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Dietary Consumption of Antioxidant Nutrients and Risk of Incident Cervical Intraepithelial Neoplasia

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Abstract

Objective—Women with human papillomavirus (HPV) infections are at risk for developing squamous intraepithelial lesions (SIL) of the cervix; however, other factors are required for infections to progress to SIL. We hypothesize that consumption of fruits and vegetables high in antioxidant nutrients may prevent, in part, the development of HPV-associated SIL.

Methods—This study is a nested case-control study of 265 HPV-positive women (93 SIL cases and 172 cytologically normal controls) in the Ludwig-McGill Cohort Study, Sao Paulo, Brazil. Diet was assessed by a self-administered food frequency questionnaire. The association between food and nutrient intake of antioxidants and incident SIL was determined by logistic regression and multinomial regression when comparing LSIL and HSILs.

Results—Higher reported consumption of papaya was inversely associated with risk of SIL (p trend=0.01) and strongest for ≥1 time/week (adjusted odds ratios (AORs)=0.19; 95%CI, 0.08-0.49). Risk of SIL was reduced among women reporting consumption of oranges ≥1 time/week (AOR=0.32; 95%CI, 0.12-0.87; p-trend = 0.02). Nutrient intakes of ß-cryptoxanthin and α-carotene were marginally protective against SIL.

Conclusions—Frequent consumption of fruits high in antioxidant nutrients appears to be associated with reduced risk of incident SIL among Brazilian women.

Keywords

cervical cancer; cervical intraepithelial neoplasia; human papillomavirus; diet; antioxidant nutrient

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INTRODUCTION

Cervical cancer is the second most common cancer among women worldwide[1]. The main etiological agent in the initiation of cervical neoplasia is human papillomavirus (HPV)[2, 3]. Prospective studies have shown that women infected with HPV are more likely to develop squamous intraepithelial lesions (SIL) of the cervix [4]. Although oncogenic HPV infection has been recognized as a necessary cause of cervical cancer, only a small proportion of HPV-infected women develop disease[5].

Nutritional status and food consumption may be important HPV-cofactors that increase risk of persistence and progression to SIL; however, there is insufficient evidence to support the association between nutritional status and cervical carcinogenesis[6]. A recent review provided evidence for an inverse association between nutritional status and HPV persistence, SIL, and cervical cancer. Specifically, antioxidant nutrients such as carotenoids, tocopherols, and retinol, were suggested to have a protective effect against HPV persistence and cervical dysplasia[6]. In a recent case-control study among Sao Paulo women, dietary intakes of dark green and deep yellow vegetables/fruit, and carrots were combined; categorized into tertiles, and examined in association with CIN I, CIN II, CIN III and cancer. Intake in the highest tertile was inversely associated with CIN III risk among HPV positive women (adjusted OR (95%CI): 0.56 (0.34-0.92). This study, however, did not assess individual fruits and vegetable consumption or individual nutrient intake and lesion development [7]. To date, the association between SIL and nutritional status has been examined in retrospective or case-control studies [7-9], which are particularly susceptible to selection and recall bias. In addition, most studies did not adequately control for HPV status or consider important confounding factors (e.g. smoking, oral contraceptive use or co-infections)[6].

We previously demonstrated that dietary intake of lutein/zeaxanthin, β-cryptoxanthin, vitamin-C, and consumption of papaya were inversely associated with type-specific HPV persistence [10], an intermediate step in SIL development. The goal of the present study was to evaluate the association between dietary intake and SIL incidence over a 5-year follow-up period.

MATERIALS AND METHODS

Cohort Study Design

Participants in the Ludwig-McGill Cohort Study were identified at random from the daily lists of outpatients attending a comprehensive maternal and child health maintenance program (1993-1997) that served low-income families in São Paulo, Brazil[11]. Enrolled participants were followed every 4-months during the first year and twice yearly thereafter. During each visit, participants underwent a gynecological exam, provided blood and were interviewed using a visit specific structured questionnaire[11]. Each study participant signed an approved informed consent document. The institutional review boards and ethical committees at all institutions approved study documents and procedures.

