

## Diet and the Risk of Vulvar Cancer

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*In this case-control study, 201 case patients with vulvar cancer and 342 community control subjects responded to a 61-item food frequency questionnaire. Risk was unrelated to intake of dark green vegetables, citrus fruits, legumes, and vitamins A and C and folate. Risk increased modestly with decreased intake of dark yellow-orange vegetables; the relative risk for the lowest versus the highest quartile was 1.6. Analyses using preliminary determinations of the major carotenoids in common fruits and vegetables suggested that alpha carotene might be the protective constituent in dark yellow-orange vegetables. Intake of beta carotene and provitamin A carotenoids was unrelated to risk.*

*Multivitamin users were at lower risk, compared to nonusers, but no trend was observed with increasing years of use, suggesting that this association was due to unmeasured differences in life-style factors. Risk increased irregularly with the number of cups of coffee consumed per week whereas consumption of alcohol was unrelated to risk. Ann Epidemiol 1991;1:427-437.*

KEY WORDS: Vulvar cancer, diet, carotenoids, alpha carotene.

### INTRODUCTION

Carcinoma of the vulva is a rare gynecologic tumor; the average annual age-adjusted incidence rate for invasive vulvar cancer in the United States is less than 2/100,000 women/y (1). Risk factors associated with vulvar cancer are similar to those reported for cervical cancer and include multiple sexual partners, cigarette smoking, a history of genital warts, and a prior abnormal finding on Papanicolaou smear (2). Indicators of low socioeconomic status have also been consistently associated with these two predominantly squamous-cell tumors (3). The frequent simultaneous occurrence of cervical and vulvar cancer provides further evidence for a possible common etiology (4).

Recent attention has focused on the possibility that certain dietary deficiencies might explain the association between low socioeconomic status and cervical cancer that persists after adjustment for sexual behavior and other risk factors. Some studies found dietary intake of dark green or orange vegetables (5, 6), vitamin A (7), carotenoids (5-8), fruit juices (6, 9), and vitamin C (6, 9-11) to be lower among individuals with cervical dysplasia or neoplasia than among comparison individuals. In addition, supplementation with folic acid has been associated with an improvement in cervical dysplasia among users of oral contraceptives (12).

We evaluated the relation between diet and vulvar cancer using interview data obtained from a large case-control study, to determine if dietary factors implicated in the etiology of cervical cancer also influence the risk of vulvar cancer. In addition, we

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examined the roles of coffee and alcohol and vulvar cancer because these were postulated as risk factors for vulvar cancer in a case-control study by Mabuchi and colleagues (13).

## METHODS

Details on the selection of case patients and control subjects, and other study methods are presented elsewhere (2). Briefly, 344 case patients with incident and pathologically confirmed vulvar cancer diagnosed between 1985 and 1987 were identified at 34 participating hospitals in Chicago and upstate New York. A total of 686 control subjects matched for age (5-year age groups), race, and residence (telephone exchange or zip code) were selected using random digit dialing techniques for controls under the age of 65 or Health Care Financing Administration rosters for those 65 and older. Home interviews were obtained from 209 case patients (61%) and 348 control subjects (51%). Reasons for nonresponse included refusal (18% of case patients versus 34% of control subjects), subject having moved or inability to locate (4% versus 9%), death (3% versus 1%), illness (6% versus 3%), and other problems (2% versus 3%). In addition, for 6% of the case patients it was not possible to obtain physician consent to conduct an interview.

