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Familial Risk in Oral and Pharyngeal Cancer

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We examined the relationship between a family history of cancer and risk of oral and pharyngeal cancer using epidemiological data from a large case–control investigation of these tumours. 487 (45.7%) of the cases and 485 (41.0%) of the controls reported cancer in a parent or a sibling. After controlling for age, race, sex, study location, respondent status and smoking and alcohol use, the OR associated with any cancer in the family was 1.1 [95% confidence interval (CI) 0.9–1.3]. Risks were non-significantly elevated among those with a history of cancers arising from the oral cavity/pharynx (OR = 1.2, 95% CI 0.7–2.3), oesophagus/larynx (OR = 1.6, 95% CI 0.7–3.8) and lung (OR = 1.2, 95% CI 0.8–1.8), with the excess risk primarily among those for whom a male relative, particularly a brother, was affected with these smoking-related cancers. In addition, an elevated risk of oral/pharynx cancer was found among those whose sisters developed other cancers (OR = 1.6, 95% CI 1.1–2.2). Subsite analyses revealed stronger elevated risks of smoking-related cancers in relatives of pharyngeal cancer cases (OR = 1.7, 95% CI 1.1–2.8) than of oral cancer patients. The data indicate that there is at most a weak familial aggregation of oral/pharynx cancers. Furthermore, since the excess familial risk of oral/pharynx cancer was associated with smoking-related cancers among male but not female relatives, it seems likely that environmental factors (notably smoking and drinking) contribute to the familial tendency observed in this study. The results underscore the need to collect risk profile information on relatives in future studies to disentangle genetic from environmental determinants.
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INTRODUCTION

TOBACCO SMOKING and alcohol consumption are the major risk factors for oral and pharyngeal cancer in most parts of the world [1]. Based on case reports of a familial occurrence of these tumours, it has been suggested that hereditary factors may also influence risk [2–4]. Most populations studied, however, have not been of sufficient size to address the question of familiality of this cancer from an epidemiological standpoint. Herein we report results from a large multicentre case–control investigation examining the relationship between a family history of cancer and risk of oral and pharyngeal cancer.

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PATIENTS AND METHODS

These data are part of a population-based case–control study of oral and pharyngeal cancer carried out in four areas of the U.S.A. [5].

Incident cases of pathologically confirmed primary oral and pharyngeal cancer [International Classification of Diseases (ICD), 9th revision], codes 141–149, excluding salivary gland cancer (ICD 142) and nasopharyngeal cancer (ICD 147), diagnosed between 1 January 1984 and 31 March 1985, were identified from population-based cancer registries covering metropolitan Atlanta, Los Angeles County, Santa Clara and San Mateo counties south of San Francisco-Oakland, and the state of New Jersey. All cases among white and black residents aged 18–79 years in these areas were eligible for participation in the study. Seventy-five per cent ($n = 1114$) of the eligible cases completed interviews.

Controls in each area were selected from two population sources. Controls under age 65 were identified by a random-digit-dialling technique for sampling households with telephones [6]. Sufficient numbers of individuals were then selected so that the age (in 5-year groups), sex and race (black, white) distribution of the controls was similar to the expected age-sex-race distribution of the cases. The control selection process was sex-specific, so that only a male or female (not

*Table 1. Odds ratios for oral/pharynx cancer associated with a family history of four cancer types and total cancers for several categories of relatives**

Familial relationship	Type of cancer in relatives of cases and controls				
	Oral/pharynx	Larynx/oesophagus	Lung	Other	Total
Any family member	1.2 (0.7–2.3)	1.6 (0.7–3.8)	1.2 (0.8–1.8)	1.0 (0.8–1.3)	1.1 (0.9–1.3)
Father or brother	1.5 (0.7–3.0)	1.9 (0.7–5.2)	1.3 (0.8–2.1)	0.9 (0.7–1.2)	1.0 (0.8–1.3)
Father	1.5 (0.5–4.7)	0.9 (0.2–3.3)	1.2 (0.6–2.2)	1.0 (0.7–1.3)	1.0 (0.8–1.3)
Brother	1.5 (0.6–3.6)	4.4 (0.8–23.5)	1.5 (0.8–3.0)	1.0 (0.6–1.4)	1.2 (0.9–1.7)
Mother or sister	0.8 (0.2–2.8)	0.9 (0.2–5.0)	0.7 (0.4–1.5)	1.2 (0.9–1.5)	1.1 (0.9–1.4)
Mother	1.3 (0.2–7.2)	1.2 (0.2–7.2)	1.2 (0.4–3.5)	1.0 (0.7–1.3)	1.0 (0.7–1.3)
Sister	0.5 (0.1–3.0)	—	0.5 (0.2–1.4)	1.6 (1.1–2.2)	1.3 (0.96–1.8)

