The role of genetic factors in predisposition to squamous cell cancer of the head and neck

S Jefferies[1], R Eeles[1], D Goldgar[2], R A'Hern[1], JM Henk[1], M Gore[1], MPT Collaborators: P Rhys-Evans[1], D Archer[1], K Bishop[1], A Murkin[1], E Solomon[4], S Hodgsun[4], M O'Connell[4], J Hibbert[4], D Easton[5] and W Foulkes[3]

[1]Institute of Cancer Research and the Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT, UK; [2]IARC, Lyon, France; [3]Division of Medical Genetics, Department of Medicine, Montreal General Hospital, McGill University, Montreal, Canada; [4]Guy's Hospital, St Thomas' Street, London, UK; [5]IPH, Cambridge, UK

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth commonest human malignancy with an estimate of nearly 900 000 new cases occurring worldwide in 1995 (Parkin et al, 1993). In this review, head and neck cancer is defined as squamous cell carcinoma occurring in the upper aerodigestive tract, superior to the clavicles, excluding skin cancer and nasopharyngeal carcinoma. The incidence of head and neck cancer is increasing in developing countries (Macfarlane et al, 1994). In England and Wales, the overall incidence is stable at 5000 cases/year ($14/10^5$ of the male and $5.5/10^5$ of the female population), but within the head and neck sites, tumours of the larynx and oral cavity are increasing.

Optimal management of SCCHN is by a multidisciplinary approach combining surgery, radiotherapy and more recently chemotherapy. The presenting tumour site and nodal status have independent implications for both treatment and prognosis. Despite therapeutic changes the overall survival rate from SCCHN remains poor (Vokes et al, 1993). A component contributing to the poor overall survival, particularly in patients initially presenting with early tumours of the larynx, oral cavity and oropharynx, is the 10–30% chance of developing a second malignancy or multiple primary tumour (MPT) of the aerodigestive tract or elsewhere within 5 years (Day, 1992; Jovanic et al, 1994).

There are various criteria for multiple primary tumour development. A classification described by Hong provides strict criteria to exclude recurrence of SCCHN (Hong et al, 1990). This includes:

1. A MPT must occur more than 3 years from the original diagnosis or be separated by greater than 2 cm of entirely normal epithelium.
2. For a MPT of different histology these criteria do not apply.
3. If occurring in the lung, a MPT must be solitary and histologically distinct if less than 3 years after the first tumour.
4. A MPT is not limited to the upper aerodigestive tract.

The increasing relevance of SCCHN, together with failure to improve survival rates, emphasizes the need for better understanding of SCCHN epidemiology. Greater understanding of the disease process may then allow targeted primary prevention of

SCCHN and secondary prevention for those at risk of MPT with subsequent improvement in both quality and duration of life.

Slaughter et al (1953) proposed the concept of field cancerization, which suggests that the whole of the upper aerodigestive tract is exposed to the damaging effects of environmental agents and therefore is at risk of multiple tumour development. The field cancerization hypothesis predicts that second or multiple primary tumours occur as independent genetic events. Environmental agents are undoubtedly very important when considering risks of developing SCCHN. There is an abundance of information on tobacco and alcohol. These agents increase risk in a dose-dependent and independent manner. In non-drinkers, the effect of smoking is to increase relative risk (RR) of developing SCCHN, the increase varies between 2 and 20-fold. In some sites, larynx, oral and pharyngeal cancer, the combined effect of alcohol and tobacco can be multiplicative for cancer risk (RR: 2–140) (Maier et al, 1992). Areca nut exposure, alone or as a component of pan/betel quid, is associated with SCCHN. Tobacco and alcohol in combination with areca nut increase the risk of developing SCCHN (van Wyck et al, 1993; Patel et al, 1994). A smaller increase in relative risk has also been demonstrated from exposure to asbestos (RR: 1.3) (Muscat and Wynder, 1992), coal products (Maier et al, 1991), viral infections (Larson et al, 1991; Fouret et al, 1995) and long-term consumption of nitrosamine-containing food (Rogers et al, 1995). Risk factors differ for different sites and, therefore, when conducting epidemiological studies this must be taken into account.

