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Dietary Inflammatory Index and ovarian cancer risk in a large Italian case-control study

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Abstract

Background—While inflammation has been shown to play an important etiologic role in ovarian carcinogenesis, little is known about the association between inflammatory properties of diet and ovarian cancer risk.

Methods—We explored the association between the dietary inflammatory index (DII) and ovarian cancer risk in a multicentric Italian case-control study conducted between 1992 and 1999. Cases were 1031 women with incident, histologically confirmed ovarian cancer from 4 areas in Italy. Controls were 2,411 women admitted to the same network of hospitals as the cases for acute, non-malignant and non-gynecological conditions, unrelated to hormonal or digestive-tract diseases or committed to long-term modifications of diet. DII scores were computed based on 31 nutrients and food items assessed using a reproducible and validated 78-item food frequency questionnaire. Odds ratios (ORs) were estimated through logistic regression models adjusting for age, total energy intake and other recognised confounding factors.

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Disclosure: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

Results—Subjects in the highest quartile of DII scores (i.e., with the most pro-inflammatory diets) had a higher risk of ovarian cancer compared to subjects in the lowest quartile (i.e., with an anti-inflammatory diet) ($OR_{\text{Quartile4vs1}} = 1.47$, 95% confidence interval, CI, 1.07, 2.01; p -trend=0.009). When analyses were carried out using continuous DII, a significant positive association with ovarian cancer was observed, the OR for one-unit increment in DII score (corresponding to approximately 8% of its range in the current study, +6.0 to −6.20) was 1.08 (95% CI=1.02, 1.14).

Conclusion—A pro-inflammatory diet as indicated by higher DII scores is associated with increased ovarian cancer risk.

Keywords

diet; inflammatory index; ovarian cancer; risk factor

INTRODUCTION

Ovarian cancer is the 7th most common cancer in women worldwide, with 239,000 new cases diagnosed in 2012 (1). Among gynecological cancers, ovarian cancer has the highest mortality rates, with dismal five-year survival rates (46% for all stages combined) (2). Risk factors for ovarian cancer include obesity, nulliparity, and family history of the disease (including mutations in BRCA1 and BRCA2 genes), while oral contraceptive (OC) use, higher parity, and tubal ligation have been shown to reduce risk (3, 4). Several studies have been conducted exploring the association between dietary factors and ovarian cancer with inconsistent results (5). While there is growing evidence linking inflammation to ovarian carcinogenesis (6, 7), to date there has been no research on the role that inflammatory potential of diet plays in ovarian cancer risk.

The dietary inflammatory index (DII) was recently developed to assess the inflammatory potential of an individual's diet (8). A pro-inflammatory diet is characterized by a high consumption of foods rich in saturated fat and carbohydrates, and a low consumption of foods rich in poly-unsaturated fatty acids, flavonoids, and other antioxidant dietary components. The DII has been validated in a variety of longitudinal and cross-sectional studies with various inflammatory markers, including C-reactive protein (CRP) (9), interleukin-6 (IL-6) (10), and tumor necrosis factor- α (11). The DII has been associated with risk of colorectal cancer in case-control studies in Spain and Italy (12, 13); in three cohort studies from the USA (14–16), and risk of pancreatic, prostate, hepatocellular and esophageal squamous cell cancers in case-control studies in Italy (17–20). Among gynecological cancers, the DII has been shown to be associated with endometrial cancer in Italy (21). Using a large case-control study conducted in Italy (22), this is the first attempt to examine the association between the DII and ovarian cancer risk. Our working hypothesis is that women with ovarian cancer are more likely to have consumed a pro-inflammatory diet compared to women with no ovarian cancer.

METHODS

Design and Participants

An unmatched case-control study of ovarian cancer was conducted between January 1992 and September 1999 in four Italian areas: the greater Milan area (northern Italy), the provinces of Pordenone, Padua and Gorizia (north-eastern Italy), the province of Latina (central Italy), and the urban area of Naples (southern Italy) (22). Cases were 1,031 women (median age 56 years) admitted to the major teaching and general hospitals in the areas under study with incident, histologically confirmed epithelial ovarian cancer. Controls were 2,411 women (median age 57) from the same catchment areas and admitted to the same network of hospitals as the cases for acute, non-malignant and non-gynecological conditions, unrelated to hormonal or digestive-tract diseases or who were engaged in long-term dietary modification. Among controls, 26% were admitted for traumas, 28% for non-traumatic orthopaedic disorders, 15% for surgical conditions and 31% for miscellaneous other illnesses, including eye, ear, nose, throat and dental disorders. Less than 4% of cases and controls approached refused interview, and the response rate did not appreciably vary across hospitals and geographic areas. All subjects signed an informed consent, according to the recommendations of the Board of Ethics of the study hospitals.

