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Dietary Inflammatory Index and Risk of Epithelial Ovarian Cancer in African American Women

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Abstract

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Chronic inflammation has been implicated in the development of epithelial ovarian cancer (EOC); yet, the contribution of inflammatory foods and nutrients to EOC risk has been understudied. We investigated the association between the dietary inflammatory index (DII), a novel literature-derived tool to assess the inflammatory potential of one's diet, and EOC risk in African American (AA) women in the African American Cancer Epidemiology Study (AACES), the largest population-based case-control study of EOC in AA women to date. The energy-adjusted DII (E-DII) was computed per 1,000 kilocalories from dietary intake data collected through a food frequency questionnaire, which measured usual dietary intake in the year prior to diagnosis for cases or interview for controls. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using multivariable logistic regression for the association between the E-DII and EOC risk. 493 cases and 662 controls were included in the analyses. We observed a 10% increase in EOC risk per a one-unit change in the E-DII (OR=1.10, 95% CI=1.03–1.17). Similarly, women consuming the most pro-inflammatory diet had a statistically significant increased EOC risk in comparison to the most anti-inflammatory diet ($OR_{Quartile4/Quartile1}$=1.72; 95% CI=1.18–2.51). We also observed effect modification by age ($p<0.05$), where a strong, significant association between the E-DII and EOC risk was observed among women older than 60 years, but no association was observed in women aged 60 years or younger. Our findings suggest that a more pro-inflammatory diet was associated with an increased EOC risk, especially among women older than 60 years.

Keywords

Ovarian cancer; African American; dietary inflammatory index; inflammation; diet

INTRODUCTION

In a seminal paper by Ness and Cottreau[1], chronic inflammation was implicated as an underlying mechanism contributing to ovarian carcinogenesis. Inflammation can influence tumor development through stimulation of DNA damage, increased cell division that can give rise to DNA repair aberrations, promotion of angiogenesis, and facilitation of invasion.[1,2] Several studies report an association between biological markers of inflammation, such as C-reactive protein (CRP) and circulating interleukins, and ovarian cancer risk.[3–5] Additionally, an increased risk of ovarian cancer has been observed for several factors that enhance inflammation (e.g., body powder applied to genital areas, endometriosis, and pelvic inflammatory disease)[6–9] and an inverse association has been observed for anti-inflammatory factors (e.g., aspirin, nonsteroidal anti-inflammatory drugs).[10,11] Dietary habits also can contribute to chronic inflammation; traditional Mediterranean diets (high intake of fruits, vegetables, and whole-grains) have been associated with lower levels of inflammation in comparison to Western diets (high intake of red meat and simple carbohydrates).[12] Yet, the impact of an inflammatory diet on the risk of ovarian cancer has been understudied.

Cavicchia and colleagues[13] developed a novel literature-derived tool to assess the inflammatory potential of one's diet, the dietary inflammatory index (DII). Since then, the DII was updated by Shivappa, et al.[14] to reflect the literature on diet and inflammation through 2010. The improved DII has been validated by examining its relationship to

inflammatory biomarkers (e.g., CRP and interleukin-6).[15–18] Additionally, a more pro-inflammatory diet, as defined by higher DII scores, has been linked to an increased risk of several cancers, including colorectal[19,20], pancreatic[21], prostate[22], breast[23], and endometrial cancer.[24] Specific to ovarian cancer, a recent study[25] observed an increased risk among Italian women who consumed a more pro-inflammatory diet. However, as that study was conducted among Italian women, the results may not be generalizable to other, non-White populations. Dietary patterns in Italy tend to be healthier than those in the United States[26] and there are considerable differences in inflammation by race among the general population, with higher levels of inflammatory biomarkers present among African Americans (AA) compared to Whites.[27–29] In this study, we will use the largest case-control study of epithelial ovarian cancer (EOC) in AA women, the African American Cancer Epidemiology Study, to examine the association between the DII and EOC risk among AA women in the United States. We hypothesize that AA women consuming a more pro-inflammatory diet will have an increased risk of EOC.