Cervical Cytology and HPV Genotyping

During each visit, a sample of ecto- and endocervical cells were collected for Pap cytology and HPV testing as previously described[11]. A conventional Pap smear was prepared and then cells were resuspended in Tris-EDTA buffer (pH7.4). Cytological diagnosis was determined according to the Bethesda system (negative for abnormality, atypical squamous or glandular cells of undetermined significance (ASCUS/AGUS), Low grade SIL (LSIL), High grade SIL (HSIL), cancer, or inconclusive[12]). HPV detection using MY09/11,[13] polymerase chain reaction (PCR) amplification, dot blot hybridization, and restriction fragment–length polymorphism (RFLP) analysis of the L1 fragment has been previously described.[11] HPV types detected were 6/11, 16, 18, 26, 31-35, 39, 40, 42, 44, 45, 51–59, 61, 62, 66-73, 82-84, and 89).

Antioxidant Nutrient Study Sample

This study is nested within the Ludwig-McGill Cohort study of 2, 282 women. Eight hundred eighteen women were identified from this cohort for the antioxidant nutrient study that demonstrated an inverse association between dietary intake of lutein/zeaxanthin, β-cryptoxanthin, vitamin-C, and consumption of papaya and type-specific HPV persistence [10], an intermediate step in SIL development. Women were considered HPV positive if they tested positive at enrollment (n=117) or least once prior to SIL diagnosis (N=137). Using a nested case-control approach, SIL cases and normal controls were frequency matched on age (±5-years) and date of enrollment (±180 days) to ensure comparable follow-up between cases and controls. Overall, 265 women (93 cases and 172 controls) were selected for the case-control analysis, with a ratio of 1:2, when possible.

Diet Questionnaire

Information on the frequency of consumption of selected food items and the consumption of vitamin and mineral supplements was obtained at the second visit (month 4). Using a self-administered questionnaire, participants were asked to recall the usual frequency of consumption of 15 food items during the past 5 years focusing on foods high in antioxidants[15](e.g. oranges, lemons, carrots, pumpkin, papaya, collard greens, spinach, broccoli, lettuce, other leafy vegetables, eggs, milk and yogurt, cheese, butter, and liver). These foods contribute substantially to the variation in intake of carotenoids and tocopherols among Brazilian women living in São Paulo. Frequency of food consumption was as follows: never, <1 time/month, 2-3 times/month, 1-3 times/week, 4-6 times/week, and ≥1 time/day. A similar questionnaire was used to demonstrate an association between specific dietary intake and risk of oral cancer in the same region of Brazil [16].

Nutrient values were calculated from the participants' reported dietary intake using the United States Drug Administration's Continuing Survey of Food Intake of Individuals (CSFII-86) and Nationwide Food Consumption Survey (NFCS 87–88). Due to variations in nutrient contents in different parts of the world, Brazilian specific intake values were generated for *α*- and *ß*-carotene, lutein/zeaxanthin, and *ß*-cryptoxanthin from published nutrient values for foods consumed in São Paulo, Brazil [17]. Dietary-intake calculations used age-specific portion sizes for women, as described elsewhere [18]. Nutrient values utilized in this study were vitamin A, carotenoids (*α*- and *ß*-carotene, lutein/zeaxanthin, and *ß*-cryptoxanthin), and vitamin C.

We examined the association between consumption of certain fruits and vegetables and corresponding serum carotenoid concentrations for 100 women of the sub-cohort[15]. Using serum carotenoid values from the first visit we observed strong associations (r >0.40) between the consumption of citrus fruits and serum lutein, zeaxanthin, *cis*-zeaxanthin, -cryptoxanthin, lycopene, *cis*-lycopene, and -carotene, and between the consumption of carrots and serum lutein, -cryptoxanthin, -cryptoxanthin, lycopene, *cis*-lycopene, -carotene, and -carotene. These correlation coefficients are similar to those observed in studies comparing the intake of specific carotenoids estimated from food frequency questionnaires with the corresponding serum concentrations [19, 20]. In addition, we evaluated the crude and energy-adjusted [21] associations between carotenoid intake and serum carotenoid concentrations and found stronger associations when the energy-adjusted carotenoid intake values were used (data not shown). The primary purpose of energy-adjustment of nutrient values was to adjust for the tendency of individuals to consistently under or over report intakes using a frequency checklist[21]. Therefore, all diet and SIL analyses utilized energy-adjusted nutrient values.

