hypertensive or hyperlipidaemic patients. It is likely, but unproved, that peak expiratory flow rate, which is more cheaply measured than FEV_1 but well correlated with it, would serve the same purpose. Spirometric results are conventionally expressed as a percentage of predicted values for a given age and height. Short stature itself, however, is a risk factor for early death, and prediction of subsequent mortality is strengthened if age adjusted FEV_1 is used, without controlling for height.[3] Further work is needed to clarify the interpretation of forced expiratory or peak flow measurements as risk indicators in day to day clinical practice.

What are the public health implications? Diminished lung function may be a cumulative indicator of environmental influences on mortality or may have direct effects on survival after myocardial infarction or stroke. Forced expiratory volume is influenced both by lung development in childhood and by destructive insults to the lung tissues during adult life. At its peak in early adult life, it is related to both prenatal and postnatal growth[4] and thus may be a better integrated measure of developmental influences on survival than adult height.[3] Arguably, taking a long term public health perspective, FEV_1 should be considered as a potentially modifiable risk factor, its association with premature mortality indicating a plausible mechanism for causal relations between family circumstances in childhood and the chances of surviving through middle age.

1 Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. *BMJ* 1995;311:1356-9.
2 Browner WS, Hulley SB. Effect of risk status on treatment criteria. Implication of hypertension trials. *Hypertension* 1989;13(suppl I): I51-6.
3 Strachan DP. Ventilatory function, height and mortality among lifelong non smokers. *J Epidemiol Community Health* 1992;46:66-70.
4 Strachan DP, Griffiths JM, Anderson HR, Johnston IDA. Association of intrauterine and postnatal growth with ventilatory function in early adult life. *Thorax* 1994;49:1052P.

Familial risks of squamous cell carcinoma of the head and neck: retrospective case-control study

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Abstract

***Objective*—To determine the contribution of inheritance to the incidence of squamous cell carcinoma of the head and neck.**

***Design*—Historical cohort study. First degree relatives of cases with squamous cell carcinoma of the head and neck made up the exposed cohort and first degree relatives of spouses of cases made up the comparison unexposed cohort.**

***Setting*—Ear, nose, and throat clinic in a large metropolitan teaching hospital.**

***Subjects*—1429 first degree relatives of 242 index cases of squamous cell carcinoma of the head and neck; as controls, 934 first degree relatives of the spouses of 156 index cases.**

***Main outcome measures*—Relative risk of developing squamous cell carcinoma in first degree relatives of cases compared with risk in first degree relatives of spouses.**

***Results*—The adjusted relative risk for developing head and neck cancer if the index case had squamous cell carcinoma of the head and neck was 3.79 (95% confidence interval 1.11 to 13.0). There were no significantly increased risks associated with a family history of cancer at other sites. The adjusted relative risk for squamous cell carcinoma of the head and neck was 7.89 (1.50 to 41.6) in first degree relatives of patients with multiple primary head and neck tumours.**

***Conclusions*—These data suggest that genetic factors are important in the aetiology of head and neck cancer, in particular for patients with multiple primary cancers. Given the prolonged exposure of these subjects to carcinogens, these genetic factors may have a role in modifying carcinogen activity or in host resistance to carcinogens. Inherited factors may be important in persons with environmentally induced cancers.**

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Introduction

Squamous cell carcinoma of the head and neck is an important cause of morbidity and mortality throughout the world. The incidence of this cancer is increasing in developing countries.[1 2] It has been known for more than 30 years that tobacco and alcohol have the major role in the aetiology of this disease.[3] Occupational risk factors include exposure to wood dust, nickel refining, and leather working.[4] In some countries, maté drinking and woodstoves have also been implicated.[5 6] Familial factors have received less attention, but there are several reasons to suppose they may be important. Multiple primary tumours are often seen in hereditary cancer syndromes; second primary tumours are a particular feature of squamous cell carcinoma of the head and neck and are found in 10-30% of these patients.[7] Chromosome breaks induced by bleomycin are more common in patients with squamous cell carcinoma of the head and neck than in controls, in particular in patients with multiple primary tumours and in patients with a family history of cancer.[8 9] Also, squamous cell carcinoma of the head and neck is featured, albeit rarely, in several inherited cancer syndromes, including hereditary non-polyposis colorectal cancer, Li-Fraumeni syndrome, Fanconi anaemia, and Bloom syndrome.[10] There is some preliminary evidence that families linked to the hereditary breast cancer gene BRCA2 show an excess of laryngeal cancer.[11]

To estimate the magnitude of the increased risk associated with a family history of squamous cell carcinoma of the head and neck and to establish whether the familial risk is independent of familial clustering of smoking and drinking habits, we studied the family history of cancer and the risk of head and neck squamous cell carcinoma in patients attending a large urban general hospital.

