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Papers

Smoking, Alcohol, Dentition and Diet in the Epidemiology of Oral Cancer

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This matched case-control study was conducted in Western New York. The smoking, alcohol consumption, dental hygiene and diet of 290 cases were compared with those of 290 sex-, age-, and neighbourhood-matched controls. The results confirm earlier findings that cigarette smoking and alcohol consumption impart substantial risks of oral cancer. The results also confirm that poor oral hygiene increases the risk of oral cancer, although this effect is much smaller than those of cigarette smoking and alcohol consumption. The results suggest that, of macronutrients, intake of fat is more likely than those of protein or carbohydrate to be related to risk. Of micronutrients, calcium, sodium, riboflavin and retinol are associated with risk, while thiamin, niacin, and dietary fibre are associated with decreased risk. Although patterns of dietary effects are discernable, these effects are in general much weaker than are those of smoking and alcohol consumption.
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INTRODUCTION

ORAL CANCER represents a major form of cancer in Asia and the Pacific Islands. It is less significant in Europe and the USA; nevertheless, it is responsible for approximately 9000 deaths in the USA each year [1].

As treatment of oral cancer is relatively ineffective and often disfiguring and debilitating, any aetiological clues which might be used in its prevention would be highly useful. Apart from the roles of tobacco and alcohol, however, little is known about the epidemiology of oral cancer in the USA. It has been clearly documented [2–9] that smoking and alcohol use increase the risk of oral cancer, and it is suspected, [7–10] that poor oral hygiene or compromised dentition might also increase risk, but the independence and magnitudes of these effects have not been studied in depth [9]. Relatively little is understood about the manner in which dentition and diet alter oral cancer risk; there is need to identify the most relevant aspects of dentition and diet [9, 16, 26–31].

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This study was designed to assess the impact of oral hygiene, dentition and diet, with adjustment for the effects of alcohol ingestion and smoking, on oral cancer risk.

PATIENTS AND METHODS

Pathologically-confirmed cases were identified from pathology records of the 20 major hospitals of the three western New York counties of Erie, Niagara and Monroe between 1975 and 1983. Securing cases from most of the hospitals in three counties, we avoided the bias which could result from obtaining them from only a few hospitals in a few communities. Six small hospitals—each saw few patients—were not included in this study. The counties include the cities of Buffalo, Niagara Falls, Lackawanna and Rochester plus many smaller towns, villages and rural populations. Controls were neighbourhood-, age- and sex-matched. Since the number of black cases was expected to be too small for meaningful analysis, blacks were excluded from the study.

Because of the uncertainty inherent in the use of surrogate-provided data with regard to the study variables, we limited responses to those directly provided by the subjects. Thus, the case sample consisted of oral cancer patients from hospitals in Erie, Niagara and Monroe Counties, deemed by their physicians to be able to withstand a lengthy interview, living by the time contacted, and willing to be interviewed.

We were not able to secure physician permission to contact 15% of the patients identified. Of the 513 contacted, 16%, were too ill, or were judged by the interviewer to be mentally incompetent; 23%, refused to participate, and 60% of those contacted, completed an interview. The 290 controls

matched to cases represented 41% of the number contacted. Given the above exigencies and limited resources, and recognising the value of population-based inquiry, we emphasise that this study is much more modest than a population-based one.

The cases interviewed were, for the most part, interviewed relatively soon after diagnosis: the median lag between diagnosis and interview was a little more than 2 months, and almost all cases were interviewed within 6 months of diagnosis. Their cancers were almost exclusively squamous cell carcinoma (90%), with site concentrated on the tongue (28%), oropharynx, (22%), floor of mouth (14%) or pharynx or hypopharynx (13%).

Neighbourhood matching was accomplished by a procedure designed to sample dwellings in the neighbourhood of the case. After the case was interviewed, the interviewer sought a control of like age (within 5 years), race and sex at the household a pre-specified number of doors to the left of the case dwelling, then the same number of doors to the right of the case dwelling, then at the next dwelling to the left of the first potential control, and so on. This procedure was intended to discourage interviewers from selecting residences that might have differed systematically from those of the cases. As soon as a matched and willing control was located, an interview was arranged. By matching on neighbourhood, we hoped to draw each control from a social milieu similar to that of the case to which he or she was compared. We used this procedure rather than assume *a priori* that we could measure and statistically adjust for all the social and demographical factors that might distinguish cases from controls.

