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Is Oral Cancer Susceptibility Inherited? Report of Five Oral Cancer Families

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All the oral cancer patients registered at the Regional Cancer Centre, Trivandrum, during January to July 1995 were subjected to detailed pedigree analysis. This revealed that oral cancer tends to aggregate in families. Like other familial cancers, a family history of oral cancer was associated mostly with an early age of onset of the disease. Family members without habits such as tobacco chewing, smoking or alcohol consumption were also affected. These observations prompt us to suggest the probable inheritance of an oral cancer susceptibility gene in these families. The familial aggregation, mostly site-specific, with an autosomal dominant mode of inheritance, was observed in 0.94% of the total oral cancers. This necessitates the need to undertake studies to elucidate the molecular lesions responsible for oral cancer susceptibility in families.

Keywords: oral cancer, familial aggregation, tobacco, alcohol, autosomal dominant inheritance, susceptibility gene

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INTRODUCTION

Oral and pharyngeal cancer is a major and growing worldwide problem. Its incidence, aetiology and natural history vary considerably in different population groups. Variation in incidence is related to exposure to known aetiological factors such as tobacco and betel nut chewing, smoking and alcohol consumption [1]. Relatively, a high incidence of oral cancer is seen in many parts of South Asia where up to 25% of all malignancies originate in the oral cavity. Oral cancer comprises about 40% of the total cancer incidence in India [2], in contrast to 2–4% of the total of malignant tumours in Western society [3]. The age adjusted rates of 24.2/100 000 for males and 11.2/100 000 for females in Trivandrum city (South India) are probably the highest reported incidence rates in the world [4].

At the Regional Cancer Centre, Trivandrum, South India, an analysis of the pedigrees of all patients with a positive family history of cancer has been started. Preliminary analysis of a familial survey revealed that oral cancer tends to aggregate in families. Here the details of five oral cancer families are presented and the genetic aspects of familial cancers are briefly reviewed.

PATIENTS AND METHODS

All the oral cancer patients attending the out-patient clinics of the Regional Cancer Centre, Trivandrum, during the period from January to July 1995 were interviewed at the time of diagnosis using a questionnaire aimed at the oncology history of first-degree relatives, with particular attention paid to oral cancer. All patients were asked to evaluate the site of tumours affecting first-degree relatives and the age at diagnosis of these tumours. The questionnaire also sought histories of tobacco and alcohol intake, dietary habits, occupation, etc. On the basis of family history analysis, oral cancer families were identified. Detailed pedigree charts of all the oral cancer families were prepared.

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RESULTS

The pedigrees of five oral cancer families are shown in Figs 1–5.

Family 1

The proband was a young female aged 35 years. She had carcinoma of the buccal mucosa. She did not chew tobacco, smoke or consume alcohol. Her mother had died at the age of 45 years with carcinoma of the buccal mucosa, her maternal grandfather also had oral cancer (specific site unknown) and had died at the age of 60 years.

Family 2

The proband was a 50-year-old male patient with carcinoma of the buccal mucosa. He was a smoker, but one of his brothers, who did not chew tobacco, smoke or consume alcohol, had also

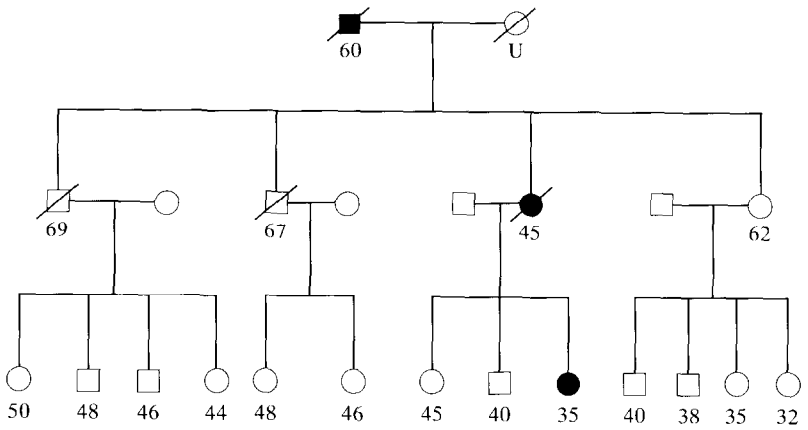


Fig. 1. Pedigree of family 1.

