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Dietary glycemic index, glycemic load and ovarian cancer risk: a case–control study in Italy

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Background: Dietary carbohydrates vary in their ability to raise blood glucose and insulin levels, which, in turn, influence levels of sex hormones and insulin-like growth factors. We analyzed the effect of type and amount of carbohydrates on ovarian cancer risk, using the glycemic index (GI) and the glycemic load (GL) measurement in a large case–control study conducted in Italy.

Materials and methods: Cases included 1031 women with incident, histologically confirmed epithelial ovarian cancer, from four Italian regions. Controls included 2411 women admitted to the same hospital networks for acute, non-neoplastic conditions. Average daily GI and GL were calculated from a validated food frequency questionnaire. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were computed using multiple logistic regression.

Results: Ovarian cancer was directly associated with dietary GI (OR for highest versus lowest quartile = 1.7, 95% CI 1.3–2.1) and GL (OR = 1.7, 95% CI 1.3–2.1). The associations were observed in pre- and post-menopausal women, and they remained consistent across strata of major covariates identified.

Conclusions: This study supports the hypothesis of a direct association between GI and GL and ovarian cancer risk and, consequently, of a possible role of hyperinsulinemia/insulin resistance in ovarian cancer development.

Key words: carbohydrate, case–control study, glycemic load, ovarian cancer

Introduction

Ovarian cancer is directly related to nulliparity, and inversely related to oral contraceptive use, but little is known of its potential dietary correlates [1]. It has been suggested that diet may have a potential influence on ovarian carcinogenesis, and several case–control studies have reported a beneficial effect on the risk of ovarian cancer of a diet rich in vegetables [2, 3]. A few case–control studies showed that women with cancer of the ovary reported more frequent meat consumption [4, 5], and others suggested that a diet rich in eggs may also increase the risk of ovarian cancer [2, 6]. Fish, on the other hand, seemed to exert a protective effect [5, 6].

With reference to specific nutrients, descriptive epidemiology and ecological studies have reported positive relationships between fat, protein and total calory intake, and ovarian cancer risk [7]. Data from analytical, mainly case–control studies supported the hypothesis of a possible increased risk in relation to various types of fat [2, 6]. Carbohydrates have also been shown to increase the risk of epithelial ovarian cancer [8].

Different carbohydrates, however, affect blood glucose and insulin levels to varying degrees depending on the nature of the carbohydrate and the type and extent of food processing [9]. On this basis they have been ranked using the glycemic index (GI) and glycemic load (GL). Foods with high GI tend to increase glucose and insulin levels to a greater extent than low GI foods [9]. In turn, it has been proposed that insulin may be directly or indirectly involved in the carcinogenic process by modulating hormonal levels such as sex hormones and insulin-like growth factors (IGF) [10]. High-GL diets have been directly associated with risk of various Western chronic conditions, including diabetes [11], coronary heart disease [12], colorectal [13] and breast [14] cancer, and high insulin levels may be one of the mechanisms of action of risk factors shared by these diseases [15].

We thus evaluated the possible differential effects of carbohydrate-rich foods on epithelial ovarian cancer risk by means of the GI and GL measurements in a large case–control study.

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Materials and methods

A multicenter case–control study of ovarian cancer was conducted between January 1992 and September 1999 in four Italian regions: Greater Milan, the provinces of Pordenone, Padua and Gorizia (north-eastern Italy); the province of Latina (central Italy); and the urban area of Naples (southern Italy).

