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# Preoperative levels of plasma micronutrients are related to endometrial cancer risk

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**Abstract**

*Objective.* To examine the relation between the plasma concentration of antioxidant micronutrients and endometrial cancer risk in Korean women. *Design.* Hospital-based case–control study. *Setting.* Seven tertiary medical institutes in Korea. *Population.* Incidence of 28 endometrial cancer cases were identified and 140 age-matched controls selected for the same period. *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. Conditional logistic regression was used to evaluate micronutrient effect after adjustment for body mass index (BMI), menopause, parity, oral contraceptive use, smoking status, and alcohol consumption status. *Main outcome measures.* Effect of micronutrients on endometrial cancer risk. *Results.* The mean concentration of plasma β-carotene ($p = 0.001$), lycopene ($p = 0.008$), zeaxanthin plus lutein ($p = 0.031$), retinol ($p = 0.048$), and γ-tocopherol ($p = 0.046$) were significantly lower in endometrial cancer patients than in controls. Plasma levels of β-carotene ($p$ for trend $= 0.0007$) and lycopene ($p$ for trend $= 0.007$) were inversely associated with endometrial cancer risk across tertiles. Women in the highest tertile of plasma β-carotene and lycopene had a 0.12-fold (95% confidence intervals (CIs) 0.03–0.48) and 0.15-fold (95% CIs 0.04–0.61) decreased risk of endometrial cancer compared to women in the lowest tertile, respectively. Other micronutrients such as zeaxanthin plus lutein ($p$ for trend $= 0.142$), retinol ($p$ for trend $= 0.108$), α-tocopherol ($p$ for trend $= 0.322$), and γ-tocopherol ($p$ for trend $= 0.087$) showed no association with endometrial cancer risk. *Conclusions.* Plasma levels of β-carotene and lycopene are inversely associated with the risk of endometrial cancer in Korean women.

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

## Introduction

Endometrial cancer is the seventh most common female-specific cancer worldwide, behind breast, lung, and colon cancer (1). The prevalences for endometrial cancer vary worldwide, suggesting that environmental and lifestyle factors are important in the etiology of endometrial cancer (1,2). A migration study in the Korean-American population indicated that there is a higher incidence of cancer of the uterine corpus (mainly endometrial cancer) in the offspring of women who move from Korea to

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America (3). Such evidence has motivated research on the effects of nutritional factors on endometrial cancer.

A diet rich in fruits and vegetables has an inverse association with endometrial cancer (4,5). Consistent with this finding, antioxidant micronutrients have been shown to be associated with a reduced risk of cancer (6,7). However, some studies have shown conflicting results (8,9). Only few studies have examined plasma micronutrients in endometrial cancer patients (10,11). These studies did not address the association with endometrial cancer risk. Here, we examine the levels of preoperative plasma micronutrients and their relation to endometrial cancer risk in Korean women.

## Materials and methods

This hospital-based case–control study was conducted in seven tertiary medical centers between June 2006 and July 2007 in Korea, after obtaining approval from the institutional review board for each center. During the study period, we included 28 women with histologically confirmed endometrial cancer and no previous history of another malignancy. Endometrial cancer cases were diagnosed by endometrial biopsy and immediately after the histologic diagnosis, mostly within 10 days, blood samples were collected and kept at $-80^{\circ}$C.

Control women included age-matched women who had visited for a routine gynecological examination during the same study period, with five women for each case. As far as could be ascertained from medical records and cancer registry records, control women were alive and free of known cancers and gynecological or endocrinological conditions. A total of 140 age-matched controls were enrolled. All patient-derived specimens were collected and archived according to protocol.

Upon study enrollment, the women were interviewed by a single trained interviewer who had no knowledge of the subject's disease status. The women were questioned regarding their socio-demographic characteristics, including education, occupation, monthly income, smoking status, alcohol consumption, and physical activity, with a detailed time frame of exposures. The women were also asked about their family history of cancer, and history of menstruation and reproduction, including age at menarche, menstrual periods, age at first live birth, and menopausal status. As part of the interview, we also questioned patients regarding their use of oral contraceptives and multivitamins. Pathological and laboratory data were collected, recorded, and entered into a database. A peripheral venous blood sample of 20 mL was obtained and stored at $-80^{\circ}$C until the time of assay.