Statistical Analyses

We compared HPV-positive women who developed an incident SIL (LSIL or HSIL) during follow-up (cases) with HPV-positive women who did not develop LSIL or HSIL over the same time period (controls). Logistic regression was performed to estimate odds ratio [OR] and 95% confidence interval (CI) between antioxidant nutrient intake (either as food consumption or estimated nutrient value) and incident SIL. Multinomial regression was preformed when estimating the OR and 95% CI across SIL groups (controls, LSIL and HSIL). Energy adjusted nutrient intake values were categorized into quartiles based on the distribution among control women.

To fully evaluate potential confounders, we examined confounding factors known to be associated with dietary nutrient intake, HPV infection and SIL. First, we compared the frequency of fruit and vegetable consumption or quartiles of nutrient intake by age, socio-demographic and lifestyle factors, including age, race, income, education, marital status, household size, smoking, oral contraceptive use, pregnancies, age at first intercourse, and number of lifetime partners (data not shown). Next, we identified those factors that altered the crude OR estimate by ≥10%. Final confounding factors were age, year of entry into cohort, total pregnancies, education, number of sexual partners in last year and oral contraceptive use. Tests for linear trend treated categorical nutrients as continuous in the multivariate models. All statistical tests performed were two-sided and declared at the 5% significance level using SAS® software, version9.1.3.

RESULTS

The goal of the present study was to evaluate the association between dietary intake and SIL incidence in the presence of HPV infection among this same sub-cohort of women. A comparison of cases and controls on follow-up, demographic and lifestyle factors is presented in Table 1. Overall, the groups were similar in age and follow-up times, demonstrating the frequency matching of the two groups. Cases were more likely to have oncogenic HPV infection, ($p<0.0001$), more pregnancies ($p=0.02$) and increased condom use ($p=0.01$) compared to controls.

Frequency of fruit and vegetable consumption and dietary intake values are presented in Table 2 for the 93 SIL cases and 172 controls. Compared to women that developed incident SIL, control women consumed papaya more frequently ($P=0.01$) and had higher mean daily intake of ß-cryptoxanthin ($P=0.048$). Fruit and vegetable consumption differed by age at menarche, ethnicity, oral contraceptive use, condom use, age and sexual partners in the last year, while quartiles of nutrient intake differed by age, ethnicity, number of sexual partners and smoking (data not shown).

The association between consumption of selected fruits and vegetables and risk of incident SIL among HPV-positive women is shown in Table-3. Higher reported consumption of papaya was inversely associated with risk of SIL for intake above once a year (p-trend=0.01) and strongest for consumption ≥1 time/week (adjusted OR (AORs)=0.19; 95%CI=0.08-0.49). Papaya intake was consistently protective for both LSIL and HSIL. SIL risk was reduced among women reporting consumption of oranges ≥1 time/week (AOR=0.32; 95%CI=0.12-0.87; p-trend=0.02), which was strongest among LSIL.

Table-4 presents the association between estimated nutrient intake and development of anytype SIL and across SIL groups. Overall intakes of individual nutrients estimated from

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the questionnaire were not significantly associated with risk of SIL. The point estimates for increasing nutrient intake of ß-cryptoxanthin and α-carotene were all below 1.0 suggesting a trend towards reduced risk of SIL; however, the p-trend was not significant. Similar inverse trends were estimated for LSIL incidence, but not HSIL.

DISCUSSION

The development of cervical cancer occurs through a series of ordered events: acquisition of HPV infection, HPV persistence and development of HPV-induced cervical lesions, progression to cervical cancer. In this study, we sought to determine whether antioxidant nutrient intake influenced risk of SIL among HPV-positive women. Previously, consumption of papaya and oranges, important sources of antioxidant nutrients, were associated with a reduced risk of type-specific HPV persistence[15]. *β*-cryptoxanthin, lutein/ zeaxanthin, and vitamin-C intakes were associated with >2-fold decreased risk of type-specific HPV persistence[15]. In the current study among the same group of HPV-positive women, we found that greater consumption of papayas was associated with a decreased risk of both LSIL and HSIL and intake of oranges with decreased risk of LSIL. However, inconsistent associations were observed when individual nutrients were examined. These data support a possible protective effect of frequent consumption of fruits high in antioxidant nutrients and development of SIL.

Most studies that have examined dietary factors in relation to cervical dysplasia were retrospective and failed to control for HPV status or confounders. Because HPV is the cause of cervical cancer[5], statistical analyses restricted to HPV positive women identify co-factors in HPV-induced carcinogenesis independent of HPV. Therefore, we restricted both cases and controls to women who tested positive for HPV during the exposure period prior to lesion detection. While this reduced our sample size, this approach is the most stringent study design to test our hypothesis.

