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ORIGINAL ARTICLE

Plasma carotenoids, retinol and tocopherol levels and the risk of ovarian cancer

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Abstract

Objective. We investigated the relation between plasma carotenoids, retinol and tocopherol levels and ovarian cancer risk in Korean women. *Design.* Hospital-based case–control study. *Setting.* Six tertiary medical institutes in Korea. *Population.* Forty-five epithelial ovarian cancers and 135 age-matched controls. *Methods.* Preoperative plasma concentrations of β-carotene, lycopene, zeaxanthin plus lutein, retinol, α-tocopherol, and γ-tocopherol were measured by reverse-phase, gradient high-pressure liquid chromatography. *Main outcome measures.* Odds ratios (OR) and 95% confidence intervals (95%CI) were estimated by tertiles to evaluate the effect of micronutrients on endometrial cancer risk after adjustment for body mass index (BMI), menopause, parity, oral contraceptive use, smoking status, and alcohol consumption status. *Results.* Women in the highest tertile for β-carotene had 0.12-times the risk of ovarian cancer of in the lowest tertile (OR 0.12; 95%CI 0.04–0.36). Women with the highest tertiles of lycopene (OR 0.09; 95%CI 0.03–0.32), zeaxanthin/lutein (OR 0.21; 95%CI 0.09–0.52), retinol (OR 0.45; 95%CI 0.21–0.98), α-tocopherol (OR 0.23; 95%CI 0.10–0.53) and γ-tocopherol (OR 0.28; 95%CI 0.11–0.70) had lower risk of ovarian cancer than women in the lowest tertiles. Results were consistent across strata of socio-epidemiologic factors. *Conclusions.* Micronutrients, specifically ß-carotene, lycopene, zeaxanthin, lutein, retinol, α-tocopherol, and γ-tocopherol, may play a role in reducing the risk of ovarian cancer.

Key words: *Carotenoids, vitamin A, tocopherol, ovarian cancer*

Introduction

Ovarian cancer is the sixth most common cancer in women and accounted for 204,000 cases and 125,000 deaths worldwide in 2002 (1). The incidence of ovarian cancer varied from country to country, with the highest rates reported in Western countries and lower rates observed in Asian and African countries (2). Compared with Western countries, Korea has a relatively low incidence of 4.74 per 100,000 women-years (3). Based on these observations, epidemiological studies hypothesized that the etiology of ovarian cancer could be related to dietary factors (4).

There has been considerable interest in micronutrients and their potential anticarcinogenic effects. A number of studies have evaluated the association between intakes of dietary carotenoids and ovarian

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cancer risk (2,5–12), but the results have been inconclusive. A few studies have examined plasma carotenoids, retinol, or tocopherols in the ovarian cancer patients (13–17). To provide further association between plasma carotenoids, retinol and tocopherols and their relation to ovarian cancer risk, we conducted a hospital-based case–control study in Korean women.

Materials and methods

The study population was recruited from six tertiary medical centers between June 2006 and July 2007 in Korea, after obtaining approval from their respective institutional review boards. Eligibility criteria for both cases and controls included not being pregnant at the time of recruitment and had no record of any gynecological surgery and cancer. The cases included 45 Korean women who had histologically confirmed incident epithelial ovarian cancer of any stage (mean age 52.8 years, range 47–61) in the participating institutes and no record of any other cancer.

For each case woman, three age-matched control women were selected from women who had visited for a routine gynecological examination in the same institutes. Control subjects were alive and free of known cancers, gynecological or endocrinological conditions, and any medical condition associated with long-term modification of their diet. A total of 135 age-matched controls (mean age 52.1 years, range 39–62) were enrolled.

At the enrollment, the women were interviewed by a trained interviewer who was blinded to each woman's disease status, using a questionnaire to obtain socio-demographic characteristics and medical information. All women filled out questionnaires, provided a blood samples, and informed consent was obtained after an explanation of the study. The questionnaire-based information collected concerned body size, reproductive and menstrual history, individual medical history, family history of ovarian and other malignancies, exogenous hormone use, and multivitamin supplements used at enrollment. Socio-demographic characteristics included education, monthly economic income, cigarette smoking, and alcohol consumption with a timeframe of exposure.

A peripheral venous blood sample of 20 mL was obtained in an anticoagulant tube from each participant preoperatively. Blood samples were wrapped so as not to expose them to light against photooxidation, and transported to the laboratory without revealing the case–control status prior to assay for antioxidant micronutrients. After separating plasma, samples were stored at –80°C until assayed.