Centrally trained and supervised interviewers collected information on socio-demographic characteristics, anthropometric measures, life-style habits, including tobacco smoking and history of selected diseases during their hospital stay using a structured questionnaire. Each subject's usual diet during the 2 years prior to cancer diagnosis (for cases) or hospital admission (for controls) was assessed using an interviewer-administered food frequency questionnaire (FFQ), consisting of 78 items on foods and beverages. Subjects were asked to indicate the average weekly frequency of consumption of each dietary item; intakes lower than once a week, but at least once a month, were coded as 0.5 per week. Nutrient and total energy intake was determined using an Italian food composition database (23). The FFQ was tested for validity (7-day dietary record was used as reference method) (24) and reproducibility (25, 26), with satisfactory results for both validity and reproducibility. This was assessed using repeated two-week diaries in different seasons (24–26).

In order to compute the DII score, dietary information for each study participant was first linked to the regionally representative database that provided a robust estimate of a mean and a standard deviation for each of the 45 parameters (i.e., foods, nutrients, and other food components) considered in the DII definition (8). These parameters then were used to derive the subject's exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the parameter's standard deviation. The purpose of deriving z-scores was to alleviate problems with using actual units of measurements as multipliers, as doing so in the original DII formulation resulted in over- or under-weighting of parameters in an effort to place them into an arbitrary "reasonable" range. For example, μg and mg differ by three orders of magnitude and some parameters, such as vitamin A and β -carotene, had to be divided by 100 and others, such as n -3 and n -6 fatty acids, multiplied by 10 in order to place them in a 'reasonable' range so as not to over- or underestimate their influence on the overall

score. The use of z-scores solved this problem entirely by eliminating problems with right-skewing of the data. By converting z-scores to percentiles, and then centering them fixes “null” values to zero. Clinical interpretation remains clear with these additional steps as inappropriate weighting is avoided and higher (i.e., more positive) DII scores still represent more pro-inflammatory diets. The resulting value was then multiplied by the corresponding food parameter effect score (derived from a literature review on the basis of 1943 articles (8)).

All of these food parameter-specific DII scores were then summed to create the overall DII score for every subject in the study. Higher scores indicate a pro-inflammatory diet while lower scores indicate a more anti-inflammatory diet. The DII computed on this study’s FFQ includes data on 31 of the 45 possible food parameters comprising the DII: carbohydrates, proteins, fats, alcohol, fibers, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega 3, omega 6, niacin, thiamin, riboflavin, vitamin B6, iron, zinc, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, beta carotene, anthocyanidins, flavan3ols, flavonols, flavanones, flavones, isoflavones, caffeine, and tea. Because we adjusted for energy in the analyses, we did not use it for DII calculation. The remaining 13 missing food parameters are pepper, saffron, turmeric, garlic, ginger, onion, eugenol, trans fat, selenium, magnesium, vitamin B12, thyme and rosemary.

