Association of Dietary Vitamin A, Carotenoids, and Other Antioxidants with the Risk of Ovarian Cancer

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Abstract

Antioxidants may protect the ovaries from oxidative damage and reduce the risk of ovarian cancer. Although a few studies have examined the relation of antioxidant intake to the risk of ovarian cancer, the results have been inconclusive. Questions still remain regarding the effects of confounding factors, such as menopause, tobacco smoking, and alcohol drinking, on the association between antioxidants and ovarian cancer development.

Objective: **To examine the association of the consumption of micronutrients from foods and supplements with the risk of ovarian cancer.**

Methods: **A structured questionnaire was administered to 558 histologically confirmed epithelial ovarian cancer cases and 607 population controls from a multiethnic, population-based case-control study conducted between 1993 and 1999 in Hawaii and Los Angeles.**

Results: **Overall, vitamin A and carotene intakes were modestly associated with a reduced risk of ovarian cancer. Inverse gradients in ovarian cancer risk with increasing dietary intake of vitamin A and β-carotene were somewhat stronger among women with mucinous histologic types, smokers, and nondrinkers. A significant positive trend in risk associated with increasing β-cryptoxanthin intake was observed among postmenopausal women, among women with nonmucinous tumors, and among nonsmokers. The intake of other carotenoids and antioxidants, either from foods or supplements, was unrelated to ovarian cancer risk.**

Conclusion: **Our findings suggest that dietary vitamin A and β-carotene are modestly protective against ovarian cancer, particularly among smokers. Our data suggest a role for retinoic acid signaling pathways in ovarian carcinogenesis.** (Cancer Epidemiol Biomarkers Prev 2005;14(3):669–76)

Introduction

Retinoids, or vitamin A derivatives, play an essential role in cell proliferation, differentiation, and apoptosis in normal and neoplastic ovarian tissues (1, 2). Retinoic acid (RA), the primary active metabolite of vitamin A, mediates numerous gene transcriptions through retinoid nuclear receptors (3). Hence, the retinoids, in targeting the nuclear receptors, are considered to be one of the most promising chemopreventive and chemotherapeutic agents against ovarian cancer (4).

Carotenoids, particularly β-carotene, from fruits and vegetables are the main sources for vitamin A in the diet, fueling controversy as to whether the pro–vitamin A or the antioxidant function is primarily responsible for the antiproliferative effects of carotenoids. Although central cleavage of β-carotene to retinoids occurs in the ovary (5), a potential direct antioxidant effect of carotenoids, independent of their pro–vitamin A function, is suggested as dietary carotenoids may be absorbed intact through the intestine and transported to blood and target tissues. Antioxidant effects of carotenoids have been reported *in vitro* and *in vivo* (6). Among the more common dietary carotenoids, lycopene probably is the most efficient singlet oxygen quencher and peroxyl radical scavenger (7).

Oxidative stress during successive ovulation increases DNA damage resulting in the malignant transformations of ovarian cells (8), which in turn gives sound support to the ''incessant ovulation'' hypothesis. High consumption of antioxidants may reduce the risk of ovarian cancer based on this hypothesis. Epidemiologic studies have examined the relation between antioxidant intake and ovarian cancer risk, and the results are inconsistent, with both inverse (9-11) and null (12-17) findings. Intervention trials of other cancer sites provide evidence that the effects of antioxidants can be modified by other risk factors. Results from two clinical trials, the α-Tocopherol, β-Carotene Cancer Prevention Study (18) and the Carotene and Retinol Efficacy Trial (19), indicate an adverse effect of β-carotene supplements on lung cancer risk among smokers and drinkers. These findings not only raise health concerns about potential pro-oxidant effects of β-carotene but also add further complexity to our understanding of the underlying antiproliferative mechanisms of antioxidants.

In this study, we examined the association of dietary vitamin A, carotenoids, other selected antioxidants, and their food sources with the risk of ovarian cancer. In particular, we were interested in how these relations were modified by histologic subtype, menopausal status, tobacco smoking, and alcohol drinking.

Materials and Methods

The details of this population-based case-control study conducted in Hawaii and Los Angeles between 1993 and 1999 have been described elsewhere (20). Briefly, eligibility criteria for participation in this investigation included (*a*) residency in Hawaii or Los Angeles County for at least 1 year before diagnosis for cases or interview for controls, (*b*) ≥18 years of age, (*c*) no prior history of ovarian cancer, and (*d*) at least one intact ovary for controls. The participation rate was 62% among eligible cases and 67% among controls. Response rates among eligible cases did not differ substantially by study location or ethnic group. A total of 558 primary epithelial ovarian cancer cases and 607 population controls with complete dietary and demographic information were included in this analysis.

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All eligible cases diagnosed with primary histologically confirmed, epithelial ovarian cancer between 1993 and 1999 were identified through two population-based cancer registries, the Hawaii Tumor Registry and the Los Angeles County Cancer Surveillance Program. Population controls were randomly selected from a neighborhood walk procedure in Los Angeles (21) and from lists of participants in a Department of Health statewide annual survey in Hawaii (22). The controls were frequency matched to cases with an ~1:1 ratio based on specific ethnicity (e.g., Japanese), age (±5 years), and study site (23).

The food frequency questionnaire included 256 food items and was modeled after the instrument used in a multiethnic cohort study of >215,000 men and women (ages 45-75 years) living in California and Hawaii that included the ethnic groups of interest to this study (24). This instrument has been intensively assessed for its reliability and validity with 24-hour dietary recalls (25, 26). Subjects were queried by interviewers for the average frequency of intake and serving size consumed for each food item eaten during the year before diagnosis for cases and before interview for controls. Intakes of alcoholic beverages and dietary supplements were also assessed.

