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Intakes of Vitamin A, C, and E, and β-Carotene Are Associated With Risk of Cervical Cancer: A Case-Control Study in Korea

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Cervical cancer is one of the most common gynecological malignancies in Korea, although the incidence has been declining in recent years. This study explored whether antioxidant vitamin intakes influenced the risk of cervical cancer. The association between antioxidant vitamin intakes and cervical cancer risk was calculated for 144 cervical cancer cases and 288 age-matched, hospital-based controls using unconditional logistic regression models. Cases reported statistically lower mean dietary intakes of vitamin A, β-carotene, and vitamin C than did controls. Total intakes of vitamins A and E, which included both dietary and supplement intake, were also lower in cases. Those patients in the highest quartiles of dietary vitamin A, β-carotene, and vitamin C intakes had statistically significantly lower cervical cancer risks than those in the lowest quartiles for vitamin A, β-carotene, and vitamin C: odds ratio (OR) = 0.36 [95% confidence interval (CI) = 0.19–0.69), OR = 0.48 (CI = 0.26–0.88), and OR = 0.36 (CI = 0.18–0.69), respectively. Total intakes of vitamins A, C, and E were strongly inversely associated with cervical cancer risk: OR = 0.35 (CI = 0.19–0.65), OR = 0.35 (CI = 0.19–0.66), and OR = 0.53 (CI = 0.28–0.99), respectively. The findings support a role for increased antioxidant vitamin intake in decreasing the risk of cervical cancer. These associations need to be assessed in large prospective studies with long-term follow-up.

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INTRODUCTION

Cervical cancer is the rapid, uncontrolled growth of severely abnormal cells in the cervix and is a particular problem among women in lower socioeconomic strata (1,2). This preventable disease kills an estimated 288,000 women every year worldwide

(3). In Korea, cervical cancer remains one of the most common gynecologic malignancies despite the fact that widespread cytological screening has reduced its incidence (4). The incidence of cervical cancer (age-standardized rate) in Korea was estimated to be 15.1 out of 100,000 women in 1999–2002, accounting for 9.8% of new cancers in women (5,6). Cervical cancer is the fifth most common cancer in Korean women after breast, stomach, colon-rectum, and thyroid cancers.

Past research has shown that infection with human papillomavirus (HPV) is the cause of most cases of cervical cancer (7). Strong and consistent associations between HPV infection and cervical cancer have been established from epidemiologic studies conducted in the West and worldwide (7–9). Among a cohort attending a sexually transmitted disease clinic in Seattle, approximately 28% of women who were infected with HPV developed cervical cancer (10). Although HPV infection is highly associated with cervical lesions, it may not be sufficient to cause cervical cancer; furthermore, cofactors such as antioxidant micronutrients might modulate the progression of HPV infection to cervical cancer (11). Although, in the final summary of the second report in World Cancer Research Fund (12), there was no strong evidence that any aspect of food and nutrition modifies the risk of cervical cancer, case-control and cohort studies have detected inverse associations between the intake of antioxidants, such as carotenoids and vitamin C, and the risk for cervical cancer (13–15). Several studies have based their analyses on dietary levels of antioxidant micronutrients, disregarding the intake of nutritional supplements (2,11,16). Clinical studies on this topic in Korea are limited. One study reported a relationship between increased oxidative stress and changes in the antioxidant system in Korean women (17). Another study investigated antioxidant vitamin intake and lipid peroxidation in Korean patients with cervical intraepithelial neoplasia (16) as apposed to cervical cancer.

In this study, we explored the association between the intake of antioxidant nutrients, such as β-carotene; retinol; vitamins A, C, and E; and cervical cancer risk among Korean women. In addition, antioxidant micronutrient intake from dietary (only food) and total (food and supplements) sources was assessed.