A structured interview was administered by trained interviewers, to obtain information on hypothesized risk factors, including demographics, pregnancy history, menstrual history and hygiene practices, cigarette smoking, sexual and contraceptive behavior, medical events, and diet. Diet was assessed using a food frequency questionnaire that included the major food sources of vitamin A, carotenoids, vitamin C, and folate in the diets of whites, blacks, and Hispanics in the United States (14, 15). For each of 61 food items, subjects provided their "usual adult intake, ignoring recent changes" in terms of the number of servings per day, week, month, or year. For foods reported to be consumed seasonally, an approximate season length was assigned from data collected in the 1977-78 US Department of Agriculture (USDA) Nationwide Food Consumption Survey (16). Fourteen subjects (8 cases, 6 controls) with missing or "don't know" responses for five or more of the food items were excluded from the dietary analyses. For the remaining subjects included in the study, complete information was available on 99% of the food items of interest. The mean ages of the final dataset of 201 case patients and 342 controls were 53.9 and 52.6 years, respectively. Non-Hispanic whites comprised 86.5% of the case patients and 85.6% of the controls.

Analyses of the dietary data were conducted using measures of both food group and nutrient intake. Food group intake was calculated as the sum of the reported frequencies of consumption of the food items included in the food group. Nutrient intake was calculated as the weighted sum of the frequencies of consumption of the food items containing the nutrient; weights used were the nutrient contents of typical servings of the food.

Portion size, food preparation practices, and nutrient content of a typical serving of a food item were estimated using methods described by Ziegler and associates (17). Estimates of portion size and preparation practices were based on 24-hour dietary recalls obtained on a representative sample of the US population (Second National Health and Nutrition Examination Survey (NHANES II)) (15). The food composition values assigned were an updated version of the values used in NHANES II (18). Estimates of vitamin A and carotenoids were updated according to the current convention that beta carotene has one-sixth the vitamin A activity of an equivalent intake of retinol (19). Folate content was obtained from the 1978-88 USDA food composition tables

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(20) with updated information from recent laboratory research and proprietary sources (21). Estimates of five major carotenoids in approximately 30 common fruits and vegetables were obtained from published reports (22) and recent preliminary measurements from the USDA (Beecher GR, personal communication, 1990). Food group and nutrient intakes were treated as categorical exposure variables; each measure was stratified into quartiles based on the frequency distribution in the control group.

Subjects were also asked whether they had used supplemental vitamins on a regular basis and, if so, for how many years. For the measurement of specific vitamin intake, subjects were queried regarding their use of vitamins A, C, and E and folic acid as individual supplements and the name brand of multivitamins typically taken.

In addition, subjects were asked about their usual adult consumption per day, week, or month of beer, wine, and spirits. Information on usual adult consumption of coffee, decaffeinated coffee, and tea was also obtained. Weekly ethanol intake was estimated assuming 1 fl oz of beer, wine, and hard liquor yields 1.1, 2.9, and 9.4 g of ethanol, and that usual servings were 8, 4, and 1 fl oz, respectively (23). A caffeine index was estimated assuming a cupful of tea and coffee yields 60 and 90 mg of caffeine, respectively (24).

The measure used to assess the strength of association between dietary exposures and vulvar cancer was the odds ratio, as an estimate of relative risk (RR). Adjusted maximum likelihood estimates and 95% confidence intervals (CI) were derived using unconditional logistic regression techniques (25). Potential confounders explored included number of sexual partners, a self-reported history of genital herpes or warts, duration and intensity of cigarette smoking, a previous abnormal result on Papanicolaou smear, income, education, age, race, and study area (upstate New York, Chicago). RRs of the various dietary indices presented were adjusted only for age, cigarette smoking (current, exsmoker, nonsmoker), and number of sexual partners, since further adjustment did not materially change any of the estimates. Tests for linear trend were obtained by assigning a score to each level of a categorical exposure variable and then treating the variable as continuous in a regression model.

## RESULTS

### Food Groups and Micronutrients

Table 1 presents the RRs of vulvar cancer associated with food groups. Reduced intake of dark yellow-orange vegetables including carrots, pumpkin, sweet potatoes, and yams was related to vulvar cancer, with risk estimates elevated among women in the two lowest quartiles of intake. No trends in risk were observed with decreasing consumption of dark green vegetables, such as broccoli, spinach, turnip greens, and collards, or legumes, including green and black-eyed peas and green, lima, and pinto beans. Intake of citrus and juices was also unrelated to risk. Furthermore, there was no consistent association between risk of vulvar cancer and intake of the basic food groups, including vegetables, fruits and juices, complex carbohydrates, meat, and dairy products.