Cases included women with incident, histologically confirmed epithelial ovarian cancer diagnosed within 1 year prior to interview and with no previous diagnosis of cancer. Overall, 1031 women aged 18–79 years (median age 56 years) were included. Controls included patients with no history of cancer who were admitted to hospitals serving the same areas as those where cases had been identified. Eligible diagnoses were acute, non-neoplastic, non-gynecological conditions, unrelated to hormonal or digestive tract diseases, or associated with long-term modifications of diet. They included 2411 women, aged 17–79 years (median age 57 years), belonging to the following diagnostic categories: trauma, mostly fractures and sprains (26%); other orthopedic disorders, such as low back pain and disc disorders (28%); acute surgical conditions (15%); and other illnesses, such as eye, ear, nose, skin and dental conditions (31%). Cases were frequency matched to controls according to quinquennium of age and area of residence. Approximately 4% of cases and controls approached for interview during their hospital stay refused to participate.

The same structured questionnaire and coding manual were used in each center, and all interviewers were centrally trained and routinely supervised. The checking of data for consistency and reliability was also conducted centrally. The questionnaire included information on sociodemographic characteristics, such as education and occupation, lifelong smoking habits, physical activity at various ages, anthropometric measures, a problem-oriented personal medical history, family history of selected cancers, menstrual and reproductive history, history of use of oral contraceptives, hormone replacement treatment, and female hormone-containing drugs for other indications. Dietary habits were investigated through an interviewer-administered food frequency questionnaire (FFQ) that included 78 items. This questionnaire was used to assess the subjects' habitual diet during the 2 years prior to cancer diagnosis or hospital admission (for controls), and included questions on the average weekly frequency of consumption of foods or food groups, as well as complex recipes. Satisfactory reproducibility [16] and validity [17] of the FFQ have been reported. Details on methodology used have been described elsewhere [13, 14]. To compute energy and nutrient intake, an Italian food-composition database was used. For each food, we expressed GI as a percentage of the glycemic response elicited using 'white bread' as a standard food. We then calculated daily average GI by summing the products of the carbohydrate content per serving for each food or recipe, multiplied by the average number of servings of that food per week, multiplied by its GI, all divided by the total amount of available carbohydrate weekly intake. This represents the 'quality of the carbohydrates', namely slow versus fast absorbable carbohydrates. A score for the daily average GL was computed as the GI, but without dividing by the total amount of carbohydrates. For these calculations we used the carbohydrate content of 50 foods or recipes, since 28 foods or recipes, chiefly cheese, meat and fish-based, contained a negligible amount of carbohydrate. With respect to GI values, we chiefly used international tables. In order to take into account Italian cooking habits (e.g. pasta 'al dente'), Italian sources were used for a few local recipes. Food items for which a GI had not been determined were assigned the GI of the nearest comparable food (e.g. tangerines were assigned the same GI as oranges).

Odds ratios (ORs) and the corresponding 95% confidence intervals (CI) for quartiles of GI and GL intake were computed using unconditional multiple logistic regression models [18]. The regression equations included terms for quinquennia of age, study center, years of education, occupational physical activity, history of diabetes, oral contraceptive use, parity, menopausal status, number of daily meals, intakes of fiber, alcohol and total energy intake. Adjustment for energy was made using the residuals method. The modifying effect of various covariates was evaluated comparing the differences between the –2 log likelihood of the model with and without interaction terms, and referring it to the chi square distribution with degrees of freedom equal to the number of interaction terms minus one.

Results

Table 1 gives the distribution of ovarian cancer cases and control subjects according to age, education, menopausal status and other potential confounding factors. Cases were better educated than controls, had a lower parity, frequently reported a family history of ovarian and/or breast cancer, and a lower occupational physical activity.

GI was positively correlated with GL (Pearson correlation coefficient, $r = 0.53$), intake of bread ($r = 0.59$), cereals ($r = 0.56$), cakes and sweets ($r = 0.33$), sugar ($r = 0.26$), available carbohydrates ($r = 0.37$), cereal fibre ($r = 0.42$), and negatively correlated with fruit ($r = –0.19$) and vegetables ($r = –0.11$). Correlations of GI with other dietary and non-dietary factors were weak (i.e. $|r| < 0.10$).

