

Diet in the Etiology of Oral and Pharyngeal Cancer among Women from the Southern United States

Deborah M. Winn,¹ Regina G. Ziegler, Linda W. Pickle, Gloria Gridley, William J. Blot, and Robert N. Hoover

Environmental Epidemiology Branch, National Cancer Institute, Bethesda, Maryland 20205

ABSTRACT

A case-control interview study involving 227 women in North Carolina with oral cavity or pharyngeal cancer and 405 matched controls showed a protective effect of a usual adult diet high in fruits and vegetables. The relative risks of 0.65 for moderate and 0.52 for high (relative to 1.0 for infrequent) consumption of fruits and vegetables were statistically significant and remained after controlling for demographic characteristics, tobacco and alcohol use, relative weight, and intake of other food groups. Risks were lower with higher bread and cereal intake but higher for those women with the lightest weights, adjusted for height. The inverse associations between oral and pharyngeal cancer and intake of fruits and vegetables and intake of breads and cereals could not be attributed to an association with general nutritional status, since meat and fish consumption was related to an increased risk of oral and pharynx cancer. Moreover, dairy and egg consumption was generally unrelated to cancer risk. The reduction in risk with greater fruit and vegetable consumption is consistent with the hypothesis that vitamin C and/or β -carotene intake is associated with a reduced risk of oral and pharyngeal cancer.

INTRODUCTION

Mortality rates from oral cavity and pharyngeal cancer among white women are higher in the Southeast than elsewhere in the United States (24). We conducted a case-control study among women in North Carolina to identify life-style, occupational, and medical characteristics contributing to the high female mortality rate for oral cavity and pharyngeal cancer in the region. Snuff dipping, cigarette smoking, and alcohol consumption were strongly related to oral and pharyngeal cancer in the study population; findings concerning these risk factors as well as dental, mouthwash, and occupational associations have been described elsewhere (4, 37-39). In this report, using the interview data on food consumption from the case-control study, the role of diet in the etiology of oral and pharyngeal cancer among women in North Carolina is evaluated.

Recent findings (21) suggest that indices of vitamins A and C intake may be inversely associated with epithelial cancers in the oral cavity. We were interested not only in exploring the relationship between these cancers and intake of food groups which are typically high in selected vitamins but also in examining some food preparation methods and overall dietary patterns. As a consequence of the persuasive findings for snuff and cigarettes, we were interested also in interactions between diet and these 2 tobacco habits, which appear to act on/at the site of physical contact.

¹ To whom requests for reprints should be addressed, at the Environmental Epidemiology Branch, Landow Building 3C09, Bethesda, MD 20205.
Received August 23, 1983; accepted November 21, 1983.

MATERIALS AND METHODS

Female oral cavity and pharyngeal cancer cases were identified through review of hospital discharges at 5 North Carolina hospitals, supplemented with tumor registry listings in 3 of the hospitals, occurring over a 3-year period ending in August 1978. Included were 156 incident and prevalent cases with cancers of the tongue, gums, buccal mucosa, floor of mouth, palate, tonsils, or pharynx and hypopharynx [International Classification of Diseases, Eighth Revision (27) Codes 141, 143 to 146, 148, 149]. Two controls per case were sought from the same hospital as the case, matched on age (± 5 years), race, and county of residence. Controls with a major oral or pharyngeal disease, cancer of the esophagus or larynx, or a mental disorder were ineligible. An additional 99 female residents who died in North Carolina of oral or pharyngeal cancer over a 2.5-year concomitant period were obtained from Vital Statistics listings and were each matched with 2 controls from the same source using the same age, race, residence, and diagnostic criteria as for hospitalized subjects. Hospital controls were obtained by review of hospital admissions subsequent to the case; death certificate controls were ascertained from lists of deaths occurring subsequent to the case's death.

Of the 405 controls, 98 (24%) had diseases of the heart as the first listed discharge diagnosis or underlying cause of death; 70 (17%) had a malignant neoplasm (12, digestive system; 16, respiratory system; 25, genitourinary system; and 17, other sites); 41 (10%) had cerebrovascular disease; 31 (8%) had diseases of the digestive system; 25 (6%) had musculoskeletal system conditions; 20 (5%) had nervous system or sense organ diseases; 19 (5%) were victims of accidents, poisonings, or violence; and 101 (25%) had other conditions.

A questionnaire was administered to the study subject or her next of kin by a trained interviewer in the home of the respondent. Interviews were conducted with the closest possible next of kin when the study subject was deceased or unable to provide an interview. Information recorded on each subject included demographic characteristics, tobacco habits, occupation, medical history, and dental status.

