A Case Control Study of Nutritional Factors and Cervical Dysplasia[1]

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Abstract

The association of nutritional factors with cervical dysplasia was examined through a case-control study. Analysis was conducted in 257 cases and 133 controls confirmed both by cytological examination and colposcopic findings. A 24-h dietary recall questionnaire was used to assess nutritional intake. Various risk factors (including age at first intercourse, number of sexual partners, parity, cigarette smoking, oral contraceptive use, human papillomavirus type 16 infection, and age and race) were adjusted for their potential confounding effects. While analyses were also performed to adjust for total calories, results were not changed significantly. Among the nutrients examined, vitamin A intake showed a significantly increased risk at the lowest quartile compared to the highest quartile, with an odds ratio of 2.2 (95% confidence interval, 1.2–4.2). A significant trend of increasing risk was also observed with lower intake of vitamin A ($P = 0.05$). Riboflavin showed increased risk at the two lower quartiles of intake with a trend test P value of 0.04. Increased risk was also found for lower intakes of vitamin C compared to the highest intake level. For folate, increased risk was found in the second highest quartile compared with the highest quartile with an odds ratio of 2.0 (95% confidence interval, 1.0–3.8). The calcium:phosphorus ratio showed an increased risk at the lowest level (odds ratio, 2.0; 95% confidence interval, 1.0–4.3). Insufficient intake of vitamin A, riboflavin, ascorbate, and folate is associated with an increased risk of cervical dysplasia.

Introduction

It is estimated that diet or nutritional factors contribute to about 35% of all cancer deaths (1). As examined recently, this estimate remains reasonable with a narrower range of acceptable percentages from 10–70% to 20–60% (2). While epidemiological studies have identified several types of risk factors for cervical cancer, much interest has been paid recently to the role of nutritional status (3–9). Two recent reviews have extensively examined the published epidemiological studies of the role of dietary components, especially fruits and vegetables, in relation to cancer (7–9). Block *et al.* (7) found evidence of a protective role for fruits and vegetables in cervical cancer or its precursor conditions in seven out of eight studies.

Cervical dysplasia, a precursor of invasive cervical cancer, may serve as a model in studying the carcinogenic effects of potential risk factors including nutrition. As an early outcome, the occurrence of cervical dysplasia is more common than invasive cancer; therefore, this provides an opportunity to study more cases. Since women with dysplasia tend to be healthier and younger, their memory and recall of previous exposures may be more accurate and less differentially biased than subjects with advanced invasive disease. Studying the effect of diet in women with cervical dysplasia may provide information concerning the temporal relationship of nutritional factors as contributory causes of cancer.

We have previously reported the association of folate deficiency, reflected by low RBC folate levels, and cervical dysplasia (10). That research showed that low RBC folate levels enhanced the effect of other risk factors for cervical dysplasia and, in particular, that of HPV-16[3] infection. In this report, we present the results from the same case-control study of the effect of diet, as assessed by a 24-h dietary recall, on cervical dysplasia.

Methods

Population. Seven hundred twenty-six women attending a county health department clinic and nine regional referral centers for family planning and routine health care were invited to participate in the study (10, 11). Informed consent was approved by subjects who agreed to participate. A questionnaire was administered through a face-to-face interview by a skilled nurse practitioner to collect demographic data, socioeconomic status, gynecological history, and personal habits. Specific information about particular risk factors of cervical cancer and dysplasia was collected about age at first intercourse, number of sexual partners, number of children, cigarette smoking, and oral contraceptive uses. Gynecological examination was conducted for all women including Papanicolaou smear and colposcopic examination, as well as a cervicovaginal scraping for cells to be tested for HPV-16. Cases were defined as women with cervical dysplasia confirmed both by cytological examination and colposcopic

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[3] The abbreviations used are: HPV, human papillomavirus; CI, confidence interval.