The methods used for the extraction of analytes from plasma and the reverse phase, gradient high-pressure liquid chromatography (HPLC) for micronutrients have previously been published (12). Plasma samples from cases and controls were arranged in random order, identified only by code numbers, and assayed in the same batch for all laboratory measurements to avoid the influence of batch-to-batch variability. Briefly, plasma carotenoids, retinol, tocopherols, retinol acetate, and tocopherol acetate were extracted with hexane, evaporated under $N_2$ and then reconstituted in ethanol. In order to correct to recoveries, retinol acetate and tocopherol acetate were added to each sample as internal standards. A portion of the final extracted sample was run through the HPLC system. The detector was set at 292 nM for tocopherols, at 340 nM for retinol, and at 450 nM for carotenoids. Individual carotenoids, retinol, and tocopherols were quantified by peak areas calibrated against the standards. Because zeaxanthin and lutein isomers cannot be separated, they were eluted together and hereafter are referred to as zeaxanthin plus lutein.

### *Statistical analysis*

Differences between cases and controls for the categorical demographic variables were analyzed by Fisher's exact test and chi-squared test. Mean differences for continuous demographic variables were tested by analysis of variance (ANOVA). Geometric means and 95% confidence intervals (CIs) were calculated for the plasma concentrations of carotenoids, retinol, and tocopherols. Differences between cases and controls for the mean levels of each analyte were tested by ANOVA. Odds ratios (OR) and 95% CIs for the risk of endometrial cancer in relation to plasma analyte concentrations were calculated by conditional logistic regression. The effects of potential confounding factors – such as BMI, menopausal status, parity, oral contraceptive use, smoking status, and alcohol consumption status, which were all controlled in the experimental design, were examined by additional regression terms into the logistic regression models. Two-sided significance tests were used ($\alpha < 0.05$). SAS version 8 was used for all analyses (SAS Institute, Inc., Cary, NC, USA).

## Results

Selected baseline characteristics for the study population are described in Table I. Cases and controls

Table I. Baseline characteristics of the endometrial cancer case/control study.

| Variables | Cases ($n=28$) | Control ($n=140$) | $p$[a] |
|---|---|---|---|
| BMI, *n* (%) | | | |
| $<18.5$ kg/m$^2$ | 1(4) | 3(2) | 0.87 |
| 18.5–23 kg/m$^2$ | 13(46) | 74(53) | |
| 23–25 kg/m$^2$ | 8(29) | 32(23) | |
| $>25$ kg/m$^2$ | 6(21) | 31(22) | |
| Means$\pm$SD, kg/m$^2$ | 23.3$\pm$2.72 | 22.9$\pm$2.74 | 0.57 |
| Education level, *n* (%) | | | |
| $\leq$Elementary | 2(7) | 18(13) | 0.87 |
| Middle school | 6(22) | 30(22) | |
| High school | 12(44) | 58(42) | |
| $\geq$University | 7(27) | 32(23) | |
| Monthly household income, *n* (%) | | | |
| $<$1,000 USD | 5(20) | 19(14) | 0.41 |
| 1,000–1,999 USD | 6(24) | 17(13) | |
| 2,000–2,999 USD | 3(12) | 26(20) | |
| 3,000–3,999 USD | 6(24) | 27(21) | |
| $\geq$4,000 USD | 5(20) | 42(32) | |
| Cigarette smoking, *n* (%) | | | |
| Non-smoker | 26(93) | 134(96) | 0.52 |
| Smoker | 2(7) | 6(4) | |
| Passive smoking, *n* (%) | 11(39.3) | 48(34) | 0.61 |
| Means$\pm$SD, min/week, home | 37.8$\pm$46.0 | 63.2$\pm$92.1 | 0.42 |
| Means$\pm$SD, min/week, office | 13.3$\pm$23.4 | 105.5$\pm$190.8 | 0.25 |
| Alcohol consumption, *n* (%) | | | |
| Non-drinker | 15(54) | 91(65) | 0.25 |
| Drinker | 13(46) | 49(35) | |
| Means$\pm$SD, year | 18.7$\pm$8.18 | 15.4$\pm$8.11 | 0.23 |
| Alcohol consumption frequency, *n* (%) | | | |
| $\leq$1–3 times/months | 7(54) | 23(49) | 0.64 |
| 1–2 times/week | 4(31) | 20(43) | |
| $\geq$3–4 times/week | 2(15) | 4(8) | |
| Ever use oral contraceptive, *n* (%) | | | |
| Never | 25(89) | 121(86) | 0.68 |
| Current/former | 3(11) | 19(14) | |
| Ever use multivitamins, *n* (%) | | | |
| No | 18(72) | 75(61) | 0.32 |
| Yes | 7(28) | 47(39) | |
| Menopause, *n* (%) | 17(60.7) | 70(50.4) | 0.32 |
| Number of childbirth, *n* (%) | | | |
| 1 | 2(11) | 16(15) | 0.68 |
| 2 | 15(83) | 77(74) | |
| $\geq$3 | 1(6) | 11(11) | |
| Age at menarche, means$\pm$SD, year | 14.9$\pm$1.38 | 14.8$\pm$1.86 | 0.78 |
| Age at first delivery, means$\pm$SD, year | 25.2$\pm$3.71 | 25.1$\pm$3.22 | 0.92 |

