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Antioxidant intake and risk of endometrial cancer: Results from the Nurses' Health Study

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Abstract

To investigate the associations between antioxidant intake and risk of endometrial cancer, the authors analyzed data from the prospective Nurses' Health Study. From 1980 to 2006, 669 invasive adenocarcinoma cases were identified over 1.3 million person-years of follow-up. Information on dietary intake was collected in 1980 and updated every 2–4 years. Cox proportional hazard models were used to calculate the multivariate relative risks (RRs), controlling for total energy and potential risk factors for endometrial cancer. Overall, the authors found no association between intakes of vitamins A, C, E or carotenoids from foods or supplements and cancer risk. The RRs and 95% confidence intervals (CIs) for the highest *vs*. lowest quintiles of vitamins A, C, E, and total carotenoids were 1.09 (95% CI: 0.85–1.39), 0.98 (95% CI: 0.76–1.25), 1.07 (95% CI: 0.83–1.38), and 1.12 (95% CI: 0.86–1.45), respectively. Similarly, use of multivitamins or specific vitamins A, C, or E supplements was unassociated with risk. In subgroup analyses, several associations appeared to vary by postmenopausal hormone (PMH) use. Our results suggest there is no overall association between dietary antioxidant intake or use of antioxidant supplements with risk of endometrial cancer.

Keywords

antioxidants; diet; endometrial neoplasms

INTRODUCTION

Endometrial cancer is the seventh most commonly diagnosed cancer worldwide with the highest incidence in the United States and Europe.[1] The role of increased levels of estrogen as a cause of endometrial cancer has been well established.[2, 3] Most endometrial cancer risk factors, such as obesity, nulliparity, and smoking, can be substantially explained within the framework of the unopposed estrogen hypothesis[4] although other mechanisms such as inflammation[5] have also been proposed.

Antioxidants from the diet, including vitamins C, E, and carotenoids, have been proposed to prevent cancers by inducing apoptosis and suppressing tumor cell growth[6–8] or by counterbalancing free radical damage by neutralizing or trapping reactive oxygen

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species.[9–11] Two *in vitro* studies reported vitamin C and lycopene had a growth inhibiting effect on endometrial cancer cells at high concentrations.[12, 13] However, epidemiological evidence addressing these associations is limited. The only prospective study (221 cases) found no overall association between vitamins A, C, E, and carotenoids with endometrial cancer.[14] Results from previous case-control studies have been inconsistent.[15–26]

In this study, we examine the associations between consumption of vitamins A, C, E, and carotenoids with risk of endometrial cancer using 26 years of prospectively collected data from the Nurses' Health Study cohort.

METHODS

Study Population

The Nurses' Health Study began in 1976, and included 121,701 female registered nurses aged 30–55 years who resided in one of 11 states in the U.S. at that time. The cohort has been followed biennially by mailed questionnaire to update exposure information and any new disease diagnoses; the follow-up rate has been at least 90% for each follow-up cycle. Deaths are confirmed through reports by family members and searching the National Death Index.

In this analysis, follow-up began in 1980 when dietary intake was first queried. At baseline, we excluded women who had had a hysterectomy (n=20,612), did not respond to or had more than 10 missing items on their 1980 Food Frequency Questionnaire (FFQ), or reported total caloric intakes <500 or >3500 kcal/day (n=28,487), died before 1980 (n=747), or reported any type of cancer before 1980 (excluding nonmelanoma skin cancer, n=3,660). Since obesity is an important risk factor for endometrial cancer, we also excluded women with missing body mass index (BMI) at baseline (n=166, these women could reenter the analysis in subsequent cycles once information on BMI was available). A total of 68,070 women remained for analysis.

At the beginning of each follow-up cycle, we excluded deaths, women with endometrial cancer or other cancer (excluding nonmelanoma skin cancer) and women who reported a hysterectomy in the previous time period. Women with missing BMI data during the prior two consecutive periods also were excluded in the next cycle but could reenter the analysis once information on BMI was available. In 1984 and later, when the FFQs queried about 130 food items, women with more than 70 blank food items, and total caloric intakes <600 or >3500 kcal/day also were excluded.

Endometrial Cancer Cases

From 1978 forward, participants were asked to report on their questionnaires any new diagnosis of endometrial cancer. From June 1, 1980 through May 31, 2006, a total of 1,384 women reported endometrial cancer. For 1,104 cases, medical records including the diagnosis, histological type, presence of invasion and stage were obtained. From these, we confirmed 669 cases of invasive adenocarcinoma defined by the International Federation of Gynecology and Obstetrics (FIGO) as stage IB to IVB. The primary reasons for exclusion were that the tumor was non-invasive (n=316) or non-epithelial (n=60) or other types of epithelial cancer (n=58) other than adenocarcinoma (*e.g.*, clear cell).