findings. Women with negative findings from both cytological and colposcopic examinations served as controls. Since all participating clinics serve primarily low-income women (12), more women with abnormal cervical dysplasia are seen than those with negative examinations. The study group consists of 294 cases and 170 controls whose status was confirmed both by cytological and by colposcopic findings. Due to incomplete dietary intake data, 257 cases and 133 controls were included in the present analysis. Comparing the characteristics between women included in the present analysis and those excluded due to incomplete dietary information revealed that 9.9% black women *versus* 26.3% white women were excluded ($P < 0.05$). Distributions of age, education, and smoking status were otherwise similar between these two groups. Subjects with the cytological finding of atypia or other than confirmed dysplasia case or control were not analyzed in this study ($n = 262$).

Dietary Recall. In this study, four 24-h dietary recalls were obtained for cases at bimonthly intervals and only one for controls who were not followed beyond the first visit. Therefore, only initial 24-h recalls were used for this analysis. The 24-h dietary recall was administered by a dietitian at the first visit to the clinic. Five trained dietitians participated in the collection of 24-h recall data over the 4-year period of data collection. The dietitians were blind to the case or control status of the study subjects since the diagnosis was made later by cytological and colposcopic confirmation. The lead dietitian trained all other dietitian interviewers and periodically reviewed the intakes as well as continuously interviewing subjects throughout the study. The 24-h dietary recall questionnaire was constructed to accommodate coding all food items. Quantitative intakes were calculated using a computerized database from the 24-h dietary recall questionnaire for the following nutrients: total calories; protein; carbohydrate; total fat; saturated fat; monounsaturated fat; polyunsaturated fat; cholesterol; fiber; vitamin A; vitamin E; vitamin C; thiamin; riboflavin; vitamin B_6; vitamin B_{12}; niacin; folate; calcium; phosphorus; iron; sodium; potassium; zinc; copper; and magnesium (12). The vitamin A intake is based on calculations which include vitamin A plus precursors (such as β-carotene). Missing folate data in the database is a potential weakness in estimating folate intake.

Statistical Analysis. Intake data were available for 257 cases and 133 controls. Each nutrient intake assessed by 24-h recall was categorized into quartiles according to the frequency distribution of the controls. For all nutrients, the highest quartile was used as the referent category for computing odds ratios for comparison among categories. For the trend test of associations, the average intake was assigned to each category as a score.

Since nonnutritional risk factors may confound the associations between nutrients and cervical dysplasia, their effects on these associations were controlled by multivariate logistic regression. The potential confounders included in the logistic regression model were age, race, age at first intercourse, number of sexual partners, parity, cigarettes smoked per day, oral contraceptive use, and HPV-16 infection.

To estimate the association between each nutrient and cervical dysplasia, both unadjusted and adjusted analyses were used to calculate odds ratio and 95% CI for each category of nutrient. *P* values of the trend tests were calculated by fitting logistic regression with the assigned scores of each nutrient as a continuous variable (13). Interaction between nutrients and nonnutritional risk factors were evaluated through general relative risk models (14). Both additive and multiplicative relative risk functions were fitted to data including interaction terms as well as main effect terms. Since total calorie intake is related to the intake of nutrients, analysis was also conducted to control for the effect of total energy consumption.

Table 1 Demographic characteristics for cases and controls

Characteristic	Cases ($n = 257$)		Controls ($n = 133$)		*P* value
	n	%	*n*	%	
Age (yr)					
<25	149	58	75	56	0.76
≥25	108	42	58	44	
Race					
White	95	37	31	23	<0.01
Black	162	63	102	77	
Education (yr)					
<12	172	67	72	54	<0.01
12	61	24	35	26	
>12	24	9	26	20	
Smoking (cigarettes/day)					
0	129	50	89	67	<0.01
1–19	66	26	27	20	
≥20	62	24	17	13	

Results

Cases and controls were young, with a median age of less than 25 years (Table 1). About two-thirds of cases and more than two-thirds of controls were black. More women with less than 12 years of education were found in the case group. Smoking, as well as heavy smoking (≥20 cigarettes/day), was more prevalent in cases than in controls.