Table 2 presents risk estimates for micronutrients, excluding intake from vitamin supplements. There were no trends in risk associated with decreasing intake of vitamin C, vitamin A, carotenoids, or folate.

### Individual Carotenoids

In Table 3, vulvar cancer risk is presented in relation to estimated dietary intake of individual carotenoids, including alpha carotene, beta carotene, lutein, lycopene, and cryptoxanthin. The RRs for women in each the three lowest quartiles of alpha carotene intake were elevated. Intake of the other individual carotenoids was unrelated to risk.

**TABLE 1** Relative risks (RRs) of vulvar cancer associated with intake of selected food groups

Food group (servings/w)	Cases (n = 201)	Controls (n = 342)	Adjusted RRs* (95% CI)
Dark yellow-orange vegetables			
Q1 $\geq 2.6$	37	86	1.00
Q2 1.5-2.5	38	86	.93 (.5-1.6)
Q3 .7-1.4	60	87	1.49 (.9-2.6)
Q4 $\leq .69$	66	83	1.59 (.9 2.7)
			P for trend = .03
Dark green vegetables			
Q1 $\geq 6.0$	60	88	1.00
Q2 4.0-5.9	45	91	.71 (.4-1.2)
Q3 2.5-3.9	51	78	1.04 (.6-1.7)
Q4 $\leq 2.4$	45	85	.71 (.4-1.2)
			P for trend = .41
Legumes			
Q1 $\geq 5.7$	60	87	1.00
Q2 3.7-5.6	43	84	.80 (.5-1.3)
Q3 2.3-3.6	58	86	1.11 (.7-1.8)
Q4 $\leq 2.2$	40	85	.70 (.4-1.2)
			P for trend = .40
Citrus fruits and juices			
Q1 $\geq 10.3$	49	85	1.00
Q2 7.1-10.2	50	86	1.11 (.7-1.9)
Q3 3.2-7.0	39	86	.78 (.5-1.4)
Q4 $\leq 3.1$	63	85	1.20 (.7-2.0)
			P for trend = .73
Vegetables			
Q1 $\geq 21.5$	56	87	1.00
Q2 16.3-21.4	38	84	.76 (.5-1.3)
Q3 11.8-16.2	45	87	.76 (.5-1.3)
Q4 $\leq 11.7$	62	84	1.09 (.7-1.8)
			P for trend = .72
Fruits and juices			
Q1 $\geq 20.9$	56	86	1.00
Q2 13.9-20.8	44	85	.79 (.5-1.3)
Q3 9.0-13.8	34	87	.54 (.3-.9)
Q4 $\leq 8.9$	67	84	1.01 (.6-1.7)
			P for trend = .76
Complex carbohydrates			
Q1 $\geq 18.1$	61	86	1.00
Q2 13.4-18.0	55	86	.96 (.6-1.6)
Q3 10.4-13.3	41	86	.70 (.4-1.2)
Q4 $\leq 10.3$	44	84	.77 (.5-1.3)
			P for trend = .19
Meat			
Q1 $\geq 13.0$	58	86	1.00
Q2 9.4-12.9	46	86	.86 (.5-1.4)
Q3 7.0-9.3	51	85	.97 (.6-1.6)
Q4 $\leq 6.9$	46	85	.70 (.4-1.2)
			P for trend = .27
Dairy products			
Q1 $\geq 16.4$	46	86	1.00
Q2 11.1-16.3	53	86	1.06 (.6-1.8)
Q3 6.5-11.0	54	87	1.15 (.7-1.9)
Q4 $\leq 6.4$	48	83	1.00 (.6-1.7)
			P for trend = .93

