Published in final edited form as:

Cancer Causes Control. 2012 June ; 23(6): 887–895. doi:10.1007/s10552-012-9958-1.

TOTAL AND INDIVIDUAL ANTIOXIDANT INTAKE AND ENDOMETRIAL CANCER RISK: RESULTS FROM A POPULATION-BASED CASE-CONTROL STUDY IN NEW JERSEY

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Abstract

We evaluated the role of total dietary antioxidant capacity and of individual antioxidants on endometrial cancer risk in a population-based case-control study in New Jersey, including 417 cases and 395 controls. Dietary intake was ascertained using a food frequency questionnaire (FFQ), and total antioxidant capacity (TAC) intake was estimated using the USDA Oxygen Radical Absorbance Capacity (ORAC) Database and the University of Oslo's Antioxidant Food Database (AFD) and FFQ-derived estimates of intake. Odds ratios and 95% confidence intervals were derived using multivariate logistic regression controlling for major endometrial cancer risk factors. Using the ORAC database, after adjusting for major covariates, we found decreased risks for the highest tertile of total phenolic intake compared to the lowest (OR: 0.62; 95% CI: 0.39–0.98). There was no association for TAC intake based on the AFD, which utilized the ferric reducing ability of plasma (FRAP) assay to assess antioxidant capacity. There was no strong evidence for an association with intake of any of the individual antioxidants. Our findings suggest that total phenolic consumption may decrease endometrial cancer risk.

Keywords

Endometrial neoplasms; antioxidants; total antioxidant capacity; vitamin C; vitamin E; beta-carotene; selenium; lutein; lycopene; diet; phenolics

INTRODUCTION

Endometrial cancer is the fourth most common cancer in women and the most common gynecologic malignancy in the United States (1). An estimated 46,470 women were diagnosed with endometrial cancer in 2011, and 8,120 died from the disease.

Many of the risk factors for endometrial cancer are modifiable (2). Obesity is among the most significant risk factors for endometrial cancer, with up to a 2 to 4.5 times increased risk

compared to those with a normal body mass index (BMI) (3). Additionally, the association with obesity is stronger than for any other cancer, with a BMI greater than 40 kg/m² associated with a 6.25 times increased risk of death from endometrial cancer compared to those with a normal BMI (4).

Obesity is associated with inflammation and oxidative stress (5), as well as with higher circulating levels of estrogen. Although it has been estimated that over 70% of patients with endometrial cancer are obese (6), the current evidence on most individual micronutrients and dietary patterns is considered to be inconsistent (7). The World Cancer Research Fund's (WCRF) Second Expert Report on Food, Nutrition, Physical Activity and the Prevention of Cancer concluded that there was limited but suggestive evidence that non-starchy vegetables were associated with a decreased risk of endometrial cancer. However, there was insufficient evidence to make any judgment on individual micronutrients and dietary patterns, and the Panel recommended that additional research be conducted in this area (8).

A number of studies have found significant inverse associations between endometrial cancer risk and individual antioxidant intake (9–22). A recent meta-analysis of studies reporting on antioxidant vitamin intake, including case-control and cohort studies published through 2009, reported decreased risks for higher intake of vitamin C, vitamin E, and beta-carotene (22). In contrast, some studies have found no association, and in some cases, increased risks have been reported (14, 16, 17, 21, 23–27). The evidence for individual micronutrients, including vitamin C, vitamin E, beta-carotene, other carotenoids, and selenium, is promising, but further studies are needed to clarify the role of these compounds in endometrial cancer prevention.

The combined role of these micronutrients in the prevention of cancer has not been established. As both individual contributions from micronutrients, as well as combined additive or synergistic effects may alter risk, understanding the combined effect of antioxidant micronutrients on the risk of endometrial cancer may also help to develop a better understanding of their role in disease prevention. We therefore sought to investigate the association between endometrial cancer risk and individual antioxidant micronutrients from food and supplements, as well as the association between endometrial cancer risk and total antioxidant capacity (TAC) intake in the EDGE Study (a study of Estrogen, Diet, Genetics, and Endometrial cancer risk), a population-based case-control study in New Jersey.