METHODS

Study Population

This study was carried out at 6 medical centers in the Republic of Korea (Department of Obstetrics and Gynecology of Korea University, Yonsei University, Chungnam National University, Gachon University, Inha University, and Ajou University) between June 2006 and July 2007. Eligibility criteria for both cases and controls included women not being pregnant at the time of recruitment as well as no past history of any cancer and cervix surgery. The age range was 20 to 75 yr. Cases consisted of 144 cervical cancer patients who were histopathologically confirmed by hospital staff pathologists to have cervical cancer; they were recruited from the participating hospitals. Controls comprised 288 age-matched ($\pm$2 yr) women without cervical cancer who had no history of abnormal Pap smears and a normal Pap smear on the day of recruitment and were enrolled from each participated hospital during the study period. All subjects filled out a questionnaire regarding their lifestyle and dietary intake. Informed consent was obtained from all subjects after a full explanation of the study that was approved by the institutional review boards of the National Cancer Center (NCCNCS-06-056) and each study center.

Data Collection

Subjects were interviewed by well trained interviewers who were blinded to each subject's disease status using both a nondietary questionnaire and a 95-item semiquantitative food frequency questionnaire (FFQ) that was developed for Korean diet and validated previously (18). In the validation study of the FFQ, the energy-adjusted and corrected Spearman rank order correlations for attenuation varied from 0.36 to 0.82. Especially correlation coefficients were 0.77, 0.54, 0.69, 0.68, and 0.72 for vitamin A, vitamin C, retinol, carotene, and vitamin E, respectively. The degree of good agreement by cross-classification between the dietary records and the FFQ ranged from 67% to 90%. In general, more than 80% of the respondents fell into good agreement for antioxidant vitamins.

A wide range of information was collected on sociodemographic characteristics, body size, reproductive and menstrual history exogenous hormone use, medical history, and family history of cervix and other cancers at the study enrollment and before the onset of disease for the control and case subjects, respectively. Sociodemographic characteristics included education, occupation, cigarette smoking, alcohol consumption, and habitual exercise, with a detailed time frame of exposures. Usual dietary factors detailing their food intakes over the year prior to enrolment to the study were collected using a 95-item, semiquantitative FFQ with their usual frequency of consumption and typical portion sizes of 95 food items. The intake of frequency in the FFQ was classified into 9 categories: almost never, once/mo, 2 to 3 times/mo, 1 to 2 times/wk, 3 to 4 times/wk, 5 to 6 times/wk, once/day, twice/day, and 3 times/day. Portion size in the FFQ was divided into 3 categories: small (half the medium portion), medium, and large (1.5 times or greater than the medium portion). The FFQ also contained questions concerning multivitamin use. Nutrient intake of each food item was calculated using the Diet Analysis program (version 4.0) for nutrients. To determine the presence of high-risk HPV, cervical smears were tested with Hybrid Capture II assay (Digene Corporation, Gaithersburg, MD) that can detect 13 high-risk HPV subtypes (numbers 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

Statistical Analyses

Data analyses were performed using SAS 9.1 (SAS Institute, Inc., Cary, NC). Descriptive statistics (means, SDs, and

percentages) stratified by case-control status were used to describe the demographic/health-related characteristics and dietary intakes of the study participants. Logistic regression analyses were used to determine whether there were statistically significant differences between cases and controls for the participant characteristics and dietary variables (19).

We calculated odds ratios (ORs) and 95% confidence intervals (95% CI) from unconditional logistic regression models to ascertain associations between antioxidant micronutrient intake (in quartiles) and cervical cancer risk. Cutoff points for quartiles of micronutrient intake were determined based on the distribution among all controls. For each analysis, dietary and total intake (taken from both food and habitual supplement intake) were applied. Antioxidant micronutrient intakes were adjusted for total energy intake using the linear residual regression method. Multivariate analyses were applied to the regression model. Potential confounders were evaluated, and these confounders were left in the multivariate analysis. Potential confounders included age, family history of cervical cancer, body mass index (BMI), smoking status, alcohol consumption status, and total energy intake. The significance level was set at 5% for all statistical tests.