Subjects and methods

CASES

We identified 250 incident and prevalent cases of squamous cell carcinoma of the head and neck who were being followed at the head and neck cancer clinic of the Sir Mortimer B Davis-Jewish General Hospital, Montreal. All patients had been diagnosed as having head and neck squamous cell carcinoma as classified under ICD-9 (international classification of diseases, 9th revision) codes 141, 143-146, 148-149, 160, and 161 (tongue, gum, floor of mouth, other parts of mouth, oropharynx, nasopharynx, hypopharynx, unspecified head and neck sites, nasal sinus, and larynx, respectively). All diagnoses were confirmed pathologically, and all histological specimens were reviewed in the department of pathology at the Jewish General Hos-

Table 1—*Ethnic origin of cases and spouse controls. Values are numbers (percentages)*

Ethnic origin of parents and grandparents	Cases (n = 250)*	Spouses (n = 159)*
French-Canadian†	99 (40)	67 (42)
British and Irish	60 (24)	30 (18)
Ashkenazi Jewish	34 (14)	23 (15)
South European	20 (8)	16 (10)
Asian or African	12 (5)	6 (4)
Eastern European	11 (4)	8 (5)
Sephardi Jewish	7 (3)	5 (3)
Other northern and western European	4 (2)	4 (3)
Native American	2 (1)	0
South American	1 (<1)	1 (<1)

*The 8 excluded cases were French-Canadian (5), British-Irish (1), and southern European (2); the 3 excluded spouses were French-Canadian (2) and Ashkenazi Jewish (1).
†Including two cases and one spouse of French origin.

pital. The presence of other tumours was confirmed by reviewing the chart and, where possible, pathology. Only those conforming to accepted criteria were accepted. We used the criteria of Hong *et al.*[12] Briefly, these are that a second primary tumour of the same histological type must be separated from the first tumour either in time (more than three years) or in space (2 cm of clinically normal epithelium); for a second primary of a different histological type, these criteria do not apply; lung second primary tumours must be solitary and histologically distinct unless they occur more than three years after the first tumour; and second primary tumours are not limited to the upper aerodigestive tract. Twenty six of our patients had second primary cancers following squamous cell carcinoma of the head and neck which fulfilled these criteria. Twenty had second primaries of the head and neck, and six had cancer at other sites. Not included here are seven who had squamous cell carcinoma of the head and neck following a cancer elsewhere.

The cases were recruited between 30 June 1994 and 31 August 1995. Most were residents of the island of Montreal, and several ethnic groups were represented (table 1). All suitable cancer clinic attenders were interviewed on the day of their clinic appointment. Those who were not seen in the clinic were interviewed over the telephone. The interviewers obtained information on date of birth, marital status, place of birth, place of parents' birth, ethnic origin (of parents and grandparents), and tobacco and alcohol use. All the patients' charts were reviewed for details of diagnosis and dates of surgery, chemotherapy, and radiotherapy. Tobacco use was recorded as age of starting, age of stopping (including periods of abstinence), and mean number of cigarettes per day. Pack years were calculated on the basis of 25 manufactured cigarettes per pack, one pack of cigarettes being equivalent to five cigars or six pipefuls of pipe tobacco. Alcohol consumption was based on age starting, age stopping (including details of periods of heavy drinking), and number of drinks per day. One drink was equivalent to one 12 ounce (355 ml) bottle of beer, one 5 ounce (148 ml) glass of wine, or 1 ounce (30 ml) of spirits. Consumption was converted to drink years: one drink per day for a year was equal to one drink year.

In all, 250 patients with squamous cell carcinoma of the head and neck were eligible for this study; 242 were included in the statistical analysis (97%). Three patients with lip cancer were excluded; two patients were rejected because they were adopted, and three were excluded because of insufficient knowledge of family history.

FIRST DEGREE RELATIVES OF CASES

The first degree relatives of cases comprised the "exposed" cohort. For each index case, a detailed pedigree which included all first degree relatives was drawn. Current age, age of diagnosis of cancer, site of cancer (where applicable), and age of death were recorded for all first degree relatives. The diagnosis of cancer in these relatives was not verified by pathological report or by death certificate, but questionable diagnoses were excluded. If the index case was sure that the relative had cancer, but was unsure of the primary site, this was recorded as cancer, primary site unknown. Tobacco and alcohol use by all first degree relatives was recorded as yes or no. The criteria for smoking were current or ever regular use (unless smoking stopped more than 20 years ago or after less than 5 pack years). Regular cigar or pipe smokers were included as smokers. Regular drinkers, ex-drinkers, and intermittent heavy drinkers were all classified as alcohol drinkers. Never drinkers and those who drank one drink (for example, one glass of wine; see above) per week or less were classified as non-drinkers. There were 1429 first degree relatives of 242 squamous cell carcinoma of the head and neck cases in the exposed cohort.