Average daily nutrient intakes were determined from a customized food composition database that has been developed and maintained at the Cancer Research Center of Hawaii (24). The 1993 U.S. Department of Agriculture-National Cancer Institute Carotenoid Database was used to estimate specific dietary carotenoid contents, including α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein/zeaxanthin in single and mixed food items (27, 28). Total vitamin A intake (IU) was calculated as the sum of the nutrients from foods and supplements using the interconversion of vitamin A and carotenoid units from the National Research Council (29).

An unconditional logistic regression model (30) was used to estimate the risk of ovarian cancer associated with daily dietary exposures by intake quartiles. The frequency-matched variables were included in all models as adjustment variables, including age as a continuous variable, ethnicity by indicator variables (Caucasian, Asian, or other), and study location (Hawaii or Los Angeles). In addition, covariates found to be important risk factors in past analysis were added as adjustment, including education (continuous), oral contraceptive pill use (ever versus never), parity (ever versus never), and tubal ligation (yes versus no). We also considered other potential risk factors as adjustment variables, such as duration of oral contraceptive use, menopausal status, family history of breast and/or ovarian cancer, body mass index, family income, recreational physical activity, dietary fat, drink-years of alcohol, and pack-years of smoking, but these did not materially alter the fit of the models. Log-transformed energy intake was included in models involving diet to identify important nutrients apart from their caloric contribution. We also employed various methods of calorie adjustment, including the residual method and the nutrient density method. We found the methods led to similar odds ratio (OR) estimates. A test for linear trend in the logit of risk was done by comparing twice the difference in log likelihoods for models with and without a trend variable, assigned the median for the appropriate quartile.

Subgroup analysis by menopausal, smoking, and drinking status was done by fitting separate logistic models. A smoker was defined as a woman who smoked cigarettes daily for at least 6 months during her lifetime. A drinker was defined as a woman who drank alcohol at least once a week for ≥6 months during her lifetime.

To statistically compare the trend variables for micronutrients among menopausal, smoking, and drinking subgroups, one model with all individuals was fit with an interaction term between membership and the trend variable. The significance of this term was based on Wald's test. Individuals with missing data were excluded from models involving that variable; one case was excluded because of missing drinking status.

To investigate the risk of ovarian cancer by histologic type, we used a polytomous logistic model (30), comparing cases with a specific histologic type with all eligible controls. Two major histologic categories of epithelial ovarian cancer were considered based on the classification scheme of the WHO (31). The model was used to simultaneously estimate the risk for mucinous tumors compared with controls and the risk for nonmucinous tumors compared with controls. Comparisons of the trend variables for micronutrients between the two histologic groups were based on Wald tests.

Results

The distribution of subject demographics and other risk factor information is shown in Table 1. Cases and controls had similar ages (mean 54.8 years for both cases and controls) and were primarily of European or Asian ancestry. Controls were better educated than cases, had more full-term pregnancies, and were more likely to have used oral contraceptives and tubal ligation. Study subject characteristics and ORs for risk factors were generally similar for the two study sites (data not shown). These factors were used as adjustment variables in subsequent analyses. The proportion of cases and controls who had reached menopause or who drank or smoked was similar. Current drinkers had a significantly reduced risk of ovarian cancer. Multivitamins, vitamin C, and vitamin E were common supplements used in our study population (Table 1). Supplement use was less common among cases than among controls, but among users dosage and duration of supplementation were similar between cases and controls and between race groups (data not shown).

Table 2 shows overall associations of total vitamin A and carotenoid intakes with ovarian cancer risk as well as stratum-specific risk by menopausal status, histologic subtype, and smoking and drinking status. Overall, high consumption of vitamin A (IU) and β-carotene from foods and supplements was significantly associated with a reduced risk of ovarian cancer, whereas β-cryptoxanthin intake was modestly associated with an increased risk. A significant inverse trend in risk with increasing vitamin A or β-carotene intake was found among smokers. The inverse associations for current smokers ($OR_{\text{highest versus lowest quartile}}$ [95% confidence interval (95% CI)], 0.18 [0.05-0.62] for vitamin A and 0.20 [0.06-0.62] for β-carotene) were somewhat stronger than for former smokers [$OR_{\text{highest versus lowest quartile}}$ (95% CI), 0.47 (0.22-1.01) for vitamin A and 0.46 (0.22-1.00) for β-carotene]. The difference between smokers and nonsmokers was significant (P for interaction = 0.03 for vitamin A and 0.0008 for β-carotene). Although the trends were stronger for nondrinkers than drinkers, the interaction was not significant (P = 0.35 for vitamin A and = 0.33 for β-carotene). Consumption of vitamin A or β-carotene seemed to be more beneficial for mucinous than for nonmucinous tumors, but the interaction was not significant (P = 0.51 for vitamin A and = 0.25 for β-carotene). In contrast to these findings, a significant positive trend in risk associated with β-cryptoxanthin intake was observed for women with nonmucinous tumors as well as among postmenopausal women or nonsmokers. Menopausal status significantly modified the effects of β-cryptoxanthin (P for interaction = 0.03) on the risk of ovarian cancer.