METHODS

Methods used in the EDGE Study have been described elsewhere (28, 29). In brief, cases were women with newly diagnosed histologically confirmed endometrial cancer. Endometrial cancer cases aged 21 years or older who spoke English or Spanish and resided in six counties of New Jersey (Bergen, Essex, Hudson, Middlesex, Morris, or Union) were eligible to participate, and were identified between 1 July 2001 and 30 June 2005. Case ascertainment was conducted by the Cancer Epidemiology Services of the New Jersey Department of Health and Senior Services (NJDHSS) via the New Jersey State Cancer Registry (NJSCR) using rapid case ascertainment, supplemented with a review of state Cancer Registry data to identify cases diagnosed out of the area. Wherever possible, representative glass slides were re-reviewed by a gynecologic pathologist to confirm the diagnosis. During the study period, 1,559 women were identified to be eligible. Of these, 1,104 were identified within a year of diagnosis, and 469 (42%) endometrial cancer cases completed the interview.

Controls were identified and recruited between the years of 2001 – 2006, and include women aged 21 years and older who were able to speak English or Spanish, and resided in same six counties of New Jersey as the cases. Women who had a hysterectomy were not eligible to participate. Controls who were 65 years or older were identified through random digit dialing, in which approximately 49% of the 355 eligible women completed the interview. Women 65 years and older were identified by random selection from lists purchased from the Centers for Medicare and Medicaid. Three hundred sixteen women were contacted, and 22% completed the interview; however, of those who declined, the eligibility of 40% was unknown. To identify additional controls > 65 years of age, area sampling was conducted starting in 2003, in which 30 consecutive households in randomly chosen neighborhoods were contacted by mail and by home visits. Women aged 55 years and older were later included to better match the age distribution of the cases. Of the 524 eligible women identified, 43% completed the interview. In total, 467 controls completed the interview.

All women participating in the study provided informed consent, and IRB approval was obtained from the Cancer Institute of New Jersey (CINJ), Memorial Sloan-Kettering Cancer Center (MSKCC), and the New Jersey Department of Health and Senior Services (NJDHSS).

Data Collection

Data on potential and established endometrial cancer risk factors were collected by telephone through a comprehensive questionnaire. The questionnaire included information on demographic characteristics, residential history, pregnancy history, occupation, oral contraceptive use and other birth control methods, menstrual history and menopausal status, personal and family history of cancer and other illnesses, height and weight, physical activity, and exposure to other potential risk factors. Participants also provided a mouthwash sample for DNA analysis and self-measured waist and hip circumferences.

Dietary intake was assessed using a validated questionnaire, the Block 98.2 FFQ, which consists of 110 food items with multiple frequency responses, as well as picture-assisted options for portion size. Participants were asked to report their regular diet in the six months prior to either their date of diagnosis for cases or date of entry into the study for controls. A total of 424 endometrial cancer cases and 398 controls completed the FFQ. Compared to those who did not complete the FFQ, the participants who completed it tended to be older, but there were no significant differences in education, BMI, or HRT use (data not shown).

Data Analysis

We excluded seven cases and three controls because they had missing data for major covariates such as menopausal status and BMI, resulting in a total analytical sample of 417 endometrial cancer cases and 395 controls.

Dietary TAC was estimated by linking data from the USDA Oxygen Radical Absorbance Capacity (ORAC) Database (<http://www.ars.usda.gov/sp2userfiles/place/12354500/data/orac/orac07.pdf>) and the University of Oslo's Antioxidant Food Database (AFD) (30) to FFQ-derived estimates of intake. Total daily intake of foods containing antioxidants was calculated first, based on food-frequency questionnaire estimates, including over 50 food items of fruits, vegetables, juices, grains, teas, chocolate and wine. The most appropriate corresponding food items from the databases were chosen to relate to food items in the FFQ. For each antioxidant food item in the FFQ, we derived daily consumption based on the frequency and portion size reported. For variables in which a range of frequency was presented, the mid-value was assigned before conversion (e.g., categories recorded as 3–4

times per day were assigned the value of 3.5 times per day). Each food value was converted from the unit of measure in the FFQ to grams per day based on standard values available from the USDA Nutrient Database for Standard Reference (www.nal.usda.gov).