MATERIALS AND METHODS

Study Population

The African American Cancer Epidemiology Study (AACES) is an ongoing, population-based case-control study of invasive epithelial ovarian cancer in AA women across eleven geographic locations in the United States, including Alabama, Georgia, Illinois, Louisiana, Michigan, North Carolina, New Jersey, Ohio, South Carolina, Tennessee, and Texas. Details on AACES methods have been described elsewhere.[30] Briefly, rapid case ascertainment at cancer registries and hospitals was used to identify cases. Eligible cases included women who self-reported AA race, were 20–79 years of age, and were newly diagnosed with invasive EOC between December 1, 2010 and December 31, 2015. Controls were identified through random digit dialing and frequency matched to cases by 5-year age groups and geographic location. Eligible controls included women who self-reported AA race, had at least one intact ovary, and did not have a history of EOC. AACES participants completed an extensive baseline survey by telephone, including but not limited to questions on demographics, reproductive history, exogenous hormone use, personal and family history of cancer, medical history, and lifestyle behaviors (e.g., smoking, physical activity). An abbreviated form of the questionnaire was offered to women who would have otherwise refused to participate in the study. Dietary intake was assessed by the widely used and validated[31,32] Block 2005 Food Frequency Questionnaire (FFQ). The FFQ was mailed to the participant's residence to obtain self-reported data on the usual consumption (frequency and portion size) of 110 foods and beverages during the year before their diagnosis (cases) or the year before their interview (controls). All FFQ data were sent to NutritionQuest, formerly known as Block Dietary Data Systems, to derive individual nutrient and total energy intake.

Dietary Inflammatory Index

The DII was calculated using the dietary intake data from the FFQ as described in Shivappa, et al.[14] In brief, the literature was searched from 1950 to 2010 to identify studies examining the association between six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP) and specific foods and nutrients. A total of 45 such parameters were identified in the

process of conducting this extensive search. Eligible studies were used to define DII scores for each food parameter, which also were weighted according to study quality. A database of 11 dietary datasets from around the world was used to estimate the global mean intake of each food parameter. Each subject's dietary data was linked to the global database and their exposure relative to the global mean was expressed as a z-score. The z-score was calculated by subtracting the standard global mean from the reported dietary intake and then dividing by the global standard deviation. Z-scores were converted to normal percentiles to reduce the effect of a positive-skewed distribution. For each food parameter, the literature-derived inflammatory effect score for each food parameter was then multiplied by the food parameter specific centered percentile for each participant. These values were then summed to calculate the overall DII score, where higher scores indicate a more pro-inflammatory diet. To control for the effect of total energy intake, the energy-adjusted DII (E-DII) was calculated per 1,000 calories of food consumed. We examined the E-DII in two ways, both with and without consideration of dietary supplements in addition to food sources of nutrients. In total, data was available on 27 food parameters (carbohydrates; protein; fat; alcohol; fiber; cholesterol; saturated, monounsaturated, and polyunsaturated fatty acids; omega3 and omega6 polyunsaturated fatty acids; trans-fat; niacin; vitamins A, B1, B2, B6, B12, C, D, E; iron; magnesium; zinc; selenium; folic acid; beta carotene; and isoflavones). The dietary supplements included vitamin A, vitamin C, vitamin D, vitamin E, iron, calcium, zinc, beta-carotene, B-1 (thiamin), B-6, B-12, folic acid, copper, selenium, riboflavin, magnesium, niacin, omega-3 fatty acids, and omega-6 fatty acids.