COMPARISON GROUP

Because we wished to control for ethnic group, social background, and other variables and to limit recall bias, we chose to study relatives of spouses as the comparison "non-exposed" cohort group. There were 159 available spouses of the 250 cases (20 of the cases were single, 33 were widowed, and 16 were divorced and had lost contact with their spouse). We asked permission of the remaining 181 cases to contact their spouses and, where possible, their ex-spouses. Twenty two cases refused to allow us to contact the spouse, or the spouses did not wish to answer the questionnaire or could not be reached after several attempts. Spouses were not excluded if they had been diagnosed as having other cancers, with the exception of one spouse who was excluded because of a history of cancer of unknown type. Two spouses were excluded because of insufficient knowledge of family history. Thus of 159 spouses, 156 (98%) were included in the statistical analysis. The same questions were asked of the spouses as of the cases, and they provided the same information on their first degree relatives as the cases. There were 934 first degree relatives of 156 spouses in the non-exposed cohort. Because relatives of spouses were chosen as the comparison group, ethnic distributions in the case and comparison groups were similar (table 1).

We excluded children from the analysis because children are related to both cases and spouses and because squamous cell carcinoma of the head and neck rarely affects those under 40. (The average age of the children of the cases and spouses was 35.5 years). In fact, only five children had cancer (one neuroblastoma, one leukaemia, one breast cancer, one lymphoma, and one thyroid cancer); none had squamous cell carcinoma of the head and neck.

STATISTICAL ANALYSIS

Each first degree relative of the cases and spouses was considered to be a study subject. We constructed two historical cohorts by obtaining information regarding current age, age of diagnosis of cancer, and age of death, where appropriate. The exposed cohort was composed of the first degree relatives of the cases, and the unexposed cohort was made up of the relatives of the spouses. Information was provided by the case or spouse regarding tobacco smoking and alcohol drinking, as described above. Using the SAS program[13] we constructed Kaplan-Meier survival curves, which describe the probability of being diagnosed as having a particular cancer over time. In univariate comparisons, we used the log rank method of assessing significant differences between variables. For multivariate comparisons we used the Cox proportional

Table 2—*Comparison of characteristics of cases and spouses*

	Cases (n = 242)	Spouses (n = 156)
Mean (range) age (years)	67.1 (34-92)	62.6 (32-86)
No (%) of males	179 (74.0)	30 (19.2)
No (%) of smokers*	205 (84.7)	80 (51.3)
Mean (range) pack years' tobacco consumption	42.6 (0-154)	16.6 (0-147)
No (%) of drinkers†	183 (75.6)	88 (56.4)
Mean (range) drink years' alcohol consumption	113.8 (0-1200)	30.1 (0-528)

Cut off points for smokers and drinkers were chosen to be comparable with those for relatives (table 3).
*Smokers = those with >4.99 pack years exposure; 88% of cases and 59% of spouses had ever smoked (pack years >0).
†Drinkers = those with >1 drink year of alcohol exposure.

Table 3—*Comparison of characteristics of relatives of cases and relatives of spouses*

	Relatives of cases (n = 1429)	Relatives of spouses (n = 934)
Mean (range) age (years)	3.5 (0.5-99)	61.1 (0.5-97)
No (%) of males	706 (49.4)	483 (51.7)
No (%) of smokers*	732 (52.9)	459 (49.8)
No (%) of drinkers†	390 (29.1)	229 (25.3)

For definition of "smokers" and "drinkers" see methods section.
*Not including 44 relatives of cases and 13 relatives of controls on whom data are missing. Percentages calculated excluding those with no information.
†Not including 88 relatives of cases and 30 relatives of spouses on whom data are missing. Percentages calculated excluding those with no information.

hazards model. The covariates in the model were ethnic group, sex of the index (case or spouse), sex of the subject, tobacco smoking in the subject (dichotomous), tobacco smoking in the case or spouse, alcohol consumption in the subjects (dichotomous), and alcohol consumption in the case or spouse. Because of the possibility of familial correlations between alcohol and tobacco use in cases and their relatives, we have included both variables in the model.

Results

In all, 242 cases and 156 spouses were studied, contributing 1429 and 934 first degree relatives, respectively. As expected, cases were more much more likely than controls to be male, tobacco smokers, and consumers of alcohol (table 2). In contrast, the two cohorts (the relatives of cases and the relatives of spouses) are closely matched (table 3). Men constituted 49.4% of the relatives of cases and 51.7% of the relatives of controls. The mean ages of the cohorts were 63.5 years (relatives of cases) and 61.1 years (relatives of spouses). Relatives of cases were only slightly more likely to be (current or former) smokers than relatives of controls (52.9% *v* 49.8%). Regular alcohol consumption was slightly more common in relatives of cases than relatives of spouses (29.1% *v* 25.9%) (table 3). Comparison of tables 2 and 3 shows that despite the differences between cases and spouses the two cohorts are closely matched on variables relating to risk of squamous cell carcinoma of the head and neck.