We calculated TAC of the diet using two separate methods: using the Oxygen Radical Absorbance Capacity (ORAC) Database and the Antioxidant Food Database (based on FRAP values). The ORAC Database, developed by the USDA Agricultural Research Service, provides the antioxidant capacities of 277 food items, in terms of hydrophilic-ORAC (H-ORAC), lipophilic-ORAC (L-ORAC), total-ORAC (T-ORAC), and total phenolics (TP). The Antioxidant Food Database (FRAP database) is a similar database detailing the antioxidant capacity of food items, developed using different methods and on a much larger scale. The antioxidant capacities of over 3100 food and beverage items are included, sampled from multiple countries, using the FRAP assay. In contrast to the ORAC database, the antioxidant capacity of supplements is included in the database. However, only total antioxidant capacity is reported (as opposed to hydrophilic, lipophilic, and total phenolics in the ORAC database). In this study, data from these two databases were utilized to develop comprehensive TAC indices among endometrial cancer patients and controls.

In the ORAC database, H-ORAC, L-ORAC, and T-ORAC are reported in μmol of Trolox Equivalents per 100 grams ($\mu\text{molTE}/100\text{g}$), and TP is reported in mg gallic acid equivalents per 100 grams (mgGAE/100g). The Antioxidant Food Database (FRAP database) provides one measure for total antioxidant content in $\mu\text{molTE}/100\text{g}$. For each food item containing antioxidants in the FFQ, respective antioxidant values were assigned based on data from the antioxidant databases, and the μmol of Trolox Equivalents per 100 grams per day and mg gallic acid equivalents per 100 grams per day were assessed. To derive the TAC indices, the respective antioxidant values for each food item for each participant, based on their consumption of those food items, was summed for all foods in the FFQ to produce total ORAC and FRAP antioxidant scores.

Separate antioxidant indices were developed for total H-ORAC, L-ORAC, T-ORAC, and TP, from the ORAC database, and an index of TAC was developed from the Antioxidant Food (FRAP) Database. As the ORAC Database does not contain values for antioxidant supplements, for comparative purposes to the T-ORAC index, two sets of TAC indices were developed from the Antioxidant Food (FRAP) Database, one including values for supplements and one without.

The individual antioxidants and TAC indices were evaluated as categorical variables. Cutpoints for tertiles were determined based on the distribution of independent variable in the controls. Age-adjusted mean antioxidant intake (for individual antioxidants and TAC indices) in cases and controls were compared using ANCOVA.

Multiple unconditional logistic regression models were developed to estimate odds ratios and 95% confidence intervals while controlling for potential confounders. Potential covariates included age, BMI, oral contraceptive use, menopausal status, reproductive factors, hormone use, physical activity, smoking, alcohol use, and total energy intake. Tests for trend were derived by assigning a median value to each tertile. Stratified analyses were conducted separately by Body Mass Index, HRT use, and smoking status (current, former/never) to assess effect modification. Interactions were evaluated by including cross-product terms in the logistic regression models. All analyses were conducted using SAS software version 9.2.

RESULTS

The age-adjusted mean intake for the TAC variables in cases and controls is shown in Table 1. Compared to controls, cases had a slightly lower intake of total hydrophilic antioxidant intake (H-ORAC) ($p=0.04$), total antioxidant intake (T-ORAC) ($p=0.04$), and total phenolics (TP) ($p=0.002$) based on antioxidant indices developed using the ORAC database. No significant differences were observed in mean TAC intake between cases and controls based on the TAC indices developed using the FRAP database. Age-adjusted mean intake of individual micronutrients is shown in Table 2. Cases tended to have a slightly higher intake of selenium than controls ($p=0.04$) and a slightly lower intake of lycopene ($p=0.01$).