In a comprehensive review, antioxidant nutrients such as carotenoids, tocopherols, and retinol, were *suggested* to be protective against cervical dysplasia; however there was a paucity of prospective studies that adequately controlled for HPV infection[6]. This study provides additional data suggesting a possible protective effect of consumption of foods high in antioxidant nutrients and cervical dysplasia. Our results are consistent with previous case-control studies suggesting an inverse association between α-carotene[9, 22, 23], *β*-cryptoxanthin[23, 24] and the risk of cervical neoplasia and a recent study among Sao Paulo women that reported a significant inverse association between higher dietary intake of dark green and deep yellow vegetables/fruits (including papayas, pumpkin and spinach) and CIN3[7]. However, the current study did not find significant associations for individual antioxidant nutrients (e.g. -carotene, lutein/zeaxanthin) and incident SIL.

The mechanism by which increased fruits and vegetables or dietary intake of antioxidants might delay the onset of HPV-associated SIL has not been clearly elucidated. Several postulated mechanisms of action[15] include: 1) quenching reactive oxygen species prior to cellular damage, deregulation cell signaling, and increased viral replication and expression; 2) enhancing the immune system thereby promoting HPV clearance; or 3) vitamin-A mediated squamous maturation. An alternative hypothesis is that women that consume more fruits and vegetables may have other healthy behaviors and overall better health than women that consume little fruits and vegetable [25].

As with all observational studies, there are limitations of our study that need to be recognized. First, due to the fact that the outcome ascertainment was based on cytologic analysis, a potential limitation is misclassification of lesion outcome. To overcome this potential limitation all cytologic assessments were carefully conducted in a reference laboratory following a strict quality-control protocol. The Ludwig-McGill cohort opted for an intensive, expert cytologic review of all subjects in the study every 4 – 6 months and referred all instances of HSIL for colposcopy. This approach reduced the likelihood of unnecessary biopsies, which may interfere with the natural history of early lesions [26]. Nevertheless, the occurrence of false-negative Pap tests could have resulted in under-estimates (or shorter estimates) of regression time and in either overestimates or underestimates of progression time, depending on whether these test results occurred at lesion outset of during the sojourn period. Women with normal and ASCUS/AGUS cytology at baseline were included, which may have led to misclassification at baseline (4% (11/265) had ASCUS/AGUS cytology at baseline and 6 developing SIL). The measures of association remained relatively unchanged when excluding them from the analysis (data not shown).

The food questionnaire assessed usual dietary intake of 15 food items and did not encompass the entire Brazilian diet. However, it contained 10 fruits and vegetables frequently consumed in Brazil that account for a majority of antioxidant nutrient intake in the study population [27]. Our approach focused primarily on the results obtained directly from the questionnaire regarding food consumption and those results were supported by the calculated nutrient intakes. Abbreviated dietary indices have been shown to account for a considerable proportion of variability in nutrient intake[28]. We increased the accuracy of our estimated carotenoid intake by using Brazil-specific carotenoid food-content values. All nutritional epidemiological studies are prone to bias due to inaccurate dietary recall, measurement error or interviewer-led recall bias. The impact of differential misclassification or interviewer bias should be minimal due to the prospective nature of this study (e.g. collection of dietary questionnaires prior to development or knowledge of the SIL outcomes).

The primary advantage of our study was its prospective design with long term follow-up and repeated measures of cervical cytology and HPV-DNA. In addition, using a nested case-control study design, we minimized the potential for selection and recall biases because exposures were collected prior to knowledge of case or control status. The prospective nature of the Ludwig-McGill Cohort study enabled the diagnosis of incident SILs. Recognizing that few persistent HPV infections progress to SIL, it was not unexpected that diagnosis of incident SIL lesions was low. Furthermore, there were no differences in nutrient intake, consumption of fruits and vegetables, or cofactors under study except older age at first intercourse between the sub-cohort and parent cohort (data not shown). Our results reflect those of the larger cohort population and are directly comparable to our previous findings associated with HPV persistence[15].

Overall, results from the current study suggest that, among populations with relatively low levels of intake of antioxidant nutrients, increasing dietary consumption of certain fruits and vegetables may lower risk of cervical neoplasia. More research is needed to elucidate the role antioxidant nutrients and foods play in reducing the risk of cervical cancer. Additional prospective studies with longer follow-up, examining both dietary and biochemical markers of nutrient intake would be best suited to achieve this goal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis Among a low income population of Brazilian women, consumption of fruits high in antioxidants (papaya and oranges) reduced risk of cervical intraepithelial neoplasia.

