RESEARCH COMMUNICATION

Cancer of the Oral Cavity and Pharynx in Karachi - Identification of Potential Risk Factors

Yasmin Bhurgri[1,2,3], Asif Bhurgri[1,2], Akbar Shah Hussainy[3], Ahmed Usman[4], Naveen Faridi[5], Jawaid Malik[5,6], Zubair Ahmed Zaidi[7], Suhail Muzaffar[3], Naila Kayani[3], Shahid Pervez[3], Sheema H. Hasan[3].

Abstract

The objective of the study was to provide an overview of the demographics of cancer of the oral cavity and pharynx in Karachi South (1995-2001), and identify potential risk factors. Cases recorded for Karachi South, at Karachi Cancer Registry during 1st January 1995 to 31st December 2002 were analysed. For maximum completion of data cancer cases, recorded from 1st January 1995 to 31st December 2001 were included for final analysis. The age standardized incidence rates per 100,000 population (ASIRs) for cancer of the oral cavity (excluding salivary gland) in Karachi South were 17.1 and 16.5 in males and females whereas the ASIRs for cancer of the pharynx (excluding nasopharynx) were 7.1 and 2.4 in males and females, respectively. The oral pharyngeal ratios were 2.4 and 6.9 for males and females and gender ratios (M F) were 1.04 for the oral cavity and 3.0 for the pharynx. The mean ages were 51 years (95% CI 49.6; 52.2) and 56.1 years (95% CI 54.4; 57.8) respectively. Cancer of the oral cavity ranked 2nd in Karachi in both genders. Cancer of the pharynx ranked 7th in males and 14th in females. Approximately 97% of the oral cavity and pharyngeal cancers were histologically confirmed. The majority of the oral (47.1%) and pharyngeal (51.9%) cancer cases presented as grade II lesions, and were discovered at advanced stages. Of the cancers reported during 1995-2001, 60.4% of the oral and 78.1% of the pharyngeal lesions had spread to a distant site at the time of diagnosis. Squamous cell carcinoma comprised 96.5% and 91.8% of the totals. The incidences of these cancers are comparable to the highest risk regions of the world. As distinct from other geographical areas oral cancer is as common in females as in males, which may reflect the pattern of exposure to known risk factors such as betal quid, arecanut and tobacco and the absence of alcohol as a risk factor in both genders. Apergillus contamination of arecanut could also be a risk factor but no confirmation studies or quantification is available. Despite the common risk factors, incidence of pharyngeal cancer is three times higher in men as compared with women. The keys to reducing the incidence and mortality due to oral and pharyngeal cancers are prevention and control, emphasizing cessation of tobacco use and cancer screening. However a targeted cancer and tobacco control program does not presently exist in Pakistan.

Key Words: Cancer - oral cavity - pharynx - Karachi - Pakistan

Asian Pacific J Cancer Prev, **4**, 125-130

Introduction

Cancers of the oral cavity (excluding salivary gland) and pharynx (excluding nasopharynx); ICD-10 (International Classification of Diseases 10th Revision) categories C00-06, and C09, C10, C12-14 affect a significant number of individuals worldwide (WHO, 1992). Cancer of the oral cavity ranks sixth overall in the world for both sexes; it is also the third most common site among males in developing countries. The age-standardized incidence rates per 100,000 population (ASIRs) vary from the lowest rates, 0.64 (males); 0.22 (females) in Egypt to the highest rates 45.81 (males); 28.8 (females) in Papua, New Guinea. The ASIR for cancer or pharynx in males vary from 0.18 in Nigeria and 0.25 in Jordan to 19.17 in France. In females the incidence rates of cancer pharynx range from 0.02 in Armenia and Azerbaijan to 5.05 in Haiti. (Ferlay, 2000)

"Cancers of the oral cavity account for 212,000 new cases

[1]Karachi Cancer Registry, [2]Sindh Medical College, Karachi, [3]Aga Khan University Hospital, Karachi, [4]Jinnah Postgraduate Medical Centre, Karachi, [5]Liaquat National Hospital, Karachi, [6]Ziauddin Cancer Hospital, Karachi, [7]Dow Medical College/Civil Hospital Karachi Address all correspondence to: Dr. Yasmin Bhurgri, Karachi Cancer Registry, Department of Pathology, Sindh Medical College, Rafiqui Shaheed Road, Cantt, Adjacent Jinnah Postraduate Medical Centre, Karachi, Pakistan.

