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The Role of Antioxidants and Vitamin A in Ovarian Cancer: Results From the Women's Health Initiative

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The Role of Antioxidants and Vitamin A in Ovarian Cancer: Results From the Women's Health Initiative

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Antioxidant nutrients and carotenoids have been inconsistently associated with ovarian cancer risk. We examined the relationship between intake of dietary and supplemental antioxidant nutrients including vitamins C, E, and selenium as well as carotenoids and vitamin A and ovarian cancer in 133,614 postmenopausal women enrolled in the Women's Health Initiative (WHI) study. Dietary intake was assessed using a food frequency questionnaire, and ovarian cancer endpoints were centrally adjudicated. Cox regression models were used to estimate the risk for invasive ovarian cancer in relation to each of the antioxidant nutrients and carotenoids under consideration using models stratified for a WHI study component. A total of 451 cases of invasive ovarian cancer were diagnosed over 8.3 yr of follow-up. Dietary intake at baseline was not significantly different for cases vs. controls. Cases reported greater intake of supplemental vitamin C (358.0 mg/day vs. 291.6 mg/day, respectively; $P = 0.024$). Multivariate modeling (P for trend) of the risk for developing ovarian cancer did not suggest any significant relationships among dietary factors and ovarian cancer risk. The results from this prospective study of well-nourished, postmenopausal women suggest that intake of dietary antioxidants, carotenoids, and vitamin A are not associated with a reduction in ovarian cancer risk.

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INTRODUCTION

One in 69 U.S. women will be diagnosed with ovarian cancer in her lifetime. Ovarian cancer accounts for 3% of all female cancers and 6% of all cancer deaths among women annually, with an estimated 22,430 new cases being diagnosed in 2007. It is the leading cause of death from a gynecologic malignancy (1–3). Median survival after a diagnosis of ovarian cancer is estimated to be 28 mo after consolidation therapy (4).

Efforts to identify lifestyle factors that might influence the risk for ovarian cancer have been ongoing and suggest that several reproductive factors, such as oral contraceptive use, bearing children, and having a tubal ligation, may influence disease risk (5,6). However, these factors are not generally modifiable. Dietary antioxidants, including select carotenoids, have been hypothesized to modify cancer risk (7,8), and evidence suggests that ovarian cancer patients demonstrate significantly higher levels of oxidative stress than age-matched controls (9). Women diagnosed with ovarian cancer have been shown to have significantly reduced plasma antioxidant (10) and vitamin A concentrations (11). Further, potential chemopreventive biological activities of foods rich in carotenoids and antioxidant nutrients, independent of their potential antioxidant activity, also exist and may influence ovarian cancer risk.

To date, studies assessing the relationship between antioxidant nutrient intake and ovarian cancer risk are limited and offer inconsistent results. The multiethnic cohort study that included dietary data from 341 postmenopausal women diagnosed with ovarian cancer and matched controls concluded that total vitamin A [odds ratio (OR) = 0.60, 95% confidence interval (CI) = 0.36–0.99] and total β-carotene (OR = 0.59, 95% CI = 0.36–0.97) were associated with a statistically significant and clinically meaningful reduction in ovarian cancer risk (12). Several other studies have also suggested that carotenoid intake, and most frequently β-carotene intake, may reduce ovarian cancer risk (13–20), including a meta-analysis of five observational studies that included 3,782 cases (21). However, data from the U.S. Nurses Health Study, which included 301 epithelial ovarian cancer cases (22), and an Italian cohort, which included 1,031 ovarian cancer cases (23), have failed to demonstrate a protective association of total dietary carotenoids or lycopene, respectively. A prospective study, the European Prospective International Cancer cohort that included 581 cases of ovarian cancer, suggested that fruit and vegetable intake, the primary food sources of carotenoids and antioxidants in the diet, was not associated with a reduced risk of ovarian cancer (24).