The dietary section of the questionnaire asked about the subject's usual adult diet. At the start of the diet history section, the interviewer stated, "This section will ask for information about your diet history from the time you were 20 years old until 1975. We are mainly concerned with your most usual diet as an adult." Frequency of consumption was determined for 21 food items. Also included were questions concerning usual adult height and weight, special diets, meal patterns (e.g., the number of meals per day), and methods of preparation of meat and fish (e.g., smoking). Three ordinal levels of frequency of consumption, high, moderate, and low, for each of the food items were created by dividing the total (cases plus controls) distribution into approximate thirds. Food groups based on traditional food groupings (e.g., fruits and vegetables) or food preparation methods (e.g., smoked meats and fish, nitrite-containing meats) were created by summing the usual weekly consumption of appropriate individual food items. The food group distributions were stratified into the lowest 25%, middle 50%, and highest 25%.

RRs,² estimated by odds ratios (20), were calculated for high and for moderate consumption relative to low consumption. Confidence intervals were calculated using the method of Gart (11). Mantel's (19) extension test was used to test (one-tailed) the progressive dependence (trend) of

² The abbreviation used is: RR, relative risk.

the odds ratio on the amount of consumption of food items or groups. Adjusted summary odds ratios (RRs) were computed from a stratified analysis according to the method of Gart (11). In addition to the stratified analysis, the logistic model (7, 31) was used to examine further the interrelationships among food groups and case-control status and to adjust for potential risk factors simultaneously. In developing the final logistic model, the statistical significance of potential correlates of exposure were evaluated by examination of the *t* statistics, as well as likelihood differences when parameters were deleted.

Relative weight was obtained by dividing the subject's reported usual adult weight by height raised to the 1.5 power ($W/H^{1.5}$). The power of 1.5 for the body mass index for women had been derived empirically in a survey of a sample of the United States population (1). Subjects were divided into 4 groups: those much heavier than "typical"; those centered around the typical value; those centered at an "ideal" value; and those much lighter than the ideal. Typical weight was based on the race- and age group-specific median weights for United States women obtained from the Health and Nutrition Examination Survey I (28). The "ideal" relative weight for adult women, $0.23 \text{ lb/inch}^{1.5}$ ($= 26.5 \text{ kg/m}^{1.5}$), was obtained from the Recommended Dietary Allowances (10).

Included in the analysis were 227 cases and 405 controls; 59% of the interviews were conducted with next of kin (husbands, 28%; children, 49%; siblings, 11%; other, 12%). More case (69.6%) than control (53.1%) interviews were with next of kin due to the fatal or disabling nature of oral and pharyngeal cancer; thus, respondent status was a key adjustment factor. The next of kin of 5 cases and 5 controls failed to respond to at least 25% of the questions in the diet section of the questionnaire; these study subjects have been excluded from the analysis. In the remaining informative questionnaires, the median intake for monthly consumers of that food item replaced the unknown value when persons were known to eat an item but with an unknown frequency per month. Substituted values accounted for not more than 2.5% of the responses to any given food item.

RESULTS

Table 1 describes general characteristics and established risk factors for oral and pharyngeal cancer in this study population.

Food Groups

Fruits and Vegetables. Table 2 shows that the estimate of the relative risk for fruits and vegetables was 0.7 for moderate and 0.5 for high consumption, a highly statistically significant trend ($p = 0.002$). In addition, for each of the 3 food items included in the fruits and vegetables grouping, lower risks were seen among both moderate and heavy consumers. The lower risks associated with fruit and vegetable consumption were consistently observed within almost every demographic subgroup examined (e.g., racial, educational, regional, urban-rural).

No differences (of more than 0.15 odds ratio units) between the adjusted and unadjusted estimates of effect for the fruit and vegetables grouping were observed for any of the potential confounders examined individually. The confounders which were evaluated included: race; education; cigarette smoking-snuff dipping; ethyl alcohol consumption; the relationship of the respondent to the study subject (self or next of kin); relative weight; presence or absence of dentures; whether 10 or more teeth were missing; reported gum-tooth quality; regular or not regular use of mouthwash; whether 3 or more meals were eaten per day; residence inland or on the coast; usual residence in a farming, rural, or urban area; and the other major food groups. The final logistic model for each food group, which adjusted for

Table 1
Odds ratios for selected oral cavity and pharynx risk factors

Factor	Cases (n = 227)	Controls (n = 405)	RR	95% confidence interval
Age				
<65	96	163		(Matching factor)
65	131	242		
Race				
White	193	344		(Matching factor)
Black	34	68		
Education				
Grade 6	63	103	1.0	
Grades 7-11	80	139	0.9	0.6-1.5
Grade 12	71	145	0.8	0.5-1.3
Missing	13	18	1.2	0.5-2.8
Tobacco and alcohol use				
No tobacco and alcohol habits	37	136	1.0	
Snuff dipper only	81	78	3.8	2.3-6.3
Snuff and cigarettes only	6	6	3.7	1.0-13.9
Snuff and alcohol only	10	26	1.4	0.6-3.4
All 3 habits	10	13	2.8	1.0-7.6
Cigarettes only	19	48	1.5	0.7-2.9
Alcohol only	4	30	0.5	0.1-1.6
Cigarettes and alcohol	60	68	3.2	1.9-5.5
Wearing of dentures (as indicator of oral problems)				
No	85	172	1.0	
Yes	142	232	1.2	0.9-1.8
Mouthwash ^a				
No	109	201	1.0	
Yes	92	149	1.1	0.8-1.6

^a Variable available on only a subset of study subjects.

the potential confounders simultaneously, yielded adjusted RRs not different from the crude RRs.