worldwide (2.2% of the total) followed by other pharyngeal cancers with 94,000 cases (1.2%)". (Parkin, 1998) In industrialized countries, men are affected two to three times as often as women, largely due to higher use of alcohol and tobacco. Ethnicity strongly influences prevalence due to social and cultural practices, as well as socioeconomic differences. "The sex ratio (M:F) is 2.0 for oral cavity cancer and 4.4 for pharynx cancer. There are some similarities to the geographic patterns for cancers of the oral cavity, and pharynx. In men, both are high in western and southern Europe, and south Asia, while oral cavity cancers (but not pharynx) have high rates in Melanesia, southern Africa, and Australia/New Zealand". (Parkin, 1998) The disease's geographical distribution may partly be explained by the major risk factors, which are dietary or nutritional composition, tobacco and alcohol. Betalquid and arecanut are additional risk factors in South Asia. Arecanut a known risk factor of submucus fibrosis has been implicated as an independent risk factor for oral cancer. (Warnakulasuriya, 2002)

Pakistan, the seventh-most populous country in the world, is a republic in south central Asia. It shares international geographical boundaries and cultural similarities with India in the east and southeast, Iran and Afghanistan on the west and northwest and China and the Soviet Central Asian Republics in the north. This cross-cultural heritage is reflected in the emerging patterns of cancer in the country. Karachi is the largest city of Pakistan, capital of Sindh Province, located on the coast of Arabian Sea (latitude: 24 -56'-00" and longitude: 67 -01'-00"). The city, also called Karachi Division is divided into 5 districts, South, Central, West, East and Malir. Karachi South (KS), the southern-most district has a population of 1,724,915 with 929,394 (54%) males and 795,521 (46%) females. (Census 1998) It includes all ethnicities of the country, namely Sindhis, Punjabis, Pathans, Baluchs and Mohajirs with a fair representation of all socio-economic categories. The Mohajirs are a mixed community, having migrated from India at the time of partition of the sub-continent and largely retaining their pre-migration cultural and social heritage. In the absence of a national cancer registration system, it qualifies as a sample population of the country. A profound affect of westernization is seen in parts of this district, in stark contrast to an extreme cultural conservativeness in some parts and moderation in other parts of the same district.

Methodology

Incident cancers of oral cavity and pharynx, diagnosed clinically or microscopically and registered at the Karachi Cancer Registry during 1st January 1995 to 31st December 2002 were analysed. For maximum completion of data, incident cases registered from 1st January 1995 to 31st December 2001 were included for final analysis. The residency status of oral cavity and pharynx cancer cases was re-ascertained and rechecked. People residing in the specified geographical regions for more than six months were considered residents. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grading and staging.

The data were classified using ICD-O2 (International Classification of Diseases-Oncology, 2nd edition) and computerized using a customized version of CANREG-3 software provided by the International Agency for Research on Cancer (IARC). (WHO, 1990) This software includes facilities for the detection of duplicate registrations and for performing internal checks on the validity of the entered data. Both manual and computerized validity checks for the cancer data were performed as per recommendations of IARC and International Association of Cancer Registries (IACR). This involved factors influencing comparability i.e. classification and coding. (Parkin, 1997; Parkin, 1994; Skeet, 1991)

The person-years of population at risk by sex and 5-year age-groups were estimated based on the 1998 census (copy obtained from the Sindh Bureau of Statistics), assuming an annual growth rate of 1.74%. The growth rate was based on the inter-census growth-rate and measures for inflow and outflow of population, calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age distribution. (Segi, 1960) 'The standardized rate is the incidence rate that, theoretically, would have been observed if the population had a standard age distribution. The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population, averaged over the number of years for which data are presented'. (Parkin, 1997) Incidence tables were based on ICD-10. (WHO, 1992)

Results

The ASIR for cancer of the oral cavity (excluding salivary gland) ICD-10 (International Classification of Diseases 10th Revision) categories C00-06, in Karachi South was 17.1 and 16.5 in males and females whereas the ASR for cancer pharynx (excluding nasopharynx) ICD-10 categories C09, C10, C12-14 was 7.1 and 2.4 in males and females. The gender ratio (M:F) was 1.04 for oral cavity and 3.0 for pharynx. The mean ages were 51 years (95% CI 49.6; 52.2) and 56.1 years (95% CI 54.4; 57.8) for oral cavity and pharynx. (Tables 1,2)

Cancer of oral cavity ranked 2nd in Karachi with an identical risk in both genders. Cancer of pharynx ranked 7th in males and 14th in females. The tumour ranking in males was lung, ICD-10 categories C33-C34 (ASIR 21.8), oral cavity ICD-10 categories C00-C06 (17.1), larynx ICD-10 category C32 (9.9), urinary bladder ICD-10 category C67 (9.6), lymphoma ICD-10 categories C81-C85; C96 (9.6/), prostate ICD-category C61 (7.5) and pharynx ICD-10 categories C09, C10, C12-C14 (7.1).