\* Adjusted for age, number of sexual partners, and cigarette smoking.

intake of selected

2)	Adjusted RRs <sup>a</sup> (95% CI)
	1.00
	.93 (.5-1.6)
	1.49 (.9-2.6)
	1.59 (.9-2.7)
	P for trend = .03
	1.00
	.71 (.4-1.2)
	1.04 (.6-1.7)
	.71 (.4-1.2)
	P for trend = .41
	1.00
	.80 (.5-1.3)
	1.11 (.7-1.8)
	.70 (.4-1.2)
	P for trend = .40
	1.00
	1.11 (.7-1.9)
	.78 (.5-1.4)
	1.20 (.7-2.0)
	P for trend = .73
	1.00
	.76 (.5-1.3)
	.76 (.5-1.3)
	1.09 (.7-1.8)
	P for trend = .72
	1.00
	.79 (.5-1.3)
	.54 (.3-.9)
	1.01 (.6-1.7)
	P for trend = .76
	1.00
	.96 (.6-1.6)
	.70 (.4-1.2)
	.77 (.5-1.3)
	P for trend = .19
	1.00
	.86 (.5-1.4)
	.97 (.6-1.6)
	.70 (.4-1.2)
	P for trend = .27
	1.00
	1.06 (.6-1.8)
	1.15 (.7-1.9)
	1.00 (.6-1.7)
	P for trend = .93

TABLE 2 Relative risks (RRs) of vulvar cancer associated with estimated intake of selected micronutrients

Micronutrient	Cases (n = 201)	Controls (n = 342)	Adjusted RRs <sup>a</sup> (95% CI)
Vitamin C (mg/d)			
Q1 $\geq$ 203	55	85	1.00
Q2 153-202	42	86	.86 (.5-1.4)
Q3 112-152	37	86	.71 (.4-1.2)
Q4 $\leq$ 111	67	85	1.15 (.7-1.9)
			P for trend = .72
Vitamin A (RE/d)			
Q1 $\leq$ 1465	61	85	1.00
Q2 1067-1464	43	86	.71 (.4-1.2)
Q3 779-1066	40	86	.67 (.4-1.1)
Q4 $\leq$ 778	57	85	.93 (.6-1.5)
			P for trend = .71
Carotenoids (RE/d) <sup>b</sup>			
Q1 $\geq$ 736	53	85	1.00
Q2 521-735	37	86	.73 (.4-1.3)
Q3 369-520	41	86	.69 (.4-1.2)
Q4 $\leq$ 368	70	85	1.20 (.7-2.0)
			P for trend = .47
Folate ( $\mu$ g/d)			
Q1 $\geq$ 299	54	85	1.00
Q2 233-298	50	86	.93 (.6-1.6)
Q3 180-232	39	86	.68 (.4-1.2)
Q4 $\leq$ 179	58	85	1.02 (.6-1.7)
			P for trend = .77

<sup>a</sup> Adjusted for age, cigarette smoking, and number of sexual partners.

<sup>b</sup> Based on USDA estimates of provitamin A carotenoids (18).

RE = retinol equivalents.

A strong correlation was observed between intake of dark yellow-orange vegetables and alpha carotene because dark yellow-orange vegetables are the major source of alpha carotene (Spearman's  $\tau = .79$ ,  $P = .0001$ ). As shown in Table 4, it was not possible to assess the independent effects of these two dietary exposures on risk because so few women had discordant intake levels of dark yellow-orange vegetables and alpha carotene.

### Supplemental Vitamins

Table 5 shows the RRs associated with years of supplemental vitamin use. Combining intake from individual vitamins and multivitamins, risk was substantially lower among users of vitamins C, A, and E and folic acid. Multivitamin users were also at lower risk than were nonusers. Limiting comparisons to within vitamin takers only, however, no reductions in risk were observed with increasing years of use of vitamin A or multivitamins. Only modest decreasing trends in risk were noted with increasing years of use of vitamins C and E and folic acid.