Studies assessing the possible protective associations of dietary antioxidants other than carotenoids are limited. International data, including a large case-control study from Australia, which included over 600 cases of invasive epithelial ovarian cancer and a second case-control study (n = 442 cases, 2,135 controls) from Canada, have shown that vitamin E intake was inversely and significantly associated with both ovarian cancer survival (25) and risk (19). These findings are supported by the significant reduction in ovarian cancer risk associated with higher dietary intakes of vitamins A, C, and E demonstrated in a cohort of Chinese women that included 254 cases of epithelial ovarian cancer and 652 controls (20). In fact, a recent analysis of carotenoid intake in this same cohort suggested a significant protective effect for intake of total as well as each individual carotenoid, in relation to ovarian cancer (26).

In the present study, we evaluated the relationship between antioxidant nutrients (vitamins C and E and selenium), vitamin A, and carotenoids and ovarian cancer risk. We used the robust prospective, longitudinal diet, dietary supplementation, and pathology-confirmed ovarian cancer events data collected within the Women's Health Initiative (WHI) study to evaluate this association.

MATERIALS AND METHODS

Study Population

The WHI clinical trial and observational study has been previously described (27). Briefly, after completing the informed consent process, a total of 68,132 postmenopausal women (age 50–79 yr) were enrolled in one or more of the three clinical trials (dietary modification, calcium-vitamin D supplementation, and/or hormone therapy), and an additional 93,676 women participated in the observational study. Specifically, 48,835 were randomized to participate in the dietary modification trial in which women were randomized in a 40:60 ratio to a low fat (20% total energy) or control diet. A total of 36,282 women were randomized to participate in the placebo-controlled calcium (1,000 mg elemental calcium) plus vitamin D (400 IU) intervention vs. placebo (ratio 1:1), and 27,347 were randomized to estrogen alone or estrogen plus progesterone also in a 1:1 ratio. Enrollment occurred at 40 clinical sites throughout the United States. Participants for this analysis were followed through December 2004, resulting in an average follow-up of 7 yr. All clinical trial and observational study participants were included in this analysis; after exclusion for history of ovarian cancer, bilateral oophorectomy, or a missing baseline dietary questionnaire, 133,614 women remained for inclusion in this analysis. All study sites (n = 40) attained human subjects committee approval prior to enrolling subjects in the WHI.

Dietary Assessment

The methodology for assessment of dietary intake was the WHI semiquantitative food frequency questionnaire (FFQ) (28,29). This questionnaire includes 19 adjustment questions used to modify food-item responses in regard to fat, fiber, and sodium intake followed by 122 specific food-item lines that capture frequency and serving size for select foods. Participants completed the FFQ at baseline and were asked to report intake over the past 3 months. For quality assurance purposes, 90% of food items and all adjustment questions had to be completed for an FFQ form to be included in the dietary assessment. Dietary nutrients included in this analysis were the antioxidant nutrients

vitamin C, E, as well as antioxidant carotenoids; dietary selenium was not included due to poor exposure estimates related to regional variability in soil selenium (and therefore food) content. Vitamin A was also assessed given that carotenoid precursors serve as the major source of vitamin A in the diet. Women also completed an interviewer-administered dietary supplement questionnaire. Women were asked to bring their supplement bottles to their baseline clinic visit, and staff transcribed dose, frequency, and duration of use for multivitamins and single nutrient supplements. Supplemental nutrients included in the analysis were vitamins A, C, E, carotenoids, and selenium.

Outcomes Ascertainment and Adjudication

Information on ovarian cancer diagnosis was initially based on self-report. Once reported, relevant medical records were collected to affirm the diagnosis including pathology reports, a process that included local adjudication of the medical data as per WHI study protocol (30). Event reports were then forwarded to the WHI study Clinical Coordinating Center in Seattle for centralized adjudication of the ovarian cancer event. Only ovarian cancers that demonstrated invasive behavior were considered cases for this analysis.