Assessment of Intake of Antioxidants

A 61-item food frequency questionnaire for collecting dietary information was asked in 1980. An expanded food frequency questionnaire with approximately 130 food items was sent to women in 1984, 1986, 1990, 1994, 1998, and 2002 to assess usual food intake in the

previous year. A common unit or portion size for each food was specified, and participants were asked how often, on average, they had consumed that amount of food or beverage during the previous year. The average daily intake of nutrients were calculated by multiplying the frequency of consumption of each item by its nutrient content per serving and totaling the nutrient intake for all food items.

The Food and Nutrition Board of the National Research Council in the United States defines a dietary antioxidant as a substance in foods which significantly decreases the adverse effects of reactive oxygen species, reactive nitrogen species, or both on normal physiologic function in humans. In our study, we investigated the associations of intakes of vitamins A, C (ascorbic acid or ascorbate), E (α tocopherol), and carotenoids from foods as well as vitamin supplements with risk of endometrial cancer. The values were calculated from the USDA database.[27] Since forms of vitamin E other than α tocopherol such as β, gamma and delta tocopherol are now assumed to have no vitamin E activity, we used only the values of α tocopherol (foods supplementation only/without supplement). The carotenoids evaluated included total carotenoids, α-and β-carotene, lutein/zeaxanthin and lycopene. In the analyses, we assessed total intake (intakes from both foods and supplements), intake without supplements (from foods only), and vitamin supplement use. To assess the total antioxidant effect from foods and supplements, we also analyzed two “antioxidants indices”, ferric-reducing ability of plasma (FRAP)[28] and an antioxidant score, calculated by adding up the quintiles of each of the individual antioxidants.

Energy-adjusted intakes were computed as the residual plus the expected nutrient intake (from a person with mean energy intake) from the regression model with total energy as the independent variable and absolute nutrient intake as the dependent variable [29] This addresses the question of whether the composition of the diet, independent of total energy intake, is most relevant to the risk of endometrial cancer. Given dietary intake was assessed up to 7 times over a 26 year period, we assessed intake in several ways: cumulative average intake (the average intake from the available FFQs up to each follow-up cycle), recent intake (current intake, intake during the previous assessment period, *i.e.*, 4 years ago), and baseline intake (in 1980) were used to assess the effect of cumulative exposure, short latency, and long latency, respectively. If intake on one or more questionnaires was missing, the cumulative average intake was calculated by averaging the available data. For recent intake, we carried forward the last available dietary data, and if data from more than one questionnaire was missing, recent intake was considered missing. We also examined use of vitamin supplements, including daily dose and duration of use of multivitamins, vitamins A, C, and E.

Assessment of Covariates

Information on most potential confounding factors, including weight, smoking, oral contraceptives (OC) use, PMH use, age at menopause, age at last birth, hypertension, and diabetes was collected in 1976 and subsequent questionnaires. If data were not available, those women were assigned to a missing category for that period. BMI was calculated from height at baseline and from the biennially updated report of current weight. We carried forward, for up to two cycles, the weight reported in the prior questionnaire cycle if it was missing in the current cycle. Participants were classified as postmenopausal from the time they returned a questionnaire reporting natural menopause. PMH was first assessed in 1976; women were queried about current and past postmenopausal hormone therapy use and duration. From 1978 forward, information on the type of hormone used was collected. OC use was queried biennially until 1984 when women were 38 to 63 years of age and few women were still current users.

Data Analyses

Each participant contributed person-time from the date of the return of the 1980 questionnaire through June 1, 2006, hysterectomy, death, loss to follow-up, or diagnosis of endometrial cancer or other cancer, whichever came first. Incidence rates of endometrial cancer in each category of the exposure variable were calculated as the number of incident cases divided by the total person-time at risk. Incidence rate ratios (IRRs) were computed as the ratio of the incidence rate in the exposure category of interest to the incidence rate in the referent category.

To adjust the RRs for multiple covariates, we used Cox proportional hazard models conditioned on age (months) and follow-up cycle. In all multivariate models, we included the following covariates (see Table 2 for detail on how covariates were defined in multivariate models): total energy, smoking, oral contraceptive use, postmenopausal hormone use, age at menopause, parity, age at last birth, age at menarche, hypertension, diabetes, BMI. With no prior rationale for specific cutpoints for intakes of antioxidants and to insure adequate numbers in each category, we categorized antioxidant intakes into quintiles. Tests for linear trend for the nutrients were calculated by including the median of each quintile in the final multivariate model.

To assess whether the relationships between antioxidant intake and endometrial cancer risk varied across categories of other risk factors, we performed stratified analyses. The interaction terms were evaluated using the likelihood ratio test. The interaction terms were calculated as the products of a binary stratification factor (*e.g.*, ever smoked *vs.* never smoked) and the median for each quintile of our dietary exposures.

RESULTS

A total of 669 cases of invasive adenocarcinoma cases were identified among about 1.3 million person-years of follow-up. Characteristics of the study population at the midpoint of follow-up (1990) are summarized in Table 1. In 1990, women with higher intakes of vitamins A, C, E and carotenoids were more likely to use PMH. Women with higher intakes of vitamin A and carotenoids were less likely to smoke, and had a lower BMI.