Non-participation by controls was greater than hoped. Our procedure amounted to a separate sampling in the neighbourhood of each case interviewed. In the bulk of these neighbourhoods, the first suitable control contacted was interviewed; for 222 of the 290 control interviews, the control was recruited after two or fewer refusals. Unfortunately, in certain neighbourhoods, the interviewer had considerable difficulty identifying a control willing to participate. Generally, however, poor response was isolated and not characteristic of the majority of subjects.

The interview, which required 2–3 h for administration, emphasised smoking and tobacco use, alcohol ingestion, dental history and diet. The use of cigarettes, cigars, pipes, snuff and chewing tobacco was considered. Cigarette exposure was arrayed in pack-years, the pack-year defined as the number of packs per day multiplied by the number of years that amount was smoked. The subject was asked the frequency with which he or she consumed each type of alcohol (beer, wine, spirits), then the amount usually consumed on each occasion. The quantity data were multiplied by reported duration of consumption. The separate quantity–frequency–duration estimates were combined to provide a total exposure index.

The dentition and oral hygiene assessment of cases and controls concerned two basic aspects of oral health. The first, tooth loss, included the loss and replacement of teeth, history of use of dentures, partials and bridges, and periods during which subjects had neither teeth nor dentures. A second dimension emphasised hygiene: tooth brushing, denture cleaning, flossing, Water Pic use, dental check-up practices, and dental irradiation exposure. Also considered were visits to the dentist for various forms of acute conditions or disease: white patches, infection or inflammation, sharp or jagged teeth, toothache or crooked teeth.

The dietary assessment emphasised food frequency. Over 120 commonly consumed food items were considered. In addition to frequency, we considered quantities usually consumed, usual cooking or preparation, storage, and addition of seasonings or condiments. These dietary data were then used to construct indices of exposure to calories and to major macro- and micronutrients.

Analysis

The data were analysed by both conditional (matched) and unconditional (unmatched) logistic regression. The results presented, based on matched analysis, represent the comparison of 290 pairs. As the matching was designed to control for age, sex, and the social class of the respondent, the unmatched summary analyses were conducted with control for age, sex and social class, the latter operationally defined by years of education. The findings presented are nearly identical to those derived by unmatched analysis.

RESULTS

Table 1 describes the overall demographic characteristics of cases and controls. The matching procedure resulted in a control series very similar in basic demographic status to the case series.

Table 2 describes the impact of cigarette smoking on oral cancer risk. Although risk did not increase in strict dose–response fashion, it was sizably and significantly elevated from the third to the seventh exposure category. Cigar and pipe smoking were also considered; their effects appeared to be of little consequence. There was a risk associated with chewing tobacco, but it was insignificant, with very few people exposed. Table 3 summarises the association of alcohol use with the risk of oral cancer; with subjects arrayed in control exposure quintile categories, risk increased in dose–response fashion from quintiles 2 to 4, with a relative risk of nearly 15

Table 1. Demographic characteristics of western New York oral cancer cases and controls

	Case		Control	
	n	%	*n*	%
Sex				
Male	201	69	201	69
Female	89	31	89	31
Total	290	100	290	100
Age				
≤50	38	13	42	14
51–55	40	14	43	15
56–60	65	22	57	20
61–65	53	18	51	18
66–70	45	16	49	17
71–75	30	10	24	8
76+	19	7	24	8
Total	290	100	290	100
Education				
Graduate school +	10	4	17	6
College graduate	21	7	21	7
Some college	28	10	32	11
Trade, tech school	24	8	26	9
High school graduate	76	26	72	25
Less than high school	129	45	122	42
Total	288	100	290	100

Table 2. Smoking and oral cancer risk in western New York: matched pairs analysis

Cigarettes (pack-years)	Odds ratios (95% C.I.)
0	1.0
1–20	1.3 (0.7, 2.4)
21–30	2.7 (1.2, 6.0)
31–40	2.9 (1.5, 5.9)
41–50	7.0 (3.3, 15.1)
51–70	7.7 (3.7, 15.9)
71+	5.7 (2.7, 12.1)

P (trend) < 0.0001.

Table 3. Alcohol use and oral cancer risk in western New York: matched pairs analysis

Quantity–frequency–duration (Quintile)	Odds ratio (95% C.I.)
1	1.0
2	2.4 (1.1, 5.2)
3	2.7 (1.2, 6.1)
4	3.4 (1.6, 7.4)
5	14.8 (6.8, 32.3)

P (trend) < 0.0001.

in quintile 5. Separate examinations of synergy between alcohol and tobacco revealed no effects beyond the additive ones noted.