[a]$p$-Values are from chi-squared test or Fisher's exact test for categorical variables and from ANOVA test for continuous variables.

were closely matched by age. The mean ages upon enrollment were 48.8 years for cases and 48.6 years for controls. Most participants were non-smokers; 93% of cases and 96% of controls ($p=0.52$). Fifty-four percentage of cases and 65% of controls did not drink alcohol ($p=0.25$). Most women did not use oral contraceptives (89% of cases and 86% of controls) or multivitamins (72% of cases and 61% of controls). Between cases and controls, there were no differences in BMI, education, or monthly income. Sixty percentage of cases and 50% of controls were postmenopausal women ($p=0.32$). The age at menarche and number of childbirths were similar between cases and controls.

The mean plasma concentrations and standard deviation (SD) of all analytes in endometrial cancer

Table II. Plasma nutrient levels between endometrial cancer cases and controls.

| | Plasma levels of analyte | | | | | | |
|---|---|---|---|---|---|---|---|
| | Cases ($n=28$) | | | Controls ($n=140$) | | | |
| Analyte | Mean | Median | Fifth–95th percentile | Mean | Median | Fifth–95th percentile | $p$[a] |
| β-Carotene (μg/dl) | 16.3 | 15.1 | 8.08–24.3 | 22.8 | 22.3 | 10.6–38.9 | 0.001 |
| Lycopene (μg/dl) | 0.50 | 0.50 | 0.44–0.57 | 0.58 | 0.55 | 0.43–0.79 | 0.008 |
| Zeaxanthin+Lutein (μg/dl) | 47.1 | 43.8 | 26.1–74.6 | 57.2 | 53.6 | 25.8–91.5 | 0.031 |
| Retinol (μg/dl) | 57.7 | 57.7 | 36.5–74.2 | 66.0 | 64.8 | 36.5–101.5 | 0.048 |
| α-Tocopherol (mg/dl) | 1.30 | 1.21 | 0.89–1.46 | 1.33 | 1.26 | 0.76–2.29 | 0.769 |
| γ-Tocopherol (mg/dl) | 0.26 | 0.25 | 0.15–0.35 | 0.30 | 0.28 | 0.16–0.49 | 0.046 |

[a]$p$-Values are from ANOVA test for continuous variables.

cases and controls are presented in Table II. Overall baseline geometric mean plasma concentrations in the endometrial cancer cases were numerically lower than in controls for all of the micronutrients except for α-tocopherol. The mean concentration of plasma β-carotene ($p=0.001$), lycopene ($p=0.008$), zeaxanthin plus lutein ($p=0.031$), retinol ($p=0.048$), and γ-tocopherol ($p=0.046$) were significantly lower in endometrial cancer patients than in controls. However, the mean concentration of α-tocopherol was not different between cases and controls ($p=0.769$).