Among the demographic and nonnutritional risk factors examined, race, age at first intercourse, number of sexual partners, parity, cigarette smoking, oral contraceptive use, and HPV-16 infection were found to be significantly related to cervical dysplasia (Tables 1 and 2). Their effects, as well as that of age, were controlled for in logistic regression analysis of nutritional factors. The crude effect of nutrients having a significant (or close to significant) association with cervical dysplasia, as assessed by 95% confidence intervals or trend test *P* values, are presented in Table 3. Among these nutrients, vitamin A showed the most significant effect of increased risk at the lowest level compared to the highest level, with an odds ratio of 2.0 (95% CI, 1.1–3.6) and a *P* value of 0.09 for the trend test.

Table 4 presents the association of these nutrients with cervical dysplasia adjusted for nonnutritional risk factors and total calories. The correlation coefficients among the nutrients studied varied markedly. However, all of the micronutrients correlated with the macronutrients and with calories. Since protein, fat, and carbohydrate and total calorie intakes are strongly related to each other, with correlation coefficients of 0.8 or above, only total calorie intake was included for adjustment in the multiple logistic regression model. Overall, effects of these nutrients were very similar, with and without adjusting for calories. However, the statistical significance was attenuated for each nutrient, as shown by the increased *P* value for the trend test and the widened confidence intervals after adjusting for total calories. Vitamin A

Table 2 Association between nonnutritional factors and cervical dysplasia from crude analysis

Factor	Cases	Controls	Odds ratio	95% CI
Age at first intercourse (yr)				
>17	55	37	1	
16–17	109	57	1.3	0.8–2.2
<16	93	39	1.6	0.9–2.8
No. of sexual partners				
1	33	27	1	
2–4	123	68	1.5	0.8–2.7
>4	101	38	2.2	1.2–4.1
Parity				
Nulliparous	56	45	1	
Parous	201	88	1.8	1.2–2.9
Oral contraceptive use				
Never	6	13	1	
Past	48	34	3.1	1.1–8.9
Current	203	86	5.1	1.9–13.9
HPV-16				
Negative	168	112	1	
Positive	71	9	5.3	2.5–11.0

Table 3 Association between nutrient intake and cervical dysplasia from crude analysis

Intake	Cases	Controls	Odd ratio	95% CI
Vitamin A (international units)				
>5483	49	33	1.0	
≤5483	55	33	1.1	0.6–2.1
≤2323	52	33	1.1	0.6–2.0
≤1426	101	34	2.0	1.1–3.6
Trend			$P = 0.09$	
Riboflavin (mg)				
>1.9	46	33	1.0	
≤1.9	58	30	1.4	0.7–2.6
≤1.2	81	35	1.7	0.9–3.0
≤0.7	72	35	1.5	0.8–2.7
Trend			$P = 0.12$	
Vitamin C (mg)				
>119.1	46	33	1.0	
≤119.1	70	33	1.5	0.8–2.8
≤52.9	66	33	1.4	0.8–2.6
≤22.2	75	34	1.6	0.9–2.9
Trend			$P = 0.12$	
Folate (μg)				
>166	45	33	1.0	
≤166	87	34	1.9	1.0–3.4
≤73	61	32	1.4	0.8–2.6
≤37	64	34	1.4	0.7–2.5
Trend			$P = 0.21$	
Calcium (mg)				
>779.8	53	33	1.0	
≤779.8	68	34	1.3	0.7–2.3
≤483.3	77	32	1.5	0.8–2.7
≤222.5	59	34	1.1	0.6–2.0
Trend			$P = 0.54$	
Phosphorus (mg)				
>1118.5	66	33	1.0	
≤1118.5	61	34	0.9	0.5–1.6
≤799.6	66	32	1.0	0.6–1.9
≤560.0	64	34	0.9	0.5–1.7
Trend			$P = 0.89$	
Calcium/phosphorus				
>0.8	26	21	1.0	
≤0.8	57	26	1.8	0.8–3.7
≤0.6	83	46	1.5	0.7–2.9
≤0.4	91	40	1.8	0.9–3.6
Trend			$P = 0.12$	

