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Null Results in Brief

Carotenoid, Vitamin A, Vitamin C, and Vitamin E Intake and Risk of Ovarian Cancer: a Prospective Cohort Study

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Introduction

It is thought that oxidative stress resulting to repeated ovulation may increase the risk of ovarian cancer by inducing DNA damage (1). Consumption of antioxidants may, therefore, decrease ovarian cancer risk by counteracting oxidative stress and the resultant DNA damage (2, 3). Currently, the epidemiologic evidence regarding associations between antioxidants and risk of ovarian cancer is mixed (4-12). Of the two prospective studies, Kushi et al. (4) and Fairfield et al. (7) both reported no association between β-carotene and ovarian cancer risk. In addition, Fairfield et al. (7) found no association with any of the other four major carotenoids (α-carotene, β-cryptoxanthin, lycopene, and lutein) or vitamins A or C. However, they did observe a statistically significant increased risk of ovarian cancer associated with relatively high intake of vitamin E from food sources (7). Given the current lack of prospective data regarding these relationships, we examined the association between intake of dietary carotenoids and vitamins A, C, and E and ovarian cancer risk in a cohort of Canadian women.

Materials and Methods

The design of the study has been described in detail elsewhere (13). Briefly, 89,835 women ages 40 to 59 years were recruited into the Canadian National Breast Screening Study between 1980 and 1985 from the general Canadian population by various means, including personal invitation by letter, group mailings to employees of large institutions and to members of professional associations, advertisements in newspapers, and public service announcements on radio and television (14).

At recruitment into the cohort, participants completed self-administered questionnaires that sought information on demographic characteristics, lifestyle factors, menstrual and reproductive history, and use of oral contraceptives and replacement estrogens. Women who reported having regular menstrual periods within the past 12 months were classified as premenopausal. Women whose menstrual periods ceased at least 12 months before enrollment into the study were considered postmenopausal (15).

Starting in 1982 (i.e., after some participants had completed their scheduled visits to the screening centers), a self-administered food frequency questionnaire was distributed to all new attendees at all screening centers and to women returning to the screening centers for rescreening. The food frequency questionnaire sought information on usual portion size and frequency of consumption of 86 food items and included photographs of various portion sizes to assist respondents in quantifying intake (16). A comparison between the self-administered questionnaire and a full interviewer-administered questionnaire, which has been subjected to both validity and reliability testing (16) and used in a number of epidemiologic studies (17), revealed that the two methods gave estimates of intake of the major macronutrients and micronutrients, which were moderately to strongly correlated with each other (reported correlation coefficients ranged from 0.47 for cholesterol to 0.72 for vegetable protein; ref. 16). A total of 49,613 dietary questionnaires were returned and available for analysis.

Data from the food frequency questionnaire were used to calculate daily total intakes of various nutrients and alcohol, using a database developed by modifying and expanding food composition tables from the U.S. Department of Agriculture to include typically Canadian foods (18, 19). The values for carotenoid intake presented here are for intake from dietary sources alone, because data on the carotenoid content of vitamin supplements were not available. The values for vitamins A, C, and E intake presented here are for intake from dietary sources only and from diet and supplements combined. Incident ovarian cancer cases and deaths amongst cohort members were ascertained, respectively, by means of computerized record linkages to the Canadian Cancer Database and to the National Mortality Database, both of which are maintained by Statistics Canada. The linkages to the databases yielded data on cancer incidence and mortality to December 31, 2000 for women in Ontario, December 31, 1998 for women in Quebec, and December 31, 1999 for women in other provinces.

Of the 49,613 women for whom dietary data were available, we excluded women with extreme energy intake values (at least 3 SDs above or below the mean value for $\log_e$ caloric intake; $n = 502$), women with prevalent ovarian cancer at baseline ($n = 20$), and women who had undergone a bilateral oopherectomy ($n = 315$). These exclusions left 48,776 women available for analysis, among whom were 264 incident cases of ovarian cancer. Study participants were considered to be at risk from their date of enrollment until the date of diagnosis

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Table 1. Intake of carotenoids and risk of ovarian cancer in the National Breast Screening Study