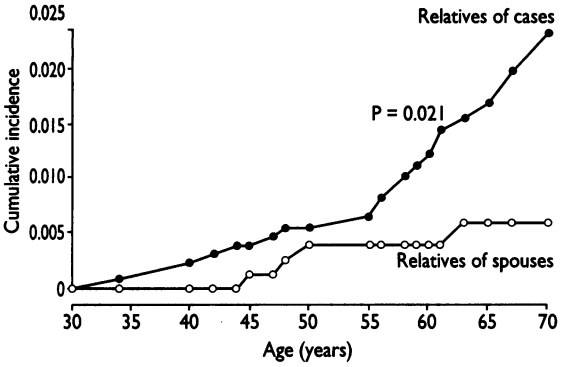

Fig 1—*Cumulative incidence of squamous cell carcinomas of the head and neck in relatives of cases and controls*

In the univariate analysis, the probability of head and neck cancer in the relatives of cases by age 70 was significantly greater than for the relatives of controls (relative risk = 3.26; P = 0.013, log rank test) (table 4 and fig 1). The cumulative risk to age 70 in the relatives of cases was 2.35%; in relatives of spouses the risk was 0.607%. The risk for relatives of cases and spouses began to diverge after age 55 (fig 1). As expected, sex, tobacco consumption, and alcohol consumption were significantly associated with risk of squamous cell carcinoma of the head and neck (P<0.001 for each); therefore the risk of squamous cell carcinoma of the head and neck associated with a family history of squamous cell carcinoma of the head and neck was reanalysed after adjustment for ethnic group, sex, and tobacco and alcohol use; the Cox proportional hazards model was used. To attain the best fit, we included terms for ethnic group, sex, smoking, and drinking in the index case, the spouse, and the relative. The

Table 4—*Relative risks for squamous cell carcinoma (SCC) of the head and neck associated with cancers at various sites in first degree relatives*

Site or type of cancer in relative	No (%) of relatives with cancer		Univariate analysis		Multivariate analysis*	
	Cases	Spouses	Relative risk (95% confidence interval)	P value	Relative risk (95% confidence interval)	P value
Any site	155/1429 (10.8)	88/934 (9.42)	1.03 (0.79 to 1.33)	0.855	0.99 (0.70 to 1.39)	0.938
Specific sites:						
SCC head and neck	22/1429 (1.54)	4/934 (0.428)	3.26 (1.12 to 9.47)	0.030	3.79 (1.11 to 13.0)	0.034
Lung	25/1429 (1.74)	13/934 (1.39)	1.21 (0.57 to 2.18)	0.756	0.89 (0.37 to 2.14)	0.800
Colorectum	17/1429 (1.19)	15/934 (1.61)	0.65 (0.32 to 1.30)	0.224	0.46 (0.18 to 1.21)	0.115
Stomach	6/1429 (0.42)	4/934 (0.43)	0.90 (0.25 to 3.20)	0.874	0.56 (0.12 to 2.59)	0.452
Breast	2/723 (2.90)	14/451 (3.10)	0.87 (0.44 to 1.70)	0.679	0.99 (0.49 to 1.98)	0.327
Prostate	6/706 (0.85)	5/483 (1.04)	0.64 (0.20 to 2.09)	0.460	0.71 (0.21 to 2.35)	0.571
Pancreas	1/1429 (0.07)	3/934 (0.32)	0.22 (0.02 to 2.07)	0.183	0.17 (0.01 to 2.37)	0.188
Leukaemia	5/1429 (0.34)	5/934 (0.54)	0.65 (0.19 to 2.24)	0.412	0.42 (0.09 to 2.08)	0.288
Primary site unknown	20/1429 (1.40)	9/934 (0.96)	1.37 (0.62 to 3.01)	0.550	1.49 (0.51 to 4.34)	0.466

*Adjusted for ethnic group, sex, and tobacco and alcohol consumption in index cases and subjects. Relatives were excluded if information on covariates was missing.

adjusted relative risk for squamous cell carcinoma of the head and neck in association with a family history of squamous cell carcinoma of the head and neck was 3.79 (95% confidence interval 1.1 1to 13.0; P = 0.03). No associations with other cancer sites reached significance at the 5% level (table 4). Of note was a lack of a significant excess of lung cancer in the relatives of cases compared with spouses. Colorectal cancer was less commonly reported in cases than in relatives of spouses (adjusted relative risk = 0.46; 0.18 to 1.21).

When the familial risks in association with specific head and neck sites in the case were examined, the greatest risk was seen in association with pharynx cancer (adjusted relative risk = 4.24; 1.02 to 17.6) and mouth cancer (3.82; 1.08 to 13.5) rather than with larynx cancer (1.65; 0.35 to 7.65). However, these differences may be due to the small numbers (P = 0.36).

Because multiple primary cancers are a characteristic of several hereditary cancer syndromes, we sought to determine whether the cancer risk was higher in the relatives of patients with multiple primary head and neck tumours than in the relatives of patients with a single primary tumour. There were 20 patients (8%) with multiple primary squamous cell carcinoma of the head and neck, and 222 patients with single primary squamous cell carcinoma of the head and neck. The adjusted relative risk for squamous cell carcinoma of the head and neck was 7.89 (1.50 to 41.6) in the first degree relatives of those with multiple primary head and neck tumours and 3.53 (1.01 to 12.3) in the relatives of cases with a single primary head and neck tumour. Therefore the risk for squamous cell carcinoma of the head and neck was significantly greater for the relatives of patients with two or more head and neck tumours than for relatives of those with only one head and neck tumour (P value for trend = 0.009).