Statistical analysis

The DII was analysed both as a continuous variable and by quartiles of exposure computed among controls. Distributions of characteristics across quartiles of DII for controls and cases were computed and differences were analyzed using the chi-square test. Differences in food groups across quartiles of DII were determined using ANOVA. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated using unconditional logistic regression models adjusted for quinquennia of age, total energy intake (quintiles among both cases and controls), year of interview, study centre, education (<7, 7–11, 12 years), body mass index (BMI, <25, 25–<30, ≥30 kg/m²), parity (0, 1–2, ≥3), OC use (never, ever use), menopausal status (pre/peri-menopause, post menopause), and family history of ovarian and/or breast cancer in first degree-relatives (no/yes). Missing values for adjustment variables (2 cases and 5 controls for menopausal status and 10 cases and 17 controls for BMI) were imputed to pre/peri menopausal status and to 20–25 kg/m² for menopausal status and BMI respectively, and then included in the models. The test for linear trend was carried out using the median value within each quartile as an ordinal variable. To investigate whether the effect of the DII was homogeneous across strata of selected covariates, we carried out stratified analyses according to menopausal status, parity, OC use, and family history of ovarian and/or breast cancer in first degree-relatives. To test heterogeneity across strata, we computed the difference in the –2 log likelihood of the models with and without the interaction terms. Statistical analyses were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Compared with controls, cases had similar age distribution, but reported higher levels of education and energy intake, and more often had a history of ovarian or breast cancer in first-degree relatives. With reference to hormonal and reproductive factors, no appreciable difference was found for menopausal status, whereas cases less frequently had 3 children and reported less frequent OC use than controls.

Characteristics of subjects across quartiles of DII are provided for controls and cases in Table 1 and 2, respectively. Controls in the highest quartile of DII were more likely to be older, nulliparous and to have never used OC (Table 1), whereas cases in the highest quartile of DII were more likely to have BMI <25kg/m² (Table 2).

Table 3 shows the distribution of 10 food groups across DII quartiles among controls. Servings of fruit, vegetables, and fish decreased significantly across quartiles, whereas servings of pork, sugar, cheese, and desserts increased significantly.

Table 4 shows adjusted ORs of ovarian cancer according to the DII quartiles and continuous DII. Subjects in the highest quartile of DII had a 47% excess risk of ovarian cancer compared to subjects in the lowest quartile (OR_{Quartile4vs1} = 1.47, 95% CI=1.07, 2.01; *p*-trend =0.009). Also when analyses were carried out using continuous DII, a significant positive association with ovarian cancer was observed, the OR for one-unit increment in the DII score (corresponding to approximately 8% of its range in the current study, +6.0 to -6.2) being 1.08 (95% CI=1.02, 1.14).

Table 5 shows multivariable ORs of ovarian cancer in strata of selected covariates. Stronger associations were observed among post-menopausal women (OR_{Quartile4vs1} = 1.63, 95% CI 1.10, 2.41), non-contraceptive users (OR_{Quartile4vs1} = 1.62, 95% CI 1.16, 2.27) and in women with no family history of ovarian and/or breast cancer in first-degree relatives (OR_{Quartile4vs1} = 1.53, 95% CI 1.10, 2.13) whereas test for heterogeneity was not significant for any of the strata (*p* values >0.10).

DISCUSSION

In this large case-control study, we observed a significant positive association between inflammatory potential of diet – as measured by increasing DII scores – and ovarian cancer among Italian women.

The same case-control study analyses showed significant trends of increasing risk for red meat, whereas inverse associations for high consumption of fish, raw and cooked vegetables, and pulses (22). An inverse relation was also found between ovarian cancer and flavonols as well as isoflavones (27), vitamin E, beta-carotene, and lutein/zeaxanthin (28). Positive associations with ovarian cancer emerged for starch intake, while inverse associations emerged for fiber (29), monounsaturated, and polyunsaturated fatty acids (30). Among fatty acids, oleic, linoleic, linolenic acids were inversely related to ovarian cancer (30). Previous results from the same case-control study also showed a positive association between dietary glycemic index (GI, i.e., the ability of carbohydrates to raise blood glucose and insulin

levels) and ovarian cancer risk (31). Several of these Anti-inflammatory components that are involved in DII calculation include flavonols, isoflavone, vitamin E, beta carotene, fiber, monounsaturated fatty acids, polyunsaturated fatty acids, linoleic and linolenic acids. By contrast, carbohydrates and starch contribute to the pro-inflammatory of diet and therefore increase DII scores (8).

Results from other studies exploring dietary components that contribute to the DII score and ovarian cancer have been inconsistent. No association with ovarian cancer was found in a case-control study in New Jersey (USA) with the Healthy Eating Index or with total antioxidant capacity (32, 33), while selenium from food sources was associated with reduced the risk (33). In the NIH-AARP cohort study, sugar consumption was inversely associated with ovarian cancer (34), whereas no association was observed with sugar in a case-control study from New Jersey (35). In a cohort study conducted in Canada, GI and carbohydrates were not associated while glycemic load (GL) or increased risk of ovarian cancer (36). The overall evidence of GI, GL, and ovarian cancer indicates only a moderate positive association (37).