Statistical Analysis

Socioeconomic, demographic, reproductive history, and nutrient intake were compared by invasive cancer case status using chi-square tests for categorical variables and Student's *t*-tests for the nutrient intake variables. Cox regression models were used to estimate the risk for invasive ovarian cancer in relation to each of the antioxidant nutrients and carotenoids under consideration. Analysis by dietary intervention (low-fat vs. control diet) did not alter the associations shown; however, to allow for a different estimate of the underlying hazard in the clinical trial and observational study components, the models were stratified by study component. Based on prior research of known ovarian cancer risk factors, all models were adjusted for age and family history of breast or ovarian cancer. Additionally, all models also included covariates for hysterectomy status, DM randomization arm, and total energy (kcals; log-transformed).

Potential confounding factors were grouped into conceptually similar sets of variables, and the confounding effect of the group as a whole was tested. The groupings were race/ethnicity, lifestyle (pack years of smoking, physical activity, NSAID use), fertility (parity, infertility), ovulatory (duration of oral contraceptive use, lifetime ovulatory cycles, partial oophorectomy), and menopause (menopausal age, hormone therapy use at baseline). The statistical significance of the addition of the group to the base model and the effect on the regression coefficients of the main exposure variable were assessed to determine inclusion of each group in the final model.

RESULTS

Table 1 provides a summary of the demographic characteristics of the study population. As shown, the study population had a mean age of 63.2 $\pm$ 7.3 yr, was predominantly non-Hispanic White, and were well educated. Mean body mass index (BMI) for the study population was 27.9 $\pm$ 5.9 kg/m^2, indicating that the average WHI participant was overweight. In terms of reproductive history, the mean age of menarche was 12.6 $\pm$ 1.5 yr, and of menopause it was 49.2 $\pm$ 5.8 yr. Most women (88.4%) reported having had children, and 51.1% of women had been taking hormone replacement therapy. There was no significant difference in oral contraceptive use, parity, or infertility between women diagnosed with ovarian cancer and those who were not. A family history of breast or ovarian cancer was reported by 19.9% of women, including 23.5% of ovarian cancer patients and 19.9% of women without an ovarian cancer diagnosis.

A total of 451 cases of invasive ovarian cancer were identified as of January 2005, 73.8% of which showed distant metastasis and 55.6% of which were poorly differentiated. Most (52.5%) were serous, 11.3% endometrioid, 5.5% clear cell, 5.5% mucinous, and only 3.3% were nonepithelial. A description of the antioxidant and vitamin A intake from diet alone, supplements, as well as total intake from diet and supplements combined within the study population is presented in Table 2. Dietary intake did not differ significantly between cases and controls regardless of the antioxidant nutrient or carotenoid studied. Supplemental vitamin C was significantly greater for cases as compared to control women, with mean intakes of 358.0 mg/day vs. 291.6 mg/day, respectively ($P = 0.024$).

Hazards ratios for developing a diagnosis of ovarian cancer related to dietary antioxidant intake are presented in Table 3. As shown, neither total dietary carotenoids nor any specific carotenoid was significantly associated with ovarian cancer risk reduction. Further, analysis of associations between vitamin C, vitamin E, selenium, and vitamin A also showed no significant relationships with ovarian cancer risk. The *P* for trend statistics also did not suggest that any significant relationships existed between antioxidant nutrient, carotenoids and/or vitamin A, and ovarian cancer risk.

DISCUSSION

Our study showed no significant associations between dietary and/or supplemental antioxidant nutrients, carotenoids, and/or vitamin A intake in later adult life and ovarian cancer risk in the largest, prospective cohort study of postmenopausal women ever undertaken in the United States, the WHI. The null findings of the present study (Table 3) are consistent with a recent epidemiological report from the Canadian National Breast Screening Study of 89,835 women age 40–59 yr, 48,776 of which met inclusion criteria for analysis and 264 of which had been diagnosed with ovarian cancer (31); and those of The Nurses Health Study that included 301 incident cases during 16 yr of follow-up (22); as well as The Iowa Women's Health Study that included