Table 1

Characteristics for cases of any-grade squamous intraepithelial lesion (SIL) and frequency-matched controls.

	SIL Groups				
	Cases (n = 93)		**Controls (n = 172)**		***P*** [1]
	N	**%**	**N**	**%**	
Age (years)					0.48
≤ 20	13	14.0	24	14.0	
21 – 30	42	45.2	66	38.4	
31 – 40	22	23.7	56	32.6	
> 40	16	17.2	26	15.1	
Time in Study (yrs)	7.2	6.3, 8.2	7.2	6.5, 8.1	0.63
Number of study visits	14	13, 15	14	12, 15	**0.02**
HPV types					**<.0001**
Oncogenic	72	77.4	100	58.1	
Non-oncogenic only	13	14.0	69	40.1	
None	8	8.6	3	1.7	
Ethnicity					0.64
White	54	58.1	105	61.0	
Non-White	39	41.9	67	39.0	
Marital Status					0.83
Common Law	33	35.5	61	35.5	
Married	36	38.7	66	38.4	
Single	15	16.1	33	19.2	
Widowed/Divorced	9	9.7	12	7.0	
Education					0.12
< Elementary	71	76.4	136	79.1	
Elementary	20	21.5	32	18.6	
≤ High School	2	2.2	4	2.3	
Monthly Income, *in US Dollars*					0.29
< 250	33	35.5	41	23.8	
250 – <450	20	21.5	47	27.3	
451 – <725	20	21.5	39	22.7	
≥ 725	19	20.4	38	22.1	
Smoking status					0.87
Never	43	46.2	79	45.9	
Former	13	14.0	28	16.3	
Current	37	39.8	65	37.8	
Oral contraceptive use					0.49
Never	19	20.4	28	16.3	
< 6 years	51	54.8	107	62.2	
≥ 6 years	23	24.7	37	21.5	

	SIL Groups				
	Cases (n = 93)		Controls (n = 172)		*P* [1]
	N	%	N	%	
Total no. of pregnancies					**0.02**
0 – 1	21	22.6	32	18.6	
2 – 3	30	32.3	85	49.4	
4 – 6	34	36.6	36	20.9	
7+	8	8.6	17	9.9	
Age at first intercourse					0.56
≤ 15	29	31.2	52	30.2	
16 – 17	22	23.7	51	29.7	
≥ 18	42	45.2	69	40.1	
Lifetime no. of sexual partners					0.08
0 – 1	36	38.7	63	36.6	
2 – 3	42	45.2	61	35.5	
≥ 4	15	16.1	48	27.9	
Total no. of sexual partners during the last year					0.11
0 – 1	86	92.5	147	85.5	
≥ 2	6	6.5	22	12.8	
Menarche					0.20
0-11	23	24.7	31	18.0	
12-19	70	75.3	141	82.0	
Condom use					**0.02**
No	85	91.4	168	97.7	
Yes	8	8.6	4	2.3	

[1] P values determined using Pearson's Chi-2 test or Kruskal Wallis test (time in study and number of study visits)

Table 2

Frequency of food consumption and energy-adjusted mean (SD) values of nutrient intake for cases of any-grade squamous intraepithelial lesion (SIL) and controls.