We already described the extraction of analytes from plasma, the quality control parameters, and the reverse-phase, gradient high-pressure liquid chromatography (HPLC) system for plasma micronutrients (18). Plasma samples from cases and controls were randomized and analyzed together in a same batch to minimize the impact of batch-to-batch variability. Laboratory technicians were blinded to case–control and quality control status of the samples. Because the separation of zeaxanthin and lutein isomers was not possible, they are hereafter referred to as zeaxanthin plus lutein.

Statistical analysis

Differences between cases and controls for demographic variables were analyzed by Fisher's exact test or chi-squared test for categorical variables, and by analysis of variance (ANOVA) for continuous variables. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated by conditional logistic regressions. The effects of potential confounding factors – such as education level, (BMI), menopausal status, parity, oral contraceptive use, smoking status, and alcohol consumption status – were examined into the logistic regression models. Two-sided significance tests were used ($\alpha < 0.05$). All analyses were performed using SAS 8 software (SAS Institute, Inc., Cary, NC, USA).

Results

We compared the demographic factors and baseline characteristics of study population in relation to developing ovarian cancer (Table I). Cases and controls were closely matched on age. The mean ages at study entry were 52.8 years for cases and 52.1 years for controls ($p = 0.68$). The mean BMI was 22.8 for cases and 23.2 for controls ($p = 0.37$). Most participants were nonsmokers; 96% of cases and 94% of controls ($p = 1.00$). Seventy-one percentage of cases and 67% of controls did not drink alcohol ($p = 0.58$). There were also no significant differences between case and age-matched control women in monthly household income ($p = 0.43$), ever use multivitamin, menopause ($p = 0.68$), number of childbirth ($p = 0.43$) and age at menarche ($p = 0.89$). Although controls had a trend to use or have used multivitamins compared with cases (39% versus 24%), the difference was not significant ($p = 0.078$). However, case subjects were less educated ($p = 0.046$) and were more likely to use or to have used oral contraceptives ($p = 0.038$) than control subjects. Twenty-seven per-

Table I. Baseline characteristics of the ovarian cancer case–control study.

Variables	Ovarian cancer		
	Cases ($N=45$)	Control ($N=135$)	P-value[a]
Age (Means ± SD, yr)	52.8 ± 12.8	52.1 ± 10.5	0.68
BMI (Means ± SD, kg/m^2)	22.8 ± 3.40	23.2 ± 2.60	0.37
Education level, *n* (%)			
≤ Elementary	18(40)	30(22)	0.046
Middle school	8(18)	28(21)	
High school	14(31)	39(29)	
≥ University	5(11)	37(29)	
Monthly household income, *n* (%)			
<1,000 USD	11(27)	28(23)	0.43
1,000–1,999 USD	9(22)	18(15)	
2,000–2,999 USD	5(13)	14(11)	
3,000–3,999 USD	9(23)	28(23)	
≥4,000 USD	6(15)	36(28)	
Cigarette smoking, *n* (%)			
Nonsmoker	43(96)	127(94)	1.00
Smoker	2(4)	8(6)	
Passive smoking, *n* (%)	37.8		
Means ± SD, min/wk, home	63.7 ± 88.5	55.2 ± 79.1	0.54
Means ± SD, min/wk, office	45.0 ± 30.0	87.0 ± 179	0.62
Alcohol consumption, *n* (%)			
Nondrinker	32(71)	90(67)	0.58
Drinker	13(29)	45(33)	
Means ± SD, yr	15.9 ± 8.32	16.8 ± 8.29	0.77
Alcohol consumption frequency, *n* (%)			
≤1–3 times/mo	9(69)	19(42)	0.12
1–2 times/wk	2(15)	21(47)	
≥3–4 times/wk	2(16)	5(11)	
Ever use oral contraceptive, *n* (%)			
Never	33(73)	117(87)	0.038
Current/former	12(27)	18(13)	
Ever use multivitamins, *n* (%)			
No	32(76)	74(61)	0.078
Yes	10(24)	47(39)	
Age at menarche (Means ± SD, yr)	15.2 ± 1.91	15.2 ± 2.14	0.89
Menopause, *n* (%)	35 (77.8)	88 (65.2)	0.68
No. of childbirth, *n* (%)			
1	5(17)	12(13)	0.43
2	15(52)	62(65)	
≥3	9(31)	21(22)	

[a]*P*-values are from chi-square test or Fisher's exact test for categorical variables and from ANOVA test for continuous variables.

centage of cases reported oral contraceptive use compared with 13% of controls.

Mean plasma concentrations and standard deviation (SD) of all analytes in ovarian cancer cases and controls are presented in Table II. Mean plasma concentrations of all analytes were significantly lower in ovarian cancer cases than controls.