TABLE 1
Demographic and lifestyle characteristics of Women's Health Initiative study participants

		Control		Invasive Ovary Cancer			
				Invasive Ovary Cancer		Total Study Population	
Variable		*N*	%	*N*	%	*N*	%
Age group at screening, yr**	50–59	44,865	33.69	117	25.94	44,982	33.67
	60–69	59,184	44.44	214	47.45	59,398	44.45
	70–79	29,114	21.86	120	26.61	29,234	21.88
Ethnicity*	White	110,769	83.18	400	88.69	111,169	83.20
	Black	11,379	8.55	24	5.32	11,403	8.53
	Hispanic	5,273	3.96	15	3.33	5,288	3.96
	American Indian	563	0.42	2	0.44	565	0.42
	Asian/Pacific Islander	3,437	2.58	8	1.77	3,445	2.58
	Unknown	1,742	1.31	2	0.44	1,744	1.31
Education	0–8 yr	2,052	1.55	5	1.12	2,057	1.55
	Some high school	4,628	3.50	20	4.48	4,648	3.51
	High school diploma/GED	22,129	16.75	73	16.37	22,202	16.75
	School after high school	49,443	37.42	160	35.87	49,603	37.41
	College degree or higher	53,880	40.78	188	42.15	54,068	40.78
Body mass index, kg/m2 (full category)	Underweight (< 18.5)	1,236	0.94	5	1.12	1,241	0.94
	Normal (18.5–24.9)	46,210	35.02	158	35.27	46,368	35.02
	Overweight (25.0–29.9)	45,727	34.65	167	37.28	45,894	34.66
	Obesity I (30.0–34.9)	23,920	18.13	79	17.63	23,999	18.13
	Obesity II (35.0–39.9)	9,718	7.36	28	6.25	9,746	7.36
	Extreme obesity III (≥40)	5,141	3.90	11	2.46	5,152	3.89
Smoking	Never smoked	66,629	50.71	205	46.17	66,834	50.70
	Past smoker	55,541	42.27	208	46.85	55,749	42.29
	Current smoker	9,212	7.01	31	6.98	9,243	7.01
Hysterectomy at randomization	No	95,874	72.04	315	69.84	96,189	72.03
	Yes	37,210	27.96	136	30.16	37,346	27.97
Oophorectomy status at baseline***	None	116,105	89.74	413	94.72	116,518	89.76
	Partial	13,276	10.26	23	5.28	13,299	10.24
Multivitamin (with or without minerals)*	No	81,216	60.99	251	55.65	81,467	60.97
	Yes	51,945	39.01	200	44.35	52,145	39.03

** $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.*

139 incident cases over 10 yr of follow-up (32); and finally, a pooled analysis of 10 cohort studies that included 2,012 ovarian cancer cases with up to 22 yr of follow-up (33). In addition, the lack of an association seen here is indirectly supported by studies that have suggested that dietary fruit and vegetable intake, the major source of antioxidant nutrients and carotenoids in the diet, is also not associated with reduced ovarian cancer risk (23,24,34), including a pooled analysis of 12 cohort studies (35).

Our findings, however, are not in agreement with those of several case-control studies, particularly those specific to carotenoid intake/exposure and several of which included study sample populations residing outside the United States (12–17,20,26,36,37), including a meta-analysis that included 3,782 adult females enrolled in 5 observational studies and concluded that ovarian cancer risk was reduced by 16% in relation to greater dietary β-carotene intake (21). Among the largest of studies was one that included 549 cases, and 516 matched controls, in which dietary intake of vitamin A (OR = 0.60, 95% CI = 0.39–0.94) and the carotenoids α- and β-carotene as well as lycopene (OR = 0.60, 95% CI = 0.39–0.90; OR = 0.58, 95% CI = 0.38–0.89; OR = 0.53, 95% CI = 0.35–0.82, respectively) (16) were each associated with a statistically significant reduced risk for ovarian cancer. Thus, it appears that the prospective studies, such as WHI, for which longitudinal assessments of dietary intake are made prior to the ovarian cancer event, have generally