Dentures, loss of teeth

Table 4 describes the associations of oral cancer risk with denture use and with loss of teeth. A significant association of risk with years with dentures was seen. Adjustment for alcohol and tobacco use, as in column 2, however, diminished the impact of duration of denture use. The number of the subject's sets of dentures was associated with little change in oral cancer risk. Having had one set of dentures, in fact, increased risk more than having had two or more, and control for smoking and alcohol use diminished even those effects to statistical insignificance. No risk elevation accompanied the use of partials or bridges.

Table 4. Denture and tooth loss history and oral cancer risk in western New York: matched pairs analysis

	Odds ratio (95% C.I.)	Odds ratio* (95% C.I.)
Years with dentures		
<1	1.0	1.0
1–5	2.0 (0.9, 4.4)	1.1 (0.4, 2.9)
6–10	2.2 (1.0, 4.6)	1.3 (0.5, 3.2)
11–20	1.5 (0.9, 2.8)	0.9 (0.4, 1.9)
21–30	1.9 (1.1, 3.3)	1.3 (0.7, 2.5)
31+	2.7 (1.4, 5.0)	2.1 (1.0, 4.5)
P trend	<0.002	<0.077
Sets of dentures		
0	1.0	1.0
1	2.0 (1.3, 2.9)	1.4 (0.9, 2.2)
2+	1.6 (1.0, 2.6)	1.0 (0.6, 1.8)
P trend	<0.004	<0.318
Teeth lost but not replaced		
0	1.0	1.0
1, 2	0.3 (0.2, 0.6)	0.5 (0.2, 1.1)
3, 4	1.0 (0.5, 1.7)	1.1 (0.6, 2.3)
5–10	1.2 (0.6, 2.1)	1.4 (0.7, 2.9)
11+	3.2 (1.5, 6.7)	2.7 (1.1, 6.5)
P trend	<0.001	<0.018

*Adjusted for smoking and alcohol by multiple logistic regression.

The risk imposed by teeth lost but not replaced (LNR) persisted with statistical control for smoking and alcohol use. The data suggested a nonlinear pattern: the loss and nonreplacement of one or two teeth associated with lower risk, the loss of 11 or more teeth with substantially elevated risk. This effect was not related to dentures; those with dentures were defined as having replaced all of their teeth. A risk increase was observed to accompany the subject's ever having been edentulous (not presented). The number of subjects with this condition, however, was small.

The subjects were also asked about long-term, prolonged oral soreness or difficulty in chewing, but no risk was observed. The subjects were questioned about visits to dentists for white patches, gum infection or inflammation, sharp or jagged teeth, toothache, or for crooked teeth. None of these conveyed any increase in risk. Nor was any noteworthy risk increase associated with any combination of them.

Hygiene

Mouthwash use was considered as an oral cancer risk factor. The only significant risk elevations were among the most recent users of mouthwash. Total duration of mouthwash use did not add to risk.

We also considered the association between tooth brushing practices and oral cancer risk. Both the frequency of brushing and the reported amount of time expended each time the teeth were brushed appeared to have only a weak, negligible bearing on risk. No risk gradient according to denture cleaning frequency was observed among those with dentures. Regular use of dental floss was associated with a statistically non-significant decrease in oral cancer risk.

Although failure to secure regular dental check-ups was associated with a statistically significant increase in oral cancer risk, no dose–response was observed. No association of X-ray exposure and risk was observed.

Because these data provided equivocal evidence that dentures and poor oral hygiene were related to oral cancer risk, and because these several oral hygiene practices could to some extent reflect a common factor, we examined whether an overall hygiene effect might be independent of the other dentition and denture exposure variables. A single standardised hygiene variable was developed composed of the strongest hygiene risk indicators: standardised brushing, flossing, and regular check-up index scores.