This absence of confounding also generally held for the other major food groups examined in detail (breads and cereals, dairy products and eggs, pork products, and fish and shellfish); differences which did occur will be noted explicitly.

Snuff dipping and cigarette smoking were 2 strong independent risk factors for oral and pharyngeal cancer in this study (39). The relationship between these 2 habits and oral and pharyngeal cancer risk was evident among low, moderate, and high consumers of each food group. As shown in Table 3, high but not moderate intake of fruits and vegetables was associated with a reduced RR in those with no tobacco habits; decreasing RRs with increasing intake of fruits and vegetables were evident in those who used cigarettes only or cigarettes and snuff.

Breads and Cereals. The complex carbohydrate food group included whole-grain breads and cereals, white bread, and cornmeal or grits products. As shown in Table 4, the inverse trend of risk with bread and cereal intake was statistically significant. Lower odds ratios with increasing bread and cereal consumption were evident in nonusers of tobacco as well as in snuff dippers and cigarette smokers. Intake of white bread and combread-grits appeared to be unrelated to oral and pharyngeal cancer risk, while consumption of whole-grain breads and cereals (moderate RR, 0.8; high RR, 0.7) was associated with lower risk. However, the odds ratio for high whole-grain breads and cereals intake was closer to 1.0 after adjustment for smoking and snuff dipping (moderate RR, 0.8; high RR, 0.9). Unlike the fruit and vegetable items, which were all positively correlated with one another, whole-grain bread consumption was negatively corre-

lated with white bread intake, and both items were unrelated to the consumption of cornbread.

Meat and Fish. Table 5 shows that for several (not mutually exclusive) combinations of the meat and fish items there is an increasing oral and pharyngeal cancer risk with increasing consumption. The pork products and fish-shellfish categories, as well as the total meat and fish group, show dose-response gradients. Individual food items in the meat-fish category for which more frequent consumption was associated with a higher, although not statistically significant, risk of mouth and throat cancer included frankfurters, luncheon meats, corned beef-pas-

trami, sausage, brains-chitterlings, ham or pork, fish, and shellfish.

Associations for pork products, which were sometimes obtained from the subjects' own farms, and for the total meat and fish group were modified by other variables, particularly socioeconomic status. The increasing risk with increasing pork products consumption was limited to women with less than a seventh grade education (moderate RR, 1.9; high RR, 3.4); in contrast, the RRs for those with a high school education were in the opposite direction (moderate RR, 0.9; high RR, 0.4), making adjustment by education inappropriate. The RRs were reduced

Table 2
Odds ratios for consumption of fruits and vegetables

	Times consumed/wk	Median weekly intake	Odds ratio	95% confidence interval	p for χ^2 trend test
Fruits and vegetables	Low (0-10.9)	8	1.0		0.002
	Moderate (11.0-20.9)	15	0.7	0.4-1.0	
	High (\geq 21.0)	21	0.5	0.3-0.8	
Fresh fruit	Low (0-1.0)	0.2	1.0		0.001
	Moderate (1.1-6.9)	3	0.7	0.5-1.2	
	High (\geq 7.0)	7	0.6	0.4-0.8	
Green leafy vegetables	Low (0-2.0)	1	1.0		0.06
	Moderate (2.1-6.9)	3	0.7	0.5-1.1	
	High (\geq 7.0)	7	0.7	0.5-1.1	
Other vegetables	Low (0-6.9)	2	1.0		0.08
	Moderate (7.0)	7	0.7	0.5-1.1	
	High (\geq 7.1)	14	0.7	0.4-1.3	

Table 3
Odds ratios for tobacco habits and fruit and vegetable intake

Fruit and vegetable intake	None			Snuff only			Cigarettes only			Both		
	No.	RR	95% CI ^a	No.	RR	95% CI	No.	RR	95% CI	No.	RR	95% CI
Low												
Cases	9			24	3.8	1.4-10.7	28	4.4	1.6-12.3	10	9.4	2.0-47.8
Controls	34	1.0 ^b		24			24			4		
Medium												
Cases	18	1.1	0.4-2.9	39	2.8	1.1-7.2	35	2.5	1.0-6.4	3	1.4	0.2-7.9
Controls	64			52			53			8		
High												
Cases	14	0.8	0.3-2.2	28	3.8	1.4-10.3	16	1.6	0.6-4.4	3	1.6	0.3-9.3
Controls	68			28			39			7		

^a CI, confidence interval.

^b Referent.