Despite the clearly defined evidence of the role of environmental agents in the development of SCCHN there is also a possibility that inherited susceptibility may be be important.

EVIDENCE SUGGESTING A GENETIC COMPONENT IN SCCHN

Familial aggregates of cancer and increased cancer risks amongst relatives

The occurrence of familial aggregations of cancer suggests existence of genetic predisposing factors. Families occur that exhibit a high number of cases of cancer, which also tend to occur at younger ages. A familial cluster of oral squamous cell cancer has been reported which also demonstrated cases occurring at younger ages (Ankathil et al, 1996). A study addressing the prevalence of

Table 1   Relative risk of SCCHN and RUDT in first-degree relatives of cases of SCCHN

Authors	Copper et al, 1995	Foulkes et al, 1995	Goldstein et al, 1995	Foulkes et al, 1996
Location	The Netherlands	Brazil	USA	Quebec, Canada
No. of cases	105	754	1065	242
Type	Consecutive	Incident	Incident and prevalent	Incident and prevalent
Source	ENT clinic	Hospital cases	Cancer registry	Head and neck clinic
No. of controls	105	1509	1182	156
Type	Spouse	Hospital	Population register	Spouse
First-degree relatives:				
Cases	617	–	–	1429
Controls	618	–	–	934
Relative details:				
Cancer	Not verified	Not verified	Not verified	Not verified
Smoking	Collected	Collected	Collected	Collected
Alcohol	Not collected	Not collected	Not collected	Collected
RR of SCCHN in relatives of SCCHN cases (95% CI)	RR = 3.4 (0.8–13.7)	RR = 3.5 (1.97–6.76)	–	RR = 3.79 (1.11–13.00)
Subgroup analysis (95% CI)	RUDT RR = 3.5 (1.90–6.40) Sibling RR = 14 (3.10–69.10)	Sibling RR = 8.57 (2.72–27.04)	Pharynx RR = 1.7 (1.10–2.80) Oral RR = 1.2 (0.80–1.70)	Pharynx RR = 4.24 (1.02–17.6) Oral RR = 3.82 (1.08–13.50) Larynx RR = 1.65 (0.35–7.61)

RUDT—respiratory and upper digestive tract; RR—relative risk; SCCHN—squamous cell carcinoma of the head and neck; CI—confidence interval.

oral cancer in an Israeli Jewish population found that, after controlling for smoking and alcohol usage, an Ashkenazi group had at least twice the risk of developing oral cancer compared with other Jewish groups (Gorsky et al, 1994).

Increased risk of cancer is noted amongst relatives of patients with SCCHN. Four recent epidemiological studies in SCCHN have addressed the issue of familial factors in detail; these are summarized in Table 1. Copper et al (1995) found that first-degree relatives of patients with head and neck cancer had an increased incidence of upper aerodigestive tract tumours (RR: 3.5). A higher rate of upper aerodigestive tract cancer was observed amongst siblings (RR: 14.6). Foulkes et al (1995) performed a study in Southern Brazil which demonstrated that relative risk for developing SCCHN, if a first-degree relative had SCCHN, was 3.5. In the same study, the relative risk of SCCHN if a sibling had developed the disease was 8.6. In a historical cohort study by the same author (Foulkes et al, 1996) in Quebec, a relative risk of 3.79 was seen for SCCHN in association with a family history of SCCHN. All three studies have shown a similar magnitude of relative risk. In contrast to this, a study by Goldstein et al (1994) found only a slight increase in relative risk of SCCHN within families of oral and pharyngeal cases.

There are a number of factors relating to these studies that need to be considered. In each of these studies cases of cancer amongst relatives were not confirmed. Attempts to collect information on relatives' alcohol consumption proved to be unreliable in all of the studies. Analysis of the first-degree relative characteristics in the studies that used spouse controls show that demographic factors and smoking were well matched. Of note in the Goldstein study is that smoking details were not collected for relatives and matching was by racial group.

