	2.5	1	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.6 (0.5–0.8)	0.8 (0.6–1.0)	7.63[e]
β-cryptoxanthin (mg)	0.4	0.4	1	1.1 (0.8–1.4)	1.1 (0.8–1.4)	1.0 (0.7–1.3)	1.2 (0.9–1.6)	1.06
Lutein/zeaxanthin (mg)	4.8	2.6	1	1.1 (0.8–1.4)	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.6 (0.5–0.8)	14.71[e]
Lycopene (mg)	6.3	3.7	1	1.0 (0.7–1.3)	1.0 (0.7–1.3)	1.1 (0.8–1.4)	1.1 (0.9–1.5)	1.35
Vitamin D (mcg)	2.9	1.3	1	0.8 (0.6–1.1)	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.7 (0.6–1.0)	2.28
Vitamin E (mg)	14.0	6.0	1	0.8 (0.6–1.1)	0.6 (0.4–0.7)	0.7 (0.5–0.9)	0.6 (0.5–0.8)	13.30[e]

[a]Estimates from multiple logistic regression models including terms for age (quinquennia), study center, year of interview, education, body mass index, parity, oral contraceptive use, occupational physical activity, and energy intake, according to the residual model.

[b]Among controls, per day.

[c]Reference category.

[d]$P<0.05$.

[e]$P<0.01$.

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