Table 4
Odds ratios for consumption of breads and cereals

	Times consumed/wk	Median weekly intake	Odds ratio	95% confidence interval	p for trend test
All breads and cereals	Low (0-8.5)	7	1.0		0.02
	Moderate (8.6-17.0)	14	0.9	0.6-1.3	
	High (>17.0)	22	0.6	0.4-1.0	
White bread	Low (0-6.9)	0.2	1.0		0.34
	Moderate (7.0-9.9)	7	1.1	0.7-1.7	
	High (\geq 10.0)	14	0.9	0.6-1.5	
Whole-grain breads and cereals	Low (0)	0	1.0		0.06
	Moderate (0.1-6.9)	1	0.8	0.5-1.2	
	High (\geq 7.0)	7	0.7	0.5-1.1	
Cornbread and grits	Low (0-1.9)	1	1.0		0.33
	Moderate (2.0-3.9)	2	1.0	0.7-1.5	
	High (\geq 4.0)	7	1.1	0.7-1.7	

Table 5
Odds ratios for consumption of meat and fish subgroups by consumption level

	Times consumed/wk	Median weekly intake	Odds ratio	95% confidence interval	p for trend test
All meat and fish	Low (0-7.5)	5	1.0		0.09
	Moderate (7.6-15.0)	11	1.2	0.8-1.9	
	High (>15.0)	19	1.4	0.9-2.2	
Pork products (ham or pork dried meats, bacon, sausage, brains, lunch meat, frankfurters, canned meats)	Low (0-4.9)	3	1.0		0.05
	Moderate (5.0-11.5)	8	1.3	0.8-2.0	
	High (>11.5)	16	1.5	0.9-2.4	
Fish and shellfish	Low (0-0.3)	0.2	1.0		0.04
	Moderate (0.4-1.0)	0.8	1.4	0.9-2.2	
	High (>1.0)	2	1.6	1.0-2.5	
Expensive meat (other beef or veal, pork or ham)	Low (0-1.9)	1	1.0		0.44
	Moderate (2.0-4.0)	3	1.4	0.9-2.1	
	High (>4.0)	6	1.0	0.6-1.7	
Convenience meat (lunch meat, canned meats, frankfurters)	Low (0-0.2)	0	1.0		0.10
	Moderate (0.3-2.0)	1	1.5	1.0-2.3	
	High (>2.0)	4	1.3	0.8-2.1	
Breakfast meat (bacon, sausage)	Low (0-2.0)	1	1.0		0.35
	Moderate (2.1-7.0)	5	1.2	0.8-1.9	
	High (>7.0)	9	1.1	0.7-1.8	
Nitrite-containing meats (corned beef, lunch meat, frankfurters, canned meat, bacon)	Low (0-2.0)	1	1.0		0.31
	Moderate (2.1-7.5)	4	1.0	0.6-1.5	
	High (>7.5)	9	1.1	0.7-1.9	

from 1.5 to 1.3 for high consumption when adjustment was made for the relationship of the respondent to the study subject. The estimated risks for fish and shellfish consumption were similar in magnitude and direction to the risks for pork products. High fish and shellfish consumers had 1.6 times the risk of low consumers; only adjustment for overall tooth and gum condition, 1 of 3 dental variables, had an impact on the magnitude of the RR leading to a change from 1.6 to 1.8. No elevated odds ratios were observed for moderate intake of either fish or shellfish, the 2 contributors to the category; however, for both items the RR for high intake was 1.4.

Only 10% of women were reported to consume pickled meats and fish; smoked meat and fish (49%) and charcoal-grilled meat and fish (37%) were more commonly consumed. There was little or no evidence for any overall association with charcoal-grilled or with pickled meats or fish. Elevated risks were seen for smoked beef (RR, 1.8; $p = 0.13$), which was eaten by 26 women; smoked poultry (RR, 3.7; $p = 0.03$); and smoked fish (RR, 3.3; $p = 0.03$), although fewer than 20 respondents reported consumption of the latter 2 foods. However, the smoking of meats and fish was not consistently related to risk, since the RR for the 302 persons who ate smoked pork was only 1.1.

Dairy Products and Eggs. High or moderate consumption of dairy products and eggs was not related to oral and pharyngeal cancer risk. The food items contributing to this food group also showed no consistent patterns of risk with consumption. Adjustment by cigarette smoking and snuff changed the odds ratios for dairy and egg consumption slightly from 0.9 for moderate and 1.0 for high intake to 1.0 and 0.8, respectively.

General Nutritional and Medical Status

The white women in the study were lighter in relative weight than other United States women of comparable age. Sixty-seven

% of the total white cases and 66% of white controls had usual adult relative weights less than the median for United States women of the same race and comparable to the case's age at hospitalization or death. More black controls were lighter than the United States median relative weight for blacks (72% were below the median), but only 47% of all black cases were below the median. Overweight women had the same oral and pharyngeal cancer risk as did those close to the United States median weight, while those with ideal or very low weights had race-adjusted relative risks (compared to those of typical weight) of 1.8 and 1.3, respectively, a statistically significant trend ($p = 0.03$). Women who usually ate 3 or more meals per day experienced a nonsignificant decreased risk relative to those who ate less often (RR, 0.8; $p = 0.24$). Although relative weight and meals per day were positively correlated, the RRs for each factor did not change with adjustment for the other factor. Relative weight was positively correlated with intake of each of the food groups, but adjustment by each of the food groups did not diminish the elevated odds ratio for underweight women. In addition, the RRs were not altered when we adjusted for tobacco use, denture wearing, or education.