RESULTS

Table 1 presents the general characteristics of the study participants. The majority of the participants were married, 40 yr of age or older, and nonsmokers. Controls were more educated, more likely to be married, with higher household incomes, and more likely to do strenuous exercise than were cases. There were no statistically significant differences between cases and controls in age, BMI, family history, and smoking and drinking habits. Also there was no a significant difference in HPV infection status between cases and controls. Table 2 shows the reproductive information of the study subjects. A larger number of cases were menopausal and had breast fed their children. There were no statistically significant differences between cases and controls in age at menarche, hormone use, parity, miscarriage, contraceptive use, age at first full-term pregnancy, and number of full-term pregnancies.

A comparison of nutrient intakes is shown in Table 3. Cases reported statistically lower mean intakes than controls in dietary vitamin A, β-carotene, and vitamin C. Total intakes of vitamins A and E from diet and supplements were also lower in cases than in controls. Specifically, although the mean dietary intakes in retinol and vitamin E and the mean total intakes in vitamin C among controls tended to be somewhat higher than for cases, these differences were not significant.

Table 4 gives crude ORs of cervical cancer based on the intake of each nutrient. We detected a significant protective association for the intake of antioxidant nutrients. These associations in the highest quartiles of dietary vitamin A; β-carotene; vitamin C; and total vitamin A, C, and E intakes were statistically significant. The subjects in the highest quartiles of dietary vitamin A, β-carotene, and vitamin C intakes had statistically significantly lower cervical cancer risk than those in the lowest quartiles, regardless of whether the statistical method used was crude or multivariate regression analyses: OR (95% CI) and P for trends for vitamin A, β-carotene, and vitamin C were OR = 0.36 (CI = 0.19–0.69), $P < 0.001$; OR = 0.48 (CI = 0.26–0.88), $P = 0.006$; and OR = 0.36 (CI = 0.18–0.69), $P = 0.001$, respectively. Vitamins A, C, and E had strong inverse associations for total intakes (both dietary and supplementary intakes) using statistical approaches: OR (95% CI), P for trends for vitamin A, vitamin C, and vitamin E were OR = 0.35 (CI = 0.19–0.65), $P < 0.001$; OR = 0.35 (CI = 0.19–0.66), $P < 0.001$; and OR = 0.53 (CI = 0.28–0.99), $P = 0.03$, respectively. However, dietary intakes of vitamin E and retinol were not significantly associated with cervical cancer risk.

DISCUSSION

Cervical cancer is a major health problem for Korean women (6). According to a recent report (5), the incidence in women 50 to 69 yr of age has been decreasing, whereas the incidence has increased in women over 60 yr of age. Although the overall corrected age-standardized cervical cancer mortality rates have decreased, the rate has increased substantially in women over 70 yr of age (6).

Cervical cancer is a complex and multifactorial disease. Because HPV is the greatest risk factor for cervical cancer, many studies have examined the association between micronutrients and HPV persistence (11,20,21). Epidemiological research has examined whether dietary and hematological antioxidants, such as carotenoids (22–25), α-tocopherol (26–28), and vitamin C (29–32), might reduce the risk of cervical dysplasia and cancer (1). In one study of the relationships between cervical dysplasia and plasma antioxidants, the strongest association between hematological antioxidants and cervical cancer risk was seen for cryptoxanthin, and a modest reduction in risk was related to vitamin C levels (20), consistent with previous reports, although showing a nonsignificant relationship between cervical cancer risk and plasma β-carotene and vitamin C (32). Moreover, evidence for an inverse association between dietary vitamin C and risk of cervical intraepithelial neoplasia is consistent with the findings of previous studies (16,29,33), although one study found no association between vitamin C intake and invasive cervical cancer (34). In a Japanese case-control study, high retinol and carotene intakes were not significantly associated with an increased risk of cervical dysplasia (35), which concurs with the results of Romney et al. (36). One possible explanation is that the lower serum carotenoids found in cases could not be accounted for by lower intake of foods rich in carotenoids. Another possibility is that the lower level of serum carotenoids was a result rather than a cause of the disease.