The average age of the cases was 67.1 years. Because early age of onset can be a feature of hereditary forms of cancer, we reanalysed the data, comparing the relative risk of head and neck cancer in the relatives of cases diagnosed at 60 years or older with that in relatives of cases diagnosed at less than 60 years of age. There was no significant difference in the risk seen (4.05; 1.08 to 15.3 *v* 3.56; 0.99 to 13.39; P = 0.79). Therefore, younger cases were not significantly more likely to have a family history of squamous cell carcinoma of the head and neck than cases who were older at diagnosis.

Discussion

FAMILIAL FACTORS IN HEAD AND NECK CANCER

In this historical cohort study from Quebec, a relative risk of 3.79 (95% confidence interval 1.11 to 13.0) was seen for squamous cell carcinoma of the head and neck in association with a family history of squamous cell carcinoma of the head and neck. Two previous case-control studies reported similar results. A matched case-spouse control study conducted in the Netherlands found a relative risk of 3.5 (significant at the 10% level) for squamous cell carcinoma of the head and neck in association with a family history of cancer of the respiratory tract and upper digestive tract.[14] A previous study of squamous cell carcinoma of the head and neck in southern Brazil (754 cases and 1507 matched controls) found an adjusted relative risk of 3.65 (1.97 to 6.76) for squamous cell carcinoma of the head and neck in association with family history of squamous cell carcinoma of the head and neck.[15] Thus all three studies have estimated relative risks of similar magnitude.

An earlier study of racial differences in risk factors for oral and pharyngeal cancer did not show any overall increased risk of these cancers in association with a family history of cancer at any site, including oral cancer. Nevertheless, black people with a brother with cancer had a greatly increased risk of oral cancer (odds ratio 7.4; 1.8 to 31.0). There was no excess risk in white people.[16] These differences in risks may reflect varying patterns of exposure to environmental risk factors in the different populations studied. Our previous study in Brazil did not show any significant differences in familial risk by head and neck site.[15] The present study and the study of Copper *et al*[14] found that a family history of head and neck cancer was more common in patients with oral and pharyngeal cancer than in those with laryngeal cancer, but these differences were not significant, possibly because of the small sizes of the subgroups. Using the Utah population database, Goldgar *et al* showed that familial relative risks were higher for laryngeal cancer and lip cancer than for oral cancer.[17] Finally, Day *et al* found no increased risk of cancer in the first degree relatives of patients with oral and pharyngeal cancer.[16] Given these differing results, larger, specific studies of individual head and neck cancer sites will be required, because the risk factors for the various anatomical sites are known to differ.[3,4]

FAMILIAL FACTORS IN OTHER AERODIGESTIVE TRACT CANCERS

Several of the risk factors for head and neck cancer are also risk factors for lung and oesophageal cancer. The data presented here are consistent with the findings of previous studies of genetic susceptibility to oesophageal cancer and lung cancer. In the Turkoman population near the Caspian Sea in Iran, which has one of the highest rates of oesophageal cancer in the world, oesophageal cancer was 4.4 times more common in blood relatives of patients with the disease than in unrelated controls. In the non-Turkoman population, which has a low rate of oesophageal cancer, no familial association was found.[18] Tobacco consumption and family history were the major determinants of carcinoma of the oesophagus and gastric cardia in Linxian, China.[19] Among Japanese men with oesophageal cancer, those with a family history of cancer had an eightfold risk of a second cancer of the upper aerodigestive tract. Family histories of smoking and alcohol consumption did not differ in patients with and without family histories of cancer.[20] Genetic factors seem to be less important for lung cancer. In some studies, relatives of patients with lung cancer have an increased incidence of tobacco related cancers[21-24]; however, a recent study of male twins with lung cancer diagnosed at age 50 or above showed that dizygotic twins were more likely to be concordant for lung cancer than monozygotic twins, making a genetic effect unlikely.[25] We found no excess of lung cancer in the relatives of cases (table 4).

MUTAGENICITY, MULTIPLE CANCERS, AND FIELD CANCERISATION

Recently, in vitro mutagenicity assays have suggested that familial factors may be important in the predisposition to squamous cell carcinoma of the head and neck. One hundred and eight patients with upper aerodigestive tract cancers were tested for chromosomal sensitivity to bleomycin. Mutagen sensitivity was defined as the presence of one or more breaks per cell.[8] The odds ratio for mutagen sensitivity was 2.63 (1.06 to 6.53) for those with a family history of any cancer in a first degree relative, and if there were two or more affected first degree relatives this increased to 6.59 (1.69 to 25.72).[8] In addition, the odds ratio was raised for patients with multiple primary head and neck neoplasms.[9]