We did not observe any consistent associations between cumulative antioxidant intake and risk of endometrial cancer (Table 2). The RRs and 95% CI for the highest *vs.* lowest quintiles of vitamins A, C, E, and total carotenoids were 1.09 (95% CI: 0.85–1.39), 0.98 (95% CI: 0.76–1.25), 1.07 (95% CI: 0.83–1.38), and 1.12 (95% CI: 0.86–1.45), respectively. Although a few relative risks were statistically significant (i.e., for vitamin A without supplements, retinol activity equivalent without supplements, and total carotenoids), these modest positive associations related intermediate levels of intake to the lowest intake (reference); 5^{th} *vs.* 1^{st} quintile category comparisons and trend tests all were non-significant. Findings for baseline, as well as simple updated intake were similarly null (data not shown). In addition, we did not find any significant associations between daily intake of multivitamins, vitamins C, or E, or duration of vitamin supplement intake with endometrial cancer (Table 3); finding were similar among the few users of vitamin A supplements (data not shown). Neither the FRAP nor antioxidant scores were significantly associated with risk of endometrial cancer (data not shown). The RRs and 95% CI for the highest *vs.* lowest quintiles of the FRAP and antioxidant scores were 0.97 (95% CI: 0.75–1.24) and 1.11 (95% CI: 0.78–1.35), respectively.

Several of the associations appeared to vary by menopausal status and PMH use (never/past *vs.* current). Specifically, α-carotene intake, and to a lesser extent total carotenoids and β-carotene, were positively associated with risk among current PMH users but not among past/

never users or premenopausal women ($P_{interaction}$: 0.03 to 0.07). The RR for the highest *vs.* lowest quintiles of α-carotene intake was 1.69 (95%CI=0.99–2.86, P_{trend} =0.05) (Table 4). No statistically significant variation in relative risks was observed within strata defined by smoking status (never *vs.* ever smoked) or BMI (BMI≥30 *vs.* BMI<30) (data not shown).

DISCUSSION

The results from our large cohort study suggest that intake of antioxidants, including vitamin supplement use, are not associated with reduced risk of endometrial cancer.

These finding are largely consistent with the one prior prospective study.[14] Over 10 years of follow-up and with 221 cases, the researchers found no associations of vitamins A, C, E, vitamin C supplements, lutein, or β-carotene with risk of endometrial cancer; only lycopene was inversely associated with risk (the RR for the highest *vs.* lowest quartile was 0.63 (95%CI: 0.43–0.94)). Results from previous case-control studies have been inconsistent. Most case-control studies reported significant inverse associations of carotene,[25] α-carotene,[18] β-carotene,[18, 21, 23, 30, 31] lycopene,[18] or lutein/zeaxanthin[18, 30–32] with risk of endometrial cancer, while others reported no significant associations with any of the carotenoids.[16, 17, 26, 33] For vitamins A, C, and E, our results are consistent with most prior studies which found no significant associations between vitamin A,[15, 17, 18, 33] C,[15–17, 23, 25, 26, 33] and E[15, 18, 23, 25, 26, 33] with endometrial cancer. In contrast, a few case-control reported significant inverse associations between vitamin A,[21, 25, 26] C,[18, 21] and E[21, 23] and endometrial cancer risk.

The prior, limited data do not support a beneficial effect of vitamin supplement use on endometrial cancer risk. An inverse association has been reported for ever use of multivitamins and duration of use of any vitamin supplement;[21] in a second study, a positive association was observed for vitamin A supplement use.[25] However, other studies found no significant association with use of multivitamin,[16, 19] vitamin C,[19, 25] or E[19, 25] with risk.

We observed possible heterogeneity in the carotenoid/cancer associations across PMH use status, with a positive association noted among current PMH users. In a previous case-control study, the association of β-cryptoxanthin intake (but not α- or β- carotene intake) and endometrial cancer risk varied by PMH use. In that study, intake of β-cryptoxanthin was associated with an increased risk of endometrial cancer among PMH users but a decreased risk among non-users[31]. We can not exclude the possibility that these are chance findings, however, and further assessment in other studies is needed. This interaction also might vary by the antioxidant activity of different compounds, and this might partially explain some of our results (*e.g.*, effect modification for α-carotene but not vitamin A). The potential mechanism is unclear, however one possibility is that, for cells which have already been mutated, higher levels of antioxidants might also protect them from excessive oxidant toxicity and apoptosis hence allowing further mutagenesis.[34] Conceivably this mechanism may be most apparent in women already at high risk (current PMH users). Although not for endometrial cancer, several intervention studies provide indirect support for this hypothesis. In the A-Tocopherol, B Carotene Cancer Prevention Study in Finland, elevated incidence rates of lung cancer (18% increase, 95% CI: 3–36%) among smokers were seen after 8-year's supplementation of β-carotene (20 mg/d).[35] In the USA, the CARET study found an elevated incidence of lung cancer among smokers after an average of 4-years of supplementation of β-carotene (30 mg/d).[36] Although we observed no effect modification by smoking status in our study, smoking is associated with a reduced (not increased) risk of endometrial cancer likely through hormonal and possibly other mechanisms.[37]