Studies on carrots and cervical cancer were investigated in 5 case-control studies (37–41) and one ecological study (42). All case-control studies were hospital-based and were not adjusted

TABLE 1
General characteristics of the study subjects[a]

Characteristic	Cases		Controls		*P* Value
	n	%	*n*	%	
Total	144		288		
Age (yr)					
∼ 29	3	2.1	6	2.1	1.00
30–39	21	14.6	42	14.6	
40–49	59	41.0	118	41.0	
50–59	42	29.2	84	29.2	
60∼	19	13.1	38	13.1	
BMI (kg/m^2)[b]					
BMI < 18.5	7	4.9	10	3.5	0.50
18.5 ≤ BMI < 23	62	43.1	145	50.4	
23 ≤ BMI < 25	36	25.0	67	23.2	
BMI ≥ 25	39	27.0	66	22.9	
Marital status					
Single	8	5.6	8	2.8	0.01
Married	97	67.4	242	84.3	
Divorced	15	10.4	13	4.5	
Living apart	3	2.1	2	0.7	
Widowed	21	14.5	22	7.7	
Education					
Elementary school	42	29.2	55	19.2	<0.001
Middle school	26	18.1	41	14.3	
High school	61	42.4	114	39.7	
≥ College	15	10.3	77	26.8	
Household income (1,000,000 won/mo)					
<1	31	21.6	41	14.2	<0.001
1–2	34	23.6	48	16.7	
2–3	29	20.1	45	15.6	
3–4	19	13.2	50	17.4	
≥ 4	17	11.8	90	31.2	
Unknown	14	9.7	14	4.9	
Family history					
No	51	35.4	103	35.8	0.94
Yes	93	64.6	185	64.2	
HPV infection					
No	25	59.5	100	62.1	0.75
Yes	17	40.5	61	37.9	
Smoking					
Nonsmoker	128	88.9	265	92.0	0.31
Current smoker	11	7.6	12	4.2	
Ex-smoker	5	3.5	11	3.8	
Drinking habit					
Nondrinker	79	54.9	153	53.1	0.08
Current drinker	52	36.1	123	42.7	
Ex-drinker	13	9.0	12	4.2	
Strenuous exercise					
No	127	88.2	221	77.3	0.01
Yes	17	11.8	65	22.7	

[a] Abbreviations are as follows: BMI, body mass index; HPV, human papillomavirus.

TABLE 2
Reproductive information of the study subjects

	Cases		Controls		
	n	%	*n*	%	*P* Value
Total	144		288		
Age at menarche (yr)					
≤ 14	57	39.6	147	51.0	0.08
15–16	54	37.5	87	30.2	
≥ 17	33	22.9	54	18.8	
Menopause					
No	51	35.4	148	51.6	0.001
Yes	93	64.6	139	48.4	
Hormone use					
No	71	78.0	97	71.3	0.25
Yes	20	22.0	39	28.7	
History of delivery					
No	11	7.6	28	9.7	0.47
Yes	133	92.4	260	90.3	
Breast feeding					
No	24	16.7	80	28.1	0.009
Yes	120	83.3	205	71.9	
Miscarriage					
No	31	21.5	68	23.6	0.62
Yes	113	78.5	220	76.4	
Contraceptive use					
No	122	84.8	242	84.0	0.11
Current	2	1.4	0	0.0	
Past	20	13.8	46	16.0	
Age at first full-term pregnancy [yr; mean (SD)]	24.2 (3.47)		24.7 (4.36)		0.27
Number of full-term pregnancies [mean (SD)]	2.38 (0.93)		2.37 (0.93)		0.90

TABLE 3
Selected nutrient intakes of study subjects[a]