TABLE 2
Mean dietary and supplemental intake of antioxidant nutrients and vitamin A in women diagnosed with invasive ovarian cancer, as well as controls, in the WHI study population[a]

	Control			Invasive Ovary Cancer			Total Study Population		
Variable	*N*	Mean	SD	*N*	Mean	SD	*N*	Mean	SD
Dietary energy (kcal)	133,163	1,641.2	642.2	451	1,607.0	616.7	133,614	1,641.1	642.1
Vitamin A									
Total vitamin A (RAE)	133,161	1,718.9	1,689.0	451	1,806.3	1,710.2	133,612	1,719.2	1,689.0
Dietary vitamin A (RAE)	133,163	748.8	406.2	451	739.1	393.5	133,614	748.8	406.2
Supplemental vitamin A (mcg RE)	133,161	970.1	1,635.2	451	1,067.2	1,650.7	133,612	970.4	1,635.3
Vitamin C									
Total vitamin C (mg)	133,161	391.5[b]	628.1	451	455.9[b]	1,072.7	133,612	391.8	630.1
Dietary vitamin C (mg)	133,163	100.0	55.4	451	98.0	52.4	133,614	99.9	55.4
Supplemental vitamin C (mg)	133,161	291.6[b]	622.9	451	358.0[b]	1,073.0	133,612	291.8	625.0
Vitamin E									
Total vitamin E (mg)	133,161	167.3	278.5	451	172.4	259.1	133,612	167.3	278.5
Dietary total α-Toc Eq (mg)	133,163	8.2	5.7	451	8.1	5.5	133,614	8.2	5.7
Supplemental α-tocopherol (mg)	133,161	159.0	278.6	451	164.3	258.8	133,612	159.0	278.5
Carotenoids[c]									
Total dietary carotenoids (mcg)	133,163	10,767.3	5,978.4	451	10,726.3	5,988.7	133,614	10,767.1	5,978.5
Dietary α-carotene (mcg)	133,163	693.8	545.3	451	696.6	490.4	133,614	693.8	545.2
Total β-carotene(mcg)	133,161	5,886.6	5,298.0	451	6,201.8	5,865.7	133,612	5,887.7	5,300.1
Total dietary β-carotene (mcg)	133,163	3,221.8	2,158.4	451	3,240.3	2,133.3	133,614	3,221.8	2,158.3
Supplemental β-carotene (mcg[c])	133,161	2,664.9	4,717.8	451	2,961.5	5,247.5	133,612	2,665.9	4,719.7
Total dietary β-cryptoxanthin (mcg)	133,163	147.2	92.9	451	143.5	90.7	133,614	147.1	92.9
Total dietary Lutein + zeaxanthin (mcg)	133,163	1,755.9	1,475.0	451	1,751.2	1,521.4	133,614	1,755.9	1,475.1
Total dietary lycopene (mcg)	133,163	4,948.7	3,222.1	451	4,894.7	3,210.5	133,614	4,948.5	3,222.1
Selenium[d]									
Supplemental selenium (mcg)	133,161	13.2	39.0	451	13.3	29.8	133,612	13.2	38.9

[a] Abbreviations are as follows: WHI, Women's Health Initiative; RAE, retinol activity equivalents; RE, retinol equivalents.
[b] P value < 0.05; Student's t-test difference of means for cases vs. controls.
[c] Only β-carotene was reported to be taken as a dietary supplement; all others reported for diet only.
[d] Only data for supplemental selenium reported, as accurate dietary exposure estimates are not available.