The range of E-DII values in our sample were −5.57 to 3.19 and −4.15 to 3.19 for the E-DII with and without including dietary supplements, respectively. The E-DII was evaluated continuously, where a 1-unit change in the E-DII with and without supplement intake was equivalent to about 11% and 14% of its range, respectively, as well as categorically by dividing the E-DII scores into quartiles based on its distribution among the controls. For the E-DII with supplements, the range of E-DII scores for each quartile are: Quartile 1 (−5.57 to −3.64), Quartile 2 (−3.63 to −2.46), Quartile 3 (−2.45 to −0.33), and Quartile 4 (−0.32 to 3.19); and for the E-DII without supplements, the range of E-DII scores for each quartile are: Quartile 1 (−4.15 to −2.18), Quartile 2 (−2.17 to −0.66), Quartile 3 (−0.65 to 1.01), and Quartile 4 (1.02 to 3.19).

Statistical Analysis

We used data from AACES participants enrolled in the study as of January 2016 and who completed the FFQ (N=1,173). We excluded data from any participants reporting extreme values for total energy intake, defined as greater than twice the interquartile range of the log energy intake (1 case and 3 controls). Distributions of participant characteristics were compared by case-control status using chi-square tests for categorical variables or t-tests for continuous variables. We also examined the distribution of selected participant characteristics by E-DII quartiles using chi-square tests. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between the E-DII (with supplements and without supplements), and odds of ovarian cancer were estimated using multivariable logistic regression. To test for linear trends, the median value within each quartile was modeled as a continuous variable. Two models with different adjustment sets were

examined. Model 1 is adjusted for the study design variables, including age (in years; age at diagnosis for cases and age at interview for controls) and study site (Alabama, Georgia and Tennessee combined [combined due to geographic similarities and sample size], Illinois and Michigan combined [combined due to geographic similarities and sample size], Louisiana, New Jersey, North Carolina, Ohio, South Carolina, Texas). Model 2 is additionally adjusted for family history of breast or ovarian cancer in a first-degree relative (yes, no), parity (0, 1, 2, 3 or more live births), duration of OC use (no use, <5 years, 5 or more years), education (high school graduate or less, some post high school training, college or graduate degree), tubal ligation that occurred 1 year prior to the date of interview for controls and the date of diagnosis for cases (yes, no), menopausal status (pre- or peri-menopause, post-menopause), and body mass index (BMI; normal weight: <25 kg/m^2; overweight: 25–29.9 kg/m^2; obese: ≥30 kg/m^2), smoking status (never, former, current smoker), and endometriosis (yes/no). For the models examining the E-DII not including supplement intake as part of the calculation, the fully adjusted model (Model 2) also was adjusted for any dietary supplement intake in the year before diagnosis for cases or year before interview in controls (yes/no), as reported in the FFQ. The following potential confounders were evaluated but not included in the model because their addition did not change the effect estimate by 10% or more: total energy intake, physical activity, arthritis, diabetes, hypertension, high cholesterol, aspirin use, non-aspirin NSAID use, pelvic inflammatory disease, and body powder use. Ten women were missing covariate data and were removed from the analyses (N=1,155). All analyses were repeated restricted to the most deadly histologic subtype of EOC, serous ovarian cancer. Based on the findings of previous literature on the DII and female malignancies[23–25], we developed *a priori* hypotheses to examine whether age (21–50 years, 51–60 years, >60 years), BMI, smoking status, and menopausal status were effect modifiers of the association between the E-DII and ovarian cancer risk. Effect modification was evaluated by adding a cross-product term (e.g., BMI × E-DII quartiles) into the regression model and a likelihood ratio test was used to compare the models with and without the cross-product term. SAS 9.4 was used to complete all analyses.

RESULTS

The distribution of participant characteristics for 493 cases and 662 controls are described in Table 1. Cases were more likely to have a family history of breast or ovarian cancer in a first-degree relative, to be nulliparous, and to have a history of endometriosis; cases were less likely to use oral contraceptives, to have a college or graduate degree, to have a tubal ligation, to be a current smoker, and to report use of dietary supplements. No statistically significant differences in total energy intake were observed for cases and controls. The majority of EOC cases were of serous histology (71%).