In accordance with the inverse association of dietary vitamin A and β-carotene with ovarian cancer risk, we also

Table 1. ORs and 95% CIs for the association of selective nondietary variables with the risk of ovarian cancer, Hawaii and Los Angeles, 1993-1999

Variable	Cases (n = 558), n (%)	Controls (n = 607), n (%)	OR* (95% CI)	P for trend†
Center				
Hawaii	200 (35.8)	283 (46.6)		
Los Angeles	358 (64.2)	324 (53.4)		
Age (y)‡				
<45	130 (23.3)	149 (24.5)		
45-54	160 (28.7)	171 (28.2)		
55-64	117 (21.0)	98 (16.1)		
≥65	151 (27.1)	189 (31.1)		
Ethnicity‡				
Caucasian	258 (46.2)	266 (43.8)		
Asian	206 (37.2)	254 (41.8)		
Other	94 (16.6)	87 (14.3)		
Education (y)				
<13	189 (33.9)	163 (26.8)	1§ (—)	
13-14	194 (34.8)	214 (35.2)	0.75 (0.55-1.02)	
15	113 (20.2)	150 (24.7)	0.63 (0.41-0.96)	
≥16	62 (11.1)	80 (13.2)	0.59 (0.41-0.83)	0.002
No. full term pregnancies				
0	159 (28.5)	107 (17.6)	1§ (—)	
1	77 (13.8)	90 (14.8)	0.60 (0.41-0.89)	
2	139 (24.9)	179 (29.5)	0.60 (0.42-0.84)	
≥3	183 (32.8)	231 (38.1)	0.53 (0.37-0.75)	0.002
Oral contraceptive pill use (y)				
0	320 (57.3)	269 (44.3)	1§ (—)	
0.1-1.8	93 (16.7)	99 (16.3)	0.74 (0.51-1.08)	
1.9-5.3	82 (14.7)	110 (18.1)	0.61 (0.42-0.88)	
≥5.4	63 (11.3)	129 (21.2)	0.36 (0.24-0.54)	<0.0001
History of tubal ligation				
No	490 (87.8)	487 (80.2)	1§ (—)	
Yes	68 (12.2)	120 (19.8)	0.70 (0.50-0.99)	
Menopausal status				
Premenopausal	217 (38.9)	256 (42.2)	1§ (—)	
Postmenopausal	341 (61.1)	351 (57.8)	1.36 (0.93-1.99)	
Drinking status				
Nondrinker	354 (63.6)	369 (60.8)	1§ (—)	
Drinker	203 (36.4)	238 (39.2)	0.88 (0.67-1.66)	
Former drinker	104 (18.6)	95 (15.6)	1.16 (0.82-1.64)	
Current drinker	99 (17.7)	143 (23.6)	0.69 (0.50-0.96)	
Smoking status				
Nonsmoker	351 (62.9)	367 (60.5)	1§ (—)	
Smoker	207 (37.1)	240 (39.5)	0.92 (0.72-1.19)	
Former smoker	143 (18.6)	161 (15.6)	0.96 (0.72-1.27)	
Current smoker	64 (17.7)	79 (23.6)	0.86 (0.59-1.25)	
Vitamin/mineral supplement use				
None	210 (37.6)	151 (24.9)		
Multivitamin	279 (50.0)	387 (63.8)		
Vitamin A or β-carotene	68 (12.2)	79 (13.0)		
Vitamin C	180 (32.2)	212 (34.9)		
Vitamin E	151 (27.1)	193 (31.8)		

*After adjustment by unconditional multiple logistic regression for age, ethnicity, study center, education, oral contraceptive pill use, parity, and tubal ligation (where appropriate).
† Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the categories.
‡ Cases and controls were frequency matched on these variables.
§Reference category.

found a dose-response relationship between carrot consumption, particularly carrot juice, and a reduced risk of ovarian cancer (Table 3). Carrots were the main food source of vitamin A (IU; 41% in cases and 44% in controls) and β-carotene (38% in cases and 40% in controls) among study subjects. Similar to vitamin A or β-carotene, we found that high consumption of carrots or carrot juice was somewhat more protective against ovarian cancer among smokers than among nonsmokers (data not shown). We found no evidence of a dose-response relation for vitamin A from supplements alone either in the form of retinol or β-carotene (data not shown).

Table 4 shows the associations of other selected vitamins and minerals, including vitamin C, vitamin E, and selenium, with ovarian cancer risk. Overall, no significant relations were found for total vitamin/mineral intake or for intakes from foods or supplements (data not shown). With the exception of a significant inverse dose-response gradient between total vitamin E intake and the risk of mucinous tumors, the stratified variables, in general, did not have a significant affect on these associations.

Discussion

In this study, high intakes of vitamin A and β-carotene, but not other antioxidants, had a protective effect against ovarian cancer, particularly for mucinous tumors and among smokers or nondrinkers. These results support the notion that alcohol and smoking status may modulate the effects of vitamin A and that different histologic subtypes derive from heterogeneous entities, which may provide some insight into the conflicting results found among epidemiologic studies. Without careful consideration of these factors, important dietary relations with ovarian cancer may be masked.

Table 2. ORs (95% CIs) for the association of quartiles of total vitamin A and carotenoid intake with ovarian cancer, Hawaii and Los Angeles, 1993-1999

	Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	*P* for trend*
All women (*n* = 558 cases and 607 controls)				
Vitamin A (IU)†	0.78 (0.55-1.10)	0.66 (0.46-0.95)	0.61 (0.42-0.89)	0.02
Vitamin A (IU)-food sources only	1.04 (0.73-1.47)	0.75 (0.52-1.08)	0.72 (0.49-1.07)	0.05
All carotenoids (μg)†	1.09 (0.77-1.54)	0.66 (0.46-0.96)	0.78 (0.52-1.17)	0.11
α-Carotene (μg)	1.19 (0.85-1.68)	0.73 (0.52-1.04)	0.81 (0.56-1.17)	0.08
β-Carotene (μg)†	0.98 (0.70-1.39)	0.70 (0.49-1.00)	0.66 (0.45-0.97)	0.02
β-Carotene (μg)-food sources only	1.26 (0.89-1.78)	0.78 (0.55-1.12)	0.82 (0.56-1.21)	0.11
β-Cryptoxanthin (μg)	1.20 (0.85-1.68)	1.18 (0.84-1.67)	1.33 (0.93-1.91)	0.14
Lycopene (μg)	0.93 (0.65-1.31)	0.96 (0.66-1.39)	0.97 (0.65-1.44)	0.91
Lutein/zeaxanthin (μg)	1.27 (0.89-1.80)	1.06 (0.73-1.53)	0.84 (0.57-1.26)	0.31
Premenopausal women (*n* = 217 cases and 256 controls)				
Vitamin A (IU)†	0.70 (0.39-1.25)	0.52 (0.29-0.93)	0.49 (0.26-0.92)	0.04
Vitamin A (IU)-food sources only	1.28 (0.72-2.27)	0.73 (0.49-1.33)	0.71 (0.38-1.35)	0.15
All carotenoids (μg)†	0.96 (0.54-1.70)	0.56 (0.30-1.92)	0.65 (0.33-1.27)	0.15
α-Carotene (μg)	1.58 (0.89-2.80)	0.60 (0.33-1.10)	0.70 (0.38-1.29)	0.06
β-Carotene (μg)†	1.27 (0.73-2.21)	0.73 (0.41-1.31)	0.61 (0.33-1.14)	0.04
β-Carotene (μg)-food sources only	1.54 (0.88-2.72)	0.70 (0.39-1.26)	0.70 (0.37-1.31)	0.10
β-Cryptoxanthin (μg)	0.81 (0.48-1.38)	0.58 (0.33-1.00)	0.79 (0.43-1.44)	0.20
Lycopene (μg)	1.01 (0.55-1.85)	0.95 (0.50-1.81)	1.04 (0.52-2.07)	0.84
Lutein/zeaxanthin (μg)	0.98 (0.55-1.75)	1.04 (0.56-1.94)	0.60 (0.31-1.16)	0.15
Postmenopausal women (*n* = 341 cases and 351 controls)				
Vitamin A (IU)†	0.77 (0.49-1.21)	0.70 (0.43-1.12)	0.60 (0.36-0.99)	0.06
Vitamin A (IU)-food sources only	0.84 (0.53-1.32)	0.70 (0.43-1.24)	0.62 (0.36-1.05)	0.06
All carotenoids (μg)†	1.13 (0.72-1.78)	0.66 (0.41-1.07)	0.76 (0.45-1.28)	0.16
α-Carotene (μg)	0.96 (0.62-1.50)	0.78 (0.50-1.22)	0.81 (0.50-1.31)	0.29
β-Carotene (μg)†	0.78 (0.49-1.23)	0.62 (0.38-0.99)	0.59 (0.36-0.97)	0.05
β-Carotene (μg)-food sources only	1.01 (0.64-1.59)	0.79 (0.40-1.26)	0.75 (0.45-1.25)	0.17
β-Cryptoxanthin (μg)	1.64 (1.03-2.60)	1.98 (1.24-3.17)	1.90 (1.17-3.07)	0.007
Lycopene (μg)	0.91 (0.59-1.42)	1.46 (0.66-1.69)	0.90 (0.54-1.50)	0.80
Lutein/zeaxanthin (μg)	1.43 (0.90-2.25)	0.97 (0.60-1.56)	0.89 (0.52-1.50)	0.45
Mucinous tumors (*n* = 109 cases and 607 controls)				
Vitamin A (IU)†	0.55 (0.31-0.99)	0.34 (0.18-0.65)	0.49 (0.26-0.93)	0.06
Vitamin A (IU)-food sources only	0.73 (0.40-1.32)	0.50 (0.26-0.95)	0.53 (0.27-1.06)	0.04
All carotenoids (μg)†	0.84 (0.46-1.52)	0.57 (0.30-1.07)	0.52 (0.25-1.07)	0.07
α-Carotene (μg)	1.02 (0.57-1.82)	0.58 (0.31-1.09)	0.70 (0.37-1.34)	0.13
β-Carotene (μg)†	0.68 (0.38-1.22)	0.52 (0.28-0.97)	0.43 (0.22-0.86)	0.02
β-Carotene (μg)-food sources only	0.80 (0.44-1.44)	0.64 (0.35-1.18)	0.48 (0.24-0.95)	0.01
β-Cryptoxanthin (μg)	1.05 (0.59-1.88)	0.91 (0.50-1.66)	0.82 (0.43-1.57)	0.50
Lycopene (μg)	1.39 (0.76-2.55)	0.89 (0.44-1.78)	1.15 (0.55-2.38)	0.99
Lutein/zeaxanthin (μg)	1.05 (0.58-1.90)	0.85 (0.45-1.62)	0.53 (0.26-1.10)	0.08
Nonmucinous tumors (*n* = 449 cases and 607 controls)				
Vitamin A (IU)†	0.87 (0.60-1.25)	0.78 (0.53-1.13)	0.65 (0.44-0.98)	0.04
Vitamin A (IU)-food sources only	1.15 (0.79-1.66)	0.84 (0.57-1.24)	0.79 (0.52-1.20)	0.13
All carotenoids (μg)†	1.17 (0.81-1.69)	0.70 (0.47-1.03)	0.86 (0.56-1.31)	0.25
α-Carotene (μg)	1.25 (0.87-1.80)	0.79 (0.54-1.14)	0.85 (0.58-1.25)	0.16
β-Carotene (μg)†	1.09 (0.76-1.57)	0.76 (0.52-1.12)	0.74 (0.49-1.10)	0.05
β-Carotene (μg)-food sources only	1.43 (0.99-2.06)	0.83 (0.56-1.21)	0.94 (0.62-1.42)	0.29
β-Cryptoxanthin (μg)	1.24 (0.86-1.78)	1.27 (0.88-1.83)	1.49 (1.02-2.19)	0.05
Lycopene (μg)	0.83 (0.57-1.20)	0.98 (0.67-1.45)	0.94 (0.62-1.43)	0.93
Lutein/zeaxanthin (μg)	1.33 (0.92-1.93)	1.13 (0.76-1.67)	0.94 (0.61-1.43)	0.63
Smokers (*n* = 207 cases and 240 controls)				
Vitamin A (IU)†	0.69 (0.38-1.24)	0.59 (0.33-1.05)	0.36 (0.19-0.66)	0.001
Vitamin A (IU)-food sources only	0.95 (0.53-1.70)	0.82 (0.45-1.47)	0.51 (0.57-0.95)	0.03
All carotenoids (μg)†	1.07 (0.59-1.92)	0.64 (0.36-1.15)	0.42 (0.22-0.78)	0.002
α-Carotene (μg)	1.36 (0.78-2.36)	0.78 (0.44-1.38)	0.74 (0.42-1.31)	0.17
β-Carotene (μg)†	0.98 (0.56-1.73)	0.78 (0.43-1.41)	0.37 (0.20-0.68)	0.0003
β-Carotene (μg)-food sources only	1.18 (0.67-2.10)	0.75 (0.42-1.34)	0.55 (0.30-1.01)	0.03
β-Cryptoxanthin (μg)	0.85 (0.50-1.43)	1.00 (0.56-1.77)	0.79 (0.44-1.43)	0.55
Lycopene (μg)	1.18 (0.64-2.16)	1.03 (0.56-1.90)	0.84 (0.43-1.63)	0.49
Lutein/zeaxanthin (μg)	1.56 (0.85-2.84)	0.81 (0.43-1.54)	0.71 (0.37-1.03)	0.10
Nonsmokers (*n* = 351 cases and 367 controls)				
Vitamin A (IU)†	0.82 (0.53-1.28)	0.69 (0.43-1.09)	0.80 (0.48-1.31)	0.48
Vitamin A (IU)-food sources only	1.11 (0.71-1.73)	0.71 (0.44-1.15)	0.87 (0.52-1.48)	0.33
All carotenoids (μg)†	1.15 (0.74-1.79)	0.69 (0.43-1.12)	1.19 (0.70-2.04)	0.63
α-Carotene (μg)	1.09 (0.70-1.71)	0.68 (0.43-1.07)	0.81 (0.51-1.28)	0.27
β-Carotene (μg)†	1.04 (0.67-1.60)	0.68 (0.43-1.08)	0.94 (0.57-1.55)	0.76
β-Carotene (μg)-food sources only	1.35 (0.87-2.10)	0.82 (0.51-1.30)	1.03 (0.61-1.73)	0.63
β-Cryptoxanthin (μg)	1.53 (0.97-2.40)	1.35 (0.86-2.11)	1.83 (1.13-2.95)	0.02
Lycopene (μg)	0.83 (0.54-1.27)	0.95 (0.59-1.52)	1.09 (0.65-1.82)	0.71
Lutein/zeaxanthin (μg)	1.14 (0.73-1.76)	1.28 (0.81-2.02)	0.93 (0.55-1.57)	0.97
Drinkers (*n* = 203 cases and 238 controls)				
Vitamin A (IU)†	0.90 (0.49-1.63)	0.83 (0.45-1.55)	0.86 (0.45-1.65)	0.70
Vitamin A (IU)-food sources only	1.13 (0.63-2.03)	0.90 (0.49-1.65)	1.04 (0.54-2.00)	0.94
All carotenoids (μg)†	1.52 (0.83-2.77)	0.61 (0.32-1.14)	1.05 (0.55-1.99)	0.79
α-Carotene (μg)	1.38 (0.78-2.44)	0.74 (0.42-1.32)	0.94 (0.51-1.64)	0.42