TABLE 3
Cox proportional Hazard Ratios (HR) of incident ovarian cancer risk among Women's Health Initiative study participants in relation to total, total dietary, or supplemental antioxidant intake[a]

Variable	Control (N)	%	Invasive Ovarian Cancer (N)	%	HR	95% CI
Vitamin A						
Total vitamin A (mcg RAE), quartiles						
<640	25,395	24	75	21		
640 to <1,209	25,838	25	79	22	1.06	(0.76–1.48)
1,209 to <2,326	26,442	25	101	29	1.23	(0.90–1.67)
2,326 +	26,860	26	97	28	1.14	(0.83–1.57)
Total dietary vitamin A (mcg RAE), quartiles						
<486	26,088	25	95	27		
486 to <677	26,174	25	91	26	0.92	(0.68–1.25)
677 to <926	26,290	25	79	22	0.80	(0.57–1.12)
926 +	25,984	25	87	25	0.91	(0.62–1.32)
Supplemental vitamin A (mcg RAE), categorized						
None	53,163	51	165	47		
≤1,500	31,135	30	113	32	1.07	(0.84–1.36)
>1500	20,237	19	74	21	1.05	(0.80–1.38)
Vitamin C						
Total vitamin C (mg), quartiles						
<90	25,016	24	70	20		
90 to <158	25,880	25	89	25	1.17	(0.85–1.61)
158 to <555	26,634	25	88	25	1.10	(0.79–1.52)
555 +	27,005	26	105	30	1.22	(0.89–1.67)
Total dietary vitamin C (mg), quartiles						
<58	25,216	24	81	23		
58 to <93	26,902	26	95	27	1.08	(0.80–1.47)
93 to <130	25,791	25	83	24	0.97	(0.70–1.33)
130 +	26,627	25	93	26	1.07	(0.77–1.48)
Supplemental vitamin C (mg), categorized						
None	44,873	43	131	37		
≤310	30,054	29	108	31	1.12	(0.87–1.45)
>310	29,608	28	113	32	1.15	(0.89–1.49)
Vitamin E						
Total vitamin E (mg ATE), quartiles						
<7.4	25,097	24	71	20		
7.4 to <34.6	25,836	25	83	24	1.20	(0.86–1.67)
34.6 to <403.2	26,511	25	96	27	1.23	(0.89–1.68)
403.2 +	27,091	26	102	29	1.22	(0.89–1.66)
Total dietary vitamin E (mg ATE), quartiles						
<4.9	25,633	25	90	26		
4.9 to <6.7	26,197	25	97	28	1.09	(0.80–1.49)
6.7 to <9.4	26,675	26	80	23	0.94	(0.65–1.35)
9.4 +	26,031	25	85	24	1.05	(0.71–1.57)
Supplemental vitamin E (mg ATE), categorized						
None	43,543	42	126	36		
≤200	30,167	29	112	32	1.17	(0.90–1.51)
>200	30,825	29	114	32	1.12	(0.86–1.45)
Total dietary carotenoids (mcg), quartiles						
<6,564	25,523	24	88	25		
6,564 to <9,408	26,180	25	78	22	0.86	(0.63–1.18)

(Table continued to next page)

TABLE 3
Cox proportional Hazard Ratios (HR) of incident ovarian cancer risk *(Continued)*