Information had been obtained by questionnaire regarding diseases previously linked with oral cancer occurrence in the literature. However, only one case and one control were reported to have had syphilis, and none of the women were said by the respondent to have Plummer-Vinson syndrome. A diet predisposing to pellagra and consisting primarily of fatback, cornmeal, and molasses was first identified in the southeastern United States in the early 1900's (12). After elevated risks for pork products were observed, a "pellagra-prone" index based on bacon, sausage, ham-pork, and cornbread intake was created. The RR of 1.3 for high consumption was less than the comparable RR for the pork products groups, and no trend with increasing intake was observed.

Table 6
Odds ratios^a with case and control series restrictions

	Consumption level	All cases (N = 227) vs. all controls (N = 405)	Hospital incident cases ^b (N = 117) vs. all controls (N = 405)	Hospital incident cases (N = 117) vs. acute controls ^c (N = 361)	Anatomic site	
					Oral cavity cases (N = 157) vs. matched controls (N = 294)	Pharynx cases (N = 69) vs. matched controls (N = 110)
Fruits and vegetables	Moderate	0.7	0.5	0.6	0.9	0.3
	High	0.5	0.5	0.5	0.6	0.4
Bread and cereals	Moderate	0.9	0.8	0.8	0.9	0.8
	High	0.6	0.6	0.6	0.6	0.5
Pork products	Moderate	1.3	1.5	1.5	1.3	1.2
	High	1.5	1.5	1.5	1.6	1.3
Fish and shellfish	Moderate	1.4	1.8	2.0	1.6	1.0
	High	1.6	1.9	1.9	1.9	0.9
Dairy products and eggs	Moderate	0.9	0.9	0.9	0.8	1.4
	High	1.0	1.0	1.0	0.9	1.1

^a Relative to low consumption.

^b Cases ascertained from participating hospitals and initially diagnosed during 3-year study period.

^c Controls with diagnoses unrelated to or unaffected by diet.

Eating Style and Spices and Condiments

Whether fluids were consumed with meals was unrelated to oral and pharyngeal cancer risk (RR, 1.0). Eating faster than other people (RR, 0.4; $p = 0.05$) and drinking beverages that are very hot (RR, 0.7; $p = 0.24$) were inversely related to risk.

Moderate (RR, 1.0) or heavy (RR, 0.9) use of condiments (mustard, ketchup, steak sauce) and spices (pepper, hot peppers, curry powder, chili sauce, hot sauce) was not significantly related to cancer risk, nor was the use of any individual condiment or spice. Only 38% of the study population used "hot" spices, a category which included hot peppers, chili sauce, or hot sauce, with an associated risk of 0.9 ($p = 0.5$).

Case and Control Subpopulations

Minimal changes in the estimated RRs were evident when the case and the control series were restricted to subsets of the study population likely to have different relationships with dietary factors (see Table 6). Relative risks for fruits and vegetables, breads and cereals, and dairy products and eggs were virtually unchanged when the 100 cases identified through death certificates and the 10 prevalent cases (those hospital cases initially diagnosed prior to the 1975–1978 study period) were excluded from the analysis. When the 117 hospitalized incident cases were compared with only the 361 controls with conditions unrelated to diet ("acute" conditions³), the patterns originally present in the total population also remained evident for the most restrictive case and control definitions. Slightly stronger associations for fish-shellfish were observed when the case and control definitions were more restricted.

When oral cavity cancer cases and their matched controls were examined separately from pharyngeal cancer cases and controls, the direction of the odds ratios remained consistently above 1 for pork products and below 1 for fruits and vegetables

³ Excluded were women with chronic conditions which might significantly influence or are influenced by dietary patterns (neoplasms of the digestive system, ulcers, diabetes, diseases of the intestine, cholelithiasis, dental and facial anomalies, esophageal inflammatory disease, and nutritional deficiencies).

and for cereals and breads; for the latter 2 food groups, the RRs were even lower for the pharyngeal cancer cases than for the oral cavity cancer cases. Elevated RRs for the oral cavity but not for the pharynx were observed with intake of fish and shellfish.

DISCUSSION

This study of diet and oral and pharyngeal cancer revealed clear differences in adult food consumption between women with cancer and controls, suggesting that nutritional factors may play an important role in the origins of these neoplasms.

The most compelling findings concerned the dose-dependent reduction in risk associated with fruit and vegetable consumption, with the high consumers (21 or more portions per week) at approximately one-half the risk of low consumers (less than 11 portions per week). The reduced risks with increasing consumption of the fruit and vegetable food group were consistently observed for the individual food items composing the food group and within subgroups reflecting a wide variety of demographic and life-style characteristics (e.g., education, race), although the reduction was most prominent among smokers. None of the many factors that we examined separately (in the stratified analysis) or together (in the logistic analysis) introduced any substantial confounding of the RR estimates.