Despite the somewhat equivocal evidence on specific dietary components, there is strong evidence suggesting the role of inflammation in the incidence of ovarian cancer (6, 7, 38, 39). In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, both higher levels of CRP and IL-6 have been shown to be associated with increased risk of ovarian cancer (7). Results from the Prostate, Lung, Colorectal And Ovarian Cancer (PLCO) screening trial suggest that CRP, IL-1 α , IL-8, and TNF- α are associated with increased risk of subsequently developing ovarian cancer (38). Similarly, in the Nurse's Health Study, higher levels of circulating CRP were associated with increased risk of ovarian cancer (39). These previous results support our hypothesis that inflammation is associated with ovarian cancer and diet plays a role in this association. In relation to inflammatory markers, DII has been shown to be associated with CRP (9), IL-6 (11), TNF- α (11) and homocysteine (10). A possible common mechanism could be the effect of pro-inflammatory diet on insulin-like growth factor (IGF), which has been shown to be a promoter of carcinogenesis (40, 41) by exerting its well-established mitotic, antiapoptotic and proangiogenic effects (42). Experimental studies have shown that IGF-I protein, receptor and mRNA are expressed in ovarian cancer cells and tissues and that they are associated with progression of ovarian cancer (43). Additionally, IL-6 act by regulating proliferation, adhesion and invasion in human ovarian cells (44).

This study has the strengths and some of the limitations characteristic of hospital-based case-control studies including possible selection and information biases. The almost complete participation of both cases and controls in this large study indicates that selection bias is unlikely to be a major concern. Attention has been paid to include in the comparison group only subjects with acute conditions, unrelated to known or likely risk factors for ovarian cancer, and unlikely to be related to long-term dietary changes. Furthermore, use of the same hospital setting for cases and controls would tend to improve the comparability of information collected, and the structured investigation of the habitual diet 2 years before the interview should reduce potential recall bias. With reference to other potential source of recall bias in the present study, awareness of any particular dietary hypothesis in ovarian

cancer aetiology was very limited in the Italian public at the time that this investigation was undertaken. Moreover, the dietary questionnaire was tested for reproducibility (25, 26) and validity (24), giving satisfactory results. In addition, no significant heterogeneity was found across strata of menopausal status, parity, OC, and family history of ovarian or breast cancer, providing further support to the consistency of the association observed with DII.

A limitation of the study may be the use of a FFQ that, with respect to the DII, did not include 14 food factors for complete calculation. However, some of the food parameters such as saffron, ginger and turmeric are consumed infrequently in this population; so, non-availability of these parameters may not have played a major impact. However, food parameters such as rosemary, thyme, garlic, magnesium, selenium are more likely to be consumed in higher quantities, so inclusion of these food parameters could have influenced our results. Further to this issue of non-availability, we have found little drop off in predictability in other studies, such as the SEASONS Study (9), in which we compared multiple (15) 24-hour recall interviews to five 7-Day Dietary Recalls and the Women's Health Initiative (11), which compared multiple 24-hour recall interviews to an FFQ. In the SEASONS study, DII was calculated from 44 food parameters using the 24-hour recalls and from 27 food parameters using 7-Day Dietary Recall (7DDR). With CRP (>3 mg/l) as the outcome, we did not observe any drop off in the effect of the DII in the 7DDR subset (9). Similarly robust results were observed with the WHI FFQ (11).

In the current study we did not have adequate information on histology of ovarian cancer; hence we could not test if there are differences in results by histological features. All cases, in any event, were epithelial ovarian cancers. Physical activity and non-steroidal anti-inflammatory drugs use have been found to reduce inflammation (45, 46) and to reduce the risk of ovarian cancer (47–50) but did not modify any of the associations observed.

In conclusion, our study suggests that subjects with ovarian cancer were more likely to have a pro-inflammatory diet, as shown by higher DII scores. However, this finding requires replication in other studies, including prospective cohorts.

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Table 1

Distribution of 2411 controls across quartiles of dietary inflammatory index (DII). Italy, 1992–1999.