Our study is large and prospective with dietary assessments collected repeatedly over 2 decades. We were able to assess vitamin intake both from food sources as well as vitamin supplements. The repeated dietary assessments should decrease exposure misclassification, and the prospective nature and high follow-up rate minimized recall and selection biases. Further, we were able to control for most known or possible endometrial cancer risk factors. Our study also has some weaknesses. We can not exclude the possibility of bias from unidentified risk factors. Also, non-differential misclassification from the FFQ assessment would attenuate our results, so that modest associations could have be missed.

In summary, in our cohort study, we found no overall association between intake of specific antioxidants and risk of endometrial cancer. However, our data also suggest that the associations may vary by PMH use, these findings warrant evaluation in additional large prospective studies.

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Abbreviations used

BMI	Body Mass Index
CI	Confidence Interval
FFQ	Food Frequency Questionnaire
FRAP	Ferric-Reducing Ability of Plasma
IRR	Incidence Rate Ratio
OC	Oral Contraceptive
PMH	Postmenopausal Hormone
RR	Relative Risk

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Table1

Age-standardized prevalence of potential endometrial cancer risk factors by quintile of cumulative average antioxidant intake* among women in the Nurses' Health Study cohort, 1990

	Vitamin A (IU/d)			Vitamin C (mg/d)			Vitamin E (mg/d)			Total carotenoids (IU/d)		
Quintiles	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Median antioxidant intake	6538	11635	20364	94	188	674	6.5	10.3	114.7	4065	7654	14097
Age (years)	55.3	55.4	55.5	55.4	55.4	55.4	55.4	55.4	55.4	55.3	55.4	55.5
Age at menopause (yrs)	49.5	49.8	49.9	49.5	49.9	49.9	49.6	49.8	50.0	49.6	49.8	49.9
Parity among parous women	3.3	3.2	3.1	3.3	3.2	3.1	3.3	3.2	3.1	3.3	3.2	3.1
Age at last birth (yrs)	31.6	31.6	31.3	31.7	31.6	31.1	31.7	31.6	31.0	31.5	31.5	31.4
Age at menarche (yrs)	12.5	12.4	12.4	12.5	12.5	12.4	12.5	12.5	12.5	12.5	12.4	12.4
BMI (continuous, kg/m^2)	25.9	25.7	25.3	25.9	25.8	25.3	25.7	25.9	25.2	26.0	25.7	25.3
BMI≥30(%)	17.9	16.6	14.5	17.5	17.0	14.6	16.8	17.8	14.3	18.9	16.5	14.2
Ever Smoked (%)	61.1	55.9	55.7	62.6	54.6	58.0	59.9	56.3	57.6	60.8	57.6	55.1
Postmenopausal (%)	58.3	60.4	59.2	58.1	60.4	59.1	57.1	60.7	60.3	57.9	60.1	59.8
Ever used oral contraceptives (%)	48.1	50.2	49.2	47.4	48.8	51.2	47.8	50.3	50.0	49.2	50.0	48.1
Ever used PMH (%) *	20.1	25.7	26.8	19.8	24.4	28.5	17.6	25.3	29.6	21.2	25.3	26.3
Diabetes (%)	3.7	4.1	3.7	3.7	3.9	3.5	3.7	4.5	3.4	4.1	4.2	3.6
Hypertension (%)	25.9	26.2	25.2	23.1	26.7	25.7	25.2	25.9	24.6	26.3	26.6	24.9

* Total antioxidant intake: antioxidants from both foods and supplements.

Table 2

Cumulative average, energy-adjusted intake of antioxidants and risk of endometrial cancer, Nurses' Health Study cohort (1980–2006)