We conducted linear regression to assess the food sources that were the highest contributors to each of the indices in our study. The highest contributor to the FRAP index was orange or grapefruit juice, accounting for 36% of the variation in the index, followed by strawberries. For both the ORAC index and the H-ORAC index, tea and fruits such as apples, pears, peaches and apricots, were the highest contributors. As expected based on previous results (31), the highest contributors to the L-ORAC index were foods that contain fat soluble antioxidants, such as cooked cereals, spinach, and broccoli (data not shown).

Agreement between the ORAC antioxidant index and the FRAP antioxidant index was assessed by classifying the participants into quantiles of total antioxidant intake, and determining whether they were in the same or a close quantile using each of the antioxidant databases. Almost 60% of the total population was classified in the same quantile. Among the remaining women who were not classified in the same quantile, the majority of women were only misclassified by one quantile (37.8%). The Spearman rank correlation between the ORAC antioxidant index and the FRAP antioxidant index for the total population was 0.86.

Risk associated with the various TAC indices compiled is shown in Table 3. After adjusting for major risk factors, a significantly decreased risk of endometrial cancer was observed for the highest tertile of total phenolics compared to the lowest (OR: 0.62; 95% CI: 0.39–0.98). The highest tertile of total hydrophilic and lipophilic antioxidant intakes, compared to the lowest, were associated with odds ratios of 0.89 and 0.74, respectively; however the confidence intervals included the null. Similar results were observed for TAC intake based on the ORAC and FRAP values. No substantial differences were observed after further adjustment for alcohol intake, physical activity, and smoking status among any of the indices.

As shown in Table 4, there was little evidence for an association of any of the individual antioxidants and endometrial cancer risk, with the exception of vitamin E supplement use, which was associated with a somewhat increased risk after adjusting for relevant confounders (OR: 1.43; 95% CI: 1.0–2.04 for users compared to non users). However, there was no association with vitamin E intake from food and supplement sources combined.

Stratified analyses by Body Mass Index, HRT use, and smoking status did not suggest effect modification (data not shown).

DISCUSSION

The major findings emerging from our study were an inverse association of endometrial cancer risk with total phenolics and a suggestion of increased risk with vitamin E supplement use. However, this may have been an artifact as we found no association when we evaluated vitamin E from food and supplements combined. There was little evidence that individual antioxidants from food sources played a role.

Our findings show similar results for TAC intake based on the ORAC database and the FRAP database; however TAC intake was almost twice as high using ORAC values compared to FRAP values. Antioxidant capacity assays are categorized into two types based on the type of reaction involved (32–34). Assays based on hydrogen atom transfer (HAT), such as the ORAC assay, act through a competitive reaction scheme where the antioxidant and substrate compete for peroxy radicals, which inhibit induced low-density lipoprotein autoxidation. The second category of antioxidant capacity assays includes assays based on electron transfer (ET), such as the ferric ion reducing antioxidant power (FRAP) assay, which measures the capacity of an antioxidant to reduce an oxidant. Among HAT assays, the ORAC assay is consistently considered to be the ideal assay to quantify an antioxidant's peroxy radical scavenging capacity, due to its relevance to human biology as the peroxy radical is the most abundant free radical in humans. The ORAC assay is considered to be a method capable of providing a basis upon which to establish dietary guidelines that may impact health outcomes (33). The FRAP assay is commonly used due to its ease of use and low costs. However, the FRAP assay has been criticized in terms of interference, reaction kinetics, and quantitation methods. As the mean daily intake based on ORAC values was found to be twice that based on FRAP values, further investigation is warranted to determine what is driving the differences between the two assays.

The dietary TAC in cancer prevention has received little attention. To our knowledge, this is the first study to evaluate the association between TAC intake and endometrial cancer risk. In the Health Professionals Follow-Up Study, TAC intake assessed through the FRAP assay was not associated with colorectal cancer (35). In the EPIC cohort, TAC intake, based on the FRAP and TRAP (total radical-trapping antioxidant parameter) assays, was associated with a reduction in gastric cancer risk (36).