To estimate the combined effect of diet and vitamin intake, we examined the risks associated with years of supplemental vitamin intake of vitamins A and C and folic acid among women at each level of dietary intake of these nutrients. The effect of dietary intake of vitamins A and C and folate was also examined separately among users and nonusers of the respective supplemental vitamin (data not shown). Similar protective effects for supplemental vitamins A and C and folic acid as shown in Table

**TABLE 3** Relative risks (RRs) of vulvar cancer associated with estimated intake of individual carotenoids

Carotenoid	Cases (n = 201)	Controls (n = 342)	Adjusted RRs (95% CI)
Alpha carotene ( $\mu\text{g}/\text{d}$ )			
Q1 $\geq 569$	32	85	1.00
Q2 350-568	55	86	1.60 (.9-2.8)
Q3 207-349	52	86	1.56 (.9-2.7)
Q4 $\leq 206$	62	85	1.74 (1.0-3.0)
			<i>P</i> for trend = .09
Beta carotene ( $\mu\text{g}/\text{d}$ )			
Q1 $\geq 3006$	44	85	1.00
Q2 2048-3005	41	86	.88 (.5-1.5)
Q3 1284-2047	54	86	1.23 (.7-2.1)
Q4 $\leq 1283$	62	85	1.26 (.7-2.1)
			<i>P</i> for trend = .23
Lutein ( $\mu\text{g}/\text{d}$ )			
Q1 $\geq 4571$	54	85	1.00
Q2 2784-4570	54	86	1.02 (.6-1.7)
Q3 1279-2783	42	86	.87 (.5-1.5)
Q4 $\leq 1278$	51	85	.98 (.6-1.6)
			<i>P</i> for trend = .81
Lycopene ( $\mu\text{g}/\text{d}$ )			
Q1 $\geq 368$	53	84	1.00
Q2 259-367	46	87	.81 (.5-1.4)
Q3 170-258	57	86	1.23 (.7-2.1)
Q4 $\leq 169$	45	85	.79 (.5-1.3)
			<i>P</i> for trend = .76
Cryptoxanthin ( $\mu\text{g}/\text{d}$ )			
Q1 $\geq 289$	49	85	1.00
Q2 186-288	43	86	.79 (.5-1.3)
Q3 126-185	50	86	.94 (.6-1.6)
Q4 $\leq 125$	59	85	.97 (.6-1.6)
			<i>P</i> for trend = .36

\* Adjusted for age, cigarette smoking, and number of sexual partners.

5 were evident among women in each quartile of dietary intake of vitamins A and C and folate. On the other hand, no relationship between risk and dietary intake of vitamins A or C or folate was observed among either users or nonusers of the respective supplement.

Closer evaluation of the effects of specific vitamins was limited because most women reported using multivitamins containing vitamins A, C, and E and folate, or individual supplements in combination with multivitamins. Among the 253 women taking vitamins C, E, or A or folic acid, 62% were taking all four, 14% were taking a combination of three, and 9% were taking a combination of two. Among women taking only one vitamin, 24 were taking vitamin C, six were taking vitamin E, and two were taking folic acid; no women reported taking only vitamin A.

### Coffee and Alcohol Consumption

The relationship of risk to consumption of caffeinated and decaffeinated hot beverages is shown in Table 6. Although risk was modestly elevated among women consuming more than three cups of coffee per day even after adjustment for age, sexual behavior, and cigarette smoking (RR = 1.72; CI, 1.0 to 3.0), the pattern of increasing risk with

h estimated intake of

Adjusted RRs (95% CI)
1.00
1.60 (.9-2.8)
1.56 (.9-2.7)
1.74 (1.0-3.0)
P for trend = .09
1.00
.88 (.5-1.5)
1.23 (.7-2.1)
1.26 (.7-2.1)
P for trend = .23
1.00
1.02 (.6-1.7)
.87 (.5-1.5)
.98 (.6-1.6)
P for trend = .81
1.00
.81 (.5-1.4)
1.23 (.7-2.1)
.79 (.5-1.3)
P for trend = .76
1.00
.79 (.5-1.3)
.94 (.6-1.6)
.97 (.6-1.6)
P for trend = .36