Table 2 shows the ORs of epithelial ovarian cancer according to the quartiles of GI and GL, and total carbohydrate intake by menopausal status. Dietary GI and GL were directly associated with ovarian cancer risk, and the ORs, for the highest versus the lowest quartile, were 1.7 (95% CI 1.3–2.1) and 1.7 (95% CI 1.3–2.1), respectively. However, ORs by quartile of GI and GL did not show linear trends, but were already elevated in the second quartile and tended to plateau thereafter. Associations, particularly for GI, were appreciably stronger in postmenopausal compared with premenopausal women, although no significant heterogeneity emerged. Total carbohydrate intake was also associated with ovarian cancer (OR = 1.8, in the highest quartile, 95% CI 1.3–2.4) in postmenopausal women (Table 2).

Table 3 shows the relationship between GI and epithelial ovarian cancer in different strata of known or suspected risk factors for ovarian cancer. No substantial effect modification was apparent in strata of: family history of ovarian or breast cancer; oral contraceptive use; and parity.

The relationship between GI and epithelial ovarian cancer risk was also analyzed in separate strata of history of diabetes, body mass index (BMI), BMI increase from age 30, waist to hip (W/H) ratio, occupational physical activity and alcohol intake (Table 4). There was no consistent pattern of risk among diabetic subjects or in different strata of BMI, BMI increase from age 30, and W/H ratio. There was, however, a significant modifying effect of alcohol, with no consistent association with GI in alcohol abstainers. The association with GI was stronger in women reporting higher physical activity.

Although risk factors, including dietary factors, may differ in their relationship to specific histological subtypes of ovarian cancer [19], no relevant difference emerged when we replicated the analyses for GI and GL in invasive serous ovarian cancer only. Other histological subtypes represented <10% of cases in our data set.

Table 1. Distribution of 1031 cases of epithelial ovarian cancer and 2411 controls[a], according to age and selected variables (Italy, 1992–99)

Characteristic	Cases		Controls		χ^{2} [b]
	n	%	*n*	%	(*P* value)
Age groups (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 (years)					
<7	570	55.6	1417	59.4	
7–11	227	22.2	620	26.0	38.90
≥12	22	22.2	349	14.6	(<0.01)
Menopausal status					
Premenopausal	346	33.6	803	33.4	0.02
Postmenopausal	683	66.4	1603	66.6	(0.89)
Parity (number of births)					
Nulliparae	184	17.8	381	15.8	
1–2	572	55.5	1268	52.6	48.20
≥3	275	26.7	762	31.6	(<0.01)
Oral contraceptive use					
Never	921	89.3	2142	88.8	0.18
Ever	110	10.7	269	11.2	(0.67)
Diabetes history					
No	986	95.6	2324	96.4	0.06
Yes	45	4.4	87	3.6	(0.81)
Family history of breast or ovarian cancer[c]					
No	902	87.5	2291	95.0	55.95
Yes	129	12.5	120	5.0	(0.01)
Occupational physical activity					
Low	331	33.2	677	28.9	
Medium	492	49.3	1237	52.9	22.75
High	175	17.5	426	18.2	(<0.01)
Alcohol intake (drinks per week)					
Abstainers	288	27.9	833	34.5	
1–6	261	25.3	542	22.5	
7–13	226	21.9	421	17.5	0.31
≥14	256	24.9	615	25.5	(0.58)
Meal frequency					
1 per day	40	3.9	83	3.5	0.47
2 per day or more	991	96.1	2325	96.5	(0.48)
Fibre intake (g/day)					
<17.5	218	21.1	647	26.8	
17.5–22.2	257	24.9	611	25.3	
22.2–27.1	280	27.2	568	23.6	6.71
≥27.1	276	26.8	585	24.3	(0.01)

[a]Some figures do not add up to the total as some values are missing.
[b]Cochran–Mantel–Haenzel χ^{2} adjusted for center and age.
[c]In immediate relatives.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs)[a] of epithelial ovarian cancer by quartile of energy-adjusted glycemic index, glycemic load and total carbohydrate intake (Italy, 1992–99)