Table III shows the associations of plasma carotenoids, retinol and tocopherols, and the risk of ovarian cancer. In conditional logistic regression analyses, significant inverse associations were observed between β-carotene ($P_{trend}<0.0001$), lycopene ($P_{trend}<0.0001$), zeaxanthin/lutein ($P_{trend}=0.0008$), α-tocopherol ($P_{trend}=0.0003$), and γ-tocopherol ($P_{trend}=0.0031$), and the risk of ovarian cancer. After adjustment for risk factors such as BMI, menopausal status, parity, oral contraceptive use, smoking status, and alcohol consumption status, these inverse trends kept their significance. Women in the highest tertile for β-carotene had 0.12-fold the ovarian cancer risk of women in the lowest tertile (OR 0.12; 95%CI 0.04–0.37) that is, this result means 88% of risk reduction in developing ovarian cancer. Women in the highest tertiles of lycopene, zeaxanthin/lutein, retinol, α-tocopherol, and β-tocopherol, respectively, had 91, 79, 55, 77, and 72% lower risk of ovarian cancer risk than women in the lowest tertiles. We did not find a significant association between

Table II. Comparison of plasma levels of carotenoids, retinol, and tocopherols between cases and controls in ovarian carcinoma.

	Plasma levels of analyte						
	Cases ($n=45$)			Controls ($n=135$)			
Analyte	Mean	Median	5th–95th percentile	Mean	Median	5th–95th percentile	*P*-value[a]
β-Carotene (μg/dl)	13.6	11	5.27–24.3	21.5	21.7	6.58–42.2	<0.0001
Lycopene (μg/dl)	0.48	0.47	0.40–0.57	0.57	0.54	0.43–0.79	<0.0001
Zeaxanthin+Lutein (μg/dl)	40.9	37.9	13.7–63.8	56.0	53.8	23.2–96.7	<0.0001
Retinol (μg/dl)	59.8	61.1	23.8–99.5	68.6	66.9	36.7–120	0.0183
α-Tocopherol (mg/dl)	1.09	1.05	0.74–1.77	1.34	1.28	0.75–2.48	0.0005
γ-Tocopherol (mg/dl)	0.23	0.21	0.12–0.38	0.31	0.29	0.15–0.67	0.0002

[a]*P*-values are ANOVA test for continuous variables.

retinol and the risk of ovarian cancer in conditional logistic regression (crude OR 0.68; 95%CI 0.34–1.36). After adjustment for potential confounding factors, the linear trend for retinol appeared to have a significant inverse association (adjusted OR 0.45; 95%CI 0.21–0.98).

Discussion

This is the first hospital-based case–control study to evaluate plasma concentrations of carotenoids, retinol, and tocopherols with respect to ovarian cancer risk in Asian population. We observed an inverse association between ovarian cancer risk and plasma concentrations of ß-carotene, lycopene, zeaxanthin plus lutein, retinol, α-tocopherol, and γ-tocopherol. Our results add to the evidence suggesting that a low plasma concentration of micronutrients is a risk factor for ovarian cancer (14).

Carotenoids, retinol, and tocopherols are thought to be cancer preventive mainly because of their antioxidant properties, which may reduce oxidative

Table III. The association of plasma carotenoids, retinol, and tocopherols and the risk of ovarian cancer.

	OR for tertiles of plasma analyte levels category cut-points (μg dl^{-1})[a]			
Analyte	1 (Ref.)	2	3	*P* for trend[b]
β-Carotene				
Range	1.73–17.1	17.1–25.2	25.2–60.1	
Crude OR	1.0	0.24 (0.04–0.36)	0.12 (0.04–0.36)	<0.0001
Adjusted OR	1.0	0.24 (0.10–0.56)	0.12 (0.04–0.37)	<0.0001
Lycopene				
Range	0.36–0.51	0.51–0.58	0.58–2.37	
Crude OR	1.0	0.31 (0.15–0.65)	0.10 (0.03–0.32)	<0.0001
Adjusted OR	1.0	0.28 (0.12–0.63)	0.09 (0.03–0.32)	<0.0001
Zeaxanthin+Lutein				
Range	6.97–41.8	41.8–59.8	59.8–135	
Crude OR	1.0	0.40 (0.19–0.85)	0.26 (0.11–0.61)	0.0008
Adjusted OR	1.0	0.33 (0.15–0.73)	0.21 (0.09–0.52)	0.0008
Retinol				
Range	23.8–56.3	56.3–72.1	72.1–134	
Crude OR	1.0	0.36 (0.16–0.84)	0.68 (0.34–1.36)	0.2257
Adjusted OR	1.0	0.28 (0.11–0.68)	0.45 (0.21–0.98)	0.0430
α-Tocopherol				
Range	335–1,070	1,070–1,381	1,381–4,063	
Crude OR	1.0	0.29 (0.13–0.67)	0.37 (0.17–0.79)	0.0043
Adjusted OR	1.0	0.21 (0.09–0.51)	0.23 (0.10–0.53)	0.0003
γ-Tocopherol				
Range	46.3–250	250–337	337–964	
Crude OR	1.0	0.36 (0.17–0.77)	0.25 (0.11–0.60)	0.0006
Adjusted OR	1.0	0.43 (0.19–0.95)	0.28 (0.11–0.70)	0.0031