(Continued on the following page)

Table 2. ORs (95% CIs) for the association of quartiles of total vitamin A and carotenoid intake with ovarian cancer, Hawaii and Los Angeles, 1993-1999 (Cont'd)

	Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	*P* for trend*
β-Carotene (μg)†	1.10 (0.62-1.95)	0.79 (0.43-1.46)	0.89 (0.48-1.63)	0.58
β-Carotene (μg)-food sources only	1.47 (0.83-2.63)	0.94 (0.51-1.72)	1.09 (0.58-2.06)	0.88
β-Cryptoxanthin (μg)	1.38 (0.81-2.35)	1.63 (0.92-2.88)	0.88 (0.47-1.63)	0.91
Lycopene (μg)	1.15 (0.62-2.12)	1.15 (0.62-2.14)	0.91 (0.48-1.74)	0.72
Lutein/zeaxanthin (μg)	1.54 (0.83-2.85)	1.04 (0.55-1.95)	1.55 (0.79-3.06)	0.39
Nondrinkers (n = 354 cases and 369 controls)				
Vitamin A (IU)†	0.68 (0.44-1.05)	0.59 (0.38-0.92)	0.47 (0.29-0.76)	0.004
Vitamin A (IU)-food sources only	0.93 (0.60-1.44)	0.63 (0.39-1.00)	0.53 (0.31-0.88)	0.006
All carotenoids (μg)†	0.91 (0.59-1.40)	0.67 (0.42-1.06)	0.61 (0.36-1.05)	0.05
α-Carotene (μg)	1.06 (0.69-1.63)	0.67 (0.42-1.06)	0.70 (0.43-1.14)	0.06
β-Carotene (μg)†	0.90 (0.58-1.40)	0.62 (0.39-0.97)	0.51 (0.31-0.84)	0.004
β-Carotene (μg)-food sources only	1.12 (0.72-1.74)	0.66 (0.42-1.05)	0.64 (0.38-1.05)	0.03
β-Cryptoxanthin (μg)	1.06 (0.68-1.67)	0.98 (0.63-1.53)	1.51 (0.95-2.39)	0.11
Lycopene (μg)	0.85 (0.55-1.32)	0.86 (0.54-1.38)	1.02 (0.60-1.73)	0.98
Lutein/zeaxanthin (μg)	1.15 (0.75-1.78)	1.10 (0.69-1.75)	0.58 (0.34-0.97)	0.06

NOTE: ORs after adjustment for age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, tubal ligation, and energy intake by polytomous logistic regression (histologic type) or unconditional logistic regression (all other variables). Quartile cut points for vitamin A and carotenoids were as follows: vitamin A (total), 9,230, 14,366, and 23,148 IU; vitamin A (food sources), 7,433, 11,444, and 18,703 IU; total carotenoids, 7,887, 12,470, and 19,597 μg; α-carotene, 470, 898, and 1,703 μg; β-carotene (total), 3,016, 5,070, and 8,252 μg; β-carotene (food sources), 2,880, 4,722, and 7,575 μg; β-cryptoxanthin, 55.2, 137.6, and 322.5 μg; lycopene, 1,542, 2,636, and 4,659 μg; lutein/zeaxanthin, 1,711, 2,707, and 4,182 μg.
*Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the categories.
† Includes both food and supplement sources.