continued to show a significant effect of increased risk at the lowest intake level compared to the highest level. The odds ratio was 2.2 with 95% confidence intervals of 1.2–4.2. Riboflavin showed an increased risk at the two lower quartiles with a trend test P value of 0.04. Increased risk was also found for lower intakes of vitamin C compared to the highest intake level. For folate, increased risk was only found in the second highest quartile compared with the first (highest) quartile, with an odds ratio of 2.0 (95% CI, 1.0–3.8). For both calcium and phosphorus alone, there was no significant association found with cervical dysplasia; however, it was observed that the lowest ratio of calcium to phosphorus intake was associated with a significantly increased risk (odds ratio, 2.0; 95% CI, 1.0–4.3).

We further examined the interaction of nutritional and nonnutritional risk factors on cervical dysplasia. No statistically significant interaction was found among the nutrients and nonnutritional risk factors. The results for interaction with vitamin A are presented in Table 5 as an example. We did not observe an increased risk of any nonnutritional factor in the lower vitamin A intake group as compared to the higher intake group.

Discussion

Studies have repeatedly found the importance of certain nutritional deficiencies in relation to cervical cancer as well as other cancers (7, 8, 15–21). Studies relating nutritional factors to precursors of invasive cervical cancer have also found that the same importance exists (22–26).

Marshall *et al.* (15) found that the index of β-carotene intake was negatively associated with cervical cancer risk. They observed a risk ratio of 2.0 with 95% confidence intervals of 1.1–3.7 comparing the lowest level to the highest level of vitamin A intake. We found similar results in this study with almost the same estimate for the risk effect. The protective effect of β-carotene, or related components of a vegetable-rich diet, against cervical cancer is also strongly supported by a study in Italy (16). In a multicenter case-control study of diet and the risk of invasive cervical cancer among United States white women, Ziegler *et al.* (19) found that risk was not affected by increased consumption of vegetables, dark green vegetables, dark yellow-orange vegetables, fruits, or legumes, which are the major sources of the four micronutrients believed to reduce the risk of cervical cancer: carotenoids; vitamin A; vitamin C; and folate. However, in another case-control study conducted in four Latin American countries, significant trends of decreasing risk were observed for vitamin C, β-carotene, and other carotenoids by using dietary indicators (20). The protective effect of β-carotene was further supported by using serological indicators (21).

While most of the epidemiological studies have concerned cervical cancer, a protective effect of antioxidant nutrients has also been found on dysplasia (7). It is possible that

Table 4 Association between nutrient intake and cervical dysplasia from multivariate analysis

Nutrient	OR[a]	95% CI[a]	OR[b]	95% CI[b]
Vitamin A (international units)				
>5483	1.0		1.0	
≤5483	1.1	0.6–2.2	1.2	0.6–2.3
≤2323	1.1	0.6–2.2	1.1	0.6–2.3
≤1426	2.2	1.2–4.2	2.2	1.1–4.3
Trend	$P = 0.05$		$P = 0.08$	
Riboflavin (mg)				
>1.9	1.0		1.0	
≤1.9	1.4	0.7–2.8	1.4	0.7–2.8
≤1.2	2.1	1.1–4.1	2.2	1.0–4.6
≤0.7	1.7	0.9–3.4	1.6	0.7–3.5
Trend	$P = 0.04$		$P = 0.07$	
Vitamin C (mg)				
>119.1	1.0		1.0	
≤119.1	1.7	0.9–3.5	1.8	0.9–3.5
≤52.9	2.0	1.0–4.1	2.0	1.0–4.0
≤22.2	1.7	0.9–3.2	1.6	0.8–3.1
Trend	$P = 0.05$		$P = 0.10$	
Folate (μg)				
>166	1.0		1.0	
≤166	2.0	1.0–3.8	2.0	1.0–3.9
≤73	1.4	0.7–2.8	1.3	0.7–2.6
≤37	1.5	0.8–2.9	1.4	0.7–2.7
Trend	$P = 0.14$		$P = 0.21$	
Calcium (mg)				
>779.8	1.0		1.0	
≤779.8	1.4	0.7–2.7	1.5	0.8–3.0
≤483.3	1.2	0.6–2.2	1.4	0.7–2.8
≤222.5	0.8	0.4–1.5	0.9	0.4–2.1
Trend	$P = 0.27$		$P = 0.58$	
Phosphorus (mg)				
>1118.5	1.0		1.0	
≤1118.5	1.0	0.5–1.9	0.8	0.4–1.7
≤799.6	1.1	0.6–2.1	0.8	0.4–1.8
≤560.0	1.0	0.5–2.0	0.6	0.2–1.5
Trend	$P = 0.97$		$P = 0.21$	
Calcium/phosphorus				
>0.8	1.0		1.0	
≤0.8	1.6	0.7–3.5	1.6	0.7–3.6
≤0.6	1.6	0.7–3.3	1.7	0.8–3.5
≤0.4	2.0	1.0–4.3	2.1	1.0–4.4
Trend	$P = 0.04$		$P = 0.04$	