[a]Each tertile was constructed by the estimation based on control subjects.[b]ORs and 95%CIs calculated by conditional logistic regression, adjusted for education level, BMI, menopause (premenopause versus postmenopause), number of parity, oral contraceptive use, smoking status (ever versus never), and alcohol consumption status (ever versus never).

stress, lipid peroxidation, and DNA damage. Retinol, along with carotenoids, has a role in the control of cellular growth kinetics (19). Despite this potential background, results from previous reports on dietary intake of carotenoids assessed from dietary questionnaires have been mixed and many have shown weak or null associations with ovarian cancer (5,7,8,10–12). Estimation of dietary carotenoid intake tends to have many measurement errors and may not reflect their actual bioavailability, which can be better estimated by measuring plasma carotenoid levels (20).

Few studies have considered pre-diagnostic blood levels of antioxidant micronutrients in association with ovarian cancer risk, and the results from previous studies were inconclusive. Originally, Heinonen et al. demonstrated that vitamin A may involve in the metabolism of patients with advanced ovarian cancer (14). In a case–control study, their 28 ovarian cancer patients had significantly lower serum levels of vitamin A than controls, while carotene and vitamin E levels were similar in both groups. Another case–control study with 35 ovarian cancer cases presented no significant association between the levels of retinol, α-tocopherol or carotenoids and ovarian cancer risk (13). In a study of 16 ovarian cancer cases, Knekt et al. found that being in the lowest quintile of tocopherol levels was associated with a 1.6-fold risk of developing ovarian cancer compared to the highest quintile (16).

In contrast to most previous studies about plasma micronutrients (13–15), our results demonstrated a dose–response trend and quantitative risk reduction in most kinds of vitamin A and E families and we found a significant inverse association and decreased risk between micronutrient levels and ovarian cancer. In our study, β-carotene and lycopene presented approximately 90% lower risk of ovarian cancer, that is, the best risk reduction among the micronutrients measured. Previous epidemiologic studies of micronutrient intakes (2,6,21) found approximately 20–50% of risk reduction of ovarian cancer of β-carotene. In case of lycopene, most epidemiologic and prospective studies did not address reduction of ovarian cancer risk except one (7). We also found that high circulating levels of zeaxanthin plus lutein were associated with a 79% reduction of ovarian cancer risk. In several epidemiologic studies (2,5,6), intakes of zeaxanthin plus lutein contributed approximately 40–55% of ovarian cancer risk reduction. Consistent with our results, a Mexican study reported that retinol intakes contributed to a 50% reduction of risk (17). With regard to α- and β-tocopherol, previous studies showed that dietary intakes (6,21) and supplemental intake of tocopherols (8) has a protective effect with a 40–60% risk reduction.

This study had several potential limitations. We collected and measured the plasma concentrations of micronutrients just before the surgery from one blood sample. It is possible that detection bias has an effect on our results, because this study had not a population-based but hospital-based design. There are some possibilities that micronutrient levels of cancer patients could be affected by the disease itself. The small number of cancer cases and selection bias in the case–control study may have had an effect on the risk association of ovarian cancer. To minimize this problem, we selected proper control women for each cancer patient. Because most of the cases and controls came from the same reference population, the age-matched control and case groups shared similar socio-economic characteristics. To obtain robust and meaningful data about the impact of micronutrient levels on ovarian cancer risk, a carefully designed prospective epidemiologic study is needed. Another minor limitation of this study is that micronutrient levels were assessed from only one blood sample. However, there is evidence to suggest that a single time measurement of micronutrients represents the long-term exposure adequately (22).

Ovarian cancer is a major public health burden. To date, there is little information about correctable risk factors. Micronutrients, specifically carotenoids, exhibit a great deal of inter-individual variation in terms of absorption, metabolism, and excretion (23). Therefore, plasma levels of micronutrients may give a more accurate approximation of the amount available to target tissues than intake estimates. Our results suggest that plasma levels of micronutrients specifically, ß-carotene, lycopene, zeaxanthin, lutein, retinol, α-tocopherol, and γ-tocopherol, may play a role in reducing ovarian cancer risk, at least in the Korean population. Further studies are needed to confirm the inverse associations observed between micronutrients and ovarian cancer risk in a population-based design.

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