Table III shows the associations between plasma nutrients and the risk of endometrial cancer. Multivariate adjustment for risk factors such as BMI, menopausal status, parity, oral contraceptive use, smoking status, and alcohol consumption status did not change the association with endometrial cancer. Based on conditional logistic regression analyses, a significant inverse association was observed between plasma β-carotene and endometrial cancer across tertiles ($p$ for trend $=0.0007$). Women in the highest tertile of plasma β-carotene had a 0.12-fold (95% CI 0.03–0.48) decreased risk of endometrial cancer compared to women in the lowest tertile. Plasma lycopene was inversely associated with the risk of endometrial cancer across tertiles ($p$ for trend $=0.007$) and showed a significant risk reduction (OR 0.15; 95% CI 0.04–0.61 for the highest versus the lowest tertiles). That is, women in the highest tertiles for β-carotene and lycopene had an 88 and 85% reduced risk of endometrial cancer, respectively, compared to the women in the lowest tertiles.

When considering tertiles of other micronutrients in plasma and endometrial cancer risk, zeaxanthin plus lutein (OR 0.50; 95% CI 0.18–1.39), retinol (OR 0.41; 95% CI 0.14–1.24), α-tocopherol (OR 0.58; 95% CI 0.20–1.71), and γ-tocopherol (OR 0.41; 95% CI 0.14–1.18) showed no significant association with endometrial cancer risk at the highest versus the lowest tertiles.

## Discussion

This is the first study to evaluate the preoperative plasma levels of antioxidant micronutrients with respect to endometrial cancer risk. We observed that plasma levels of β-carotene and lycopene were inversely associated with endometrial cancer risk in Korean women. Plasma β-carotene and lycopene reduced the endometrial cancer risk for women in the highest tertile (88 and 85% compared with women with the lowest tertiles, respectively). We found no effect of other micronutrients, including zeaxanthin plus lutein, retinol, α-tocopherol, and γ-tocopherol. Carotenoids including β-carotene and lycopene can function as distinctive antioxidants, which reduce the potential carcinogenic effects of oxygen-free radicals, lipid peroxidation, and DNA damage (13), and also act against endometrial cancer and other hormone-dependent malignancies (14). Carotenoids are postulated to inhibit estrogen signaling and attenuate their deleterious effect in hormone-dependent malignancies (15).

Most previous results addressing associations between micronutrients and endometrial cancer risk, derived data from questionnaires about micronutrient intake. Those previous results showed that β-carotene intake from vegetables and fruits had an inverse association with endometrial cancer risk (6–9,16), except in one study (17). Similarly, we found that the plasma level of β-carotene was inversely related to endometrial cancer risk. With lycopene, inverse associations have been demonstrated between lycopene intake and endometrial cancer risk (6,16,17). According to an Italian study, a null association between lycopene and endometrial cancer risk was reported (16). Our findings involving zeaxanthin plus lutein, retinol, and tocopherol

Table III. Odds ratios of endometrial cancer and 95% confidence intervals according to tertiles of plasma nutrients between endometrial cancer cases and controls.