In agreement with our findings, several case-control investigations have reported a significant inverse association between dietary intake of vitamin A and/or β-carotene and ovarian cancer risk (9-11, 32). However, in other studies, no association has been found (14, 16, 33, 34). Two prospective studies found no association (12, 17). A meta-analysis of five observational studies reported that a high intake of β-carotene was significantly associated with a reduced risk of ovarian cancer (relative risk, 0.84; 95% CI, 0.75-0.94; ref. 35). Significant inverse relationships for lutein/zeaxanthin (9, 36), lycopene, α-carotene (10), and total carotenoids (37) with ovarian cancer risk have been reported, although we found no significant relation to risk for carotenoids other than for β-carotene. Some studies have reported a significant and inverse association between the consumption of specific vegetables, such as carrots (10, 11), dark green vegetables (12, 33), and tomato sauce (10), and ovarian cancer risk, in accordance with the association of dietary vitamin A, β-carotene, and lycopene intakes. We observed protective effects for carrots, but not for other vegetables or fruits, against ovarian cancer. Bosetti et al. (38) reported that high vegetable consumption was significantly associated with a decreased risk of ovarian cancer. Similar to most previous studies (9, 14, 17), we did not find a significant association between total fruit or vegetable intake and ovarian cancer risk, nor did we observe a significant dose-response relation for other antioxidants. In contrast to our results, two studies reported a significant inverse association with ovarian cancer risk for vitamin E and/or vitamin C either from food and supplement sources combined or from food sources alone (9, 34).

The lack of consistency in the dietary findings of epidemiologic studies of ovarian cancer may be due in part to the diversity in food intakes of different study populations and the limitations inherent in quantifying dietary consumption. Interindividual variation in bioavailability of these nutrients partially due to the diverse food preparations or cooking methods may also account for some of the inconsistencies between studies (39-41). Unfortunately, we did not obtain this information in our investigation. Finally, some of the inconsistencies may be attributed to the lack of adjustment for important confounders of the diet-ovarian cancer relation, such as menopausal status, tobacco smoking, and alcohol drinking.

Fairfield et al. (17) found that the inverse association of ovarian cancer with total fruit and vegetable consumption was strongest for adolescent dietary exposures. Similarly, Byers et al. (13) reported an inverse association of vitamin A intake from vegetables and fruits with ovarian cancer in younger but not older (>50 years) women. Both results raise the possibility that the role of vitamin A and carotenoids in ovarian malignancies may be more important in earlier rather than in later life. In support of this theory, Cramer et al. (10) found that the protective effects of lycopene and β-cryptoxanthin intakes against ovarian cancer risk were stronger in premenopausal women. However, the protective effect of α-carotene on ovarian cancer risk was stronger in postmenopausal women. We observed a significant adverse effect of β-cryptoxanthin on postmenopausal but not on premenopausal ovarian cancer risk. Associations for other carotenoids were similar between premenopausal and postmenopausal women. It is unclear whether the positive association for β-cryptoxanthin was a real or chance finding. β-Cryptoxanthin has been consistently shown to reduce lung cancer (42). As an oxycarotenoid or xanthophylls (C-OH), it is biologically plausible that β-cryptoxanthin may act on ovarian cells differently from other hydrocarbon carotenoids (C-H). In this study, a high intake of oranges, tangerines, and papaya, the most common food sources of β-cryptoxanthin, had modest positive associations with the risk of ovarian cancer.

Consistent with the results of Cramer et al. (10), we found that high intakes of vitamin A, β-carotene, and vitamin E were somewhat more protective against mucinous tumors than against nonmucinous tumors, although the differences were not significant. Similar histologic differences were observed between borderline and invasive ovarian tumors (data not shown). Cramer et al. reported a significant negative dose-response relationship between α-carotene intake and mucinous tumors and invasive serous tumors and between lycopene intake and borderline serous tumors. In addition, Britton et al. (15) reported a significant decreasing trend in the risk of benign serous tumors with increasing retinol and vitamin A intake. Based on the distinct genetic aberrations observed among histologic types of ovarian cancer (43), it is possible that nuclear retinoid receptor profiles may differ by tumor histology (44). Only Katsetos et al. (45) showed RA receptor (RAR) α gene expression in serous tumors. Further studies are warranted to explore this possibility.