[a] Odds ratio and confidence intervals adjusted for age, race, age at first intercourse, number of sexual partners, parity, cigarette smoking, oral contraceptive use, and HPV-16 infection.

[b] Odds ratio and confidence intervals adjusted for age, race, age at first intercourse, number of sexual partners, parity, cigarette smoking, oral contraceptive use, HPV-16 infection, and total calories.

Table 5 Interactive effect between vitamin A intake and nonnutritional risk factors on cervical dysplasia

Factor	Vitamin A, >2323 IU[a]			Vitamin A, ≤2323 IU		
	Cases	Controls	OR	Cases	Controls	OR
HPV-16						
Negative	64	60	1.0	104	52	1.9
Positive	33	3	10.3	38	6	5.9
Oral contraceptive						
Never use	2	6	1.0	4	7	1.7
Past user	15	15	3.0	33	19	5.2
Current user	87	45	5.8	116	41	8.5
Smoking (cigarettes/day)						
0	53	44	1.0	76	45	1.4
1–19	27	15	1.5	39	12	2.7
≥20	24	7	2.9	38	10	3.2
Parity						
Nulliparous	20	23	1.0	36	22	1.9
Parous	84	43	2.3	117	45	3.0
Age at first intercourse (yr)						
>17	20	21	1.0	35	16	2.3
16–17	49	28	1.8	60	29	2.2
<16	35	16	2.3	58	22	2.8
No. of partners						
1	13	13	1.0	20	14	1.4
2–4	42	35	1.2	81	33	2.5
>4	49	18	2.7	52	20	2.6

[a] IU, international units.

the magnitude of these associations could be diluted in studies of preinvasive disease, since dysplasia does not always progress into invasive cancer. Low levels of vitamin A, vitamin C, β-carotene, and folate have all been found to be related to an increased risk of dysplasia or *in situ* carcinoma (22–27). Among the results found in the current study, the association between low vitamin A intake and high risk of dysplasia is the most convincing. Although this 24-h dietary recall did not separate animal sources from vegetable sources of vitamin A, it could be assumed that the major effect of vitamin A represented the effects of β-carotene and other carotenoids from fruit and vegetable sources, also rich in vitamin C, which did show a probable protective effect in this study. Steinmetz and Potter (9) recently reviewed the protective mechanisms of vegetables and fruit against cancer. They summarized that important mechanisms of carotenoids in the protection against cancer may include the conversion to vitamin A, which plays a role in the regulation of epithelial cell differentiation, as well as their ability to quench singlet oxygen and trap free radicals, which protects cells against oxidative DNA damage. Carotenoids may also function without vitamin A activity (9).