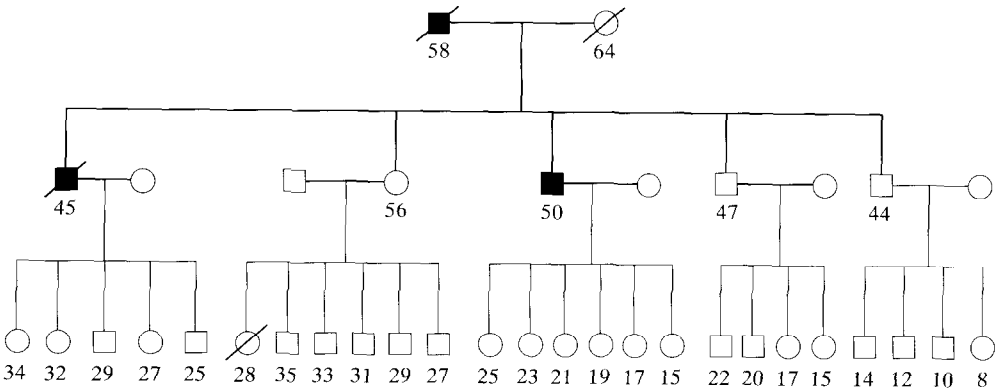


Fig. 2. Pedigree of family 2.

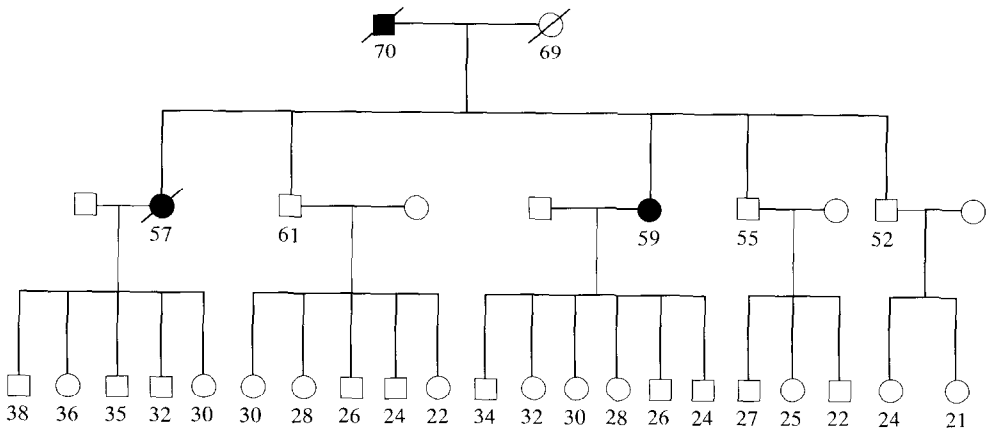


Fig. 3. Pedigree of family 3.

had buccal mucosal cancer and had died at the age of 45 years. His father was also an oral cancer patient (cancer of the tongue) and had died at the age of 58 years.

Family 3

A 59-year-old female presented with carcinoma of the lip. She did not smoke, chew tobacco or consume alcohol. Her sister, a habitual chewer, had also had cancer of the lip and had died at the age of 57 years; her father who was a smoker also had carcinoma of the tongue and had died at the age of 70 years.

Family 4

A 70-year-old female, who was an occasional tobacco chewer presented with carcinoma of the buccal mucosa. Her brother had buccal mucosal cancer and had died at the age of 60 years. Her son, 50 years old at the time of the study, also had carcinoma of the buccal mucosa and has been undergoing treatment at the centre for the last 2 years. He was a smoker.