Table 5 reflects the results of our simultaneous analyses of multiple dental factors: we considered the effects of dentures, teeth lost and not replaced, and the hygiene index, adjusting for alcohol use and smoking. The data indicated that, although denture use was associated with increased risk, the confidence intervals about the estimates of that effect all included unity. There was little evidence of a dose–response. The LNR effect was significant, revealing the loss and nonreplacement of 11 or more teeth to be associated with a near quadrupling of oral cancer risk. Although hygiene may be protective, the confidence intervals about the effect of each

*Table 5. Dentures, loss and non-replacement of teeth, and hygiene and oral cancer risk in western New York: simultaneous matched pairs analysis**

Risk factor	Odds ratio (95% C.I.)
Baseline	1.0
Dentures (years)	
1–10	1.7 (0.7, 4.4)
11–20	1.0 (0.4, 2.8)
21–30	1.5 (0.6, 3.9)
31+	2.6 (0.9, 7.7)
P trend	<0.069
Teeth lost, not replaced	
1–2	0.8 (0.3, 2.0)
3–4	1.9 (0.8, 4.5)
5–10	1.9 (0.8, 4.3)
11+	3.9 (1.3, 11.3)
P trend	<0.004
Hygiene (Quintile)†	
2	0.7 (0.4, 1.5)
3	1.1 (0.5, 2.4)
4	0.6 (0.2, 1.7)
5 (best)	0.7 (0.3, 2.1)
P trend	<0.479

*Analysis adjusted for smoking, alcohol consumption.
†Quintile defined by control exposure distribution.

level of oral hygiene included the no-effect point. With tobacco and alcohol consumption held constant, the effects of denture exposure and hygiene practices appeared negligible.

We also considered the extent to which combinations of cigarette, alcohol and LNR exposure increase the risk of oral cancer. For Table 6, cigarette and alcohol intake were dichotomised at the control medians. The upper LNR category was the loss and non-replacement of one or more teeth. Above-the-median alcohol use alone tripled risk, while tobacco exposure alone multiplied risk by a little more than two; poor dentition alone had a more substantial impact. The combination of all three risk factors was the most potent marker of risk: associated with a 12-fold multiplication of oral cancer risk.

Diet and nutrition

Table 7 describes the association of Quetelet Index status 1 year before interview and oral cancer risk. According to categorical analysis (a) by control quartile, those with a higher Quetelet Index were at a decidedly lower risk. This same pattern was seen in part (b), with the Quetelet Index used as a continuous variable. Moreover, this pattern persisted as statistically significant with adjustment for smoking, alcohol consumption and LNR.

Table 6. Oral cancer risk associated with smoking, alcohol consumption and poor dentition in western New York: matched pairs analysis

Dentition (teeth lost, not replaced)	Cigarettes	Alcohol	Odds ratio (95% C.I.)
–	–	–	1.0
–	–	+	3.3 (1.2, 9.2)
–	+	–	2.3 (0.8, 6.2)
+	–	–	8.6 (3.6, 20.9)
–	+	+	0.9 (0.3, 2.7)
+	–	+	2.3 (0.8, 7.0)
+	+	–	3.4 (1.1, 10.8)
+	+	+	12.8 (4.9, 33.8)

Table 7. Quetelet index and oral cancer risk in western New York: matched pairs analysis

(a) Categorical analysis Quetelet index	Odds ratio (95% C.I.)
15–23	1.0
24–25	0.5 (0.3, 0.8)
26–27	0.4 (0.2, 0.6)
28+	0.4 (0.2, 0.6)
(b) Continuous analysis	
Control variables	**Odds ratio (95% C.I.)**
(1) —	0.9 (0.8, 0.9)
(2) Age, education, smoking, alcohol, LNR	0.9 (0.9, 1.0)*

*95% confidence interval does not include 1.0.

Table 8 considers the bearing of calorie and macronutrient (protein, carbohydrate, fat) intake to risk. The estimated impact of total calories was not statistically significant with smoking, alcohol, Quetelet and LNR status considered. To increase interpretability, we standardised each nutrient and ratio variable, so that the logistic coefficient described the relative risk accompanying a single standard-deviation increase in intake or the ratio of intakes. As Willett and Stampfer have recommended, we adjusted for calories in considering the impact of macronutrients; in general, however, the data provide little or no evidence that any one macronutrient is related to risk. We also considered the ratio of each

Table 8. Calories, macronutrients and oral cancer risk in western New York: matched pairs logistic regression