In this study, we applied subject characteristic restriction to classify cases and controls; *i.e.*, we used both cytological and colposcopic findings in order to eliminate or minimize misclassification. Our results are similar to previous reports considering both direction and magnitude. While recall bias might exist in this study, the effect of misclassification would be mostly nondifferential rather than differential, since both interviewers and women in this study were not aware of the status of dysplasia at their initial visit to the clinic. Since nondifferential misclassification would likely attenuate the effect, our estimates of risk ratio are believed to be conservative. Adjusting for calories attenuated the statistical significance of most nutrients, as adding variables to the model usually reduces the precision of parameter estimation. However, the validity of risk estimation would be increased when total calories, a potentially confounding factor, was adjusted.

While adjustments were made for most known risk factors, in this study we did not find any statistically significant interaction among nutritional and non-nutritional risk factors. However, the biological effects of these factors are com-

plex. Smoking has been found repeatedly to be related to cervical cancer even after controlling for other risk factors (28, 29). Biochemical studies have also found that cervical nicotine and cotinine levels are related to smoking history and intensity (30, 31). In other studies smoking has been shown to depress the blood level of vitamin C and folate (32). This evidence further supports the biological plausibility of smoking as a cause of cervical cancer.

Among the risk factors of cervical cancer, HPV infection has the strongest association (10). Much progress has been made in exploring the role of HPV in human cancer, especially cervical cancer, mostly due to the advances in molecular biology and biotechnology (33–35). While HPV is one of the most important risk factors of cervical cancer, the effect of specific types, or new types, needs to be further studied. Also other types of viruses, such as herpes simplex virus 2, may still play a role in carcinogenesis (34, 36, 37).

The role of nutritional factors in carcinogenesis is still poorly understood (32). Nutritional deficiency might play a carcinogenic role at different stages of cancer development. Folate deficiency may act at the initiation stage (10, 11, 32), while other vitamin deficiencies, such as vitamin A, may act as promoters (27). A special comment seems to be in order regarding folate, since it has been reported that high levels of RBC folate appear to be protective against HPV-16-associated dysplasia (10). In that study, analyses were conducted using laboratory indices of nutritional status. It was found that the protective effect of RBC folate was primarily apparent in the highest tertile; a progressively greater risk was not observed in the lowest *versus* the middle tertile. Somewhat similar findings were observed in the present analysis of dietary folate intake patterns among the same subjects. It does not seem unreasonable to suggest that folate deficiency may interfere with the proliferation of virus-infected cells, thus explaining the potential value of folate antagonists in the treatment of cancer, while allowing for cancer initiation to occur during a period of mild or transient deficiency. In the previous report using laboratory indices, neither retinol nor carotenoids nor ascorbate was found to be significantly associated with dysplasia risk (10). The inconsistencies of associations between using laboratory indices and dietary intakes should be mainly due to measurement differences. The present analysis was based on a 24-h dietary recall that is subject to certain limitations, such as day-to-day variation and not being representative of long-term intake. The laboratory assessments reflect both long-term and recent dietary intakes, as well as homeostatic mechanisms of the body.

It is generally acknowledged that RBC folate levels provide a better indication of long-term nutritional status than serum levels. By comparing the correlation between 24-h recalls and laboratory assessments for vitamin A, only weak correlations were found in this population (correlation coefficient, 0.15) (12). The differences of measures from these two assessment methods may be due to real differences of nutritional status and instrumental measurement errors as well. The weak correlation between dietary recall and laboratory assessment in this study is not unique. Similar findings have been reported by others (38, 39) comparing food frequency questionnaire estimates with laboratory measurements. While the ability of each of these measurements to represent past dietary intake may vary from study to study (40), consistency of associations between nutrients such as vitamin A, and dysplasia risk among studies, does lend support for potentially etiological roles.

In this case-control study, we found that insufficient intake of vitamin A, riboflavin, ascorbate, and folate is associated with an increased risk of cervical dysplasia. Further study of these nutritional factors promises to improve understanding of mechanisms of cancer development and progression, as well as appropriate intervention at corresponding stages (41).

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