	Cases:controls[b]	Quartile, OR (95% CI)				χ^2_1 (trend) (*P* value)
		1[c]	2	3	4	
Glycemic index						
Upper limit[d]		70.8	74.4	77.7	–	
Premenopausal	346:803	1	1.33 (0.88–2.00)	1.42 (0.95–2.14)	1.36 (0.90–2.05)	2.12 (0.15)
Postmenopausal	683:1603	1	1.83 (1.36–2.47)	2.10 (1.57–2.82)	1.84 (1.37–2.48)	16.29 (<0.01)
All cases	1031:2411	1	1.61 (1.27–2.04)	1.80 (1.43–2.27)	1.65 (1.30–2.09)	16.81 (<0.01)
Glycemic load						
Upper limit[d]		147	185	234	–	
Premenopausal	346:803	1	1.49 (0.99–2.25)	1.68 (1.09–2.57)	1.39 (0.92–2.10)	2.31 (0.13)
Postmenopausal	683:1603	1	1.37 (1.02–1.84)	1.49 (1.11–2.00)	1.83 (1.36–2.46)	15.58 (<0.01)
All cases	1031:2411	1	1.40 (1.11–1.78)	1.54 (1.22–1.96)	1.65 (1.30–2.09)	16.89 (<0.01)
Total carbohydrate intake (g)						
Upper limit[d]		7.57	9.44	11.55	–	
Premenopausal	346:803	1	1.31 (0.86–1.98)	1.33 (0.86–2.06)	1.39 (0.90–2.15)	1.87 (0.17)
Postmenopausal	683:1603	1	1.49 (1.11–1.99)	1.55 (1.14–2.10)	1.75 (1.28–2.39)	11.40 (<0.01)
All cases	1031:2411	1	1.44 (1.13–1.82)	1.48 (1.16–1.90)	1.62 (1.27–2.08)	12.93 (<0.01)

[a]Adjusted for age, study center, years of education, occupational physical activity, meal frequency, alcohol consumption, fibre and energy intake, history of diabetes, oral contraceptive use, parity and menopausal status (when appropriate).
[c]Some figures do not add up to total because of some missing value.
[c]Reference category.
[d]In overall population of cases and controls.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs)[a] of epithelial ovarian cancer by strata of selected variables and quartile of energy-adjusted glycemic index (Italy, 1992–99)

	Cases:controls[b]	Quartile, OR (95% CI)				χ^2_1 (*P* value)
		1[c]	2	3	4	
Upper limit[d]		70.8	74.4	77.7	–	
Family history of breast and/or ovarian cancer[e]						
Yes	129:120	1	2.05 (0.85–4.96)	1.59 (0.72–3.53)	1.45 (0.61–3.44)	0.51 (0.48)
No	902:2291	1	1.64 (1.27–2.11)	1.84 (1.44–2.37)	1.70 (1.32–2.19)	16.67 (<0.01)
Oral contraceptive use						
Yes	110:269	1	2.25 (1.06–4.76)	2.02 (0.98–4.18)	1.53 (0.71–3.28)	0.84 (0.36)
No	921:2142	1	1.52 (1.18–1.96)	1.77 (1.38–2.28)	1.61 (1.25–2.07)	14.52 (<0.01)
Parity (no. of births)						
Nulliparae	184:381	1	2.30 (1.26–4.20)	2.01 (1.10–3.66)	1.39 (0.77–2.51)	0.98 (0.32)
1–2	572:1268	1	1.51 (1.10–2.07)	1.75 (1.27–2.40)	1.62 (1.16–2.25)	8.90 (<0.01)
≥3	275:762	1	1.95 (1.20–3.18)	2.39 (1.51–3.81)	2.26 (1.42–3.59)	11.67 (<0.01)

[a]Adjusted for age, study center, years of education, occupational physical activity, meal frequency, alcohol consumption, fibre and energy intake, history of diabetes, oral contraceptive use, parity and menopausal status (when appropriate).
[b]Some figures do not add up to the total as some values are missing.
[c]Reference category.
[d]In the overall population of cases and controls.
[e]In immediate relatives.