*All OR adjusted for age, race, study location, respondent status, smoking and drinking (95% confidence intervals presented in parentheses).

both) was selected from any individual household. Controls age 65 years and over were systematically selected after a random start from rosters of residents in each area provided by the Health Care Financing Administration. Registry data on oral and pharyngeal cancer from prior years were used to determine the age (5-year groups), sex and race distribution of the controls. Overall, 76% ($n=1268$) of the eligible controls completed interviews.

A structured questionnaire (the questionnaire is available upon request from Dr W.J. Blot, Epidemiology and Biostatistics Program, Executive Plaza North, Room 431, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland 20892, U.S.A.) specifically designed for the study was administered in-person by trained interviewers. For cases who had died or were too ill or incapacitated, interviews were sought with proxy respondents, first a spouse and then a first-degree relative if the spouse was unavailable. Next-of-kin interviews were conducted for 22% of the cases and 2% of the controls. The questionnaire sought histories of tobacco and alcohol intake, dietary habits, residence, occupation, the occurrence and type of cancer in parents (mothers, fathers) and siblings (brothers, sisters), and other variables.

We examined the association between a family history of cancer and the risk of oral/pharynx cancer for the four categories of relatives. Categories of cancer among family members were oral/pharynx (ICD codes 141–149 excluding 142 and 147), larynx/oesophagus (ICD codes 150 and 161), lung (ICD code 162), and other cancers (all ICD codes excluding those listed above). No attempt was made to verify reported cancers in family members through medical records or other sources.

The measure of association between oral/pharynx cancer risk and a family history of total or specific categories of cancer used in this analysis was the odds ratio (OR). Point estimates and 95% confidence intervals (CI) of summary (adjusted) OR were calculated using unconditional logistic regression analyses [7, 8]. All analyses were adjusted for age (<50, 50–59, 60–69, ≥70 years), race (black, white), sex (male, female), study location (New Jersey, Atlanta, Los Angeles, San Francisco/Oakland), and respondent status (self vs. next-of-kin interview). For these analyses, all white subjects of Hispanic origin were excluded (49 cases and 86 controls). Previous analyses of the smoking and drinking variables in this study population showed that both were significantly associated with oral/pharynx cancer risk and that these variables combine to account for approximately 75% of all oral and pharyngeal cancers in the U.S.A. Adjustments for smoking and drinking used the categories previously designated [5]. Smoking categories were: 0=non-smoker, 1=light/former smoker, 2=pipe/cigar only, 3=1–19 cigarettes/day for 20+ years, 4=20–39 cigarettes/day for 20+ years, and 5=40+ cigarettes/day for 20+ years. Alcohol categories were 0=<1 drink/week, 1=1–4 drinks/week, 2=5–14 drinks/week, 3=15–29 drinks/week, and 4=30+ drinks/week. For additional details about the data collection methods and procedures used, see [5].

RESULTS

Among the cases, 68% were male and 82% were white. The median age at diagnosis of the patients was 63 years, with 62% being 60 years and older. Of the cases, 33% had cancers arising in the pharynx (ICD codes 146, 148–149), 29% the tongue (ICD 141), and 38% other oral sites (ICD 143–145).