	SIL Groups		
	Cases (n = 93)	Controls (n = 172)	p [1]
Food Consumption	**N (%)**	**N (%)**	
Papaya			
Never or <1 time/year	18 (19)	11 (6%)	**0.01**
≥1 time/year, <1 time/month	16 (17)	31 (18)	
1-3 times/month	19 (20)	40 (23)	
≥1 time/week	40 (43)	90 (52)	
Carrots			
Never or <1 time/year	10 (11)	11 (6)	0.09
≥1 time/year, <1 time/month	7 (8)	18 (11)	
1-3 times/month	26 (28)	30 (17)	
≥1 time/week	50 (54)	113 (66)	
Orange			
Never or <1 time/month	13 (14)	11 (6)	0.10
1-3 times/month	19 (20)	32 (19)	
≥1 time/week	61 (66)	129(75)	
Pumpkin			
Never or <1 time/year	20 (22)	36 (21)	0.99
≥1 time/year, <1 time/month	32 (35)	63 (37)	
1-3 times/month	20 (22)	37 (22)	
≥1 time/week	20 (22)	36 (21)	
Spinach			
Never or <1 time/year	60 (65)	98 (57)	0.69
≥1 time/year, <1 time/month	14 (15)	31 (18)	
1-3 times/month	11 (12)	25 (15)	
≥1 time/week	8 (9)	18 (10)	
Broccoli			
Never or <1 time/month	42 (45)	83 (48)	0.50
≥1 time/year, <1 time/month	19 (20)	25 (15)	
1-3 times/month	20 (22)	46 (27)	
≥1 time/week	12 (13)	18 (10)	
Nutrient Intake	**Energy-adjusted mean [2] (SD)**		
	Cases (n = 93)	Controls (n = 172)	
Vitamin A, μg,RE[3]	1,151 (843)	1,159 (672)	0.56
Vitamin E, α-TE[2], mg	1.5 (0.5)	1.6 (0.5)	0.52

	SIL Groups		
	Cases (n = 93)	Controls (n = 172)	*P* [1]
Food Consumption	**N (%)**	**N (%)**	
Vitamin C, mg	52 (29)	55 (28)	0.39
β-Carotene, μg[4]	1,024 (570)	1,053 (587)	0.57
α-Carotene, μg[4]	137 (134)	153 (139)	0.15
β-Cryptoxanthin, μg[4]	223 (198)	259 (201)	**0.05**
Lutein plus zeaxanthin, μg[4]	3,927 (3121)	4,389 (4146)	0.59

[1]One-way analysis of variance of log-transformed energy-adjusted[23] nutrient intake values.

[2]Means are presented as untransformed values.

[3]RE, retinol equivalent; TE, tocopherol equivalent.

[4]Nutrient intake based on Brazilian values [21].

Table 3

Association between consumption of select fruits and vegetables and incident squamous intraepithelial lesion (SIL) diagnosis among HPV positive women[1]: Overall and by SIL diagnosis

	Controls	All Cases[2]					LSIL[3]				HSIL[3]			
	n	**n**	**Crude OR**	**(95% CI)**	**AOR[3]**	**(95% CI)**	**n**	**Crude OR**	**AOR[3]**	**(95% CI)**	**n**	**Crude OR**	**AOR[3]**	**(95% CI)**
Papaya														
Never or <1 time/year	11	18	1.00		1.00		13	1.00	1.00		5	1.00	1.00	
≥1 time/year, <1 time/month	31	14	0.28	(0.10, 0.74)	**0.22**	**(0.07, 0.63)**	12	0.33	**0.28**	**(0.09, 0.87)**	2	0.14	**0.09**	**(0.01, 0.59)**
1-3 times/month	39	16	0.25	(0.10, 0.65)	**0.19**	**(0.07, 0.55)**	15	0.33	**0.28**	**(0.09, 0.84)**	1	0.06	**0.03**	**(0.00, 0.34)**
≥1 time/week	88	37	0.26	(0.11, 0.60)	**0.19**	**(0.08, 0.49)**	26	0.25	**0.21**	**(0.08, 0.56)**	11	0.28	**0.18**	**(0.04, 0.80)**
p-trend						***0.01***				***0.01***				***0.18***
Carrots														
Never or <1 time/year	10	9	1.00		1.00		8	1.00	1.00		1	1.00	1.00	
≥1 time/year, <1 time/month	18	7	0.43	(0.12, 1.52)	0.44	(0.11, 1.73)	4	0.28	0.29	(0.06, 1.33)	3	1.67	1.46	(0.11, 19.36)
1-3 times/month	30	23	0.85	(0.30, 2.44)	1.11	(0.34, 3.60)	18	0.75	0.96	(0.28, 3.23)	5	1.67	2.12	(0.19, 23.89)
≥1 time/week	111	46	0.46	(0.18, 1.21)	0.44	(0.15, 1.26)	36	0.41	0.39	(0.13, 1.16)	10	0.90	0.72	(0.07, 7.14)
p-trend						*0.10*				*0.11*				*0.31*
Oranges														
Never or <1 time/month	11	12	1.00		1.00		10	1.00	1.00		2	1.00	1.00	
1-3 times/month	32	18	0.52	(0.19, 1.40)	0.45	(0.15, 1.40)	15	0.52	0.45	(0.14, 1.46)	3	0.52	0.42	(0.05, 3.48)
≥1 time/week	126	55	0.40	(0.17, 0.96)	**0.32**	**(0.12, 0.87)**	41	0.36	**0.28**	**(0.10, 0.80)**	14	0.61	0.52	(0.09, 3.13)
p-trend						***0.02***								
Pumpkin														
Never or <1 time/year	35	18	1.00		1.00		14	1.00	1.00		4	1.00	1.00	
≥1 time/year, <1 time/month	61	32	1.02	(0.50, 2.08)	0.74	(0.34, 1.61)	23	0.94	0.70	(0.30, 1.63)	9	1.29	1.10	(0.27, 4.51)
1-3 times/month	37	18	0.95	(0.43, 2.11)	0.67	(0.28, 1.61)	14	0.95	0.73	(0.28, 1.86)	4	0.95	0.54	(0.10, 3.02)
≥1 time/week	36	17	0.92	(0.41, 2.06)	0.69	(0.29, 1.64)	15	1.04	0.79	(0.31, 2.00)	2	0.49	0.33	(0.05, 3.30)
p-trend						*0.41*				*0.74*				*0.16*