		Quintiles					
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	P_{trend}
Vitamin A							
Total	Median (IU/d)	6268	9217	11796	14932	21098	
	Case #	113	126	134	140	156	
	RR (95% CI)						
	Age adjusted*	1.00	1.04 (0.80–1.34)	1.06 (0.82–1.36)	1.06 (0.82–1.36)	1.13 (0.89–1.45)	0.30
	Multi-adjusted†	1.00	1.01 (0.78–1.30)	1.01 (0.79–1.30)	1.00 (0.78–1.29)	1.09 (0.85–1.39)	0.49
w/o supplements	Median (IU/d)	5543	7812	9773	12165	16642	
	Case #	105	120	126	174	144	
	RR (95% CI)						
	Age adjusted*	1.00	1.06 (0.82–1.38)	1.07 (0.82–1.39)	1.41 (1.10–1.80)	1.12 (0.86–1.44)	0.17
	Multi-adjusted†	1.00	1.03 (0.79–1.34)	1.03 (0.79–1.34)	1.33 (1.04–1.70)	1.06 (0.82–1.36)	0.37
Retinol activity equivalents							
Total	Median (mcg/d)	668	1010	1390	1960	3145	
	Case #	110	143	128	145	143	
	RR (95% CI)						
	Age adjusted*	1.00	1.21 (0.94–1.55)	1.04 (0.81–1.35)	1.17 (0.81–1.49)	1.11 (0.89–1.43)	0.71
	Multi-adjusted†	1.00	1.14 (0.89–1.46)	0.96 (0.74–1.24)	1.07 (0.83–1.38)	1.04 (0.81–1.34)	0.98
w/o supplements	Median (mcg/d)	579	782	952	1159	1548	
	Case #		136	126	155	157	
	RR (95% CI)						
	Age adjusted*	1.00	1.34 (1.03–1.74)	1.19 (0.91–1.55)	1.40 (1.08–1.80)	1.35 (1.05–1.75)	0.05
	Multi-adjusted†	1.00	1.27 (0.98–1.65)	1.10 (0.84–1.44)	1.27 (0.98–1.64)	1.10 (0.93–1.56)	0.31
Vitamin C							
Total	Median (mg/d)	90	140	190	295	693	
	Case #	115	133	138	146	137	
	RR (95% CI)						

		Quintiles					
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	P_{trend}
	Age adjusted*	1.00	1.08 (0.84–1.39)	1.07 (0.83–1.37)	1.12 (0.88–1.44)	1.02 (0.80–1.31)	0.84
	Multi-adjusted†	1.00	1.01 (0.79–1.30)	0.99 (0.77–1.27)	1.05 (0.82–1.35)	0.98 (0.76–1.25)	0.79
w/o supplements	Median (mg/d)	75	106	131	157	201	
	Case #	108	126	144	133	158	
	RR (95% CI)						
	Age adjusted*	1.00	1.10 (0.85–1.42)	1.21 (0.95–1.56)	1.08 (0.84–1.40)	1.23 (0.96–1.58)	0.15
	Multi-adjusted†	1.00	1.03 (0.80–1.34)	1.13 (0.84–1.45)	0.99 (0.77–1.28)	1.15 (0.90–1.48)	0.35
Vitamin E							
Total	Median (mg/d)	6.2	8.1	10.5	17.6	129.3	
	Case #	109	144	140	133	143	
	RR (95% CI)						
	Age adjusted*	1.00	1.28 (1.00–1.64)	1.22 (0.95–1.56)	1.14 (0.88–1.47)	1.16 (0.90–1.49)	0.99
	Multi-adjusted†	1.00	1.17 (0.92–1.51)	1.10 (0.86–1.42)	1.05 (0.81–1.36)	1.07 (0.83–1.38)	0.90
w/o supplements	Median (mg/d)	5.7	6.7	7.4	8.2	9.6	
	Case #		138	128	143	152	
	RR (95% CI)						
	Age adjusted*	1.00	1.24 (0.96–1.57)	1.12 (0.87–1.45)	1.21 (0.94–1.55)	1.24 (0.96–1.58)	0.17
	Multi-adjusted†	1.00	1.14 (0.89–1.47)	1.00 (0.77–1.29)	1.05 (0.82–1.35)	1.08 (0.84–1.38)	0.79
Total carotenoids							
	Median (IU/d)	3821	5942	7720	10113	14641	
	Case #	104	132	135	157	141	
	RR (95% CI)						
	Age adjusted*	1.00	1.19 (0.92–1.55)	1.18 (0.91–1.52)	1.31 (1.02–1.68)	1.13 (0.88–1.46)	0.46
	Multi-adjusted†	1.00	1.18 (0.91–1.53)	1.14 (0.88–1.48)	1.26 (0.98–1.62)	1.12 (0.86–1.45)	0.53
α-carotene							
	Median (mcg/d)	282	457	620	902	1487	
	Case #	114	118	134	154	149	
	RR (95% CI)						

		Quintiles					
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	P_{trend}
	Age adjusted*	1.00	0.99 (0.76–1.28)	1.08 (0.84–1.38)	1.20 (0.94–1.53)	1.14 (0.89–1.45)	0.17
	Multi-adjusted†	1.00	0.98 (0.76–1.27)	1.07 (0.83–1.37)	1.16 (0.91–1.49)	1.12 (0.87–1.43)	0.24
β-carotene							
	Median (mcg/d)	1930	2966	3952	5236	7748	
	Case #	110	127	145	148	139	
	RR (95% CI)						
	Age adjusted*	1.00	1.09 (0.85–1.41)	1.21 (0.94–1.55)	1.19 (0.93–1.52)	1.08 (0.84–1.39)	0.68
	Multi-adjusted†	1.00	1.09 (0.84–1.40)	1.19 (0.93–1.53)	1.15 (0.90–1.47)	1.06 (0.83–1.37)	0.80
Lycopene							
	Median (mcg/d)	1843	3440	4408	5531	7444	
	Case #	136	135	127	123	148	
	RR (95% CI)						
	Age adjusted*	1.00	1.00 (0.79–1.27)	0.95 (0.75–1.21)	0.92 (0.72–1.17)	1.10 (0.87–1.39)	0.55
	Multi-adjusted†	1.00	1.01 (0.79–1.28)	0.93 (0.73–1.19)	0.90 (0.70–1.15)	1.09 (0.86–1.37)	0.68
Lutein and							
Zeaxanthin	Median (mcg/d)	1492	2291	3019	4245	6795	
	Case #	137	123	123	148	138	
	RR (95% CI)						
	Age adjusted*	1.00	0.87 (0.68–1.11)	0.85 (0.67–1.09)	1.01 (0.80–1.27)	0.92 (0.73–1.17)	0.99
	Multi-adjusted†	1.00	0.88 (0.69–1.12)	0.88 (0.68–1.12)	1.01 (0.80–1.28)	0.93 (0.73–1.18)	0.99