Our study showed a strong inverse association between phenolic intake and endometrial cancer risk. It has been suggested that phenolics may have stronger antioxidant properties than vitamin C, vitamin E, and beta-carotene (37). A number of mechanisms have been proposed for the anticancer effect of phenolics. Phenolics inhibit phase I enzymes, induce phase II enzymes, stimulate DNA repair, promote anti-inflammation, induce cell cycle arrest and apoptosis, and inhibit cell proliferation (38). Although phenolics are widely consumed, their health effects have only recently begun to receive attention. Epidemiologic studies as well as in vitro and in vivo studies have reported protective effects of phenolics on cardiovascular disease, neurodegenerative diseases, and some cancers. In vitro studies show that berry extracts, isolated polyphenols from strawberry, wine extracts, tea extracts, olives, legumes, citrus, apples, and curcumin as well as other phenolics have been shown to inhibit the growth of oral, breast, colon, prostate, leukemia, lymphoma, lung, pancreas, liver, stomach, cervix, and head and neck tumor cell lines (38). Animal studies on colon, lung, breast, liver, prostate, stomach, esophagus, small intestine, pancreas, mammary gland, and skin tumors have also shown protective effects (38). Few human intervention studies have been conducted; however protective effects have been observed in Barrett's esophagus patients (39) and hemodialysis patients at a high risk of cancer (40). Our findings contribute to the growing pool of evidence that phenolics may have a protective effect on oxidative stress-induced disease.

We found no association with dietary vitamin C intake and endometrial cancer risk. Similar to our findings, a cohort study which investigated the association between vitamin C and endometrial cancer risk reported no association with dietary intake; however increased risks were observed with supplement use (16). Results from the Nurses' Health Study show no association from diet or supplements (23). A meta-analysis of vitamin C intake, based on data from case-control studies, reported a random-effects summary odds ratio of 0.85 (95% CI: 0.73–0.98) per 50mg/1,000kcal (I^2 : 66.1%; $p < 0.01$) (22). We found no association

between vitamin C supplement use and endometrial cancer risk. Results from previous studies are inconsistent (11, 15, 21).

Similarly, we found no association between beta-carotene from food sources and endometrial cancer risk. Previously conducted studies investigating beta-carotene report conflicting results (9, 10, 12–17, 21, 25, 26, 41, 42). However, the majority of studies report an inverse association (10, 12–16). Most case-control studies reported decreased risks with increasing dietary intake. A meta-analysis of beta-carotene intake, based on data from selected case-control studies, reported a random-effects summary odds ratio of 0.88 (95% CI: 0.79–0.98) per 1,000mcg/1,000kcal (I^2 : 77.7%; $p < 0.01$) (22). In line with our findings, Jain *et al* (16) evaluated beta-carotene from supplements and found no association.

In contrast to our findings, the few studies that have investigated the association between lutein and endometrial cancer risk report risk estimates below one (10, 13, 15, 16, 18). The same five studies also evaluated lycopene and three of them reported decreased risks (10, 15, 16). We found no association with lutein and a trend towards a decreased risk for lycopene; however the result did not reach statistical significance.

Similar to our study, almost all studies investigating dietary vitamin E intake and endometrial cancer risk have reported decreased risks which did not reach statistical significance (10, 12, 13, 15, 21), with the exception of two cohort studies (16, 23) and one small hospital-based case-control study (14) which reported null results. All of the confidence intervals included the null value. A meta-analysis of vitamin E intake, based on data from selected case-control studies, reported a random-effects summary odds ratio of 0.91 (95% CI: 0.84–0.99) per 5mg/1,000kcal (I^2 : 0.0%; p : 0.45) (22). Jain *et al*. (15) also evaluated vitamin E intake with supplements, and reported no association. We found somewhat increased risks for vitamin E supplement users, compared to non-users, but intake of vitamin E from food and supplement combined was not associated with risk. The only other three studies reporting on vitamin E supplement intake did not report an association (11, 21, 23).