Variable	Control (N)	%	Invasive Ovarian Cancer (N)	%	HR	95% CI
Carotenoids[b]						
9,408 to <13,642	26,288	25	96	27	1.06	(0.78–1.45)
13,642 +	26,545	25	90	26	0.99	(0.72–1.38)
Total dietary α-carotene (mcg), quartiles						
<335	25,432	24	77	22		
335 to <553	26,197	25	91	26	1.11	(0.82–1.51)
553 to <885	26,301	25	95	27	1.15	(0.84–1.57)
885 +	26,606	25	89	25	1.06	(0.77–1.48)
Total β-carotene (mcg), quartiles						
<2,331	25,263	24	66	19		
2,331 to <4,677	25,816	25	84	24	1.23	(0.88–1.70)
4,677 to <7,605	26,543	25	102	29	1.38	(1.00–1.89)
7,605 +	26,913	26	100	28	1.30	(0.94–1.80)
Total dietary β-carotene (mcg), quartiles						
<1,750	25,711	25	85	24		
1,750 to <2,686	26,083	25	87	25	0.99	(0.73–1.34)
2,686 to <4,122	26,233	25	88	25	0.99	(0.72–1.35)
4,122 +	26,509	25	92	26	1.02	(0.74–1.41)
Supplemental β-carotene (mcg), categorized						
None	57,256	55	176	50		
≤4,500	32,179	31	117	33	1.09	(0.86–1.38)
>4,500	15,100	14	59	17	1.13	(0.84–1.53)
Dietary β-cryptoxanthin (mcg), quartiles						
<78	25,466	24	85	24		
78 to <133	26,244	25	85	24	0.96	(0.71–1.30)
133 to <196	26,392	25	91	26	1.00	(0.74–1.36)
196 +	26,434	25	91	26	1.02	(0.74–1.41)
Total dietary lutein + zeaxanthin (mcg), quartiles						
<902	25,886	25	91	26		
902 to <1,332	26,244	25	81	23	0.88	(0.65–1.19)
1,332 to <2,090	26,144	25	88	25	0.96	(0.71–1.31)
2,090 +	26,262	25	92	26	1.00	(0.73–1.36)
Total dietary lycopene (mcg), quartiles						
<2,736	25,456	24	81	23		
2,736to <4,214	26,118	25	85	24	1.03	(0.75–1.40)
4,214 to <6,325	26,515	25	103	29	1.24	(0.92–1.69)
6,325 +	26,447	25	83	24	1.02	(0.73–1.43)
Selenium[c]						
Supplemental selenium (mcg), categorized						
None	65,900	63	208	59		
≤ 20	24,240	23	96	27	1.16	(0.91–1.48)
>20	14,395	14	48	14	1.00	(0.73–1.37)

[a] Abbreviations are as follows: CI, confidence interval; RAE, retinol activity equivalents; ATE, α-tocopherol equivalents. Cox models stratified on clinical trial and/or observational study participation adjusted for age, log calories, No. breast/ovary cancer relatives, dietary modification randomization arm, hysterectomy status, minority race, pack-years smoking, physical activity, nonsteroidal anti-inflammatory drug use, parity, infertility, duration of oral contraceptive use, lifetime ovulatory cycles, partial oophorectomy, age at menopause, and HT usage at entry. [b] Only β-carotene was reported to be taken as a dietary supplement; all others reported for diet only. [c] Only data for supplemental selenium reported, as accurate dietary exposure estimates are not available.

reported a lack of association between antioxidant intake and ovarian cancer risk, whereas case-control studies (for which recall bias or incomplete case dietary data collection related to the high mortality of ovarian cancer may have reduced the ability to assess the true exposure prior to a diagnosis) are more likely to report protective associations.

A possible explanation for why our findings are consistent with some published reports and not others may be related to the relatively high dietary antioxidant intake (Table 2) reported in this study population of predominantly well-educated White women as compared to the overall adult population (38), a population not dissimilar to those participating in the Nurses Health Study and The Iowa Women's Health Study. Although there is a possibility that these dietary factors may be associated with ovarian cancer risk among subgroups such as histological cancer types, as has been suggested in other studies, the relatively small number of cases prevented us from evaluating subgroup effects. For example, Chiaffarino and colleagues (39) reported a 10% reduction in serous ovarian cancer among women in the highest quintile of β-carotene and vitamin E intake, a protective association not demonstrated for mucinous, endometrial, or other histological types.