*Adjusted for age and follow-up period

†Adjusted for total energy (continuous), smoking [never(reference), past, current], oral contraceptive use [never (reference), < 3 years, 3–5 years, > 5 years], postmenopausal hormone use [premenopausal, postmenopausal never(reference), past, current E only, current E+P], age at menopause [pre/unknown menopause, <45 yr, 45–46 yr, 47–48 yr (reference), 49–50 yr, 51–52 yr, 53+ yr] parity [nulliparous (reference), 1–2 & age at last birth<30, 1–2 & age at last birth>=30, 3–4 & age at last birth<30, 3–4 & age at last birth>=30, 5+], age at menarche [< 12, 12 (reference), > 12], hypertension (yes, no), diabetes (yes, no), BMI (continuous).

Table 3

Vitamin supplement use and risk of endometrial cancer, Nurses' Health Study cohort (1980–2006)

			Relative Risks (95% CI)				P_{trend}
Vitamin supplements							
Multivitamins	Numbers used /week	0	2 or less	3–5	6–9	10+	
	Case #	391	19	51	189	19	
	RR (95% CI)						
	Age adjusted*	1.00	0.95 (0.60–1.51)	1.03 (0.77–1.38)	0.92 (0.77–1.10)	1.10 (0.69–1.75)	0.57
	Multi-adjusted†	1.00	0.96 (0.60–1.52)	1.05 (0.78–1.40)	0.92 (0.77–1.10)	1.09 (0.69–1.73)	0.54
Vitamin C supplements	mg/day	0	<400	400–700	750–1250	1300	
	Case #	458	28	110	53	20	
	RR (95% CI)						
	Age adjusted*	1.00	0.83 (0.56–1.21)	1.04 (0.85–1.29)	0.86 (0.64–1.14)	1.23 (0.78–1.92)	0.90
	Multi-adjusted†	1.00	0.83 (0.57–1.22)	1.05 (0.85–1.30)	0.86 (0.65–1.15)	1.23 (0.79–1.93)	0.96
Vitamin E supplements	IU/day	0	<250	300–500	600+		
	Case #	472	41	128	28		
	RR (95% CI)						
	Age adjusted*	1.00	1.12 (0.82–1.55)	0.95 (0.78–1.17)	0.91 (0.62–1.33)		0.59
	Multi-adjusted†	1.00	1.16 (0.84–1.60)	0.95 (0.78–1.17)	0.88 (0.60–1.30)		0.55
Duration of used vitamin supplements							
Multivitamins	Categories	0	<24 months	24–59 months	60+ months		
	Case #	139	27	375	128		
	RR (95% CI)						
	Age adjusted*	1.00	0.65 (0.43–0.98)	0.98 (0.78–1.24)	1.02 (0.77–1.36)		0.93
	Multi-adjusted†	1.00	0.64 (0.42–0.97)	0.98 (0.77–1.23)	1.01 (0.76–1.35)		0.99
Vitamin A	Case #	595	22	43	9		
	RR (95% CI)						
	Age adjusted*	1.00	1.04 (0.68–1.59)	1.07 (0.78–1.45)	1.22 (0.63–2.35)		0.52

		Relative Risks (95% CI)				P_{trend}
	Multi-adjusted†	1.00	1.03 (0.67–1.57)	1.08 (0.79–1.47)	1.21 (0.62–2.34)	0.49
Vitamin C	Case #	377	63	144	85	
	RR (95% CI)					
	Age adjusted*	1.00	0.93 (0.71–1.21)	1.06 (0.87–1.29)	1.06 (0.83–1.36)	0.55
	Multi-adjusted†	1.00	0.90 (0.69–1.17)	1.05 (0.86–1.27)	1.08 (0.85–1.39)	0.53
Vitamin E	Case #	182	56	391	40	
	RR (95% CI)					
	Age adjusted*	1.00	1.04 (0.77–1.41)	1.18 (0.95–1.45)	1.07 (0.73–1.56)	0.21
	Multi-adjusted†	1.00	1.02 (0.75–1.38)	1.18 (0.95–1.46)	1.10 (0.75–1.61)	0.17