Macronutrient	Control variables*	Odds ratio (95% C.I.)
Total calories		
a		1.2 (1.0, 1.4)
b	2–5	1.2 (0.9, 1.5)
Protein (g)		
a		1.1 (1.0, 1.4)
b	1	0.9 (0.6, 1.4)
c	1–5	0.8 (0.5, 1.4)
Carbohydrates (g)		
a		1.1 (0.9, 1.3)
b	1	0.6 (0.4, 0.9)
c	1–5	0.8 (0.4, 1.3)
Fat (g)		
a		1.3 (1.1, 1.6)
b	1	2.1 (1.3, 3.4)
c	1–5	1.6 (0.9, 3.0)
Protein/(carbohydrate, fat)		
a		1.1 (0.9, 1.3)
b	2–5	1.0 (0.8, 1.2)
Carbohydrate/(fat, protein)		
a		0.8 (0.7, 0.9)
b	2–5	0.9 (0.7, 1.1)
Fat/(carbohydrate, protein)		
a		1.5 (1.3, 1.9)
b	2–5	1.3 (1.0, 1.7)

*Control variables 1–5 include, respectively, total calories, smoking, alcohol, Quetelet, and LNR.

macronutrient to the other two; only that of fat to carbohydrate and protein was statistically significant.

Table 9 considers micronutrient intake and risk, with both bivariate odds ratios and those adjusted for total calories, Quetelet, smoking, alcohol intake and LNR status. Again, the logistic coefficient describes the change in relative risk accompanying a single standard-deviation increase in intake. Calcium, sodium, riboflavin, vitamin D and retinol were associated with increased relative risk, and those increased risks tended to persist with adjustment for the noted control variables. Vitamin C and carotene were associated with negligible risk alterations, regardless of whether the noted confounding variables were considered. Thiamine, niacin and dietary fibre were associated with significant protective effects, with total calories and the other control variables taken into account. These protective effects were not significant unless calories were controlled in the analysis. The impacts of several other micronutrients, including ash, phosphorous, iron, and vitamin E were considered, but these were in general quite weak. In addition, the impacts of nutrients were considered by general food source category. For example, the association of dietary fibre and risk was evaluated with fibre from fruits, vegetables, and other sources considered separately. In general, however, these analyses lent little additional clarity to the patterns observed in Table 9. The partial effects of alcohol, smoking, dentition and Quetelet, adjusted for diet, are not displayed. These effects were not, in general, affected to any noticeable degree by adjustment for dietary practices.

Table 9. Micronutrients and oral cancer risk in western New York: matched pairs logistic regression

Micronutrient	Control variables*	Odds ratio (95% C.I.)
Calcium (g)		
a		1.4 (1.2, 1.7)
b	1–5	1.6 (1.2, 2.3)
Sodium (mg)		
a		1.4 (1.2, 1.7)
b	1–5	2.3 (1.4, 3.8)
Thiamine mg		
a		1.0 (0.9, 1.2)
b	1–5	0.4 (0.2, 0.7)
Riboflavin (mg)		
a		1.4 (1.1, 1.7)
b	1–5	1.8 (1.2, 2.9)
Niacin (mg)		
a		1.0 (0.9, 1.2)
b	1–5	0.5 (0.3, 0.8)
Vitamin C (mg)		
a		0.9 (0.8, 1.1)
b	1–5	0.9 (0.7, 1.2)
Vitamin D (iu)		
a		1.3 (1.1, 1.6)
b	1–5	1.3 (1.0, 1.7)
Dietary fibre (g)		
a		0.9 (0.8, 1.1)
b	1–5	0.6 (0.4, 0.9)
Carotene (iu)		
a		0.9 (0.8, 1.1)
b	1–5	1.0 (0.8, 1.2)
Retinol (iu)		
a		1.5 (1.2, 1.9)
b	1–5	1.4 (0.9, 2.1)

*Control variables 1–5 include, respectively, total calories, Quetelet, smoking, alcohol, and LNR.

DISCUSSION

These findings support those of several other epidemiological studies of smoking and alcohol use in the epidemiology of oral cancer [2–9]. They confirm that cigarette smoking and alcohol consumption impart substantial, significant risks.

These data suggest that the effects of pipe and cigar smoking as practiced in recent years may be much less significant than cigarette smoking. In this study, the effects of pipe and cigar smoking were considered with and without adjustment for cigarette smoking; in each case the associations of pipe and cigar smoking with risk were minimal. We are not sure why earlier studies [8, 9] showed increased risk with cigar and pipe smoking, while ours did not. The evidence indicting cigarette smoking as a health risk factor may have led some health-conscious cigarette and cigar smokers to shift to pipe smoking to lessen their risk of cancer. Such individuals could have had low risk lifestyles in general. Pipe smokers in this study were, in general, exposed to lower smoke levels than were those in earlier studies.