There is a growing interest on the role of selenium on carcinogenesis. We found a decreased risk with increasing dietary selenium intake; however the risk estimate did not reach statistical significance. Only two studies have investigated the role of selenium in endometrial cancer prevention, both reporting results similar to our study. In both studies, serum selenium levels were found to be significantly lower in women with endometrial cancer compared to those in the control groups (19, 20). Our results similarly suggest a trend towards a decreased risk associated with selenium.

This study is subject to limitations of case-control studies, such as recall bias and selection bias. We also had a low participation rate. To determine whether our study participants differed from the general population, we compared those who participated to women with endometrial cancer diagnosed in the same counties during this time period. The cases who participated in the study tended to be younger, and they were more likely to have localized disease (81% of our study participants versus 70% of all eligible cases). We do not have information on controls who did not participate. However, we found the distribution of established risk factors among endometrial cancer and controls to be in line with what has been reported in other published studies.

We used a validated FFQ to assess dietary intake and assigned antioxidant values based on the FRAP and OCAC assays to the different foods to estimate a total index of TAC intake. Measurement error in dietary assessment is always a possibility, leading to non-differential misclassification and, in turn, hampering our ability to detect an association. This may have explained, at least in part, our null findings for most of the variables.

In summary, our study shows that total phenolic antioxidant intake may be associated with a decreased risk of endometrial cancer. Further research investigating the role of phenolic antioxidants is needed to confirm their role on endometrial cancer prevention.

Acknowledgments

Funding: This work was funded in part by NIH-K22CA138563 and R01CA83918.

We thank the research staff who were involved in this study at Memorial Sloan-Kettering Cancer Center (Sharon Bayuga, Katherine Pulick, Silvia Brendel, Nora Geraghty, June Kittredge, Elinor Miller, Louise Salant, Mathilde Saxon, Elizabeth Ward, Doreen Wass, Kay Yoon), the New Jersey Department of Health and Senior Services personnel (Sandy Wilcox, Tara Blando, Joan Kay, Betsy Kohler, Kevin Masterson, and Helen Weiss), as well as all the participants who generously donated their time to the study.

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Table 1

Age-adjusted mean total antioxidant intake based on antioxidant indices in cases and controls

	Mean (SE)		p value
	Cases	Controls	
H-ORAC, $\mu\text{molTE}/100\text{g}$	13,058 (341)	13,809 (351)	0.045
L-ORAC, $\mu\text{molTE}/100\text{g}$	429 (15)	442 (15)	0.313
T-ORAC, $\mu\text{molTE}/100\text{g}$	13,358 (348)	14,133 (358)	0.039
TP, mgGAE/100g	1805 (47)	1895 (48)	0.002
FRAP, $\mu\text{molTE}/100\text{g}$	5,428 (146)	5,669 (150)	0.251
FRAP, with supplements, $\mu\text{molTE}/100\text{g}$	12,958 (536)	13,025 (551)	0.931

H-ORAC: Hydrophilic oxygen radical absorbance capacity; L-ORAC: Lipophilic oxygen radical absorbance capacity; T-ORAC: Total oxygen radical absorbance capacity; TP: Total phenolics; TE: Trolox equivalents; GAE: Gallic acid equivalents