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TABLE 4 Relative risks<sup>a</sup> of vulvar cancer associated with level of intake of alpha carotene and dark yellow-orange vegetables

Quartile of dark yellow-orange vegetable intake	Quartile of alpha carotene intake <sup>b</sup>			
	Q1 (High)	Q2	Q3	Q4 (Low)
Q1 (High)	1.00 <sup>c</sup> (26,63)	.97 (9,20)	.80 (1,2)	3.70 (1,1)
Q2	.51 (4,15)	1.08 (22,45)	.96 (10,22)	1.07 (2,4)
Q3	.39 (1,4)	2.18 (18,17)	1.52 (28,43)	1.18 (13,23)
Q4 (Low)	.65 (1,3)	2.69 (6,4)	1.42 (13,19)	1.61 (46,57)

<sup>a</sup> Adjusted for age, cigarette smoking, and number of sexual partners.  
<sup>b</sup> In parentheses are numbers of case patients and control subjects.  
<sup>c</sup> Referent category.

increasing coffee consumption was irregular. Among nonsmokers, the pattern of risk was also irregular (RR = 1.0, 1.75, 1.47, 1.37, 1.79). Consumption of decaffeinated coffee and tea was unrelated to risk. The caffeine index also showed no clear relation with risk.

There was no association between the overall amount of ethanol consumed and risk of vulvar cancer (data not shown). When specific types of alcohol beverages including beer, wine, and spirits were examined, risk was not appreciably increased with increasing intake after adjustment for age, sexual behavior, and cigarette smoking.

### Interrelationship between Dietary Risk Factors

Finally, to determine if the dietary factors found to be associated with risk in this study were confounded by each other, dark yellow-orange vegetable or alpha carotene intake, supplemental vitamin use, and coffee consumption were entered together into a regression model along with age, cigarette smoking, and number of sexual partners. There was no evidence of confounding as the risk estimates presented earlier in the text were unchanged.

TABLE 5 Relative risks<sup>a</sup> of vulvar cancer associated with years of supplemental vitamin use

Type of vitamin	Years taken <sup>b</sup>					P for trend	Unknown
	0	1-3	4-9	10-15	16+		
Vitamin C	1.0 (123,162)	.65 (16,33)	.68 (22,40)	.58 (13,32)	.47 (22,65)	.006	.75 (5,10)
Vitamin A	1.0 (135,193)	.66 (12,25)	.72 (15,28)	.44 (8,26)	.56 (20,53)	.07	1.12 (11,17)
Vitamin E	1.0 (123,180)	.86 (17,28)	.85 (21,35)	.50 (9,26)	.57 (22,60)	.09	1.23 (9,13)
Folic acid	1.0 (141,208)	.74 (12,23)	.79 (15,27)	.50 (7,22)	.59 (16,44)	.11	1.00 (10,18)
Multivitamins	1.0 (135,186)	.58 (11,26)	.59 (13,30)	.41 (11,38)	.59 (17,41)	.08	1.05 (14,21)

<sup>a</sup> Adjusted for age, cigarette smoking, and number of sexual partners.  
<sup>b</sup> In parentheses are numbers of case patients and control subjects.