The ORs associated with familial cancer according to various groups of first-degree relatives and four types of cancer are shown in Table 1. Three of the four categories of cancers involve cancers known to be induced by smoking: oral/pharynx, larynx/oesophagus and lung. All analyses were adjusted for smoking and alcohol use, in addition to age, race, study location and respondent status of the study subjects (but not their relatives). Approximately 45.7% (487/1065) of the cases and 41.0% (485/1182) of the controls reported cancer in a nuclear family member. The overall adjusted OR for oral/pharynx cancer associated with any cancer in the family was 1.1 (95% CI 0.9–1.3). There were slightly but non-significantly elevated risks of oral/pharynx cancer associated with a family history of oral/pharynx cancer (OR=1.2, 43 cases and 24 controls with a positive family history of oral/pharynx cancer), larynx/oesophagus (OR=1.6, 18 cases, 13 controls), lung cancer (OR=1.2, 76 cases, 72 controls). The risks tended to be somewhat higher when the oral/pharynx, larynx/oesophagus and lung cancers arose in a male relative (ORs=1.5, 1.9, 1.3, respectively), and especially in a brother (ORs=1.5, 4.4, 1.5, respectively). In addition, a significant oral/pharynx cancer risk was associated with other cancers among sisters, with an OR=1.6 (95% CI 1.1–2.2), mainly due to an increased frequency of several cancers including cancers of the breast, liver, stomach, colon and cervix among sisters of cases vs. controls. The numbers of site-specific cancers were very small for all sites except breast (51 cases/41 controls). Controlling for number of sisters or brothers had no effect on the results.

*Table 2. Odds ratios for a family history of cancer and oral or pharyngeal cancer risk**

Familial relationship	Oral cancer risk Type of cancer in relatives		Pharyngeal cancer risk Type of cancer in relatives	
	Smoking-related†	Other	Smoking-related†	Other
Any family member	1.2 (0.8–1.7)	1.0 (0.8–1.4)	1.7 (1.1–2.8)	1.0 (0.7–1.4)
Father or brother	1.4 (0.9–2.1)	0.9 (0.6–1.2)	1.7 (1.0–2.9)	1.0 (0.6–1.5)
Father	1.2 (0.7–2.2)	0.9 (0.7–1.3)	1.2 (0.6–2.5)	1.0 (0.6–1.6)
Brother	1.5 (0.9–2.7)	0.9 (0.6–1.3)	2.3 (1.2–4.8)	1.3 (0.7–2.3)
Mother or sister	0.6 (0.3–1.2)	1.2 (0.9–1.6)	1.6 (0.7–3.4)	1.2 (0.8–1.7)
Mother	0.9 (0.3–2.4)	1.0 (0.7–1.4)	2.4 (0.8–6.9)	0.9 (0.6–1.4)
Sister	0.4 (0.1–1.0)	1.7 (1.2–2.4)	1.0 (0.4–3.0)	1.4 (0.9–2.4)

*All OR adjusted for age, race, sex, study location, respondent status, smoking and drinking (95% confidence intervals are presented in parentheses). †Smoking-related cancers are oral/pharynx, oesophageal/laryngeal and lung cancer.

The relative risk patterns were generally similar among whites tested separately, among self-respondents and among males vs. females (data not shown). The numbers of black cases and their relatives with cancer were too small to permit a separate detailed analysis, as were the number of surrogate respondents. However, the excess risk associated with the occurrence of cancer in brothers was higher among blacks than whites, because of a deficit of cancer in brothers of black controls compared to brothers of white controls. The subsites of oral and pharyngeal cancer were also assessed separately. Because of the small numbers of cancers in the relatives of cases and controls, the three categories of smoking-related cancers were combined for these analyses. Table 2 shows the site-specific ORs for family histories of the smoking-related cancers and other sites. For pharyngeal cancer, significantly elevated risks were associated with occurrences of smoking-related cancer in any relative (OR = 1.7, 95% CI 1.1–2.8), a male relative (OR = 1.7, 95% CI 1.0–2.9), and particularly a brother (OR = 2.3, 95% CI 1.2–4.8); the risks of pharyngeal cancer were also elevated when a female relative (OR = 1.6, 95% CI 0.7–3.4) or a mother (OR = 2.4, 95% CI 0.8–6.9) had a smoking-related cancer. For oral cancer, there was a similar pattern of elevated risk associated with smoking-related cancers among male but not female relatives. In addition, a significant increase of oral cancer was associated with a sister having other cancers (OR = 1.7, 95% CI 1.2–2.4), whereas a decreased risk was seen when sisters had a smoking-related cancer (OR = 0.4, 95% CI 0.1–1.0). Controlling for number of sisters did not alter the results.