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs)[a] of epithelial ovarian cancer by strata of selected variables and quartile of energy-adjusted glycemic index (Italy, 1992–99)

	Cases:controls[b]	Quartile, OR (95% CI)				χ^2_1 (trend) (*P* value)
		1[c]	2	3	4	
Upper limit[d]		70.8	74.4	77.7	–	
Diabetes						
Yes	45:87	1	0.75 (0.16–3.47)	1.66 (0.37–7.55)	1.04 (0.22–5.05)	0.13 (0.71)
No	986:2324	1	1.69 (1.32–2.15)	1.88 (1.48–2.39)	1.69 (1.33–2.16)	17.44 (<0.01)
Body Mass Index (BMI)						
<25	549:1266	1	1.63 (1.16–2.28)	1.84 (1.32–2.54)	1.48 (1.06–2.07)	4.97 (0.03)
≥25	472:1128	1	1.66 (1.18–2.35)	1.71 (1.20–2.43)	1.79 (1.26–2.54)	9.77 (<0.01)
BMI increase from age 30 years[e]						
≤0	228:467	1	1.57 (0.96–2.57)	1.79 (1.11–2.87)	1.74 (1.07–2.83)	5.07 (0.02)
>0 to 4	465:1001	1	1.73 (1.20–2.50)	1.75 (1.22–2.52)	1.65 (1.14–2.37)	6.31 (0.01)
>4	233:716	1	1.61 (0.99–2.62)	2.09 (1.28–3.40)	1.67 (1.01–2.75)	4.89 (0.03)
Waist to hip ratio						
<0.83	319:922	1	1.62 (1.08–2.44)	1.95 (1.31–2.90)	1.43 (0.93–2.19)	3.99 (0.05)
≥0.83	407:925	1	1.82 (1.23–2.68)	1.80 (1.23–2.63)	1.95 (1.33–2.84)	10.04 (<0.01)
Occupational physical activity						
Low	331:677	1	1.58 (1.01–2.48)	1.62 (1.05–2.49)	1.27 (0.82–1.97)	1.14 (0.29)
Medium	492:1237	1	1.55 (1.11–2.18)	1.68 (1.20–2.36)	1.56 (1.11–2.21)	6.32 (0.01)
High	175:426	1	1.95 (1.03–3.68)	3.16 (1.72–5.81)	3.05 (1.64–5.67)	14.70 (<0.01)
Alcohol intake (drinks per week)						
Abstainers	288:833	1	1.56 (1.01–2.40)	1.32 (0.86–2.03)	0.98 (0.63–1.51)	0.16 (0.69)
1–6	261:542	1	1.78 (1.09–2.93)	2.54 (1.55–4.15)	2.22 (1.35–3.63)	11.65 (<0.01)
7–13	226:421	1	1.34 (0.75–2.37)	2.29 (1.29–4.07)	2.15 (1.20–3.84)	8.93 (<0.01)
≥14	256:615	1	1.89 (1.15–3.11)	1.96 (1.21–3.16)	2.24 (1.37–3.66)	9.62 (<0.01)

[a]Adjusted for age, study centre, years of education, occupational physical activity, meal frequency, alcohol consumption, fibre and energy intake, history of diabetes, oral contraceptive use, parity and menopausal status (when appropriate).
[b]Some figures do not add up to the total as some values are missing.
[c]Reference category.
[d]In the overall population of cases and controls.
[e]For subjects aged 35 years or more.