Overall, the mean and standard deviation (SD) of the E-DII including supplement intake was −1.82 ± 2.16; as expected, the mean E-DII score excluding supplement intake was greater or more pro-inflammatory (−0.51 ± 1.87) compared to the E-DII score including supplements. For both measures of the E-DII, cases, on average, had a more pro-inflammatory diet compared to controls (mean ± SD of the E-DII including supplements: cases = −1.70 ± 2.19 and controls = −1.91 ± 2.13, and for the E-DII not including supplements: cases = −0.43 ± 1.84 and controls = −0.57 ± 1.89). Supplementary Tables 1 and 2 provide the distribution

of selected characteristics across E-DII quartiles for the E-DII calculated with and without supplement intake among controls. Across both measures of the E-DII, a more pro-inflammatory diet was observed among women who were younger, less educated, pre- or peri-menopausal, current smokers, and who did not engage in any physical activity.

The estimated ORs and 95% CIs for the E-DII and EOC risk are provided in Table 2. When evaluating the E-DII including supplement intake continuously, we observed a 10% increase in the risk of EOC for every one unit change in E-DII score (OR=1.10, 95% CI=1.03–1.17). As the E-DII quartiles increased from more anti-inflammatory to more pro-inflammatory, a significant trend in EOC risk was observed (p_{trend}=0.01). Women in the highest quartile of the E-DII had a statistically significant increased risk of EOC in comparison to the lowest quartile, $OR_{Q4/Q1}$ = 1.72, 95% CI=1.18–2.51. For the E-DII not including supplements, the associations were weaker and not statistically significant. When the analyses were repeated restricted to serous EOC cases versus all controls, the ORs were slightly attenuated but no substantial differences in the results were observed (data not shown).

We observed statistically significant effect modification by menopausal status (Table 3) and age (Table 4) for the E-DII excluding dietary supplement intake ($p<0.05$), but not for the E-DII including dietary supplement intake. Among pre- and peri-menopausal women, no associations were observed between the E-DII not including supplements and EOC risk; however, among post-menopausal women, the highest, more pro-inflammatory, quartile (Quartile 4) was associated with a statistically significant increased risk of EOC ($OR_{Q4/Q1}$ = 1.63, 95% CI=1.05–2.54). Similarly, women older than 60 years of age had much higher risks of EOC for both E-DII measures in comparison to women aged 60 and younger. An increased risk was observed for a one-unit change in the E-DII with and without supplements among women older than 60 years of age, OR=1.22; 95% CI=1.09–1.37 and OR=1.27; 95% CI=1.11–1.45, respectively. The highest increase in EOC risk was observed for women older than 60 years of age and in the fourth, most pro-inflammatory, quartile, $OR_{Q4/Q1}$ = 3.23 (95% CI=1.63–6.40) for the E-DII including supplements and $OR_{Q4/Q1}$ = 3.77 (95% CI=1.82–7.77) for the E-DII excluding supplements. No evidence of effect modification by BMI or smoking status was observed (data not shown).

DISCUSSION

In a population of AA women in the United States, a more pro-inflammatory diet was positively associated with EOC risk. These findings are consistent with the only other study examining the DII and EOC risk.[25] Although few studies have looked specifically at the inflammatory potential of one's diet in relation to ovarian cancer, individual nutrients and dietary patterns that contribute to inflammation have been assessed previously, yet the results have been fairly inconsistent.[33] Although fruit and vegetable intake is associated with lower levels of inflammatory biomarkers[12,34], a protective effect of fruit and vegetable intake on ovarian cancer risk was observed neither in a pooled analysis of 12 cohort studies[35] or in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study.[36] Simple carbohydrates and high-glycemic carbohydrates have pro-inflammatory effects[12] and an increase in EOC risk has been observed for high glycemic index, especially among overweight and obese women.[37] Similarly, an increased risk of EOC was observed in

the AACES population for women consuming a carbohydrate-rich diet.[38] Our findings coupled with the previous studies evaluating food-specific effects on EOC risk suggest that a diet full of fruits, vegetables, and complex carbohydrates, would result in reductions in inflammation and potentially a reduced risk of EOC. It is important to note that a more pro-inflammatory diet is highly correlated with the Western diet[12], which is characterized by high intake of red meat and simple carbohydrates, making it difficult to disentangle whether the increased risk of EOC is due to the inflammatory potential of these foods or other consequences of consumption of the Western diet.