The apparent protective effect noted for high consumption of total fruits and vegetables is consistent with several biological mechanisms. Fruits and vegetables are the primary source of β -carotene, which is metabolized to retinol (vitamin A) in humans. Numerous animal and cell culture studies have shown cancer inhibition by retinoids (34), and evidence is mounting from epidemiological studies of several epithelial cancers that high intake of vitamin A-containing foods may be protective (2, 14, 15, 25). There is also evidence that mean serum retinol levels are lower in those who ultimately develop cancer (17, 36).

β -Carotene itself, the level of which in serum is far more closely related to dietary intake than is retinol, has been postulated to have an effect independent of that for retinol (30). One small follow-up survey implicated dietary β -carotene, rather than re-

tinol, in the reduced risk of lung cancer (33). We did not obtain information on all major retinol- and carotene-containing foods and could not develop indices of consumption to evaluate adequately the relative contributions of these 2 micronutrients. However, retinol is present in substantial amounts in milk, cheese, and eggs, whereas β -carotene is present in fruits and vegetables. Our finding of a very weak and inconsistent association between oral and pharyngeal cancer and dairy products and eggs suggests that retinol may not be a protective factor.

Vitamin C also has been suggested as an anticancer agent primarily because it inhibits the formation of nitrosamines from amines (or amides) and nitrite (26). Vitamin C is found almost exclusively in fruits and vegetables. Since we asked only about the consumption of fresh fruit, green leafy vegetables, and other vegetables, we were unable to examine separately the contributions of total fruits and vegetables, vitamin C, and β -carotene.

The inverse association between intake of the breads and cereals food group and cancer risk was close in magnitude to that for fruits and vegetables and appeared independent of the effect of the other food groups including fruits and vegetables. This absence of confounding implies that the distribution of other food groups cannot account for this association. However, the effect seemed to be limited to whole-grain breads and cereals. One hypothesis that could account for an apparent protective effect of both fruits and vegetables and bread and cereals is that the bulk and fiber of these foods may cleanse the mouth and throat of ingested carcinogens.

In contrast to the apparent reduction in risk with high fruit and vegetable and high bread and cereal consumption, increasing consumption of pork products and of fish and shellfish were related to increasing oral and pharyngeal cancer risk. The association with pork consumption was inconsistent, the positive association coming entirely from a strong relationship among the lowest social class while those in the highest social class who consumed a large amount of pork were actually at a decreased risk. This inconsistency casts doubt on the association. Alternatively, the form of pork consumed or a pork preparation or storage method used by the least educated might account for the increased risk, since many study subjects ate pigs which had been killed and prepared on their own farms. Thus, while the pork products and fish-shellfish associations persisted after controlling for fruit and vegetable intake, the biological meaningfulness of these associations is unclear.

There are several studies of nutrition and oral cancer with which to compare our findings. No differences were found between oral cancer cases and controls in the percentage of patients with an "adequate diet" (9), in the intake of a number of specific food items in a New York study (13), or in a population based study of oral cavity, pharyngeal, and esophageal cancer in Puerto Rico (23). In a case-control study of oral cavity cancers in New York (40), no consistent patterns of risk in both men and women were observed for specific food items and food groups. However, Marshall *et al.* (21) did find in their questionnaire survey lower dietary intake of vitamins A and C in cases compared to non-cancer controls. Studies in India have shown that serum vitamin A and carotene levels are lower in oral and oropharyngeal cancer cases than in controls (5, 35); however, changes in serum vitamin A levels as a consequence of the cancer cannot be ruled out.

A common criticism of case-control studies of diet and cancer is that differences between cases and controls may be a con-

sequence of the disease process in the cases. Cancer in general and oral and pharyngeal cancer in particular may interfere with the patient's ability to eat and may lead to dietary disturbances. To avoid this form of bias, the questionnaire was oriented to usual adult dietary patterns and not to recent habits. In addition, we analyzed subsets of the cases and controls in several ways because of our concerns that the cases' or controls' dietary patterns may have changed due to the symptoms of disease. The associations observed with the entire case group were observed in those whose onset of disease was most recent (the incident cases). In addition, the associations were specific for certain food groups, while one might expect more of an across-the-board effect resulting from disease symptomatology.

When a hospital control group is used, there is a possibility that the conditions of the patients in the control group may have influenced their diet, or conversely dietary factors may have contributed to disease occurrence in some members of the control group. However, we found no substantial differences in the relative risks even when we further restricted the study population by including in the control series only those with "acute" conditions presumably unrelated to dietary factors.