Nutrients	Cases	Controls	*P* Value
Energy (kcal/day)	1,805 ± 588	1,821 ± 589	0.79
Fat (g/day)	32.7 ± 14.7	34.9 ± 15.3	0.15
Protein (g/day)	63.7 ± 22.1	66.4 ± 24.0	0.26
Carbohydrate (g/day)	306 ± 107	304 ± 101	0.83
Dietary vitamin A (RE/day)	739 ± 277	836 ± 335	0.002
Dietary retinol (μg/day)	80.2 ± 43.9	87.7 ± 49.9	0.12
Dietary β-carotene (μg/day)	4,001 ± 1,574	4,518 ± 1,861	0.004
Dietary vitamin C (mg/day)	106 ± 36.9	122 ± 50.6	< 0.001
Dietary vitamin E (mg/day)	6.10 ± 2.48	6.55 ± 2.62	0.09
Total vitamin A[b] (RE/day)	825 ± 415	958 ± 461	0.003
Total vitamin C[b] (mg/day)	119 ± 60.5	141 ± 70.2	0.07
Total vitamin E[b] (mg/day)	7.42 ± 5.36	8.42 ± 5.58	0.001

[a] Abbreviation is as follows: RE, retinol equivalents.
[b] Total vitamins intake from dietary and supplement source.

TABLE 4
Odds ratios (OR) and 95% confidence interval (CI) of cervical cancer by quartile of antioxidant vitamin intake[a]

Nutrient[b]	Quartiles of Nutrient Intakes[c]	No. of Controls	No. of Cases	Crude OR	Multivariate OR[d]
Energy (kcal/day)					
	Q1 (≤1,412)	72	28	1 (ref.)	1 (ref.)
	Q2 (1,412–1744)	72	45	1.61 (0.91–2.85)	1.49 (0.83–2.69)
	Q3 (1,744–2107)	72	39	1.39 (0.78–2.50)	1.36 (0.74–2.52)
	Q4 (>2,107)	72	32	1.14 (0.63–2.09)	1.13 (0.60–2.13)
	P for trend[4]			0.90	0.91
Fat (g/day)					
	Q1 (≤23.9)	72	43	1 (ref.)	1 (ref.)
	Q2 (23.9–31.9)	72	38	0.88 (0.51–1.52)	0.89 (0.51–1.55)
	Q3 (31.9–42.0)	72	37	0.86 (0.50–1.49)	0.88 (0.50–1.56)
	Q4 (>42.0)	72	26	0.61 (0.34–1.09)	0.67 (0.36–1.23)
	P for trend			0.10	0.21
Fat (% kcal)					
	Q1 (≤13.4)	72	40	1 (ref.)	1 (ref.)
	Q2 (13.4–16.8)	72	41	1.03 (0.60–1.77)	1.00 (0.57–1.74)
	Q3 (16.8–20.5)	72	37	0.93 (0.53–1.61)	0.94 (0.53–1.68)
	Q4 (>20.5)	72	26	0.65 (0.36–1.18)	0.70 (0.38–1.31)
	P for trend			0.15	0.28
Protein (g/day)					
	Q1 (≤50.0)	72	48	1 (ref.)	1 (ref.)
	Q2 (50.0–61.0)	72	31	0.65 (0.37–1.13)	0.68 (0.39–1.20)
	Q3 (61.0–77.9)	72	39	0.81 (0.47–1.39)	0.85 (0.49–1.47)
	Q4 (>77.9)	72	26	0.54 (0.30–0.97)	0.61 (0.34–1.11)
	P for trend			0.067	0.161
Carbohydrate (g/day)					
	Q1 (≤239)	72	28	1 (ref.)	1 (ref.)
	Q2 (239–300)	72	39	1.39 (0.78–2.50)	1.33 (0.72–2.45)
	Q3 (300–344)	72	35	1.25 (0.69–2.27)	1.13 (0.61–2.12)
	Q4 (>344)	72	42	1.50 (0.84–2.68)	1.37 (0.74–2.55)
	P for trend			0.21	0.41
Dietary vitamin A (RE/day)					
	Q1 (≤609)	72	51	1 (ref.)	1 (ref.)
	Q2 (609–798)	72	47	0.92 (0.55–1.54)	0.86 (0.51–1.46)
	Q3 (798–999)	72	28	0.55 (0.31–0.97)	0.52 (0.29–0.92)
	Q4 (>999)	72	18	0.35 (0.19–0.66)	0.36 (0.19–0.69)
	P for trend			<0.001	<0.001
Dietary retinol (μg/day)					
	Q1 (≤51.6)	72	43	1 (ref.)	1 (ref.)
	Q2 (51.6–77.0)	72	29	0.67 (0.38–1.20)	0.67 (0.37–1.20)
	Q3 (77.0–118)	72	39	0.91 (0.53–1.56)	0.95 (0.54–1.68)
	Q4 (118>)	72	33	0.77 (0.44–1.34)	0.81 (0.45–1.46)
	P for trend			0.54	0.71
Dietary β-carotene (μg/day)					
	Q1 (≤3277)	72	49	1 (ref.)	1 (ref.)
	Q2 (3,277–4,213)	72	46	0.94 (0.56–1.58)	0.89 (0.52–1.52)
	Q3 (4,213–5,476)	72	26	0.53 (0.30–0.95)	0.51 (0.28–0.93)
	Q4 (>5,476)	72	23	0.47 (0.26–0.85)	0.48 (0.26–0.88)
	P for trend[e]			0.004	0.006