	Cases	Incident ovarian cancer risk	
		Person-years	Hazard ratio (95% confidence interval)
β-Carotene (μg/d)			
0-3,274	67	201,510	1.00 (reference)
>3,274-4,800	64	201,159	0.95 (0.65-1.38)
>4,800-7,000	66	200,319	1.00 (0.69-1.45)
>7,000	67	198,426	0.97 (0.66-1.43)
P_{trend}			0.95
α-Carotene (μg/d)			
0-5,839	73	201,908	1.00 (reference)
>5,839-9,700	67	201,501	0.92 (0.64-1.32)
>9,700-15,500	58	200,008	0.85 (0.59-1.25)
>15,500	66	197,996	0.94 (0.64-1.38)
P_{trend}			0.65
Lycopene (μg/d)			
0-4,708	68	200,504	1.00 (reference)
>4,708-8,600	62	200,630	0.88 (0.61-1.27)
>8,600-15,000	67	200,790	0.95 (0.66-1.37)
>15,000	67	199,490	0.92 (0.63-1.34)
P_{trend}			0.75
Lutein (μg/d)			
0-1,838	69	200,068	1.00 (reference)
>1,838-2,775	54	200,285	0.64 (0.43-1.96)
>2,775-4,278	67	200,672	0.90 (0.62-1.30)
>4,278	74	200,388	0.98 (0.68-1.41)
P_{trend}			0.69
β-Cryptoxanthan (μg/d)			
0-48	58	199,184	1.00 (reference)
>48-88	72	200,753	1.15 (0.78-1.67)
>88-143	71	200,673	1.17 (0.80-1.71)
>143	63	200,803	1.01 (0.67-1.51)
P_{trend}			0.94
Total carotenoid (μg/d)			
0-26,272	62	200,925	1.00 (reference)
>26,272-38600	62	201,094	1.00 (0.68-1.46)
>38,600-51,000	64	200,305	1.00 (0.68-1.47)
>51,000	76	199,088	1.19 (0.81-1.74)
P_{trend}			0.40

NOTE: Results are adjusted hazard ratio and 95% confidence interval and show association based on increasing quartiles of intake. Multivariate adjusted for age (time to event variable), pack-years of smoking (none plus three levels), menopausal status, use of oral contraceptives (ever versus never), body mass index (<25, 25 to 29, ≥30 kg/m^2), education (≤12 versus >12 years), participation in vigorous physical activity (any, none, missing), energy intake at baseline (continuous), study center, and randomization group (intervention versus control).

of ovarian cancer, the date of termination of follow-up (the date to which cancer incidence data were available for women in the corresponding province), or the date of death, whichever occurred earliest. Cox proportional hazards models (using age as the time scale) were used to estimate hazard ratios and 95% confidence intervals for the association between the intake of each of the five major carotenoids (separately and summed) and consumption of vitamins A, C, and E and ovarian cancer risk. Multivariate models included the variables listed in the footnote to Table 1. All estimates of antioxidant intake were adjusted for energy intake using the residual method (20). To test for trends in risk with increasing levels of the exposures of interest, we assigned each dietary variable their respective category median and then fitted the assigned value of each risk factor as a continuous variable in the risk models. We then evaluated the statistical significance of the corresponding coefficient using the Wald test (20). Use of the life test procedure in SAS showed that the proportional hazards assumption was met in the fitted models. All analyses were done using SAS version 9 (SAS Institute, Cary, NC). All statistical tests were two sided, and Ps < 0.05 were considered statistically significant.

Results

The average duration of follow-up for cohort members was 16.4 years (with a total of 801,467 person-years of follow-up). The mean (SD) age at baseline was 48.6 (5.6), and the mean age at diagnosis for the cases was 59.4 (7.2) years. For the cohort as a whole, the mean (SD) mean energy adjusted was 22,484 (16,723) μg/d for total carotenoid intake, 9,660 (4,818) IU/d for vitamin A, 21.7 (6.9) mg/d for vitamin E, and 167.4 (77.4) mg/d for vitamin C (data not shown).