Table 2

Age-adjusted mean antioxidant micronutrient intake from foods and supplements

	Mean (SE)		<i>p</i> value
	Cases	Controls	
Vitamin C, mg/1,000kcal			
Food	123.7 (3.4)	120.9 (3.5)	0.200
Supplements	292.5 (21.5)	284.6 (22.1)	0.645
Total intake	416.2 (21.8)	405.5 (22.4)	0.598
Vitamin E, aTE/1,000kcal			
Food	10.1 (0.3)	10.3 (0.3)	0.267
Supplements	116.5 (7.8)	108.9 (8.1)	0.711
Total intake	126.6 (7.9)	119.2 (8.1)	0.711
Beta-carotene, mcg/1,000kcal			
Food	3799.2 (158.3)	3483.9 (162.6)	0.661
Supplements	1853.4 (60.1)	2321.9 (267.3)	0.264
Total intake	5652.6 (309.5)	5805.9 (318.1)	0.467
Selenium, mcg/1,000kcal			
Food sources	81.3 (2.0)	77.7 (2.1)	0.045
Supplements	22.3 (2.3)	22.5 (2.3)	0.183
Total intake	103.7 (3.1)	100.2 (3.2)	0.129
Lutein (food), mcg/1,000kcal	1935.2 (101.7)	1852.3 (104.6)	0.786
Lycopene (food), mcg/1,000kcal	4852.0 (219.5)	4962.9 (225.6)	0.011

Table 3

Total antioxidant intake based on antioxidant indices and endometrial cancer risk

	Cases (n)	Controls(n)	OR1	95% CI	OR2	95% CI
ORAC Database						
H-ORAC (μmolTE/100g)						
1 (<9,949)	141	130	1.00		1.00	
2 (9,949–15,758)	164	134	1.19	0.82–1.75	1.24	0.85–1.83
3 (15,759)	112	131	0.87	0.56–1.35	0.89	0.57–1.39
p for trend				0.12		0.09
L-ORAC (μmolTE/100g)						
1 (<281)	144	131	1.0		1.0	
2 (281–469)	146	133	0.86	0.59–1.2	0.85	0.58–1.25
3 (470)	127	131	0.75	0.49–1.1	0.74	0.49–1.13
p for trend				0.96		0.96
T-ORAC (μmolTE/100g)						
1 (<10,079)	140	130	1.00		1.00	
2 (10,079–16,281)	168	135	1.21	0.83–1.77	1.26	0.86–1.85
3 (16,282)	109	130	0.85	0.55–1.32	0.87	0.56–1.36
p for trend				0.08		0.06
Total Phenolics (mgGAE/100g)						
1 (<1,379)	144	131	1.00		1.00	
2 (1,379–2,231)	174	134	1.09	0.76–1.59	1.13	0.78–1.65
3 (2,232)	99	130	0.60	0.38–0.95	0.62	0.39–0.98
p for trend				0.03		0.02
FRAP Database						
FRAP (μmolTE/100g)						
1 (<4,081)	105	131	1.00		1.00	
2 (4,081–6,618)	156	134	1.21	0.83–1.77	1.19	0.81–1.75
3 (6,619)	156	130	0.84	0.54–1.30	0.84	0.54–1.33
p for trend				0.18		0.22
FRAP with supplements (μmolTE/100g)						
1 (<6,420)	105	130	1.00		1.00	
2 (6,420–14,357)	150	134	1.03	0.66–1.60	1.11	0.70–1.74
3 (14,357)	162	131	1.23	0.77–1.96	1.29	0.80–2.08
p for trend				0.93		0.81

ORAC: Oxygen radical absorbance capacity; H-ORAC: Hydrophilic oxygen radical absorbance capacity; L-ORAC: Lipophilic oxygen radical absorbance capacity; T-ORAC: Total oxygen radical absorbance capacity; TP: OR: Odds Ratio; CI: Confidence interval. OR1: adjusted for age (continuous), education, race, age at menarche (continuous), menopausal status and age at menopause for postmenopausal women, parity, OC use, HRT use, BMI (continuous), antioxidant supplement intake, dietary fat, and total calories. OR2: further adjusted for physical activity (METs), smoking status, and alcohol (g/1000 kcal)