**TABLE 6** Relative risks (RRs)<sup>a</sup> of vulvar cancer associated with intake of caffeinated and decaffeinated beverages

Beverage	Cases	Controls	Unadjusted RRs	Adjusted RRs (95% CI)
<b>Coffee (cups/d)</b>				
0	48	105	1.00	1.00
1	51	99	1.13	1.19 (.7-2.0)
2	35	48	1.60	1.59 (.9-2.9)
3	20	41	1.07	1.03 (.5-2.0)
4+	47	49	2.09	1.72 (1.0-3.0)
				<i>P</i> for trend = .09
<b>Decaffeinated coffee (cups/d)</b>				
0	134	202	1.00	1.00
1	48	104	.70	.77 (.5-1.2)
2+	19	36	.80	.89 (.5-1.7)
				<i>P</i> for trend = .40
<b>Tea (cups/d)</b>				
0	56	69	1.00	1.00
1	114	221	.64	.66 (.4-1.0)
2	17	30	.70	.77 (.4-1.6)
3+	14	22	.78	1.02 (.4-2.3)
				<i>P</i> for trend = .71
<b>Caffeine index (mg/d)</b>				
0	13	24	1.00	1.00
1-63	34	79	.80	.76 (.3-1.7)
64-154	47	80	1.09	1.11 (.5-2.5)
155-271	49	82	1.10	1.13 (.5-2.5)
272+	58	77	1.39	1.21 (.5-2.7)
				<i>P</i> for trend = .18

<sup>a</sup> Adjusted for age, cigarette smoking, and number of sexual partners.

## DISCUSSION

Among the various food groups, micronutrients, and individual carotenoids examined in this study, only two closely correlated dietary exposures were associated with vulvar cancer. An increased risk of vulvar cancer was observed among women with decreased intake of dark yellow-orange vegetables or alpha carotene. However, we could not separate an alpha carotene effect from the effect of dark yellow-orange vegetables per se because the most common dark yellow-orange vegetable eaten by women in this study, carrots, is rich in alpha carotene and there are only a few sources of alpha carotene other than dark yellow-orange vegetables (e.g., peaches, corn).

Dark yellow-orange vegetables are also a rich dietary source of beta carotene; however, we found no beta carotene effect using either USDA estimates of provitamin A carotenoids or with beta carotene measured directly. The results of this study are therefore inconsistent with the findings of protective effects of beta carotene that have been reported in several studies of cervical cancer (5-8). On the other hand, our results are in agreement with a large study of in situ cervical cancer in which provitamin A carotenoids were not associated with risk but dark yellow-orange vegetable intake did appear to exert some protective effect (26). Furthermore, Murakoshi and colleagues (27) reported that alpha carotene has nearly ten times the antiproliferative activity of beta carotene on a human retinoblastoma cell line, providing evidence for the biologic plausibility of our finding an effect for alpha carotene but not for beta carotene.

intake of caffeinated and

Unadjusted RRs	Adjusted RRs (95% CI)
1.00	
1.19 (.7-2.0)	
1.59 (.9-2.9)	
1.03 (.5-2.0)	
1.72 (1.0-3.0)	
P for trend = .09	
1.00	
.77 (.5-1.2)	
.89 (.5-1.7)	
P for trend = .40	
1.00	
.66 (.4-1.0)	
.77 (.4-1.6)	
1.02 (.4-2.3)	
P for trend = .71	
1.00	
.76 (.3-1.7)	
1.11 (.5-2.5)	
1.13 (.5-2.5)	
1.21 (.5-2.7)	
P for trend = .18	

dual carotenoids examined were associated with vulvar cancer among women with decreased intake. However, we could not adjust for intake of low-orange vegetables per se (e.g., peaches, corn). The primary source of beta carotene in our study was provitamin A. The results of this study are consistent with those of other studies of beta carotene that have been published. On the other hand, our study did not show an association between vulvar cancer and low-orange vegetable intake. This is in contrast to the results of Murakoshi and colleagues, who found an inverse association between the antiproliferative activity of beta carotene and vulvar cancer risk. This provides some evidence for the biologic activity of beta carotene, but not for beta carotene.

A relationship of dietary vitamin C with cervical cancer risk has been suggested (4, 5), though our data do not indicate that reduced vitamin C intake increases the risk of vulvar cancer. Intake of vitamin C or foods rich in this compound (i.e., citrus fruits and juices, dark green vegetables) was similar between case patients and control subjects.