This study was designed primarily to build on our earlier study of dentition, [9] to distinguish the effects of dentition from those of tobacco and alcohol use, and to examine the contribution of diet to risk. The results suggest that only one aspect of poor dentition is clearly relevant to oral cancer risk: Increases in the number of teeth lost and not replaced may increase risk. This finding, revealed in both bivariate and multivariate statistical analyses, parallels our earlier finding [9] that the risk of oral cancer is positively associated with an index of decayed, missing and repaired teeth. This effect does not appear to be nearly as strong as those of alcohol consumption and smoking. It is also apparent that it is only the loss and replacement of a substantial number of teeth that increases risk; there appears to be little in the way of a dose–response.

Although the extent of denture use appears to be associated with oral cancer risk, that risk, only weakly demonstrated, is eliminated by statistical control for smoking and alcohol consumption. Winn *et al.* [27] reported a similar result. Oral hygiene, whether indicated by single variables or a multivariate index, appears to bear only a negligible association with oral cancer risk. Lower risk is associated with increased tooth brushing and with flossing and greater reliance on dental check-ups, but these effects are insignificant if alcohol and tobacco are taken into account. Even with these variables regarded as indicators of an underlying tendency to pay attention to oral hygiene, the decrease in risk is not statistically significant. Similarly insignificant trends were noted by Franco *et al.* [31].

Although our data support other studies which suggest that mouthwash use is associated with elevated oral cancer risk, [11–14] the temporal patterning of this association in our data, with recent use bearing the greatest risk, indicates [5] that mouthwash use is probably a response to, not a cause of the pathology which eventuates in oral cancer. This will be considered in more detail in a subsequent report.

It is important to consider the bearing of these dentition findings on diet in the epidemiology of oral cancer. Diet has been identified as a potential oral cancer risk factor [16, 26–28, 30, 31]. Diet may have a long-term impact on oral health, and hence on dentition; at the same time, dentition imposes

substantial, immediate limitations on diet. Individuals missing many or all of their teeth will find it difficult or impossible to eat many foods, such as raw vegetables, fruits or whole grain products. While diet and dentition may confound estimates of the effects of each other, it is likely that diet is more immediately determined by dentition than dentition by diet.

Thus, the most reasonable estimate of any dietary factor—calories, Quetelet, or any one nutrient—is its partial effect, adjusted for the other effects. Adjustment for caloric intake is necessary. This is important, because the effects of those dietary variables which are statistically significant are significant only if the other factors, especially calorie intake, are held constant [15–17].

It is important to emphasise the need for caution in evaluating the results of our dietary analysis. First, regardless of the control variables employed, obesity, as indicated by the Quetelet Index one year before interview, was associated with lower risk. Thinness, in other words, was associated with higher risk. This could be partly a result of debilitation resulting from smoking, alcohol use, and poor hygiene and diet. Control for these, however, did not eliminate the effect associated with Quetelet status. Also, many of the dietary effects we observed to be significant have not been noted in other studies. Although vitamin D and calcium have been proposed as protective against cancer at several sites, [18] our data indicate that intake of these is associated with (marginally significant) increased oral cancer risk. Dietary fat has been shown to increase the risk of large bowel cancer; [19] it has not been so consistently linked to oral cancer risk, although McLaughlin *et al.* [30] and Winn *et al.* [27] found meat consumption to be associated with increased risk, and Franco *et al.* [31] found consumption of charcoal grilled meat to increase risk. McLaughlin *et al.* [30] found an index of saturated fat to be associated with increased risk of oral–pharyngeal cancer risk. Dietary fibre has been proposed as protective against cancer of the lower bowel [19] but not against cancer of the oral cavity. Thiamine has not been proposed as protective, nor riboflavin as risk inducing. Niacin has been noted as possibly protective in one recent study [26]. On the other hand, although retinol, beta carotene and vitamin C appeared in our earlier study [16] and in others [27, 28, 31] to be protective against oral cancer; we see little evidence of such protective effects, with or without consideration of other factors, in this study. In a careful analysis, McLaughlin *et al.* [30] found an index of fruit consumption to be more protective than indices of carotene or vitamin C. It is certainly possible that our earlier results were biased: The measures of exposure to these nutrients in this study are much more detailed than in our earlier study.

It bears emphasising that, although the list of nutrients considered in this report is large, the list of nutrients contained in the foods that constitute the American diet is orders of magnitude larger. As we have recognised before [16], it is readily possible that the nutrient indices considered are surrogates for yet other nutrients or biologically active substances in the foods considered.