Although the Chiaffarino study (39) did specifically assess the relationship between dietary vitamin E and ovarian cancer, additional epidemiological studies that have assessed the relationship between antioxidants other than carotenoids and ovarian cancer risk are sparse. In the present study population, no significant association between vitamin E and ovarian cancer risk was found. Dietary vitamin E was associated with a statistically significant reduced ovarian cancer risk in an Italian case-control study, which included 1,031 cases of epithelial ovarian cancer and 2,411 controls (OR = 0.6, 95% CI = 0.5–0.8) (37), and in a case-control study that included 254 cases of ovarian cancer in China (OR = 0.41, 95% CI = 0.24–0.70) (20). Supplemental vitamin E was associated with reduced ovarian cancer risk in a study among women residing in North Carolina (40) and a case-control study among Canadians; but in the Canadian study, the protective association was only demonstrated after 10 yr of supplementation (19). Yet neither supplemental nor dietary vitamin E was shown to reduce ovarian cancer risk in a study conducted among U.S. women (22). There is sufficient evidence that vitamin E can favorably modulate oxidative stress, including significant reductions of lipid peroxidation (41,42); however, whether exposure levels in our cohort were sufficient to induce this biological effect is not known. Given that the major sources of dietary vitamin E in the diet are foods rich in dietary fat (nuts, seeds, oils, etc.) and that a significant percentage of the WHI cohort was adherent to a low-fat diet as participants in the intervention group of the dietary modification trial, it may be that dietary intake levels were not high enough (mean of 8.2 mg α-tocopherol equivalents vs. dietary reference recommended intake of 15 mg) to enhance antioxidant capacity and in turn modulate disease risk.

The Chinese case-control study by Zhang et al. (20) also provided evidence that vitamin C intake may be associated with reduced ovarian cancer risk (OR = 0.31, 95% CI = 0.18–0.53), although dietary vitamin C was not associated with reduced ovarian cancer risk in our study or in the Cramer study of women residing in the Northeastern United States (16). In fact, our findings indicate that supplemental vitamin C intake was significantly higher in cases as compared to controls. Although this could be by chance, other plausible biological explanations for this deleterious effect may be that supplemental vitamin C may act as a pro-oxidant alone or may promote iron absorption and thus indirectly promote iron-associated oxidative stress and/or neoplastic transformation and proliferation (43,44,45). Additionally, evidence suggests low plasma vitamin C levels in ovarian cancer patients may be the result of increased sequestration of ascorbic acid by tumor cells, implying that supplementation could provide a survival advantage to tumor cells (44). Clearly more research is needed to more fully characterize these associations mechanistically. Among the Chinese women, quartiles of vitamin C intake ranged from $<$66.5 mg/day to $>$140.25 mg/day (20), similar to the mean and range of dietary intake we identified among WHI participants. However, among Chinese women, the major source of vitamin C exposure was reported to be from raw fruits and vegetables; whereas in our cohort, 56% of WHI participants (270 cases and 74,409 controls) also took supplemental vitamin C, increasing mean exposure to just under 400 mg/day (median 158 mg/day with skewed distribution). It is possible that other constitutive phytochemicals in fruits and vegetables found in the Chinese diet, some of which may demonstrate antioxidant capacity, may account for the differential association between vitamin C and ovarian cancer in this Chinese versus American study population.

Although the WHI is among the largest prospective studies of postmenopausal women, certain limitations to the present study may have influenced the ability to test hypotheses relating intake of antioxidants and vitamin A to ovarian cancer risk. First, participants in the WHI study were generally well nourished and reported high intake of antioxidant nutrients. Over 69% of WHI study participants reported regular use of either multivitamin or specific antioxidant supplements at baseline, and 79% of baseline dietary supplement users remained on supplementation throughout the study. Further, there is the possibility that dietary intake just prior to the ovarian cancer diagnosis does not reflect longer term dietary antioxidant intake levels that may have relevance to ovarian cancer risk given the fact that ovarian cancer develops of over years if not decades. Finally, we did not test the association between plasma levels of antioxidant nutrients and ovarian cancer risk. A biomarker approach would have the advantage of reducing measurement error associated with self-report of dietary intake (46,47).

Our results suggest that antioxidant intake, either dietary or supplemental, at current levels of reported intake among postmenopausal women residing in the United States are not

associated with ovarian cancer risk. Our results contribute to an increasing body of epidemiological evidence that has suggested similar results (22,31,32).

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