We observed statistically significant effect modification by both menopausal status and age; among post-menopausal women and women older than 60 years of age, a more pro-inflammatory diet was strongly associated with an increased risk of EOC, while no association was seen for pre-menopausal women and women 60 years of age and younger. Studies in breast[23], endometrial[24], and ovarian[25] cancer observed similar results, where a positive association between the DII and cancer risk was present only among post-menopausal women, albeit not statistically significant. In these three studies, age was not assessed as a potential effect modifier. Age and menopausal status are highly correlated with one another, and in this study, the age group where we see the strongest association, women older than 60 years, are a subset of post-menopausal women. As the relationship observed in older women is stronger than that in post-menopausal women and the results were essentially null in the other age subset of post-menopausal women (ages 51–60 years), age seems to be driving the effect modification present in this study, not menopausal status. It also is important to note that we found no evidence of effect modification of E-DII scores by BMI or smoking status. Both BMI and tobacco are known to work through inflammation-related mechanisms[39,40], yet there is no apparent modification of the effect of diet-associated inflammation by either of these two factors in this study.

It is unclear as to why a stronger association between the E-DII and EOC risk was observed mainly among older women. It is possible that these findings are consistent with the observation that environmental or lifestyle factors, such as the E-DII, may be stronger determinants of hormonally sensitive cancers diagnosed in older women compared to cancers diagnosed in younger women, which are more genetically determined.[41] In addition, our findings may reflect a cumulative effect of consumption of pro-inflammatory foods over the life-course. Another explanation could also be related to variations in insulin with aging since insulin resistance is associated with both older ages[42] and increases in inflammation.[43] In fact, using diabetes as a proxy for insulin resistance, we observed a higher prevalence of diabetes among women older than 60 years of age in the AACES population compared to those 60 years old and younger (48% vs. 18%, respectively). Insulin resistance also increases with obesity, which is highly prevalent in AACES (57%).

In contrast to much of the published DII literature, we incorporated dietary supplement intake as part of the E-DII calculation and as a potential confounder for the association between the E-DII without supplements and ovarian cancer risk. Although dietary supplements are not classified as a typical dietary food item, they are important contributors to nutrient intake as they often contain nutrient doses which surpass those available from food sources. Moreover, approximately half of the U.S. population uses dietary supplements,

with a higher prevalence of supplement use among women and older individuals.[44] Supplement intake has been linked to lower levels of inflammation[45] and several studies[46–50] have observed protective effects of supplement use on ovarian cancer risk. In contrast, high doses of some supplements have been shown to increase cancer risk.[51] As supplement intake is associated with both inflammation and cancer risk, not including this factor could lead to residual confounding. In fact, in this study, we observed significant positive confounding (approximately a 40% change in the OR) when adjusting for supplement intake in the models examining the E-DII without supplements and EOC risk. With such a substantial effect on our results, it is important for future studies to evaluate dietary supplements either as a contributor to the E-DII or to evaluate supplements as a potential confounder.