Table 3. ORs (95% CIs) for the association of quartiles of carotenoid-rich food intake with ovarian cancer, Hawaii and Los Angeles, 1993-1999

	Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	*P* for trend*
All vegetables with juice	1.35 (0.96-1.91)	1.03 (0.72-1.49)	1.20 (0.79-1.83)	0.61
Carrots with juice	1.13 (0.80-1.58)	0.70 (0.50-0.99)	0.77 (0.58-1.02)	0.05
Carrot-raw or cooked	1.18 (0.84-1.65)	0.70 (0.49-0.99)	0.80 (0.56-1.15)	0.05
Carrot juice	1.08 (0.84-1.64)	0.87 (0.58-1.29)	0.79 (0.58-1.10)	0.03
Spinach	1.19 (0.84-1.67)	1.02 (0.73-1.44)	0.94 (0.66-1.34)	0.64
Tomatoes	0.82 (0.57-1.16)	1.23 (0.85-1.77)	0.82 (0.55-1.24)	0.77
Tomato Juice	1.18 (0.73-1.90)	1.20 (0.72-1.99)	0.94 (0.57-1.55)	0.78
Broccoli	0.94 (0.67-1.31)	0.90 (0.61-1.26)	0.86 (0.61-1.22)	0.39
Pumpkin	0.93 (0.55-1.53)	0.99 (0.71-1.38)	1.09 (0.77-1.55)	0.75
All fruits with juice	1.00 (0.71-1.40)	1.10 (0.78-1.56)	0.86 (0.60-1.25)	0.65
Papaya	1.42 (0.99-2.02)	1.07 (0.73-1.56)	1.19 (0.80-1.78)	0.28
Oranges	1.00 (0.72-1.39)	1.21 (0.87-1.69)	1.25 (0.90-1.74)	0.12
Tangerines	1.52 (1.05-2.19)	1.02 (0.71-1.46)	1.33 (0.94-1.86)	0.12

NOTE: ORs after adjustment for age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, tubal ligation, and energy intake by unconditional logistic regression. Quartile cut points for specific foods were as follows: all vegetables, 253.9, 388.0, and 560.6 g; total carrot, 9.2, 18.4, and 36.8 g; carrot, 9.0, 18.0, and 36.0 g; carrot juice, 0, 0.21, and 0.53 g; spinach, 0.7, 5.0, and 14.5 g; tomatoes, 26.5, 46.8, and 77.6 g; tomato juice, 0, 9.9, and 33.9 g; broccoli, 8.3, 20.1, and 35.1 g; pumpkin, 0, 2.5, and 6.3 g; all fruits, 177.5, 218.0, and 359.6 g; papaya, 0, 5.7, and 22.3 g; orange, 4.3, 11.1, and 46.3 g; tangerine, 0, 7.0, and 14.0 g.
*Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the categories.

We found for the first time that the inverse associations of vitamin A and β-carotene with ovarian cancer risk were significantly stronger in smokers than in nonsmokers. Similar inverse associations were observed among light (pack-years ≤12) and heavy (pack-years >12) smokers (data not shown). The inverse associations for current smokers were somewhat stronger than for former smokers. Fleischauer et al. (34) reported that vitamin C intake may be more beneficial against ovarian cancer among nonsmokers than among smokers but found little heterogeneity in the overall null relation between consumption of antioxidants and ovarian cancer risk by smoking history. Cho et al. (46) reported that vitamin A and

Table 4. ORs (95% CIs) for the association of quartiles of selected total antioxidant intake with ovarian cancer, Hawaii and Los Angeles, 1993-1999

	Q2 vs Q1	Q3 vs Q1	Q4 vs Q1	*P* for trend*
All women				
Vitamin C (mg)	0.98 (0.69-1.38)	0.75 (0.52-1.08)	0.89 (0.62-1.26)	0.65
Vitamin E (total α-E mg)	1.12 (0.78-1.60)	0.93 (0.64-1.37)	0.80 (0.56-1.16)	0.10
Selenium (mg)	1.18 (0.81-1.71)	1.22 (0.80-1.87)	0.98 (0.58-1.66)	0.66
Premenopausal women (*n* = 217 cases and 256 controls)				
Vitamin C (mg)	0.97 (0.56-1.69)	0.52 (0.29-0.91)	0.89 (0.50-1.59)	0.83
Vitamin E (total α-E mg)	1.00 (0.57-1.76)	0.93 (0.50-1.71)	0.83 (0.42-1.66)	0.57
Selenium (mg)	1.12 (0.56-2.23)	1.18 (0.56-2.49)	1.05 (0.42-2.62)	0.94
Postmenopausal women (*n* = 341 cases and 351 controls)				
Vitamin C (mg)	1.05 (0.66-1.66)	0.99 (0.60-1.62)	0.91 (0.57-1.46)	0.55
Vitamin E (total α-E mg)	1.31 (0.81-2.21)	1.01 (0.61-1.67)	0.99 (0.50-1.24)	0.06
Selenium (mg)	1.26 (0.80-1.98)	1.34 (0.78-2.32)	0.59 (0.36-0.97)	0.05
Mucinous tumors (*n* = 109 cases and 607 controls)				
Vitamin C (mg)	0.67 (0.38-1.19)	0.41 (0.22-0.76)	0.50 (0.26-0.95)	0.09
Vitamin E (total α-E mg)	0.94 (0.53-1.67)	0.53 (0.27-1.06)	0.39 (0.19-0.81)	0.02
Selenium (mg)	1.86 (0.93-3.71)	1.77 (0.79-3.93)	0.78 (0.27-2.21)	0.18
Nonmucinous tumors (*n* = 449 cases and 607 controls)				
Vitamin C (mg)	1.11 (0.76-1.61)	0.90 (0.61-1.32)	1.03 (0.71-1.51)	0.95
Vitamin E (total α-E mg)	1.18 (0.80-1.73)	1.08 (0.72-1.61)	0.94 (0.64-1.39)	0.34
Selenium (mg)	1.06 (0.72-1.57)	1.12 (0.72-1.76)	1.03 (0.60-1.80)	0.98
Smokers (*n* = 207 cases and 240 controls)				
Vitamin C (mg)	1.23 (0.69-2.21)	0.45 (0.24-0.84)	0.69 (0.40-1.19)	0.17
Vitamin E (total α-E mg)	1.32 (0.72-2.45)	0.60 (0.31-1.15)	0.75 (0.40-1.38)	0.34
Selenium (mg)	1.38 (0.70-2.51)	1.12 (0.55-2.26)	0.69 (0.29-1.68)	0.17
Nonsmokers (*n* = 351 cases and 367 controls)				
Vitamin C (mg)	0.87 (0.56-1.35)	0.90 (0.57-1.43)	1.00 (0.62-1.61)	0.72
Vitamin E (total α-E mg)	1.15 (0.61-2.17)	0.78 (0.39-1.56)	0.73 (0.38-1.41)	0.23
Selenium (mg)	1.11 (0.70-1.76)	1.27 (0.74-2.20)	1.19 (0.61-2.32)	0.67
Drinkers (*n* = 203 cases and 238 controls)				
Vitamin C (mg)	0.89 (0.49-1.60)	0.54 (0.29-1.02)	0.69 (0.39-1.24)	0.34
Vitamin E (total α-E mg)	1.09 (0.59-2.01)	0.84 (0.45-1.56)	1.07 (0.56-2.05)	0.86
Selenium (mg)	0.98 (0.51-1.86)	1.05 (0.50-2.21)	0.72 (0.30-1.72)	0.33
Nondrinkers (*n* = 354 cases and 369 controls)				
Vitamin C (mg)	0.98 (0.64-1.52)	0.84 (0.54-1.32)	0.99 (0.62-1.57)	0.93
Vitamin E (total α-E mg)	1.01 (0.65-1.59)	0.97 (0.61-1.55)	0.80 (0.51-1.27)	0.26
Selenium (mg)	1.34 (0.84-2.13)	1.33 (0.78-2.27)	1.18 (0.60-2.35)	0.87