Characteristics	DII quartiles				<i>p</i> value ^b
	< -1.63	-1.63, -0.32	-0.31, 1.35	> 1.35	
	N (%)	N (%)	N (%)	N (%)	
Age (years)					0.05
<45	121 (20.1)	108 (17.9)	109 (18.1)	105 (17.4)	
45–54	165 (27.4)	162 (26.8)	156 (25.9)	132 (21.9)	
55–64	179 (29.7)	187 (31.0)	183 (30.4)	175 (29.0)	
65	137 (22.8)	147 (24.3)	154 (25.6)	191 (31.7)	
Education (years)					0.07
<7	351 (58.3)	366 (60.6)	363 (60.3)	362 (60.0)	
7–11	173 (28.7)	148 (24.5)	163 (27.1)	136 (22.6)	
12	78 (13.0)	90 (14.9)	76 (12.6)	105 (17.4)	
Menopausal status ^a					0.36
Pre/perimenopause	216 (35.9)	205 (34.0)	193 (32.1)	189 (31.5)	
Postmenopause	386 (64.1)	398 (66.0)	408 (67.9)	411 (68.5)	
Parity					0.004
0	84 (14.0)	76 (12.6)	94 (15.6)	127 (21.1)	
1–2	328 (54.5)	324 (53.6)	319 (53.0)	296 (49.1)	
3	190 (31.6)	204 (33.8)	189 (31.4)	180 (29.8)	
Oral contraceptive use					0.03
Never	518 (86.1)	539 (89.2)	534 (88.7)	551 (91.4)	
Ever	84 (13.9)	65 (10.8)	68 (11.3)	52 (8.6)	
Body mass index (kg/m ²) ^a					0.99
<25	309 (51.6)	318 (52.7)	317 (53.1)	320 (53.8)	
25–30	207 (34.6)	205 (34.0)	203 (34.0)	195 (32.8)	
30	83 (13.8)	80 (13.2)	77 (12.8)	80 (13.3)	
Family history of ovarian/breast cancer					0.38
No	571 (94.8)	581 (96.2)	572 (95.0)	567 (94.0)	
Yes	31 (5.2)	23 (3.8)	30 (5.0)	36 (6.0)	

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The sum does not add up to the total because of some missing values, i.e., 5 controls for menopausal status and 17 controls for body mass index.
 p value for Chi-square test

Table 2
Distribution of 1031 ovarian cancer cases across quartiles of dietary inflammatory index (DII). Italy, 1992–1999.

Characteristics	DII quartiles				<i>p</i> value ^b
	< -1.63	-1.63, -0.32	-0.31, 1.35	> 1.35	
	N (%)	N (%)	N (%)	N (%)	
Age (years)					0.43
<45	33 (14.3)	45 (17.6)	47 (17.6)	58 (20.9)	
45–54	73 (31.7)	66 (25.8)	73 (27.3)	75 (27.0)	
55–64	73 (31.7)	85 (33.2)	76 (28.5)	91 (32.7)	
65	51 (22.2)	60 (23.4)	71 (26.6)	54 (19.4)	
Education (years)					0.81
<7	124 (53.9)	143 (55.9)	153 (57.3)	157 (56.5)	
7–11	52 (22.6)	60 (23.4)	61 (22.8)	54 (19.4)	
12	54 (23.5)	53 (20.7)	53 (19.9)	67 (24.1)	
Menopausal status ^a					0.48
Pre/perimenopause	74 (32.2)	85 (33.2)	84 (31.5)	103 (37.3)	
Postmenopause	156 (67.8)	171 (66.8)	183 (68.5)	173 (62.7)	
Parity					0.24
0	39 (17.0)	49 (19.1)	36 (13.5)	60 (21.6)	
1–2	130 (56.5)	146 (57.0)	152 (56.9)	144 (51.8)	
3	61 (26.5)	61 (22.8)	79 (29.6)	74 (26.6)	
Oral contraceptive use					0.30
Never	200 (87.0)	227 (88.7)	246 (92.1)	248 (89.2)	
Ever	30 (13.0)	29 (11.3)	21 (7.9)	30 (10.8)	
Body mass index (kg/m ²) ^a					0.006
<25	109 (47.8)	148 (58.5)	123 (46.6)	169 (61.2)	
25–30	76 (33.3)	70 (27.7)	88 (33.3)	65 (23.6)	
30	43 (18.9)	35 (13.8)	53 (20.1)	42 (15.2)	
Family history of ovarian/breast cancer					0.08
No	210 (91.3)	216 (84.4)	229 (85.8)	247 (88.8)	
Yes	20 (8.7)	40 (15.6)	38 (14.2)	31 (11.2)	