(*Continued on next page*)

TABLE 4
Odds ratios (OR) and 95% confidence interval (CI) of cervical cancer by quartile of antioxidant vitamin intake[a] *(Continued)*

Nutrient[b]	Quartiles of Nutrient Intakes[c]	No. of Controls	No. of Cases	Crude OR	Multivariate OR[d]
Dietary vitamin C (mg/day)					
	Q1 (≤87.0)	72	47	1 (ref.)	1 (ref.)
	Q2 (87.0–113)	72	48	1.02 (0.61–1.72)	0.97 (0.58–1.64)
	Q3 (113–146)	72	33	0.70 (0.40–1.22)	0.70 (0.40–1.23)
	Q4 (>146)	72	16	0.34 (0.18–0.66)	0.36 (0.18–0.69)
	P for trend			<0.001	0.001
Dietary vitamin E (mg/day)					
	Q1 (≤4.67)	72	45	1 (ref.)	1 (ref.)
	Q2 (4.67–6.01)	72	38	0.84 (0.49–1.45)	0.81 (0.47–1.41)
	Q3 (6.01–8.24)	72	36	0.80 (0.46–1.38)	0.81 (0.46–1.42)
	Q4 (>8.24)	72	25	0.56 (0.31–1.00)	0.58 (0.32–1.07)
	P for trend			0.05	0.09
Total vitamin A[f] (RE/day)					
	Q1 (≤631)	72	55	1 (ref.)	1 (ref.)
	Q2 (631–869)	72	43	0.78 (0.47–1.31)	0.76 (0.45–1.29)
	Q3 (869–1183)	72	26	0.47 (0.27–0.84)	0.51 (0.28–0.92)
	Q4 (>1183)	72	20	0.36 (0.20–0.67)	0.35 (0.19–0.65)
	P for trend			<0.001	<0.001
Total vitamin C[f] (mg/day)					
	Q1 (≤94)	72	53	1 (ref.)	1 (ref.)
	Q2 (94–123)	72	44	0.83 (0.50–1.39)	0.80 (0.47–1.35)
	Q3 (123–174)	72	28	0.53 (0.30–0.93)	0.59 (0.33–1.05)
	Q4 (>174)	72	19	0.36 (0.19–0.67)	0.35 (0.19–0.66)
	P for trend			<0.001	<0.001
Total vitamin E[f] (mg/day)					
	Q1 (≤4.78)	72	43	1 (ref.)	1 (ref.)
	Q2 (4.78–6.57)	72	40	0.93 (0.54–1.60)	0.92 (0.53–1.60)
	Q3 (6.57–9.67)	73	38	0.87 (0.51–1.50)	0.98 (0.56–1.72)
	Q4 (>9.67)	71	23	0.54 (0.30–0.99)	0.53 (0.28–0.99)
	P for trend			0.03	0.03

[a] Abbreviations are as follows: Q, quartile; ref, reference; RE, retinol equivalents.
[b] Nutrients are energy adjusted by residual method.
[c] The quartiles of nutrient intakes are based on the distribution of values among controls.
[d] Adjusted for age, smoking status, alcohol consumption status, exercise, family history, body mass index, and human papillomavirus infection status.
[e] Tests for linear trend are based on continuous variables.
[f] Total vitamins intake from dietary and supplement source.