In patients with multiple primary tumours there is an increased likelihood of an underlying genetic basis for the cancers seen. Multiple primary tumours of cancers of the head and neck are common.[7] Multiple tumours may be due to field cancerisation. In this model, carcinogen damage to the epithelial surface renders it susceptible to malignant change.[26] There is molecular

Key messages

- Squamous cell carcinomas of the head and neck are common worldwide
- Tobacco and alcohol are established risk factors, but some affected persons are non-smokers and non-drinkers
- Genetic makeup may determine how individuals respond to carcinogens
- This study found a significantly increased relative risk of 3.79 for developing head and neck cancer if a first degree relative had squamous cell carcinoma of the head and neck
- As with other cancers, people with multiple primary cancers of the head and neck may represent a susceptibility group as the familial risks are higher

evidence that this process may occur in squamous cell carcinoma of the head and neck.[27] In the presence (or even absence) of continued exposure to carcinogens the occurrence of frank neoplastic lesions may reflect underlying susceptibility. If this is the case, we might expect to see an increased incidence of squamous cell carcinoma of the head and neck in the families of patients with second primary tumours. In this study, we showed that the risk of squamous cell carcinoma of the head and neck was significantly greater in relatives of patients with multiple primary squamous cell carcinoma of the head and neck than for relatives of those with a single primary squamous cell carcinoma of the head and neck (relative risks 7.89 *v* 3.53; P value for trend 0.009). This result suggests that inherited susceptibility may contribute to the risk of multiple primary tumours of the head and neck. A larger genetic epidemiology study focused on patients with second primary tumours may be justified.

INTERACTIONS OF GENETIC AND ENVIRONMENTAL FACTORS

Numerous case-control studies have confirmed that the two most important risk factors for squamous cell carcinoma of the head and neck are tobacco and alcohol consumption.[3 5 6 28-30] The relative risk for squamous cell carcinoma of the head and neck rises with increasing exposure. While exposure to alcohol and tobacco is almost universal in patients with squamous cell carcinoma of the head and neck, the level of exposure can vary widely. In this study, 19% of cases had less than 10 pack years of exposure to tobacco: among affected women, this figure was 38%. It is perhaps in people with relatively low exposure to tobacco that differences in genetic susceptibility may have a larger role. For example, it has been shown that the glutathione *S*-transferase M1 (GSTM1) null genotype was significantly associated with lung cancer (odds ratio 1.77; 1.11 to 2.82) only in patients who had less than 40 pack years of tobacco exposure.[31] As this genotype is involved in carcinogen metabolism, further large studies of this type are warranted in squamous cell carcinoma of the head and neck.

POSSIBLE CONFOUNDING AND BIAS

We controlled for differences in tobacco and alcohol consumption between cases and controls, as well as for consumption in first degree relatives. Tobacco and alcohol consumption in relatives was dichotomised. A spurious increase in risk could be explained only if the relatives of cases smoked or drank much more heavily than the relatives of spouses. However, this explanation is implausible and is unlikely to explain a risk of the size seen. It is of interest that the crude, univariate, and multivariate relative risks are all very close to each other (3.60, 3.26, 3.79, respectively), further suggesting that this explanation is unlikely. We used surrogate respondents (the cases and spouses) to provide dichotomous levels of tobacco and alcohol consumption, but it is thought that information on smoking provided by surrogate respondents is reliable.[32 33] In a study of deceased relatives, the responses to questions regarding smoking habits that had been taken from the decedent did not differ greatly from those received from a surrogate respondent 10 years after the death of the relative.[32] In another study, agreement between respondents on questions about smoking reached 85% or more.[33]

It is also possible that recall bias has influenced the results. Patients with squamous cell carcinoma of the head and neck may be more likely to recall first degree relatives with squamous cell carcinoma of the head and neck than are unaffected controls. However, in our experience, wives of cancer patients are often equally aware of a family history of cancer on both sides of the family. In addition, reports of cancer in first degree relatives are generally accurate[34 35]; they may be more accurate than average for head and neck cancer because there is often significant disfigurement, functional impairment, and prolonged rehabilitation associated with the diagnosis. Furthermore, we compared the number of reported cases of squamous cell carcinoma of the head and neck in the relatives of spouses with that expected from the age specific cancer incidence for Quebec for 1990.[36] Four cases were observed and 4.55 were expected (P = 0.95). Thus the spouses did not significantly underreport squamous cell carcinoma of the head and neck in their relatives. The incidence of cancer at any site other than head and neck in the relatives of cases was not significantly greater than in relatives of spouses (table 4) and the incidence of cancer at all sites was nearly identical (adjusted relative risk 0.99; 0.70 to 1.39) in the relatives of cases and the relatives of spouses, the latter consistent with the findings of Day *et al.*[16]

We noted a deficit of colon and rectal cancer in the first degree relatives of cases compared with the first degree relatives of spouse controls (table 4; adjusted relative risk 0.46; 0.18 to 1.21). This was not due to overreporting by the spouses: by applying age specific cancer rates (to age 65) for the Quebec population to the first degree relatives of spouses, we expected a colon cancer rate of 1888.7 per 100 000, and the spouses reported 11 cases of colon cancer in their first degree relatives, resulting in a standardised rate of 1801.9 per 100 000 for colon cancer (P = 0.88). A deficit of colorectal cancer was seen in relatives of patients with squamous cell carcinoma of the head and neck in a large Brazilian dataset[15] and has also been reported in the relatives of non-smoking women with lung cancer.[37] The reason for this deficit is not known. The absence of an increased incidence of lung cancer in the first degree relatives of cases is also not due to over reporting of lung cancer by spouses (12 cases observed in first degree relatives to age 65, 17.05 expected; P = 0.27).