The rationale for suspecting that folate might affect risk of vulvar cancer is derived from a small clinical trial in which cervical dysplasia in users of oral contraceptives regressed on folic acid administration (12). The lack of a folate effect on vulvar cancer risk is, however, consistent with several case-control studies of cervical cancer (9, 17, 26).

If individuals in this study were seriously misclassified with respect to their nutrient intake, underlying true associations between diet and vulvar cancer might have been obscured. Although potential problems in assessing usual adult diet using food frequency questionnaires have been described, instruments similar to the one employed in this study have been shown to agree well with more exhaustive food diaries, to give comparable results when administered to the same individuals at two different points in time, and to correlate with micronutrient levels in serum or plasma (17). Particular caution should be exercised in interpreting our findings for the individual carotenoids because laboratory values for the five carotenoids were available only on selected fruits and vegetables. In addition, the variability of individual carotenoids across different foods, growing seasons, and cooking practices has yet to be determined.

We observed a protective effect associated with self-reported use of supplemental vitamins but risk increased minimally with increasing years of intake. No one of the five vitamins examined appeared to influence risk more strongly, but our ability to examine this issue was limited because of the common use of multivitamins by women in this study. Taking supplemental vitamins A and C and folic acid was found to be equally protective among women at relatively high and relatively low levels of dietary intake of these respective vitamins. Dietary intake of vitamins A and C and folic acid, however, had no effect on risk among either users or nonusers of these respective supplements. These patterns suggest that the association of supplemental vitamin use with vulvar cancer is most likely due to differences in life-style factors between women who choose to take vitamins and those who do not. Obtaining similar results for invasive cervical cancer, Ziegler and colleagues proposed the possibility that only women taking supplemental vitamins achieve high enough serum micronutrient levels to affect carcinogenesis (17).

An earlier case-control study of this neoplasm reported that coffee drinkers were at increased risk of vulvar cancer, compared to nondrinkers (13). The effect for coffee in this study was modest and there were irregular changes in risk with increased frequency of coffee intake. As neither our study nor the study by Mabuchi and colleagues (13) indicated that caffeine, a primary ingredient in coffee with possible carcinogenic activity (28), influences vulvar cancer risk, the most probable explanation for the observed association is unidentified confounding.

This study supports the report by Mabuchi and colleagues (13) that neither ethanol consumption nor intake of specific types of alcoholic beverages is associated with vulvar cancer. With respect to the amount of ethanol consumed, the heaviest drinkers in this study were not shown to be at excess risk. In addition, intake of wine, beer, and hard liquor did not appreciably alter risk, after controlling for sexual behavior and other risk factors.

A major concern in interpreting our results is the low response rate. The possibility that participation was related to dietary intake and that our results are in some

way biased cannot be excluded. However, when we examined the limited data on nonrespondents, there was no indication that particular age or racial groups were less likely to participate. In addition, the range of dietary intake levels observed in this study is comparable to that in epidemiologic studies with higher response rates (11, 17). It is also reassuring that an earlier analysis of data from this case-control study identified several suspected risk factors for vulvar cancer, including multiple sexual partners, cigarette smoking, and a self-reported history of genital warts (2). While there is also the possibility of differential case recall in this study, every attempt was made to orient case patients and control subjects to their usual adult dietary practices.

Despite the limitations of this study, the data presented do not suggest that dietary factors postulated to influence cervical cancer risk are associated with vulvar cancer, with the possible exception of alpha carotene or other correlates of dark yellow-orange vegetables. It should be noted that even in cervical cancer the role of diet is not yet resolved; risk was not related to any of the postulated dietary risk factors in a recent study of invasive cervical cancer (17). This study does suggest, however, that additional research directed toward the potential anticancer activity of individual carotenoids may provide insight into the role of nutrition in carcinogenesis and cancer prevention.

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