Two other concerns in the interpretation of case control investigations of nutrition and cancer are the validity of the diet history method of data collection and the value of interviews conducted with next of kin rather than with the subject herself. In a review of dietary assessment methods, Block (3) suggests that diet history methods, like the one used here, usually are in reasonable agreement with results obtained from other dietary methods (e.g., 24-hr recall) and with certain clinical measurements (e.g., serum vitamin C). Moderately high correlations for dietary items are observed with reinterview of study subjects, especially when the interval between interviews is relatively short (e.g., 6 months) (8, 16, 29), indicating that diet history methods can provide acceptable test-retest reliability. Surveys of comparability of responses between subjects and surrogates also have generally shown adequate agreement on dietary or height and weight questions when the surrogates are close relatives (18, 22, 32). Most surrogate respondents in our research were close relatives of the study subjects who would be expected to be familiar with the subjects' dietary habits. In addition, our estimates of risk adjusted for respondent type were virtually the same as the initial estimates. Because next of kin were respondents for some of the cases (and also because the dietary component of the questionnaire was designed to generate rather than test hypotheses), portion size information was not collected. However, since the study population of women was relatively homogeneous in age and region of the country, it was assumed that food frequencies would vary more than portion size.

Finally, any misclassification of dietary habits due to deficiencies in the method or recall of the subjects is likely to be random (i.e., similar for cases and controls), since the study population was unaware of the specific suspicions about links between diet and oral cancer. Such random misclassification could not produce a spurious association but could tend to obscure a real one (6). Thus, while such difficulties could have caused us to miss an important finding, they are unlikely to be responsible for the observed associations.

In summary, the reduction in risk associated with fruit and vegetable consumption is dose dependent and unconfounded by other aspects of life-style. Risks are of modest magnitude, which may be expected in a population which is relatively ho-

mogeneous with respect to diet. However, the association has biological plausibility and is consistent with findings for epithelial cancer in other studies. Although this study does not provide definitive answers, it does add to the enthusiasm for additional work to confirm and refine our understanding of the role of diet and micronutrients in cancer etiology.

ACKNOWLEDGMENTS

We thank Westat, Inc., Rockville, MD, for data collection activities; ORI, Inc., Bethesda, MD, for computer programming support; the Environmental Epidemiology Section of the National Cancer Institute's Environmental Epidemiology Branch for their insightful comments; and Theresa Pino and Michele Rasa for valuable secretarial support.