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The sum does not add up to the total because of some missing values, i.e. 2 cases for menopausal status and 10 cases for body mass index.
 p value for Chi-square test

Table 3

Distribution of servings of food groups across quartiles of dietary inflammatory index (DII) among 241 1 controls (mean $\pm$ standard deviation). Italy, 1992–1999.

	Food item (standard serving size)	DII quartiles				p value ^a
		< -1.63	-1.63, -0.32	-0.31, 1.35	> 1.35	
Fruit	10 items: apples and pears (1 medium size); bananas (1 medium size); kiwi (1 medium size); 1/2 cooked fruits (1 fruit bowl); unsweetened fruit juices (1 glass); citrus fruits (150 g); peaches, apricots, and prunes (100 g); melon (75 g); grapes (230 g); strawberries and cherries (150 g)	26.0 $\pm$ 12.8	20.5 $\pm$ 8.6	16.6 $\pm$ 9.6	11.2 $\pm$ 8.4	<0.0001
Vegetables	10 items: green and red salad (50 g); raw carrots (75 g); cooked carrots (130 g); onion (80 g); artichokes (1 whole); cruciferae (125 g); spinach/other greens (200 g); tomatoes (150 g); salad with carrots, cucumbers, peppers (100 g); zucchini, eggplants, bell peppers (150 g)	17.4 $\pm$ 6.5	14.2 $\pm$ 5.6	11.3 $\pm$ 5.4	8.3 $\pm$ 5.1	<0.0001
Fish	3 items: Boiled or broiled fish or mollusks (150 g); Fried fish or mollusks (150 g); Tuna or sardines packed in oil (80 g)	2.0 $\pm$ 1.2	1.9 $\pm$ 1.1	1.6 $\pm$ 1.1	1.4 $\pm$ 1.0	<0.0001
Egg	Eggs	1.3 $\pm$ 1.1	1.4 $\pm$ 1.1	1.3 $\pm$ 1.3	1.3 $\pm$ 1.3	0.21
Coffee	4 items: coffee (50 ml); decaffeinated coffee (50 g); cappuccino (125 ml); tea (125 ml)	18.3 $\pm$ 12.6	18.7 $\pm$ 11.8	16.8 $\pm$ 11.3	17.8 $\pm$ 12.4	0.15
Red meat	8 items: steak/roast-beef/lean ground beef, veal or horse meat (120 g); boiled beef (150 g); beef or veal stew/meat balls (150 g); Wiener Schnitzel (120 g); pork chop/paillard or pork roast (150 g); liver (150 g); 1/2 pasta/rice with meat sauce (80 g); 1/2 lasagne/cannelloni (250 g)	3.6 $\pm$ 2.0	3.9 $\pm$ 2.1	3.6 $\pm$ 2.1	3.4 $\pm$ 2.4	0.01
Pork	3 items: Prosciutto, lean processed meat (50 g); ham (50 g); salami, bologna, sausages, bacon, hot dog (50 g)	2.1 $\pm$ 1.5	2.5 $\pm$ 1.8	2.5 $\pm$ 2.0	2.6 $\pm$ 2.2	<0.0001
Sugar	4 items: sugar (1 tablespoon); honey and jams (1 tablespoon); chocolate and candy bars (1); candies (1)	24.1 $\pm$ 23.9	27.3 $\pm$ 22.9	27.2 $\pm$ 25.0	33.6 $\pm$ 29.4	<0.0001
Cheese	5 items: Ricotta/mozzarella cheese (100 g); other cheeses (80 g); 1/3 any type of cheese in addition or as snack (25 g); 1/15 grated cheese (1 tablespoon); 1/2 pizza (250 g)	4.0 $\pm$ 2.2	4.7 $\pm$ 2.5	4.7 $\pm$ 2.6	4.5 $\pm$ 3.6	0.01
Desserts	7 items: cookies (50 g); croissants and doughnuts (50 g); pastry, doughnuts with cream or custard (50 g); pound cakes, plain cakes, Christmas and Easter cakes (100 g); fruit or jam pies, fruit tarts (100 g); ice-creams (100 g); 1/2 cooked fruits (1 fruit bowl)	3.6 $\pm$ 3.5	4.5 $\pm$ 4.4	5.4 $\pm$ 5.6	6.7 $\pm$ 9.2	<0.0001