	Controls	All Cases[2]					LSIL[3]				HSIL[3]			
	n	n	Crude OR	(95% CI)	AOR[3]	(95% CI)	n	Crude OR	AOR[3]	(95% CI)	n	Crude OR	AOR[3]	(95% CI)
Spinach														
Never or <1 time/year	96	54	1.00		1.00		42	1.00	1.00		12	1.00	1.00	
≥1 time/year, <1 time/month	31	14	0.80	(0.39, 1.64)	0.79	(0.36, 1.71)	11	0.81	0.83	(0.37, 1.90)	3	0.77	0.59	(0.11, 3.13)
1-3 times/month	24	9	0.67	(0.29, 1.54)	0.76	(0.31, 1.86)	8	0.76	0.85	(0.33, 2.16)	1	0.33	0.37	(0.04, 3.32)
≥1 time/week	18	8	0.79	(0.32, 1.94)	0.83	(0.32, 2.20)	5	0.64	0.65	(0.21, 2.01)	3	1.33	1.35	(0.29, 6.21)
p-trend						*0.52*				*0.44*				*0.89*
Broccoli														
Never or <1 time/month	81	40	1.00		1.00		30	1.00	1.00		10	1.00	1.00	
≥1 time/year, <1 time/month	25	17	1.38	(0.67, 2.84)	1.74	(0.78, 3.86)	13	1.40	1.90	(0.81, 4.49)	4	1.30	1.36	(0.31, 5.92)
1-3 times/month	45	17	0.77	(0.39, 1.50)	0.84	(0.41, 1.76)	14	0.84	0.98	(0.45, 2.17)	3	0.54	0.42	(0.09, 1.88)
≥1 time/week	18	11	1.24	(0.53, 2.87)	1.43	(0.58, 3.51)	9	1.35	1.52	(0.17, 5.87)	2	0.90	1.00	(0.17, 5.87)
p-trend						*0.77*				*0.57*				*0.51*

[1] Restricted to HPV+ women (n=254)

[2] Logistic Regression comparing all cases and controls.

[3] Multinomial Regression comparing controls, LSIL and HSIL

[4] Adjusted OR (AOR) is adjusted for age, year of entry into cohort, education, no. of sex partners during the past year, oral contraceptive use, and total no. of pregnancies

Table 4

Association between energy-adjusted intake of carotenoids and antioxidant vitamins and incident squamous intraepithelial lesion (SIL) diagnosis among HPV positive women[1]: Overall and by SIL diagnosis