Discussion

The present study shows direct associations between dietary GI and GL and epithelial ovarian cancer risk. An elevated risk was found in the second quartile of GI and GL, but did not show a further increase in the third and fourth (highest) quartile. These associations were consistent across different strata of known or potential risk factors for ovarian cancer. However, the relationship between GI and epithelial ovarian cancer in our study was somewhat stronger in post- compared with premenopausal women, and in women without a family history and in parae.

Diets with high GI or GL are associated with a high consumption of refined carbohydrates, which are quickly absorbed and are capable of elevating blood glucose and insulin level to a greater extent than slowly absorbed ones, such as pulses and whole grains, which are low GI foods [20]. The main sources of carbohydrates in the Italian population are bread, a high GI food, and pasta, a medium-low GI food, representing 20.5% and 13.4% of total carbohydrate intake, respectively [13].

High insulin levels have been suggested as a potential unifying mechanism for the risk of several Western chronic diseases related to high intakes of energy, fat, refined carbohydrates, and low physical activity and obesity [15]. Central obesity (i.e. high W/H ratio) was associated with ovarian cancer risk in this study [21]. Diabetes, which is characterized by high insulin levels in its early stages, was considered as a possible correlate of ovarian cancer risk. However, in line with other studies [22, 23] a history of diabetes was not found to consistently affect ovarian cancer

risk in the present study. This could, however, have resulted from the small absolute number of diabetic subjects (~4%).

Insulin is a growth factor for cancer cells, and it has been shown to act as a cancer promoter in *in vitro* and in animal studies [15, 24]. Insulin also has affinity for IGF receptors, particularly the IGF-1 receptor, which has strong mitogenic effects on normal and neoplastic cells, including ovarian carcinoma cell lines, where it has been found at higher levels than in non-malignant cells [25]. Epidemiological evidence suggests a promoting effect of hyperinsulinemia [15] and of IGF-1 in carcinogenesis [25].

Insulin and IGF-1 are also powerful negative regulators of sex hormone-binding globulin (SHBG) synthesis *in vitro*, and they may stimulate ovarian cancer proliferation through a hormonal pathway [26]. An interaction between insulin, IGFs and sex hormones has also been suggested for breast cancer [27].

As in most case–control studies, recall and selection biases are possible [18]. However, awareness about any dietary hypotheses, and particularly those related to GI and GL, for ovarian cancer was limited in the Italian population when the study was conducted. While it is conceivable that dietary habits of hospital controls may have differed from those of the general population, great attention was paid in this study to minimize bias by excluding control subjects admitted for conditions that might have been associated with special dietary habits. Of greater concern is the early weight loss often occurring in ovarian cancer patients, which may have led cases to increase their energy and, hence, carbohydrate intake [21]. We had, however, information on weight loss during the year prior to cancer diagnosis or interview. Stratification and adjustment for weight or recent weight loss did not modify the association with GI and GL. Interviewing all subjects in a hospital setting may have allowed greater comparability of dietary history between cases and controls [28], and adjustment for total energy intake should have controlled for potential dietary over- and under-reporting. Furthermore, participation among eligible patients was practically complete and the catchment areas for cases and controls were highly comparable.

GI estimates have some limitations. Some GI estimates have been derived from small samples and their variability is unclear [13]. Statistics on the average dietary GI and GL in the general Italian population are not available, but intakes of bread and pasta in the present study were similar to those reported in the Italian population [29]. In addition, it would be important to confirm the association between GI, GL and ovarian cancer in different populations, since the genotype for insulin resistance may vary between ethnic groups [30].

The major strength of this study is its uniquely large dataset, which allowed reasonably precise risk estimates. Other strengths include consistency of findings, when major categories of controls were used separately, and its reliance on a validated food frequency questionnaire [16, 17].

In conclusion, this study found associations between dietary GI, GL and ovarian cancer risk, thus supporting a possible role of insulin and insulin-related factors in ovarian carcinogenesis. Similar associations were observed for colorectal [13] and breast [14] cancer, indicating the potential role of these factors on several common neoplasms.

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