*Adjusted for age and follow-up period

†Adjusted for total energy (continuous), smoking [never(reference), past, current], oral contraceptive use [never (reference), < 3 years, 3–5 years, > 5 years], postmenopausal hormone use [premenopausal, postmenopausal never(reference), past, current E only, current E+P], age at menopause [pre/unknown menopause, <45 yr, 45–46 yr, 47–48 yr (reference), 49–50 yr, 51–52 yr, 53+ yr] parity [nulliparous (reference), 1–2 & age at last birth<30, 1–2 & age at last birth>=30, 3–4 & age at last birth<30, 3–4 & age at last birth>=30, 5+], age at menarche [< 12, 12 (reference), > 12], hypertension (yes, no), diabetes (yes, no), BMI (continuous).

Table 4

Energy-adjusted antioxidant intakes and risk of endometrial cancer stratified by menopausal status, Nurses' Health Study cohort (1980–2006)*

			Postmenopausal				$P_{interaction}$†
	Premenopausal		Never/past PMH users		Current PMH users		
	# of Cases	RR (95% CI)	# of Cases	RR (95% CI)	# of Cases	RR (95% CI)	
Vitamin A							
Q1	22	1.00	65	1.00	22	1.00	
Q2	20	0.99 (0.54–1.82)	74	1.01 (0.72–1.42)	28	1.06 (0.60–1.85)	
Q3	30	1.07 (0.58–1.98)	68	0.88 (0.63–1.25)	40	1.35 (0.80–2.28)	
Q4	15	0.80 (0.41–1.55)	78	0.99 (0.71–1.39)	39	1.16 (0.68–1.97)	
Q5	16	1.01 (0.52–1.94)	86	1.07 (0.77–1.48)	45	1.20 (0.71–2.02)	
P_{trend}		0.85		0.61		0.59	0.30
Vitamin A w/o supplements							
Q1	26	1.00	50	1.00	25	1.00	
Q2	14	0.62 (0.32–1.20)	72	1.28 (0.89–1.83)	25	0.83 (0.48–1.45)	
Q3	14	0.63 (0.33–1.22)	73	1.24 (0.86–1.78)	35	1.11 (0.66–1.86)	
Q4	23	1.09 (0.62–1.94)	94	1.47 (1.04–2.08)	53	1.51 (0.93–2.46)	
Q5	16	0.85 (0.45–1.60)	82	1.23 (0.86–1.76)	36	0.95 (0.56–1.60)	
P_{trend}		0.88		0.33		0.66	0.59
Vitamin C							
Q1	22	1.00	69	1.00	21	1.00	
Q2	19	0.87 (0.47–1.63)	67	0.85 (0.61–1.19)	42	1.64 (0.97–2.79)	
Q3	19	0.93 (0.50–1.73)	81	0.98 (0.70–1.35)	30	1.08 (0.61–1.89)	
Q4	21	1.13 (0.62–2.08)	83	1.05 (0.76–1.45)	34	1.03 (0.59–1.80)	
Q5	12	0.65 (0.32–1.31)	71	0.91 (0.65–1.27)	47	1.32 (0.78–2.22)	
P_{trend}		0.27		0.82		0.72	0.26
Vitamin C w/o supplements							
Q1	19	1.00	58	1.00	27	1.00	
Q2	21	1.12 (0.60–2.09)	66	1.02 (0.72–1.46)	35	1.07 (0.64–1.77)	
Q3	18	1.00 (0.52–1.91)	83	1.18 (0.84–1.65)	36	1.06 (0.64–1.76)	