In females the ranking was breast ICD-10 category C50 (ASIR 58.3), oral cavity ICD-10 categories C00-08 (17.5),

Table 1. Age-standardized Incidence Rate (ASIR), Basis of Diagnosis, Religion, and Ethnicity

	Oral cavity (N=1153)	Pharynx (N=329)	Oral/pharyngeal
ASIR per 100,000 population			
Males	17.1	7.1	2.4
Females	16.5	2.4	6.9
Gender ratio M/F	1.0	3.0	
Basis of Dignosis	%	%	
Clinical	2.3	3.7	
Histological	97.7	96.3	
Religion			
Muslim	94.5	96.8	1.0
Christian	1.7	0.9	1.9
Hindus	1.8	1.8	1.0
Parsees	0.7	0.5	1.4
Ethnicity			
Sindhi	14.9	15.6	1.0
Punjabi	11.9	9.8	1.2
Pushtu	5.1	5.7	0.9
Baluch	19.2	9.0	2.1
Mohajir (urdu)	24.3	23.0	1.1
Mohajir (gujrati)	10.8	10.7	1.0
Mohajir (memon)	12.4	25.4	0.5
Afghan migrants	1.4	0.8	2.3

ovary ICD-10 category C56 (ASIR 9.8), cervix ICD-10 category C53 (7.6), esophagus ICD-10 category C15 (7.6), lymphoma ICD-10 categories C81-85; C96 (7.0), uterus ICD-10 categories C54-C55 (5.9), gall bladder ICD-10 category C23 (5.4), colo-rectum ICD-10 categories C18-20 (5.2), skin ICD-10 category C44 (5.0), thyroid ICD-10 category C73 (3.9), liver ICD-10 category C22 (3.8), urinary bladder ICD-10 category C67 (3.2) and pharynx ICD-10 categories C09, 10, 12-14 (2.4).

Approximately 97% of the oral cavity and pharyngeal cancers were histologically confirmed. The majority of the oral (47.1%) and pharyngeal (51.9%) cancer cases presented as grade II lesions, and were discovered at advanced stages. 60.4% of the oral and 78.1% of the pharyngeal cancers reported during 1995-2001 had spread to a distant site at the time of diagnosis. (Table 2) Squamous cell carcinoma comprised 96.5% and 91.8% of the oral and pharyngeal cancers. (Table 3). Border of the tongue and mucosa cheek comprised approximately 80% of oral cancer lesions. (Table 4)

The race or ethnicity specific incidence rates were not calculated as ethnicity specific population figures are yet to be released by the census department. However the oral pharyngeal ratio for Baluchs (2.1) and Afghan migrants (2.3) was high and for Mohajir Memons (0.5), a group of migrants from Mumbai, India was low (Table 1).

Figure 1 a and b show the age specific incidence rates for cancer oral cavity and pharynx in the males and females. In the males the age specific rates for oral cancer showed a gradual rise from 15 to 19 years of age to a maximum in the 7th decade, cancer pharynx showed a gradual rise from 30 to 34 years of age to a maximum in the 8th decade. In the females the age specific rates for oral cancer showed a gradual rise

Table 2. Distribution of Cases According Grade, Extent, and Mean Ages

	Oral cavity (N=1153) %	Pharynx (N=329) %
Grade		
I – mild	44.6	13.0
II – moderate	47.1	51.9
III – severe	7.8	33.3
IV – undifferentiated	0.5	1.8
Extent		
In-situ	0.4	1.2
Localized	39.2	20.7
Regional spread	56.5	73.2
Distant spread	3.9	4.9
Mean Ages	51	56.1

Table 3. Distribution of Cases According to Morphology

	Oral cavity (N=1153) %	Pharynx (N=329) %
Morphology		
Squamouscell carcinoma	96.5	91.8
Adenocarcinoma	0.3	0.5
Other specified carcinomas	0.7	3.1
Unspecified carcinomas	2.4	2.3
Sarcoma	-	-
Other specified morphology	-	0.9
Other unspecified morphology	-	1.4

Table 4. Topographic Distribution of Cancer Cases Oral Cavity

	Males	Females
Topography	%	%
Lip	4.9	2.4
Tongue (base)	3.9	2.8
Tongue (border)	24.8	32.6
Gum	3.2	4.8
Floor of mouth	0.7	0.7
Palate	7.3	6.5
Cheek (mucosa)	55.2	50.2