It is possible that, in spite of our effort to induce subjects to focus on pre-illness diet, the cases' dietary reports were influenced by their very recent, post-disease diets. For example, it is possible that dietary fibre protects against oral cancer, but it is also possible that cases, consuming less dietary fibre as a result of difficulty in chewing or swallowing fibrous foods, had their memories of earlier diet coloured by their more recent diet. Cases were not more likely than controls to report having had difficulty chewing food, but this possibility cannot be definitively rejected.

Several other aspects of the study design also demand interpretive caution. This study cannot be regarded as population-based; it represents comparisons of cases from all but six hospitals in Erie, Niagara, and Monroe Counties in Western New York with neighbourhood controls who were able and willing to submit to a lengthy interview. This could mean that these findings are more representative of people who respond to symptoms and seek treatment early and are, therefore, physically able to participate. They may have had more restorative work than the "typical" oral cancer patient. This may be because the case series included an excess of more educated or affluent oral cancer patients. Since the matching procedure ensured that cases and controls were equivalent in terms of social class, and since lower class subjects are less likely to participate in survey studies, our subjects were probably higher in social class than the typical oral cancer patient. Thus, it is possible that patterns observed (or not observed) in this comparison do not typify all oral cancer patients.

Although we speculated above that the responding cases were likely of higher social class than non-responding cases, whether the lack of response in controls could lead to bias is difficult to definitively assess. The non-respondents were not interviewed, and their traits are not known. Whether subject willingness to respond was a function of major demographic variables such as sex, age or education is unknown. We did examine the distribution of control non-respondents according to the age, sex and education of the case to whom they would have been matched, and it did not appear that there was any identifiable excess of non-respondents in any specific demographic category. Even so, non-demographic characteristics associated with willingness to talk to an interviewer could represent a source of bias. It is possible that alcoholics, or those with disfiguring dental conditions, could be under-represented among controls; this could lead to underestimation or overestimation of the impact of alcohol intake or dentition. Again, however, for there to be serious bias, such factors would have to be independent of age, sex and education; on these factors, cases and controls were closely matched. The likelihood of bias due to non-response in this study design is discussed in more detail elsewhere [19].

It was decided in the design of this study to risk non-response and even non-representativeness in the interest of securing a complete and detailed interview from respondents who had the interest and stamina to provide it. Because of the difficulty of securing data from sick cases, and from controls who will not participate in epidemiological studies, many investigators have used surrogate respondents in recent studies of oral cancer [27–30]. In light of the advice of Gordis [20], McLaughlin, *et al.* [21] and Lyon [22], that serious problems reside in the use of surrogate data, we chose not to interview surrogates. Confidence in the reliability of surrogate data [23] does not legitimise the substitution of surrogate for subject data [24]. If surrogates are needed more for cases than controls and, as Kolonel has shown, surrogates tend to report dietary or other practices at a different level than subjects do, and surrogate data are substituted, bias will likely result. Although smoking and alcohol consumption may be recalled with fair reliability by both subjects and surrogates [24], there have not been good studies of the reliability of reports of

dentition. Dentition and hygiene are probably reported relatively well by subjects, but it is less likely that surrogates can provide useful data on such intimate conditions and practices as numbers of missing teeth, the duration of tooth brushing, or the frequency of mouthwash use. The use of surrogate data in this situation might be expected to induce a conservative bias, although that cannot be determined with certainty.

The conditions under which a less than complete response rate could contribute to bias have been discussed elsewhere, [25]. If, for example, people with lower exposure to protective factors tend to get more ill or die more quickly than those with higher exposure, then the protective effects of the factors could be underestimated: only those with higher exposure would survive long enough to be interviewed. The opposite effect would occur with a risk-increasing factor.

In the last analysis, only the concordance of the findings of this and other human-based studies will provide convincing evidence that they are not biased. Thus, it is worth noting that the findings of this study that smoking and alcohol consumption impart sizable elevations of oral cancer risk are in keeping with those of several other studies [3, 4, 6, 8, 9, 16, 28, 29, 31]. It is also reassuring that the evidence of an elevation of risk with compromised dentition provides limited support to the findings of our earlier investigation [9].

Finally, it must be emphasised that the effects of dentition and dietary practice we observed appear quite modest. They pale when compared with those of cigarette smoking and alcohol consumption.

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