DISCUSSION

After controlling for smoking and alcohol use, our population-based case–control data showed a consistent pattern of slightly increased risks of oral and pharyngeal cancer associated with family history of a smoking-related cancer (oral/pharynx, larynx/oesophagus, lung) for any nuclear relative, a male relative or a brother. The ORs were higher when a smoking-related cancer occurred in brothers than in any other relative category, but reached a significant level only when pharyngeal cancer was evaluated. The absence of a consistent pattern of excess risk associated with smoking-related cancers among female relatives suggests that environmental factors, notably smoking and drinking, contribute to the familial tendency suggested among males in this study. Alternatively, genetic (or heritable) predisposition may be more evident in the presence of the major risk factors—smoking and drinking.

Although tobacco and alcohol are the major risk factors for oral/pharynx cancer, the role of genetic susceptibility has been suggested by clinical reports of high-risk families [2–4]. In addition, patients with head and neck cancer have shown sensitivity to mutagen-induced chromosome damage [9, 10], genetic polymorphisms at heterochromatic regions [11], and deletions of multiple chromosomal regions in tumour tissue, suggesting the role of tumour suppressor genes in the pathogenesis of these tumours [12, 13]. p53 mutations in human head and neck carcinomas have been demonstrated by immunocytochemistry, complementary DNA sequencing and single strand conformation polymorphism (SSCP) analysis, a loss of p53 heterozygosity in oral cancers has been detected by the polymerase chain reaction [14–18]. Field *et al.* [19] observed a correlation between heavy smoking and heavy drinking, and overexpression of the p53 gene in 48 patients with squamous cell carcinomas of the head and neck. The authors concluded that the results point to a genetic link between heavy smoking and heavy drinking and the aberrant expression of the p53 gene in oral and pharyngeal cancer. Confirmation of this finding in a larger sample would help begin to unravel the gene–environment complexities of oral and pharyngeal cancer.

Our data came primarily from self-reports (only a minority of the interviews were with surrogates) by cases and controls of cancer in their relatives. No reports of cancer in relatives were confirmed through medical records or other sources. It is possible that cases may have been more aware of cancer occurrences among their parents and siblings than were controls, leading to biased estimates of excess risk. This possibility, however, seems unlikely in this study because of (1) the absence of an overall excess occurrence of cancer among relatives; (2) a concentration of the excess in one gender (males); and (3) the lack of change in ORs with control for number of brothers or sisters (data not shown).

Since data on smoking and drinking were unavailable for family members, we could only adjust for these practices using information about the study subjects themselves. Had information on risk status been available for relatives, it would have helped to distinguish genetic from environmental determinants of the familial effects observed in this study.

It is noteworthy that adjustment for smoking and alcohol consumption of the cases and controls reduced the ORs

associated with the occurrence of cancer in a family member. When we conducted logistic regression analyses controlling only for age, race, study location and respondent status, there was a significant risk associated with having an oral/pharynx cancer in any relative (OR = 1.9, 95% CI 1.1–3.2). However, when smoking and alcohol were additionally and appropriately controlled for, the OR dropped to 1.2 (Table 1), because subjects with a family occurrence of oral/pharynx cancer tended to have higher intakes of tobacco and alcohol. The results were very similar if an interaction term for smoking and alcohol consumption was included in the analysis model.

An unanticipated excess risk of oral and pharyngeal cancer was seen when sisters of cases were reported to have non-smoking-related cancers. The association resulted mainly from a disproportionate number of cancers of the breast, cervix, colon, liver and stomach in sisters of cases compared to sisters of controls. The numbers of site-specific cancers were very small for all sites except breast. Controlling for numbers of sisters of the cases and controls did not affect the results, and information on the age distribution of the sisters was not available. Although the familial occurrence of oral and certain other cancers may be due to chance, especially considering the large number of comparisons evaluated, further investigation is needed, including the possible role of alcohol intake which has been reported to increase the risk of liver, breast, colon and possibly stomach cancers [20].

In conclusion, we examined the relationship of oral/pharynx cancer risk to family cancer history in a large population-based case–control study conducted in the U.S.A. After controlling for smoking and drinking in the subjects, there were slight but non-significant excess risks when an oral/pharyngeal, larynx/oesophagus or lung cancer occurred in parents or siblings. The risks were higher when these smoking-related cancers arose in a male relative, particularly a brother, and were statistically significant when pharyngeal cancer was examined separately. Interpretation of these findings is limited by the lack of data on smoking and alcohol consumption among the relatives. In future evaluations of familial tendency in oral and pharyngeal cancer, it will be essential to collect risk profile information on family members to separate genetic from environmental factors.

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