REFERENCES

1. Abraham, S., Carroll, M., Najjar, M., and Fulwood, R. Obese and overweight adults in the U.S. (Vital and Health Statistics; Ser. 11, Data from the National Health Surveys No. 230). DHHS Publication No. (PHS) 83-1680. Hyattsville, MD: National Center for Health Statistics, 1983.
2. Bjelke, E. Dietary vitamin A and human lung cancer. *Int. J. Cancer*, 15: 561-565, 1975.
3. Block, G. A review of validations of dietary assessment methods. *Am. J. Epidemiol.*, 115: 492-505, 1982.
4. Blot, W. J., Winn, D. M., and Fraumeni, J. F., Jr. Mouthwash and oral cancer. *J. Natl. Cancer Inst.*, 70: 251-253, 1983.
5. Chaudhy, N. A., Jafarey, N. A., and Ibrahim, K. Plasma vitamin A and carotene levels in relation to the clinical stages of carcinoma of the oral cavity and oropharynx. *JPMA*, 30: 221-223, 1980.
6. Copeland, K. T., Checkoway, H., McMichael, A. J., and Holbrook, R. H. Bias due to misclassification in the estimation of relative risk. *Am. J. Epidemiol.*, 105: 488-495, 1977.
7. Cox, D. R. *The Analysis of Binary Data*. London: Methuen, 1970.
8. Dawber, T. R., Pearson, G., Anderson, P., Mann, G. V., Kannel, W. B., Shurtleff, P., and McNamara, P. Dietary assessment in the epidemiologic study of coronary heart disease: the Framingham study. II. The reliability of measurement. *Am. J. Clin. Nutr.*, 11: 226-234, 1962.
9. Feldman, J. G., and Hazan, M. A case-control investigation of alcohol, tobacco, and diet in head and neck cancer. *Prev. Med.*, 4: 444-463, 1975.
10. Food and Nutrition Board. *Recommended Dietary Allowances*, Revised Ed. 9. Washington, D.C.: National Academy of Sciences, 1980.
11. Gart, J. J. The comparison of proportions: review of significance tests, confidence intervals, and adjustments for stratification. *Rev. Int. Statist. Inst.*, 39: 148-169, 1971.
12. Goldberger, J. The cause and prevention of pellagra. In: M. Terris (ed.), *Goldberger on Pellagra*, pp. 23-26. Baton Rouge, LA: Louisiana State University Press, 1964.
13. Graham, S., Dayal, H., Rohrer, T., Swanson, M., Sultz, H., Shedd, D., and Fischman, S. Dentition, diet, tobacco, and alcohol in the epidemiology of oral cancer. *J. Natl. Cancer Inst.*, 59: 1611-1618, 1977.
14. Graham, S., Mettlin, C., Marshall, J., Priore, R., Rzepka, T., and Shedd, D. Dietary factors in the epidemiology of cancer of the larynx. *Am. J. Epidemiol.*, 113: 675-680, 1981.
15. Hirayama, T. Diet and cancer. *Nutr. Cancer*, 1: 67-81, 1979.
16. Jain, M., Howe, G. R., Johnson, K. C., and Miller, A. B. Evaluation of diet history questionnaire. *Am. J. Epidemiol.*, 111: 212-219, 1980.
17. Kark, J. D., Smith, A. H., Switzer, B. R., and Hames, C. G. Serum vitamin A (retinol) and cancer incidence in Evans County, Georgia. *J. Natl. Cancer Inst.*, 66: 7-16, 1981.
18. Kolonel, L. N., Hirohata, T., and Nomura, A. Adequacy of survey data collected from substitute respondents. *Am. J. Epidemiol.*, 106: 476-484, 1977.
19. Mantel, N. Chi-square tests with one degree of freedom, extensions of Mantel-Haenszel procedure. *J. Am. Statist. Assoc.*, 58: 690-700, 1963.
20. Mantel, N., and Haenszel, W. Statistical aspects of the analysis of data from retrospective studies of disease. *J. Natl. Cancer Inst.*, 22: 719-748, 1959.
21. Marshall, J., Graham, S., Mettlin, C., Shedd, D., and Swanson, M. Diet in the epidemiology of oral cancer. *Nutr. Cancer*, 3: 145-149, 1982.
22. Marshall, J., Priore, R., Haughey, B., Rzepka, T., and Graham, S. Spouse-subject interviews and the reliability of diet studies. *Am. J. Epidemiol.*, 112: 675-683, 1980.
23. Martinez, I. Factors associated with cancer of the esophagus, mouth, and pharynx in Puerto Rico. *J. Natl. Cancer Inst.*, 42: 1069-1094, 1969.
24. Mason, T. J., McKay, F. W., Hoover, R., Blot, W. J., and Fraumeni, J. F., Jr. *Atlas of Cancer Mortality for U. S. Counties, 1950-1969*. DHEW Publication No. (NIH) 75-780. Washington, DC: Government Printing Office, 1975.
25. Mettlin, C., and Graham, S. Dietary risk factors in human bladder cancer. *Am. J. Epidemiol.*, 110: 255-263, 1979.
26. Mirvish, S. S., Wallcave, L., Eagen, M., and Shubik, P. Ascorbate-nitrite reaction: possible means of blocking the formation of N-nitroso compounds. *Science (Wash. DC)*, 177: 65-68, 1972.
27. National Center for Health Statistics. *Eighth Revision International Classification of Diseases (Adapted for Use in the United States)*, Vol 1. DHEW Publication No. (PHS) 1693. Washington, DC: Government Printing Office, 1968.
28. National Center for Health Statistics. *Overweight Adults in the United States*. Advance data, No. 51. Hyattsville, MD: National Center for Health Statistics, 1979.
29. Nomura, A., Hankin, J. H., and Rhoads, G. G. The reproducibility of dietary intake data in a prospective study of gastrointestinal cancer. *Am. J. Clin. Nutr.*, 29: 1432-1436, 1976.
30. Peto, R., Doll, R., Buckley, J. D., and Sporn, M. B. Can dietary beta-carotene materially reduce human cancer rates. *Nature (Lond.)*, 290: 201-208, 1981.
31. Prentice, R. Use of the logistic model in retrospective studies. *Biometrics*, 32: 599-606, 1976.
32. Rogot, E., and Reid, D. D. The validity of data from next-of-kin in studies of mortality among migrants. *Int. J. Epidemiol.*, 4: 51-54, 1975.
33. Shekelle, R. B., Liu, S., Raynor, W. J., Lepper, M., Maliza, C., Rossof, A. H., Paul, O., Shryock, A. M., and Stamler, J. Dietary vitamin A and the risk of cancer in the Western Electric study. *Lancet*, 2: 1185-1189, 1981.
34. Sporn, M. B., Dunlop, N. M., Newton, D. L., and Smith, J. M. Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). *Fed. Proc.*, 35: 1332-1338, 1976.
35. Wahi, P. N., Kehar, U., and Lahiri, B. Factors influencing oral and oropharyngeal cancers in India. *Br. J. Cancer*, 19: 642-660, 1965.
36. Wald, N., Idle, M., Boreham, J., and Bailey, A. Low serum-vitamin-A and subsequent risk of cancer. *Lancet*, 2: 813-815, 1980.
37. Winn, D. M., Blot, W. J., and Fraumeni, J. F., Jr. Snuff dipping and oral cancer. *N. Engl. J. Med.*, 305: 230-231, 1981.
38. Winn, D. M., Blot, W. J., Shy, C. M., and Fraumeni, J. F., Jr. Occupation and oral cancer among women in the South. *Am. J. Indust. Med.*, 3: 161-167, 1982.
39. Winn, D. M., Blot, W. J., Shy, C. M., Pickle, L. W., Toledo, A., and Fraumeni, J. F., Jr. Snuff dipping and oral cancer among women in the southern United States. *N. Engl. J. Med.*, 305: 745-749, 1981.
40. Wynder, E. L., Bross, I. J., and Feldman, R. M. A study of the etiologic factors in cancer of the mouth. *Cancer (Phila.)*, 10: 1300-1323, 1957.