A major strength of this study is the utilization of the AACES population, which includes the largest number of AA women with EOC to date and is uniquely positioned to examine race-specific effects in ovarian cancer. Another strength is using the E-DII to assess the inflammatory potential of one's diet because this approach allows simultaneous assessment of both pro- and anti-inflammatory factors instead of looking at each inflammatory dietary component individually. Despite these strengths, there are several limitations. Due to the case-control study design, there is a possibility of recall bias. However, given that the influence of dietary factors on ovarian cancer risk is still relatively unknown, it is unlikely that AACES participants were aware of hypotheses related to diet and EOC. Yet, there is a general belief that diet is an important determinant of health and well-being. If any misclassification of exposure occurred, it is unlikely that cases recalled their dietary intake differently compared to controls, which would bias the results toward the null. Given that the FFQ reflects usual dietary intake a year prior to diagnosis among the cases, there is a possibility that symptoms of an undiagnosed ovarian cancer (e.g., pelvic or back pain, fatigue, loss of appetite) may have spurred changes in diet during the time period captured by the FFQ. Another limitation is that only 27 of the 45 food parameters identified in the original literature search were available to calculate the E-DII in this study. We were also unable to validate the E-DII scores with inflammatory biomarkers in the AACES population; however, a recent study[18] validated the E-DII in an African American population by correlating the E-DII scores and CRP concentrations. The literature search for the DII has not been updated since 2010; however, with each literature update, the DII scores have remained relatively stable over time.[14] Although AACES is a relatively large sample overall, we had limited power in the stratified analyses, resulting in imprecise estimates with wide confidence intervals. Additionally, we were unable to perform stratified analyses by histology due to the small number of cases diagnosed with non-serous EOC and could only repeat the overall analyses restricted to the most common histology, serous EOC.

In summary, a more pro-inflammatory diet was associated with an increased risk of EOC in AA women, especially among women older than 60 years of age. Given that only one other study has examined the relationship between the inflammatory potential of one's diet and ovarian cancer, it is important to confirm these findings, especially among racially diverse populations that may have varying dietary habits. With very few modifiable risk factors for ovarian cancer currently known, our results suggest that modifying dietary intake to include fewer inflammatory foods may contribute to ovarian cancer prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 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.

ABBREVIATIONS

AA	African American
AACES	African American Cancer Epidemiology Study
BMI	body mass index
CI	confidence interval
CRP	C-reactive protein
DII	dietary inflammatory index
E-DII	energy-adjusted dietary inflammatory index
FFQ	food frequency questionnaire
EOC	epithelial ovarian cancer
OC	oral contraceptives
OR	odds ratio

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NOVELTY AND IMPACT

Although ovarian carcinogenesis has been linked to inflammation, the impact of an inflammatory diet on ovarian cancer risk is understudied. We examined the association between the inflammatory potential of one's diet, as assessed by a novel literature-derived tool, the dietary inflammatory index (DII), and ovarian cancer risk among African American women. A more pro-inflammatory diet was associated with an increased risk of ovarian cancer, especially among women older than 60 years of age.

Table 1

Distribution of AACES participant characteristics for 493 cases and 662 controls (N=1,155)

	Cases (n=493)	Controls (n=662)	
	n (%) or Mean (SD)	n (%) or Mean (SD)	p-value
Age at Diagnosis or Interview			
21–50 years	122 (25)	198 (30)	0.007
51–60 years	177 (36)	261 (39)	
>60 years	194 (39)	203 (31)	
Total Energy Intake			
Kilocalories	1763.8 (1187.0)	1720.4 (1112.8)	0.52
Education			
HS or less	214 (44)	244 (37)	0.08
Some post HS training	125 (25)	191 (29)	
College or graduate degree	154 (31)	227 (34)	
BMI (kg/m^2)[a]			
<25	75 (15)	125 (19)	0.26
25–29.9	129 (26)	163 (25)	
30+	289 (59)	374 (56)	
Family History of Breast or Ovarian Cancer			
No	364 (74)	542 (82)	0.001
Yes	129 (26)	120 (18)	
Menopausal Status			
Pre/Peri-menopause	138 (28)	199 (30)	0.44
Post-menopause	355 (72)	463 (70)	
Parity			
Nulliparous	95 (19)	84 (13)	0.01
1	98 (20)	121 (18)	
2	119 (24)	180 (27)	
3+	181 (37)	277 (42)	
Duration of OC Use			
Never	163 (33)	154 (23)	<0.001
<5 years	191 (39)	282 (43)	
5+ years	139 (28)	226 (34)	
Tubal Ligation			
No	324 (66)	389 (59)	0.02
Yes	169 (34)	273 (41)	
Smoking Status			
Never smoker	273 (55)	381 (57)	<0.001
Former smoker	167 (34)	150 (23)	
Current smoker	53 (11)	131 (20)	
Endometriosis			