Family 5

The proband, a male aged 53 years, had carcinoma of the tongue. His brother had had cancer of the tongue and had died

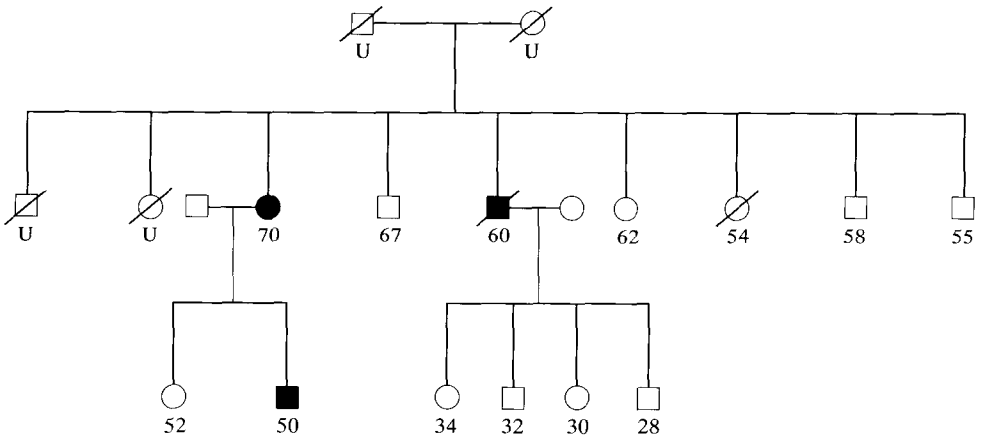
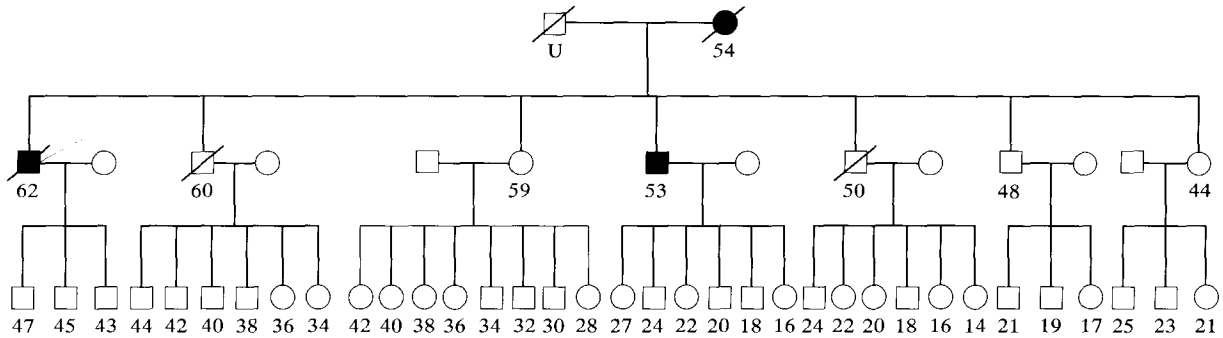


Fig. 4. Pedigree of family 4.



General symbols

Squares	– Males
Circles	– Females
Solid symbols	– Oral cancer patients
Numbers below symbols	– Age at tumour diagnosis, or age at last observation
U	– Age unknown
All open or solid symbols with a diagonal	– Deceased

Fig. 5. Pedigree of family 5.

at the age of 62 years. His mother also had cancer of the tongue and had died at the age of 54 years. These three patients and the majority of other family members were heavy tobacco chewers and/or smokers.

DISCUSSION

A pedigree analysis of oral cancer patients registered at our Centre from January 1995 onwards was carried out. Within a period of 6 months, familial aggregation of oral cancer was observed in 0.94% of the total oral cancer cases. This shows that the incidence of familial oral cancer is more significant than previously thought. In these oral cancer families, the aggregation was found to be mostly site-specific, whereas occasionally oral cancer was found in nearby, associated, anatomic sites. In the present study, a family history of oral cancer was associated with an early age of onset of the disease compared with the usual onset age in the sixth or seventh decade in sporadic oral cancers. In breast cancer, colorectal cancer, basal cell carcinoma, etc., a family history of the disease has also been associated with early onset of the disease [5, 6].

There have only been a few reports on familial aggregation of oral cancer. Goldstein *et al.* [7] examined the relationship between a family history of cancer and risk of oral and pharyngeal cancer using epidemiological data from a case–control investigation of these tumours. According to their data, there was at most a weak familial aggregation of oral/pharynx cancers. Since the excess familial risk of oral/pharynx cancer was associated with smoking-related cancers among male, but not female, relatives, they concluded that environmental factors (notably smoking and drinking) contributed to the familial tendency observed in their study. However, in our oral cancer families 1–3, at least one member who did not chew tobacco, smoke or consume alcohol had succumbed to oral cancer. This indicates that factors other than tobacco and alcohol are also involved in oral oncogenesis.