Table 1 shows that in age-adjusted models neither individual nor total carotenoid intake was associated with altered risk of ovarian cancer. After multivariate adjustment, the hazard ratios for each of the carotenoids remained essentially the same. Likewise, there were no associations between intake of vitamins A, C, and E from diet alone or from diet and supplements combined and ovarian cancer risk in either the age-adjusted or multivariate adjusted models (Table 2). The results for each of the analyses presented above were similar after exclusion of case subjects diagnosed within 1 year of recruitment (n = 10), after exclusion of subjects

Table 2. Intake of vitamins A, C, and E (from dietary and supplemental sources) and risk of ovarian cancer in the National Breast Screening Study

	Cases	Incident ovarian cancer risk	
		Person-years	Hazard ratio (95% confidence interval)
Vitamin A, diet only (IU/d)			
<6,589	70	201,093	1.00 (reference)
>6,589-8,647	65	201,093	0.85 (0.59-1.22)
>8,647-11,534	69	200,263	0.96 (0.67-1.38)
>11,534	60	198,756	0.77 (0.52-1.14)
P_{trend}			0.51
Vitamin A, diet and supplements (IU/d)			
<6,595	64	201,113	1.00 (reference)
>6,595-8,659	70	201,357	0.83 (0.57-1.20)
>8,659-11,560	66	200,292	0.96 (0.57-1.38)
>11,560	64	198,651	0.79 (0.53-1.16)
P_{trend}			0.37
Vitamin C, diet only (mg/d)			
<115	59	199,535	1.00 (reference)
>115-159	74	200,106	1.27 (0.78-1.64)
>159-206	68	201,052	1.14 (0.63-1.91)
>206	63	200,720	0.90 (0.58-1.37)
P_{trend}			0.54
Vitamin C, diet and supplements (mg/d)			
<122	53	199,310	1.00 (reference)
>122-172	61	199,903	1.22 (0.82-1.81)
>172-247	77	200,331	1.31 (0.89-1.94)
>247	73	201,869	1.11 (0.75-1.66)
P_{trend}			0.59
Vitamin E, diet only (mg/d)			
<17	60	201,349	1.00 (reference)
>17-21	76	201,000	1.31 (0.91-1.89)
>21-25	77	200,191	1.27 (0.88-1.85)
>25	51	198,873	0.87 (0.57-1.31)
P_{trend}			0.31
Vitamin E, diet and supplements (mg/d)			
0-17	57	200,892	1.00 (reference)
>17-22	68	200,436	1.27 (0.87-1.86)
>22-28	64	199,304	1.01 (0.58-1.52)
>28	75	200,780	1.24 (0.85-1.82)
P_{trend}			0.48

NOTE: Results are adjusted hazard ratio and 95% confidence interval and show association based on increasing quartiles of intake. Multivariate adjusted for age (time to event variable), pack-years of smoking (none plus three levels), menopausal status, use of oral contraceptives (ever versus never), body mass index (<25, 25 to 29, >30 kg/m^2), education (≤12 versus >12 years), participation in vigorous physical activity (any, none, missing), energy intake at baseline (continuous), study center, and randomization group (intervention versus control).

(cases and noncases) with prevalent cancers (other than ovarian cancer) at baseline (n = 56) and after the exclusion of subjects who reported having used multivitamin supplements (n = 9,798 subjects, including 65 incident cases; data not shown).

Discussion

In the prospective study reported here, there was no evidence of an association between ovarian cancer risk and dietary intake of carotenoids or vitamins A, C, or E. Given the size of our study population, we had 74% power to detect a hazard ratio of 1.5 at the two-sided 5% significance level. Our results are similar to those of Kushi et al. (ref. 4; 139 incident cases) and Fairfield et al. (ref. 7; 301 incident cases), who likewise found no association between antioxidant intake and ovarian cancer risk.

As with other studies, our data are limited by the possibility of error with respect to the measurement of carotenoid and vitamins A, C, and E consumption, which may have resulted from inaccurate recall (21). We were unable to account for carotenoid intake from vitamin supplements, as this information was not available. Nevertheless, as mentioned above, exclusion of women who reported multivitamin use from the analyses did not alter our findings with respect to carotenoid intake and ovarian cancer risk. In addition, although we adjusted our estimates for a range of potentially confounding variables, uncontrolled confounding by dietary and other factors cannot be excluded.

In conclusion, the results of this study indicate that there is no association between dietary intake of each of the five major carotenoids or vitamins A, E, or C and ovarian cancer risk.

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