	Premenopausal		Postmenopausal				$P_{interaction}$†
			Never/past PMH users		Current PMH users		
	# of Cases	RR (95% CI)	# of Cases	RR (95% CI)	# of Cases	RR (95% CI)	
Q4	16	0.97 (0.49–1.89)	74	0.97 (0.69–1.38)	35	1.00 (0.66–1.67)	
Q5	19	1.22 (0.64–2.33)	90	1.12 (0.80–1.57)	41	1.21 (0.74–2.00)	
P_{trend}		0.68		0.60		0.50	0.40
Vitamin E							
Q1	19	1.00	64	1.00		1.00	
Q2	24	1.23 (0.67–2.27)	78	1.12 (0.80–1.56)	27	1.19 (0.70–2.03)	
Q3	17	0.87 (0.44–1.69)	81	1.19 (0.85–1.66)	35	0.99 (0.58–1.69)	
Q4	20	1.13 (0.59–2.14)	67	1.03 (0.73–1.46)	34	0.95 (0.56–1.61)	
Q5	13	0.79 (0.39–1.62)	81	1.18 (0.84–1.64)	38	0.96 (0.57–1.70)	
P_{trend}		0.35		0.53	40	0.68	0.90
Vitamin E w/o supplements							
Q1	15	1.00	65	1.00	16	1.00	
Q2	22	1.27 (0.81–3.05)	74	1.02 (0.73–1.42)	33	1.08 (0.95–1.82)	
Q3	17	1.24 (0.61–2.50)	76	0.99 (0.71–1.39)	32	0.98 (0.59–1.66)	
Q4	19	1.41 (0.71–2.81)	70	0.86 (0.61–1.21)	45	1.21 (0.74–1.97)	
Q5	20	1.28 (0.81–3.13)	86	1.02 (0.73–1.41)	48	0.95 (0.57–1.58)	
P_{trend}		0.29		0.88		0.88	0.93
Total carotenoids							
Q1	22	1.00	61	1.00	19	1.00	
Q2	18	0.95 (0.50–1.77)	79	1.21 (0.86–1.69)	26	1.18 (0.65–2.14)	
Q3	22	1.22 (0.67–2.23)	77	1.12 (0.79–1.56)	31	1.29 (0.72–2.29)	
Q4	16	0.91 (0.48–1.75)	75	1.03 (0.73–1.45)	61	2.31 (1.37–3.89)	
Q5	15	0.97 (0.49–1.89)	79	1.10 (0.78–1.55)	37	1.25 (0.71–2.20)	
P_{trend}		0.87		0.97		0.25	0.07
α-carotene							
Q1	20	1.00	69	1.00	21	1.00	
Q2	16	0.93 (0.48–1.81)	63	0.87 (0.62–1.23)	32	1.38 (0.79–2.40)	

	Premenopausal		Postmenopausal				$P_{interaction}$†
			Never/past PMH users		Current PMH users		
	# of Cases	RR (95% CI)	# of Cases	RR (95% CI)	# of Cases	RR (95% CI)	
Q3	22	1.46 (0.79–2.71)	75	0.95 (0.68–1.32)	31	1.24 (0.71–2.16)	
Q4	18	1.14 (0.60–2.17)	88	1.09 (0.79–1.50)	44	1.69 (1.00–2.86)	
Q5	17	1.19 (0.62–2.31)	76	0.93 (0.67–1.29)	46	1.69 (0.99–2.86)	
P_{trend}		0.59		0.98		0.05	0.03
β-carotene							
Q1	20	1.00	68	1.00	21	1.00	
Q2	17	0.98 (0.51–1.88)	78	1.09 (0.79–1.51)	25	1.01 (0.56–1.81)	
Q3	21	1.31 (0.70–2.43)	79	1.06 (0.77–1.48)	39	1.48 (0.87–2.52)	
Q4	21	1.29 (0.70–2.40)	73	0.93 (0.67–1.30)	48	1.59 (0.95–2.68)	
Q5	14	0.94 (0.47–1.89)	73	0.95 (0.68–1.34)	41	1.29 (0.75–2.19)	
P_{trend}		0.95		0.48		0.29	0.05
Lycopene							
Q1	21	1.00	73	1.00	34	1.00	
Q2	16	0.94 (0.48–1.81)	78	1.10 (0.80–1.52)	35	0.94 (0.58–1.52)	
Q3	20	1.09 (0.58–2.03)	69	0.96 (0.69–1.33)	32	0.88 (0.54–1.43)	
Q4	20	1.12 (0.60–2.11)	64	0.87 (0.62–1.23)	36	0.99 (0.62–1.06)	
Q5	16	0.87 (0.46–1.72)	87	1.17 (0.85–1.60)	37	1.05 (0.65–1.69)	
P_{trend}		0.88		0.60		0.74	0.59
Lutein and Zeaxanthin							
Q1	23	1.00	79	1.00	32	1.00	
Q2	17	0.82 (0.43–1.54)	70	0.90 (0.65–1.24)	31	0.81 (0.49–1.32)	
Q3	17	0.88 (0.47–1.66)	73	0.92 (0.67–1.27)	27	0.70 (0.42–1.17)	
Q4	20	1.02 (0.55–1.86)	74	0.92 (0.67–1.26)	47	1.10 (0.70–1.73)	
Q5	16	0.79 (0.42–1.52)	75	0.93 (0.68–1.28)	37	0.85 (0.52–1.37)	
P_{trend}		0.68		0. 18		0.97	0.52

*Adjusted for total energy (continuous), smoking [never(reference), past, current], oral contraceptive use [never (reference), < 3 years, 3–5 years, > 5 years], postmenopausal hormone use [premenopausal, postmenopausal never(reference), past, current E only, current E+P], age at menopause [pre/unknown menopause, <45 yr, 45–46 yr, 47–48 yr (reference), 49–50 yr, 51–52 yr, 53+ yr] parity [nulliparous

(reference), 1–2 & age at last birth<30, 1–2 & age at last birth>=30, 3–4 & age at last birth<30, 3–4 & age at last birth>=30, 5+], age at menarche [< 12, 12 (reference), > 12], hypertension (yes, no), diabetes (yes, no), BMI (continuous).

†Effect modification of past/never PMH use *vs.* current PMH use among postmenopausal women