	Cases (n=493)	Controls (n=662)	
	n (%) or Mean (SD)	n (%) or Mean (SD)	p-value
No	437 (89)	631 (95)	<0.001
Yes	56 (11)	31 (5)	
Any Dietary Supplement Use (Past Year)			
No	143 (29)	142 (21)	0.003
Yes	350 (71)	520 (79)	
Histology			
Serous	333 (71)		
Mucinous	24 (5)		
Endometrioid	62 (13)		
Clear cell	12 (3)		
Mixed	14 (3)		
Other Epithelial	23 (5)		
Missing	25		

BMI: body mass index; HS: high school; OC: oral contraceptives

[a]BMI 1 year before diagnosis date for cases and interview date for controls.

Table 2

Estimated ORs and 95% CIs for the association between energy-adjusted DII and ovarian cancer risk (N=1,155)

	Cases	Controls	Model 1[a]	Model 2[b]
Quartile of Energy-adjusted DII	**n (%)**	**n (%)**	**OR (95% CI)**	**OR (95% CI)**
E-DII including supplements				
Quartile 1	108 (22)	167 (25)	1.00 (Referent)	1.00 (Referent)
Quartile 2	125 (25)	164 (25)	1.22 (0.86–1.73)	1.40 (0.97–2.01)
Quartile 3	123 (25)	166 (25)	1.20 (0.85–1.69)	1.33 (0.92–1.92)
Quartile 4	137 (28)	165 (25)	1.52 (1.07–2.14)	1.72 (1.18–2.51)
P_{trend}			0.03	0.01
Per 1 unit of E-DII			1.08 (1.02–1.14)	1.10 (1.03–1.17)
E-DII excluding supplements[c]				
Quartile 1	117 (24)	167 (25)	1.00 (Referent)	1.00 (Referent)
Quartile 2	113 (23)	166 (25)	0.95 (0.67–1.35)	0.94 (0.65–1.34)
Quartile 3	129 (26)	164 (25)	1.15 (0.82–1.62)	1.16 (0.80–1.68)
Quartile 4	134 (27)	165 (25)	1.37 (0.97–1.93)	1.35 (0.93–1.97)
P_{trend}			0.04	0.06
Per 1 unit of E-DII			1.08 (1.01–1.16)	1.08 (1.00–1.16)

OR: odds ratio; CI: confidence interval; E-DII: energy-adjusted dietary inflammatory index; OC: oral contraceptives; BMI: body mass index

[a] Model 1 is adjusted for the study design variables, age and study site.

[b] Model 2 is adjusted for the variables in Model 1 as well as family history of breast or ovarian cancer in a first degree relative, parity, OC use, education, BMI, tubal ligation, menopausal status, smoking status, and endometriosis.

[c] Model 2 is also adjusted for any use of dietary supplements in the past year.