for HPV status. Among all the case-control studies (37–41), three (37–39) were consistently and statistically significant showing reduced risk. In the only ecological study (42), however, nonsignificant increased risk was found in the group of high intake in carrots. According to the second report of the World Cancer Research Fund (12), in general, food and nutrition are not significant factors in modification of the risk of cervical cancer, although some nutritional status may affect a woman's vulnerability to infection. In the judgment of the Panel in the report (12), there is limited evidence suggesting that carrots may protect against cervical cancer. In spite of the fact that the evidence on association between carrots and cervical cancer, mostly from hospital-based case-control studies, is consistent, the data on antioxidant vitamins were either too sparse or the number of studies too few to allow conclusions to be reached.

In terms of a biologically plausible mechanism, antioxidants such as vitamins A, C, E, and carotenoids induce cell differentiation and growth inhibition to varying degrees in animal and human cancer cells (43). It has been reported that the effects of these vitamins depend on the type, form, and concentration

of the vitamins; the type of tumor; and the specific clone of that tumor. These vitamins might selectively inhibit the growth of tumor cells while being less toxic to normal cells. Experimental studies have shown that vitamin A and its derivatives (carotenoids and retinoids) play important roles in regulating the growth, differentiation, and apoptosis of normal and malignant cells (44). The role of vitamin C as an antioxidant is indicated by its known free radical scavenging activity (45). Vitamin C also has an important function in sparing vitamin E, which is a lipid soluble antioxidant. The level of vitamin C might influence the activity of vitamin E as an antioxidant and influence where it gets utilized. The synergism between vitamins C and E results in the utilization of vitamin C and the sparing of vitamin E, observed as a significant decline in plasma ascorbic acid levels (46,47).

Furthermore, antioxidants can prevent damage due to oxidative stress caused by free radicals (48,49), which are known to produce a decrease in immune function (50) and an increase in viral replication (51). Antioxidants have been shown to modify the expression of genes associated with the transcriptional AP-1 complex through their ability to quench free radicals and alter the redox status of cells (11). It has been proposed that among antioxidants, vitamins A and E regulate cell differentiation and proliferation, whereas vitamins C and E, carotenoids, and other dietary constituents act as efficient scavengers of free radicals and oxidants (52,53). It was also hypothesized that vitamins C and E could protect against HPV persistence and inhibit cervical carcinogenesis by enhancing immunological function and by modulating the inflammatory response to infection. Vitamins C, E, and other dietary constituents might also inhibit DNA adduct formation (54,55).

In this case-control study of Korean women, we observed a strong association between cervical cancer and the dietary and total intakes of antioxidant micronutrients such as vitamins A, C, and E and β-carotene. However, we observed no significant association between retinol and cervical cancer in contrast with previous reports (15,56).

The present study is the first to explore the association between antioxidant vitamin intakes and the risk of cervical cancer in a Korean population, taking total nutrient intakes (food and supplements) into consideration. The data were gathered through a detailed face-to-face interview, enabling the collection of comprehensive information on related lifestyle factors and thus lessening the potential for misclassification and measurement errors. In spite of such strengths, this study also possesses some of the limitations usually inherent to case-control study designs (i.e., selection and recall biases). There is also the possibility for differential recall characteristics between cases and controls. Due to their symptomatic and diagnostic status, cases may differ from controls in their recall of dietary habits. Therefore, we advise that such information be collected as soon as possible after diagnosis. Another limitation is that we were not able to obtain completely the information on HPV infection status for the study subjects.

In conclusion, the results from this study support a role for increased antioxidant intake in a decreased risk of cervical cancer. In terms of preventing cervical cancer, this study suggests that an increased intake of fresh fruits and vegetables, foods that contain antioxidants, might decrease the risk for developing cervical cancer. These associations need to be assessed in large prospective studies with long-term follow-up.

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