^a p values were obtained from ANOVA

Odds ratios (ORs) of ovarian cancer and corresponding 95% confidence intervals (CIs) according to dietary inflammatory index (DII) among 1031 cases and 2411 controls. Italy, 1992–1999.

Table 4

		DII quartiles, OR (95% CI)			<i>p</i> value for trend ^a	DII continuous ^b
		< -1.63	-1.63, -0.32	-0.31, 1.35		
Case/Controls	230/602	256/604	267/602	278/603		1031/2411
Model 1 ^e	1 ^d	1.10 (0.89, 1.36)	1.32 (1.05, 1.67)	1.68 (1.27, 2.22)	<0.0001	1.11 (1.06, 1.17)
Model 2 ^e	1 ^d	1.00 (0.79, 1.27)	1.19 (0.91, 1.54)	1.47 (1.07, 2.01)	0.009	1.08 (1.02, 1.14)

^aTest for linear trend was carried out using the median approach

^bOne unit increase equals 8% increase of DII in the current study(+6.0 to -6.2).

^cAdjusted for quinquennia of age and energy intake.

^dReference category.

^eAdjusted as in Model 1 and additionally adjusted for year of interview, study centre, education, body mass index, parity, oral contraceptive use, menopausal status, and family history of ovarian and/or breast cancer in first degree-relatives.

Table 5

Odds ratios (ORs) of ovarian cancer and corresponding 95% confidence intervals (CIs) according to dietary inflammatory index (DII), among 1031 cases and 2411 controls. Italy, 1992–1999.

	Cases/Controls	DII quartiles, OR (95% CI) ^d			<i>p</i> value for trend ^b	DII continuous ^c
		< -1.63	-1.63, -0.32	-0.31, 1.35		
Menopausal status ^e						
Pre/peri-menopause	346/803	1 ^d	0.94 (0.62, 1.41)	0.97 (0.62, 1.52)	0.52	0.99 (0.89, 1.09)
Post-menopause	683/1603	1 ^d	1.06 (0.78, 1.43)	1.34 (0.97, 1.85)	0.007	1.13 (1.05, 1.22)
Parity						
Nulliparous	184/381	1 ^d	1.54 (0.81, 2.93)	1.49 (0.75, 2.96)	0.04	1.17 (1.01, 1.36)
Parous	847/2030	1 ^d	0.91 (0.70, 1.18)	1.14 (0.86, 1.51)	0.10	1.06 (0.99, 1.13)
Oral contraceptive use						
Never	921/2142	1 ^d	0.98 (0.75, 1.26)	1.23 (0.93, 1.63)	0.002	1.10 (1.04, 1.18)
Ever	110/269	1 ^d	1.12 (0.55, 2.28)	0.82 (0.38, 1.78)	0.25	0.90 (0.76, 1.08)
Family history of ovarian and/or breast cancer in first degree-relatives						
No	902/2291	1 ^d	0.99 (0.77, 1.27)	1.17 (0.87, 1.53)	0.007	1.08 (1.02, 1.15)
Yes	129/120	1 ^d	1.62 (0.65, 4.07)	1.66 (0.63, 4.42)	0.80	1.01 (0.82, 1.25)

^a Adjusted for quinquennia of age, energy intake, year of interview, study centre, education, body mass index, parity, oral contraceptive use, menopausal status, and family history of ovarian and/or breast cancer in first degree-relatives, when appropriate.

^b Test for linear trend was carried out using the median approach.

^c One unit increase equals 8% increase in range in the current study (6.0 to -6.20).

^d Reference category.

^e The sum does not add up to the total because of some missing values, i.e. 2 cases and 5 controls