CONCLUSION

This study suggests that familial factors are important in determining individual susceptibility to head and neck cancer, and that the familial excess cannot be wholly explained by patterns of tobacco and alcohol consumption. The relative risk associated with a family history of squamous cell carcinoma of the head and neck was higher for cases with multiple rather than single primary tumours, implying that members of these families may be at especially high risk. Molecular epidemiology studies may be used to uncover the relevant interactions between environmental and genetic factors.

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1 Parkin DM, Laara E, Muir CS. Estimates of the worldwide incidence of sixteen major cancers in 1980. *Int J Cancer* 1988;41;184-97.
2 Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. *Int J Cancer* 1993;54:594-606.
3 Wynder EL, Bross IJ, Feldman RM. A study of the etiological factors in cancer of the mouth. *Cancer* 1957;19:1300-23.
4 Vokes EE, Weichselbaum RR, Lippman SM, Hong WK. Head and neck cancer. *N Engl J Med* 1993;328:184-94.
5 Pintos J, Franco EL, Oliveira BV, Kowalski LP, Curado MP, Dewar R. Maté, coffee and tea consumption and the risk of cancers of the upper aerodigestive tract in southern Brazil. *Epidemiology* 1994;5:583-90.
6 Franco EL, Kowalski LP, Oliveira BV, Curado MP, Pereira RN, Silva MS, *et al.* Risk factors for oral cancer in Brazil: a case-control study. *Int J Cancer* 1989;43:992-1000.
7 Day GL, Blot WJ. Second primary tumours in patients with oral cancer. *Cancer* 1992;70:14-9.
8 Bondy ML, Spitz MR, Halabi S, Fueger JJ, Schantz SP, Sample D, *et al.* Association between family history of cancer and mutagen sensitivity in upper aerodigestive tract cancer patients. *Cancer Epidemiol Biomark Prevent* 1993;2:103-6.
9 Spitz MR, Hoque A, Trizna Z, Schantz SP, Amos CI, King TM, *et al.* Mutagen sensitivity as a risk factor for second malignant tumours following malignancies of the upper aerodigestive tract. *J Natl Cancer Inst* 1994;86:1681-4.
10 Trizna Z, Schantz SP. Hereditary and environmental factors associated with risk and progression of head and neck cancer. *Otolaryngol Clin North Am* 1992;25:1089-103.
11 Wooster R, Neuhausen S, Mangion J, Quirk Y, Ford D, Collins N, *et al.* Localisation of a breast cancer susceptibility gene (BRCA2) to chromosome 13q by genetic linkage analysis. *Science* 1994;265:2088-90.
12 Hong WK, Lippman SM, Itri LM, Karp DD, Lee JS, Byers RM, *et al.* Prevention of second primary tumours with isotretinoin in squamous-cell carcinoma of the head and neck. *N Engl J Med* 1990;323:795-801.
13 SAS Institute. *SAS/STAT user's guide, release 6.03 edition.* Cary, NC: SAS Institute, 1988.
14 Copper MP, Jovanovic A, Nauta JJP, Braakhuis BJM, de Vries N, van der Waal I, *et al.* Role of genetic factors in the etiology of squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 1995;121:157-60.
15 Foulkes WD, Brunet J-S, Kowalski LP, Narod SA, Franco EL. Family history of cancer is a risk factor for squamous cell carcinoma of the head and neck in Brazil: a case-control study. *Int J Cancer* 1995:63:769-73.
16 Day GL, Blot WJ, Austin DF, Bernstein L, Greenberg RS, Preston-Martin S, *et al.* Racial differences in risk of oral and pharyngeal cancer: alcohol, tobacco and other determinants. *J Natl Cancer Inst* 1993;85:465-73.
17 Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first degree relatives of cancer probands. *J Natl Cancer Inst* 1994;86:1600-8.
18 Ghadirian P. Familial history of oesophageal cancer. *Cancer* 1985;56:2112-6.
19 Li J-Y, Ershow AG, Chen Z-J, Wacholder S, Li G-Y, Guo W, *et al.* A case-control study of cancer of the oesophagus and gastric cardia in Linxian. *Int J Cancer* 1989;43:755-61.
20 Morita M, Kuwano H, Ohno S, Sugimachi K, Seo Y, Tomoda H, *et al.* Multiple occurrence of carcinoma in the upper aerodigestive tract associated with oesophageal cancer: reference to smoking, drinking and family history. *Int J Cancer* 1994;58:207-10.
21 Tokuhata GK, Lilienfeld AM. Familial aggregation of lung cancer in humans. *J Natl Cancer Inst* 1963;30:289-312.
22 Ooi WL, Elston RC, Chen VW, Bailey-Wilson JE, Rothschild H. Increased familial risk for lung cancer. *J Natl Cancer Inst* 1986;76:217-22.
23 Samet JM, Humble CG, Pathak DR. Personal and family history of respiratory disease and lung cancer risk. *Am Rev Resp Dis* 1986;134:466-70.
24 Sellers TA, Ooi WL, Elston RC, Chen VW, Bailey-Wilson JE, Rothschild H. Increased familial risk for non-lung cancer among relatives of lung cancer patients. *Am J Epidemiol* 1987;126:237-46.
25 Braun MM, Caporaso NE, Page WF, Hoover RN. Genetic component of lung cancer: cohort study of twins. *Lancet* 1994;344:440-3.
26 Slaughter DP, Southwick HW, Smejkal W. Field cancerisation in oral stratified squamous epithelium. *Cancer* 1953;6:963-8.
27 Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S, *et al.* Genetic progression model for head and neck cancer: implications for field cancerization. *Cancer Res* 1996;56:2488-92.
28 Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, *et al.* Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* 1988;48:3282-7.
29 Elwood JM, Pearson JCG, Skippen DH, Jackson SM. Alcohol, smoking, social and occupational factors in the aetiology of cancer of the oral cavity, pharynx and larynx. *Int J Cancer* 1984;34:603-12.
30 Wynder ES, Stellman SD. Comparative epidemiology of tobacco-related cancers. *Cancer Res* 1977:37:4608-22.
31 London SJ, Daly AK, Cooper J, Navidi WC, Carpenter CL, Idle JR. Polymorphism of glutathione *S*-transferase and lung cancer risk among African-Americans and Caucasians in Los Angeles County, California. *J Natl Cancer Inst* 1995;87:1246-53.
32 McLaughlin JK, Dietz MS, Mehl ES, Blot WJ. Reliability of surrogate information on cigarette smoking by type of informant. *Am J Epidemiol* 1987;126:144-6.
33 Herrmann N. Retrospective information from questionnaires. I. Comparability of primary respondents and their next-of-kin. *Am J Epidemiol* 1985;121:937-47.
34 Love RR, Evans AM, Josten DM. The accuracy of patient reports of a family history of cancer. *J Chron Dis* 1985;38:289-93.
35 Aitken J, Bain C, Ward M, Siskind V, MacLennan R. How accurate is self-reported family history of colorectal cancer? *Am J Epidemiol* 1995;141:863-71.
36 Statistics Canada. *Cancer in Canada 1990.* Ottawa: Statistics Canada:28-55,128.
37 Wu AH, Fontham ETH, Reynolds P, Greenberg RS, Buffler P, Liff J, *et al.* Family history of cancer and risk of lung cancer among lifetime non-smoking women in the United States. *Am J Epidemiol* 1996;143:535-42.