| | OR for tertiles of plasma analyte levels category cut-points (μg $dl^{-1}$)[a] | | | |
|---|---|---|---|---|
| Analyte | 1 (Ref.) | 2 | 3 | *p* for trend |
| β-Carotene | | | | |
| Range | 1.73–18.0 | 18.0–25.3 | 25.3–60.1 | |
| Control, *n* | 46 | 47 | 47 | |
| Case, *n* | 20 | 5 | 3 | |
| Crude OR | 1.0 | 0.25(0.09–0.71) | 0.15(0.04–0.53) | 0.0008 |
| Adjusted OR | 1.0 | 0.20(0.07–0.62) | 0.12(0.03–0.48) | 0.0007 |
| Lycopene | | | | |
| Range | 0.36–0.51 | 0.51–0.59 | 0.59–1.58 | |
| Control, *n* | 46 | 47 | 47 | |
| Case, *n* | 15 | 8 | 3 | |
| Crude OR | 1.0 | 0.48(0.19–1.22) | 0.18(0.05–0.64) | 0.010 |
| Adjusted OR | 1.0 | 0.45(0.16–1.22) | 0.15(0.04–0.61) | 0.007 |
| Zeaxanthin+Lutein | | | | |
| Range | 19.9–44.0 | 44.0–65.0 | 65.0–135.0 | |
| Control, *n* | 46 | 47 | 47 | |
| Case, *n* | 14 | 7 | 7 | |
| Crude OR | 1.0 | 0.49(0.18–1.32) | 0.49(0.18–1.32) | 0.135 |
| Adjusted OR | 1.0 | 0.38(0.13–1.09) | 0.50(0.18–1.39) | 0.142 |
| Retinol | | | | |
| Range | 23.8–55.4 | 55.4–72.0 | 72.0–128.0 | |
| Control, *n* | 46 | 47 | 47 | |
| Case, *n* | 13 | 8 | 7 | |
| Crude OR | 1.0 | 0.60(0.23–1.59) | 0.53(0.19–1.44) | 0.195 |
| Adjusted OR | 1.0 | 0.52(0.19–1.46) | 0.41(0.14–1.24) | 0.108 |
| α-Tocopherol | | | | |
| Range | 0.33–1.08 | 1.08–1.42 | 1.42–4.06 | |
| Control, *n* | 46 | 47 | 47 | |
| Case, *n* | 10 | 11 | 7 | |
| Crude OR | 1.0 | 1.08(0.42–2.78) | 0.69(0.24–1.95) | 0.496 |
| Adjusted OR | 1.0 | 0.88(0.32–2.43) | 0.58(0.20–1.71) | 0.322 |
| γ-Tocopherol | | | | |
| Range | 0.12–0.25 | 0.25–0.33 | 0.33–0.56 | |
| Control, *n* | 46 | 47 | 47 | |
| Case, *n* | 15 | 5 | 8 | |
| Crude OR | 1.0 | 0.33(0.11–0.97) | 0.52(0.20–1.35) | 0.138 |
| Adjusted OR | 1.0 | 0.26(0.08–0.85) | 0.41(0.14–1.18) | 0.087 |

[a]ORs and 95% CIs are calculated by conditional logistic regression, adjusted for BMI, menopause (premenopause versus postmenopause), number of parity, oral contraceptive use, smoking status (ever versus never), and alcohol consumption status (ever versus never).

yielded negative results, which are inconsistent with previous epidemiologic studies which have shown that endometrial cancer is inversely associated with zeaxanthin plus lutein intake (16), and the intake of retinol and tocopherol (7). These inconsistencies between epidemiologic studies regarding micronutrient intakes can be explained by differences in dietary patterns; specifically, food resources, amount, and associated dietary characteristics between various populations and measurements (18). Free from this potential error, our study has given a better estimation by measuring plasma micronutrients levels.

The small number of cancer cases and selection bias in a hospital-based study must be considered in the interpretation of our results. In this study, controls were from an outpatient clinic while cases were hospitalized. However, the participating institutions were regarded as proper matching because most of the cases and controls resided in the area near the hospital where the study was performed, and the age-matched control group shared similar socio-economic characteristics with the cases. Another limitation was that the assessment of plasma micronutrients was conducted after the diagnosis of endometrial cancer. But we obtained the samples

from cases immediately after histologic diagnosis, so the time interval from diagnosis to blood collection is unlikely to have caused a significant change in dietary habits, while effects from the disease itself would be negligible. These data have demonstrated a significant inverse association of β-carotene and lycopene with endometrial cancer risk that must be investigated in a population-based study.

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