NOTE: ORs after adjustment for age, ethnicity, study site, education, oral contraceptive pill use, pregnancy status, tubal ligation, and energy intake by polytomous logistic regression (histologic type) or unconditional logistic regression (all other variables). Quartile cut points for antioxidants were as follows: vitamin C, 149.1, 252.4, and 555.3 mg; vitamin E, 10.5, 19.9, and 52.1 mg; selenium, 81.4, 109.9, and 146.3 mg. Total antioxidant intake includes both food and supplement sources.
*Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the categories.

β-carotene intakes were associated with a reduced risk of breast cancer among smokers but not among nonsmokers in the Nurses' Health Study II. β-Carotene supplements, however, increased lung cancer incidence and mortality among smokers, most particularly among current smokers. The mechanism by which smoking interacts with vitamin A or β-carotene is unclear. The activation of cytochrome *P*450 enzymes induced by tobacco smoke would increase RA catabolism and results in RA depletion in the blood (47) and tissues (48). The subsequent decrease in tissue RA levels may down-regulate the expression of RARs and diminish retinoid signaling pathways that mediate the growth inhibitory effects of retinoids (49). It is possible that high consumption of vitamin A or β-carotene counteracts the depletion of RA in tissues caused by tobacco exposure and activates RARs. Vitamin A or β-carotene may also stimulate the effects of reactive oxygen species from cigarettes that act as essential mediators in the induction of apoptosis (50). Furthermore, high consumption of β-carotene at elevated, nonphysiologic oxygen tensions may behave as a pro-oxidant (51), which may plausibly explain the opposing modulation effects of β-carotene on risks of lung, ovarian, or breast cancer, among smokers.

Alcohol consumption reduced the inverse association of vitamin A and β-carotene consumption with risk of ovarian cancer. Ethanol plays an important role in vitamin A metabolism and may have an indirect effect on RA signaling pathways. Both alcohol dehydrogenases and cytochrome *P*450 enzymes are involved in catalyzing RA biosynthesis and/or catabolism. Alcohol exposure may lower RA levels by either blocking alcohol dehydrogenase–activated RA biosynthesis or inducing CYP2E1- or CYP26-activated RA catabolism due to the competition, as dehydrogenase substrates, between alcohol and vitamin A (52). Alcohol intake has also been reported to reduce plasma carotenoid levels by interfering with lipoprotein metabolism in the liver. As indirect evidence, Ratnasinghe et al. (53) observed an inverse association of serum carotenoids among nondrinkers for lung cancer, but a positive association of serum β-carotene and β-cryptoxanthin with lung cancer was observed among drinkers.

Our results do not support a major antioxidant effect on ovarian carcinogenesis (54) in spite of the notable oxidative stress on the ovarian epithelium during ovulations. We found a significant inverse association for β-carotene on ovarian cancer risk but not for other prominent antioxidants, including vitamin E, vitamin C, and lycopene. Although mucinous tumors were less likely to be associated with ovulation than nonmucinous tumors in an earlier analysis of these data (55), we found that the protective effect of β-carotene against ovarian cancer was somewhat stronger for mucinous than nonmucinous histologic types. The stronger relation of β-carotene than other nutrients to risk may result from the heterogeneous distribution of carotenoids and other antioxidants by tissue type (56).

Several limitations of this case-control study may have influenced the validity of our results. Dietary information was based on intake during the year preceding the interview, whereas exposures in adolescence or early adulthood may be more relevant to ovarian cancer risk. Our findings may be subject to recall bias, although it is unlikely that this occurred because vitamin A or carotenoid intake is not a well-established risk factor for ovarian cancer. The smoking and drinking findings are unlikely to result from an underlying socioeconomic status effect, as we adjusted for education in all models, and the effect of smoking and drinking on protection from vitamin A and β-carotene did not vary by educational level. The modest participation rate among cases and controls may have affected the generalizability to our results.

In summary, our findings suggest that dietary vitamin A and β-carotene are modestly protective against ovarian cancer, particularly among smokers. We also found that β-cryptoxanthin consumption was associated with an increased risk of postmenopausal ovarian cancer. We found no evidence of a dose-response relation for other antioxidant vitamins or minerals. Although the possibility that vitamin A or β-carotene intake is more beneficial among smokers than among nonsmokers is intriguing, this result requires confirmation and should be taken cautiously. Further investigations regarding the antiproliferative effects of vitamin A and carotenoids on ovarian cancer development are necessary to better understand these complex mechanisms and relationships.

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