What can be concluded from these studies? The study by Goldstein suggested that, at most, there was a weak familial link between oral/pharyngeal cancer. In this study, black racial groups with a brother with cancer had an increased risk of oral cancer

Table 2   Relative risk of SCCHN and RUDT in first-degree relatives of MPT cases

Authors	Foulkes et al, 1996	Bongers et al, 1996
No. of cases of single SCCHN	222	100
No. of cases of MPT	20	97
Hong criteria	Yes	Yes
Endpoints	RR of SCCHN in first-degree relatives	Incidence of SCCHN and RUDT in first-degree relatives (%)
Single SCCHN	RR = 3.79	2.5%
MPT	RR = 7.89	8.9%
P-value	P = 0.009	P < 0.00001

RUDT—respiratory and upper digestive tract; RR—relative risk; MPT—multiple primary tumours; SCCHN—squamous cell carcinoma in the head and neck.

(odds ratio (OR): 7.4; confidence interval (CI): 1.8–31). This effect was not seen in whites. The studies by Copper (1995) and Foulkes et al (1996) (Quebec) found that familial factors may be stronger for oral and pharyngeal than for laryngeal cancer. The Brazilian study did not show any differences by tumour site for familial risk. It therefore appears that there may be a familial susceptibility to SCCHN, which is not entirely accounted for by a shared environment.

Multiple primary tumours

There is evidence from other sites that genetically predisposed individuals tend to develop multiple cancers (e.g. bilateral breast cancer is more likely to be familial) (Ottman et al, 1983). A study comparing family history of upper aerodigestive tract tumours amongst 100 patients with second primary tumours and 100 patients

with single-site SCCHN (prevalent cases at least 6 years from diagnosis) was performed by Bongers et al (1996) (Table 2). This demonstrated that, if one or more relatives had an upper aerodigestive tract tumour, this was a risk factor for MPT (OR: 3.8; CI: 2.0–7.6) (Bongers et al, 1996). Foulkes et al demonstrated that the familial risk for SCCHN in relatives of cases with multiple primary SCCHN was greater than for relatives with a single primary SCCHN (RR: 7.89 vs. 3.53) and statistically significantly greater than for controls. However, this was based upon only 26 cases with MPT (Foulkesl, 1996). Taken together with the markedly increased RR of cancer in relatives of individuals with MPT, the occurrence of MPT increases the likelihood of an underlying genetic basis for SCCHN, at least within the individuals with MPT.

Rare cancer syndromes

A number of rare syndromes occur that are clearly genetically determined where there is a marked increased cancer risk amongst gene carriers. Cancer tends to occur at younger ages and occurs in the absence of carcinogen exposure. SCCHN is occasionally featured in several inherited cancer syndromes, including families with hereditary non-polyposis colo-rectal cancer, Fanconi's anaemia, Bloom's syndrome, Xeroderma Pigmentosum and Li-Fraumeni syndrome (Trizna and Schantz, 1992). *P*16 germline mutations have been seen in individuals from families with melanoma, pancreatic tumours and SCCHN (Yarbrough et al, 1996; Sun et al, 1997).

CONCLUSION AND FUTURE CLINICAL IMPLICATIONS

The aetiology of SCCHN has been clearly defined in terms of the environmental factors that predispose to this condition but until recently little attention has been paid to the possible role of genetic factors in SCCHN. Three recent case-control studies indicate that family history of SCCHN is a significant risk factor for SCCHN particularly if MPT has occurred; however, only very small numbers of patients with MPT have been studied. Despite the influence of environmental factors on the development of SCCHN, it is now important to link epidemiological and clinical data with molecular markers from tumour specimens in prospective clinical studies. This information may have important preventative and therapeutic implications. We have commenced a prospective collaborative study, supported by the Cancer Research Campaign, to address exactly these issues.*

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