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Adequacy of cervical cytology sampling with the Cervex brush and the Aylesbury spatula: a population based randomised controlled trial

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Abstract

***Objective*—To compare the adequacy of cervical cytology sampling with two sampling instruments commonly used in primary care—namely, the Aylesbury spatula and the Cervex brush.**

***Design*—Pair matched, population based randomised controlled trial.**

***Setting*—86 general practices and family planning clinics in Greater Manchester.**

***Subjects*—15 882 cervical smears taken from women aged 20-64 years as part of the national cervical screening programme.**

***Interventions*—Participating centres were allocated to sample with either the Cervex brush or the Aylesbury spatula.**

***Main outcome measure*—Inadequate smear rate.**

***Results*—5.4% and 5.5% (433/8086 and 426/7796) of smears taken with the Cervex brush and the Aylesbury spatula respectively were reported as inadequate (odds ratio 0.95; 95% confidence interval 0.74 to 1.22).**

***Conclusion*—The Cervex brush offers no advantage over the Aylesbury spatula in reducing inadequate smear rates in the primary care setting.**

Introduction

Inadequate cervical smears are not only a cause of needless anxiety and inconvenience to women but are also an additional cost to the NHS. Attempts to reduce the rate of inadequate smears have focused on improving the competence of smear takers and the design of sampling instruments, but these instruments have rarely been evaluated in population based settings. We compared the adequacy of cytological sampling in a primary care setting with two commonly used instruments, the Cervex brush and the Aylesbury spatula.

Methods

The unit of randomisation was a general practice or family planning clinic. Fifty four general practices and 32 family planning clinics in Greater Manchester participated. Participating centres were stratified by primary care setting (general practice or family planning clinic) and then pair matched for their rate of inadequate smears during a preceding six month period (the "historical inadequate smear rate"). Within each pair one centre was randomly allocated to use the