The occurrence of familial cancer aggregations indicates the existence of genetic predisposing factors. According to Knudson's two-step mutation hypothesis [8], familial and nonfamilial (sporadic) forms of a cancer involve the same gene(s). In sporadic cancers, no mutation is inherited and a minimum of two somatic mutations must occur within one cell. Hereditary

cancer results from a germline mutation inherited from a parent and propagated in all somatic cells of susceptible family members, a second or further mutation(s) transforms the cell [9]. According to Mendelian genetics, the mode of transmission of an inherited trait can be determined by the number of altered alleles required to establish the phenotype and whether or not the allele resides on a sex or autosomal chromosome. Pedigrees of oral cancer families in the present study clearly indicate an autosomal mode of inheritance among affected family members.

Cancer susceptibility in humans has a genetic basis involving inheritance of a susceptibility gene [10]. In humans, it has been reported [11] that heterozygosity at a cancer susceptibility locus is characteristic of hereditary predispositions involving tumour suppressor genes. The *NF1* gene in neurofibromas, *p53* gene in Li Fraumeni syndrome, *BRCA1* and *BRCA2* genes in familial breast and ovarian cancers, *hMSH2* gene in hereditary colon cancer, etc., are examples of inherited tumour suppressor genes involved in cancer predisposition [12–16]. Most of these inherited cancer predispositions involve the inheritance of a mutated tumour suppressor gene and the loss (mutation) of the corresponding wild type allele in the neoplasms that eventually arise. The familial aggregation, early age of onset, dominant mode of autosomal inheritance, etc., observed in these oral cancer families reported suggests the probability of an oral cancer susceptibility gene. It is presumed that vertical transmission of a defective or altered gene from generation to generation plays a causative role in familial oral cancer development. This may be the first step in familial oral oncogenesis. Expression of mutated or phenotypically altered oncogenes, such as *ras*, *myc*, *erbB-1* and the tumour suppressor gene *p53*, has been implicated in sporadic oral cancer development [17, 18]. Maestro *et al.* [19] indicated that at least three oncosuppressor genes mapping on 3p may be involved in head and neck cancer development. However, the number of steps, their chronological order and the nature of particular genetic events have to be elucidated. These are the objectives of several ongoing studies.

The fact that all the members in an oral cancer family are not affected can be explained as resulting from interindividual differences in susceptibility at some stage of the carcinogenic process. Host factors may operate to confer greater or lesser susceptibility to carcinogenic action [20]. Variations in activity of metabolising enzymes and DNA repair competence among individuals also contribute to cancer susceptibility [6]. In head and neck squamous cell carcinoma patients, Schantz and Hsu [21] demonstrated a mild chromosomal instability after induction with the mutagen bleomycin. Schantz *et al.* [22] also demonstrated a significant relationship between an increasing risk of multiple primary cancers of the head and neck and an incrementally increasing mutagen sensitivity value. Mutagen sensitivity was also demonstrated to be a significant predictor of risk of developing second malignant tumours in patients with upper aerodigestive tract cancers [23]. Cloos *et al.* [24, 25], after studying mutagen sensitivity on head and neck squamous cell carcinomas, proposed that mutagen sensitivity was a constitutional factor which reflects the way in which genotoxic compounds are dealt with and is thereby directly related to cancer risk. So, genetically determined DNA repair capacity may be one of the factors influencing mutagen sensitivity and hence carcinogenesis in head and neck cancers. We have initiated, and intend to continue, mutagen sensitivity studies in familial oral cancer patients and their first-degree relatives to determine whether this may give any clues to cancer-predisposing factors in familial oral cancers.

Certain questions regarding the pathology of familial oral cancer have to be answered. If there is an oral cancer susceptibility gene, where is it located? Is there a premalignant genetic marker for familial oral cancer? Does the hereditary oral cancer have distinctive histological features? Identification of the oral cancer susceptibility gene and the inherited germline mutations of the susceptibility gene may help to determine who is or who is not genotypically affected in oral cancer families. Knowledge of the molecular mechanisms responsible for oral cancer susceptibility in families will facilitate new opportunities for diagnosing and treating sporadic, as well as familial, oral cancers.

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