	Controls	All Cases[2]					LSIL[3]					HSIL[3]				
Nutrient	**n**	**n**	**Crude OR**	**(95% CI)**	**AOR[4]**	**(95% CI)**	**n**	**Crude OR**	**AOR[4]**	**(95% CI)**	**n**	**Crude OR**	**AOR[4]**	**(95% CI)**
β-Carotene (μg)														
Quartile 1	43	27	1.00		1.00		23	1.00	1.00		4	1.00	1.00	
Quartile 2	41	15	0.58	(0.27, 1.25)	0.57	(0.26, 1.25)	12	0.55	0.51	(0.22, 1.19)	3	0.79	0.93	(0.19, 4.65)
Quartile 3	43	20	0.74	(0.36, 1.52)	0.76	(0.36, 1.61)	14	0.61	0.60	(0.26, 1.37)	6	1.50	1.79	(0.44, 7.23)
Quartile 4	42	23	0.87	(0.43, 1.76)	0.83	(0.40, 1.73)	17	0.76	0.70	(0.32, 1.55)	6	1.54	1.56	(0.39, 6.33)
p-trend						*0.73*				*0.41*				*0.42*
α-Carotene (μg)														
Quartile 1	42	32	1.00		1.00		24	1.00	1.00		8	1.00	1.00	
Quartile 2	43	16	0.49	(0.23, 1.02)	**0.39**	**(0.17, 0.85)**	15	0.61	0.49	(0.21, 1.13)	1	0.12	**0.08**	**(0.01, 0.72)**
Quartile 3	41	16	0.51	(0.25, 1.07)	0.46	(0.21, 1.02)	14	0.60	0.55	(0.24, 1.27)	2	0.26	0.22	(0.04, 1.22)
Quartile 4	43	21	0.64	(0.32, 1.29)	0.55	(0.26, 1.14)	13	0.53	0.44	(0.19, 1.01)	8	0.98	0.96	(0.30, 3.02)
p-trend						*0.14*				*0.07*				*0.86*
β-Cryptoxanthin (μg)														
Quartile 1	43	34	1.00		1.00		29	1.00	1.00		6	1.00	1.00	
Quartile 2	42	14	0.42	(0.20, 0.90)	**0.33**	**(0.15, 0.75)**	10	0.37	**0.28**	**(0.11, 0.67)**	4	0.68	0.68	(0.16, 2.88)
Quartile 3	42	17	0.51	(0.25, 1.05)	**0.46**	**(0.21, 0.98)**	12	0.44	**0.38**	**(0.16, 0.88)**	5	0.85	0.95	(0.25, 3.69)
Quartile 4	42	20	0.60	(0.30, 1.21)	0.57	(0.27, 1.21)	16	0.59	0.52	(0.23, 1.16)	4	0.68	0.91	(0.21, 3.94)
p-trend						*0.16*				*0.11*				*0.99*
Lutein plus Zeaxanthin (μg)														
Quartile 1	43	19	1.00		1.00		15	1.00	1.00		4	1.00	1.00	
Quartile 2	43	22	1.16	(0.55, 2.44)	1.16	(0.53, 2.54)	18	1.20	1.11	(0.48, 2.58)	4	1.00	1.33	(0.29, 6.05)
Quartile 3	43	24	1.26	(0.61, 2.64)	1.30	(0.59, 2.86)	19	1.27	1.22	(0.52, 2.87)	5	1.25	1.52	(0.35, 6.55)
Quartile 4	40	20	1.13	(0.53, 2.42)	1.17	(0.53, 2.59)	14	1.00	0.98	(0.41, 2.36)	6	1.61	1.93	(0.47, 7.85)
p-trend						*0.65*				*0.98*				0.35

	Controls	All Cases[2]					LSIL[3]				HSIL[3]			
Nutrient	**n**	**n**	**Crude OR**	**(95% CI)**	**AOR[4]**	**(95% CI)**	**n**	**Crude OR**	**AOR[4]**	**(95% CI)**	**n**	**Crude OR**	**AOR[4]**	**(95% CI)**
Vitamin C (mg)														
Quartile 1	43	29	1.00		1.00		22	1.00	1.00		7	1.00	1.00	
Quartile 2	42	18	0.64	(0.31, 1.31)	0.58	(0.27, 1.23)	17	0.79	0.71	(0.32, 1.56)	1	0.15	0.13	(0.02, 1.15)
Quartile 3	42	17	0.60	(0.29, 1.25)	0.53	(0.25, 1.13)	9	0.42	**0.38**	**(0.15, 0.94)**	8	1.17	0.98	(0.31, 3.13)
Quartile 4	42	21	0.74	(0.37, 1.50)	0.70	(0.33, 1.49)	18	0.84	0.76	(0.34, 1.71)	3	0.44	0.47	(0.10, 2.10)
p-trend						*0.31*				*0.29*				0.77

[1] Restricted to HPV+ women (n=254)

[2] Logistic Regression comparing all cases and controls.

[3] Multinomial Regression comparing controls, LSIL and HSIL

[4] Adjusted OR (AOR) is adjusted for energy intake (Kcal), age, year of entry into cohort, and total no. of pregnancies