Table 4

Antioxidant micronutrients from food and supplements and endometrial cancer risk

	Cases (n)	Controls(n)	OR1	95% CI	OR2	95% CI
<u>Vitamin C</u>						
Food (mg)						
1 (<82.7)	126	132	1.00		1.00	
2 (82.7–142.5)	161	133	1.35	0.93–1.96	1.35	0.92–1.98
3 (142.6)	130	130	1.21	0.78–1.87	1.26	0.81–1.96
<i>p</i> for trend				0.19		0.24
Supplements						
No	124	115	1.00		1.00	
Yes	293	280	1.26	0.89–1.77	1.22	0.86–1.73
Combined food and supplements (mg)						
1 (<145.6)	140	131	1.00		1.00	
2 (145.6–450.0)	138	134	1.11	0.76–1.64	1.17	0.79–1.74
3 (451.1)	139	130	1.33	0.91–1.94	1.37	0.93–2.02
<i>p</i> for trend				0.84		0.99
<u>Vitamin E</u>						
Food (αTE)						
1 (<7.4)	145	132	1.00		1.00	
2 (7.4–11.5)	146	134	0.92	0.61–1.40	0.95	0.63–1.45
3 (11.6)	126	129	0.79	0.47–1.33	0.78	0.46–1.33
<i>p</i> for trend				0.80		0.64
Supplements						
No	119	116	1.00		1.00	
Yes	298	279	1.46	1.04–2.07	1.43	1.00–2.04
Combined food and supplements (αTE)						
1 (<22.1)	136	131	1.00		1.00	
2 (22.1–123.0)	141	134	0.69	0.47–1.02	0.70	0.47–1.04
3 (>123.0)	140	130	0.96	0.67–1.39	0.97	0.67–1.40
<i>p</i> for trend				0.04		0.05
<u>Beta-carotene</u>						
Food (mcg)						
1 (<2,070)	132	131	1.00		1.00	
2 (2,070–3,649)	132	134	0.95	0.65–1.39	0.93	0.63–1.36
3 (3,650)	153	130	1.06	0.71–1.58	1.12	0.74–1.66
<i>p</i> for trend				0.61		0.45
Supplements						
No	154	143	1.00		1.00	
Yes	263	252	1.17	0.85–1.61	1.15	0.83–1.59
Combined food and supplements (mcg)						
1 (<3,040)	144	131	1.00		1.00	
2 (3,040–4,995)	123	134	0.89	0.61–1.31	0.92	0.63–1.35
3 (4,996)	150	130	1.09	0.74–1.61	1.12	0.75–1.65
<i>p</i> for trend				0.34		0.41
<u>Selenium</u>						
Food (mcg)						
1 (<59.4)	139	131	1.00		1.00	
2 (59.4–87.6)	137	134	0.92	0.60–1.40	1.00	0.66–1.54
3 (87.7)	141	130	0.62	0.36–1.07	0.64	0.37–1.10
<i>p</i> for trend				0.36		0.17

	Cases (n)	Controls(n)	OR1	95% CI	OR2	95% CI
Supplements						
No	165	153	1.00		1.00	
Yes	252	242	1.23	0.82–1.53	1.11	0.81–1.52
Combined food and supplements (mcg)						
1 (<72.4)	150	131	1.00		1.00	
2 (72.4–103.1)	124	134	0.81	0.55–1.19	0.85	0.57–1.26
3 (103.2)	143	130	0.74	0.47–1.17	0.74	0.47–1.17
<i>p</i> for trend				0.68		0.92
<u>Lutein</u>						
Food (mcg)						
1 (<1,015)	134	131	1.00		1.00	
2 (1,015–1,882)	146	134	1.11	0.76–1.61	1.14	0.78–1.66
3 (1,883)	137	130	1.01	0.68–1.49	1.07	0.72–1.59
<i>p</i> for trend				0.54		0.57
<u>Lycopene</u>						
Food (mcg)						
1 (<2,492)	129	131	1.00		1.00	
2 (2,492–5,443)	157	134	1.04	0.71–1.52	0.99	0.67–1.46
3 (5,444)	131	130	0.76	0.50–1.15	0.74	0.48–1.12
<i>p</i> for trend				0.29		0.39

OR1: adjusted for age (continuous), education, race, age at menarche (continuous), menopausal status and age at menopause for postmenopausal women, parity, OC use, HRT use, BMI (continuous), dietary fat, and total calories. OR2: further adjusted for physical activity (METs), smoking status, and alcohol (g/1000 kcal)