Table 3

Estimated ORs and 95% CIs for the association between the energy-adjusted DII and ovarian cancer risk stratified by menopausal status (N=1,155)

	Menopausal Status			
	Pre- and Peri-menopausal Women		Post-menopausal Women	
Quartile of Energy-adjusted DII	No. of cases/controls	OR[a] (95% CI)	No. of cases/controls	OR[a] (95% CI)
E-DII including supplements				
Quartile 1	25/39	1.00 (Referent)	83/128	1.00 (Referent)
Quartile 2	36/42	2.35 (1.05–5.26)	89/122	1.23 (0.81–1.87)
Quartile 3	33/47	1.82 (0.80–4.16)	90/119	1.29 (0.85–1.97)
Quartile 4	44/71	2.14 (0.96–4.76)	93/94	1.84 (1.18–2.87)
P_{trend}		0.24		0.008
Per 1 unit of E-DII		1.09 (0.96–1.24)		1.13 (1.05–1.21)
E-DII excluding supplements[b]				
Quartile 1	27/36	1.00 (Referent)	90/131	1.00 (Referent)
Quartile 2	29/48	0.89 (0.40–1.99)	84/118	0.97 (0.64–1.46)
Quartile 3	39/39	2.14 (0.94–4.86)	90/125	1.01 (0.66–1.55)
Quartile 4	43/76	1.17 (0.53–2.58)	91/89	1.63 (1.05–2.54)
P_{trend}		0.39		0.04
Per 1 unit of E-DII		1.10 (0.94–1.28)		1.10 (1.01–1.20)

OR: odds ratio; CI: confidence interval; E-DII: energy-adjusted dietary inflammatory index; OC: oral contraceptives; BMI: body mass index

[a]ORs are adjusted for age, study site, family history of breast or ovarian cancer in a first degree relative, parity, OC use, education, BMI, tubal ligation, smoking status, and endometriosis.

[b]ORs additionally adjusted for any use of dietary supplements in the past year.

Table 4

Estimated ORs and 95% CIs for the association between energy-adjusted DII and ovarian cancer risk stratified by age at diagnosis or interview (N=1,155)

	Age at Diagnosis or Interview					
	21–50 years		51–60 years		>60 years	
Quartile of Energy-adjusted DII	No. of cases/controls	OR[a] (95% CI)	No. of cases/controls	OR[a] (95% CI)	No. of cases/controls	OR[a] (95% CI)
E-DII including supplements						
Quartile 1	23/37	1.00 (Referent)	39/64	1.00 (Referent)	46/66	1.00 (Referent)
Quartile 2	29/38	1.64 (0.71–3.82)	40/73	0.99 (0.53–1.84)	56/53	1.96 (1.07–3.59)
Quartile 3	26/49	1.13 (0.47–2.70)	49/62	1.49 (0.78–2.81)	48/55	1.52 (0.83–2.79)
Quartile 4	44/74	1.33 (0.61–2.92)	49/62	1.29 (0.67–2.46)	44/29	3.23 (1.63–6.40)
P_{trend}		0.79		0.30		0.004
Per 1 unit of E-DII		1.02 (0.90–1.15)		1.06 (0.96–1.18)		1.22 (1.09–1.37)
E-DII excluding supplements[b]						
Quartile 1	23/33	1.00 (Referent)	48/68	1.00 (Referent)	46/66	1.00 (Referent)
Quartile 2	23/43	0.66 (0.27–1.63)	38/64	0.81 (0.44–1.49)	52/59	1.14 (0.65–2.03)
Quartile 3	35/42	1.40 (0.60–3.28)	41/67	0.84 (0.45–1.56)	53/55	1.36 (0.75–2.48)
Quartile 4	41/80	0.73 (0.32–1.65)	50/62	0.91 (0.49–1.69)	43/23	3.77 (1.82–7.77)
P_{trend}		0.70		0.83		<0.001
Per 1 unit of E-DII		0.97 (0.83–1.13)		1.00 (0.89–1.13)		1.27 (1.11–1.45)

OR: odds ratio; CI: confidence interval; E-DII: energy-adjusted dietary inflammatory index; OC: oral contraceptives; BMI: body mass index

[a]ORs are adjusted for study site, family history of breast or ovarian cancer in a first degree relative, parity, OC use, education, BMI, tubal ligation, menopausal status, smoking status, and endometriosis.

[b]ORs additionally adjusted for any use of dietary supplements in the past year