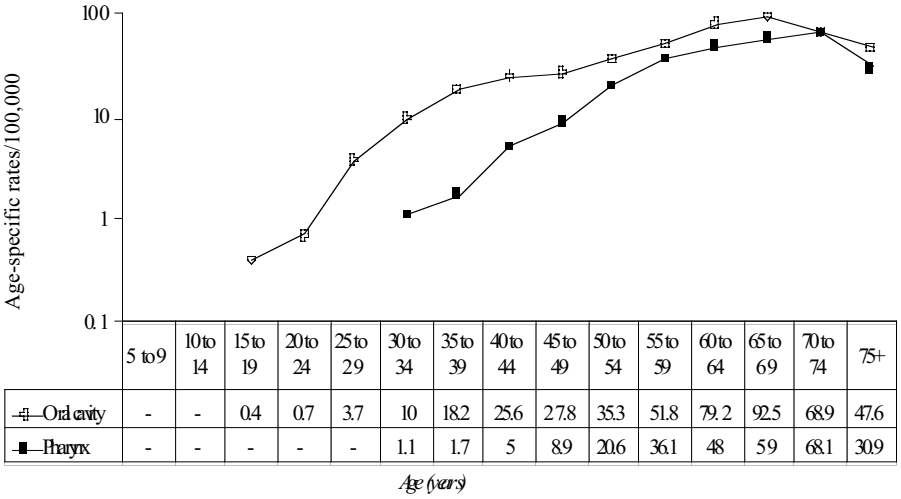
from 10 to 14 years of age to a maximum in the 8th decade whereas the rates for cancer pharynx showed a gradual rise from 20 to 24 years of age to a maximum in the 7th decade. A flattening or an actual apparent decrease in the risk is seen in the 75+ age group for both cancer types and genders.

Discussion

The registry in Karachi South covers a stable population. The data has a good completion rate with adequate coverage of clinically diagnosed and death certified cases (Table 1). The percentage of cases reported with microscopic verification is high with values similar to developed countries. Easily available and affordable biopsies and cytolologies have improved the microscopic verifications and minimized under-registration of cases. Death registration system in Karachi South is computerized and well organized. The registered data are valid. Collection from multiple reporting centres, regular scrutiny, re-abstracting and recoding exercises and the use of CANREG-3 data management software have enhanced the validity of the data. Checks for duplication of registered data, exclusion of prevalent and non-resident cases are conducted manually and with CANREG-3 inbuilt check systems.

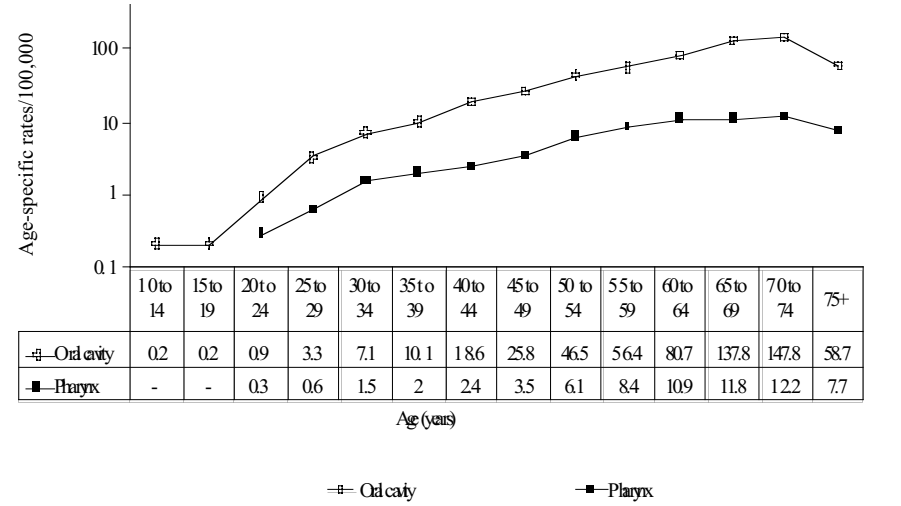
Oral cancer is an important health issue. The WHO predicts a continuing worldwide increase in the number of patients with oral cancer, extending this trend well into the next several decades. (Sciubba, 2001) Significant agents involved in the etiology of oral cancer in Western countries include sunlight exposure, smoking and alcohol consumption. In developing countries tobacco, alcohol, betal quid chewing, together with poor diet are the most important

a) Males



	5 to 9	10 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75+
Oral cavity	-	-	0.4	0.7	3.7	10	18.2	25.6	27.8	35.3	51.8	79.2	92.5	68.9	47.6
Pharynx	-	-	-	-	-	1.1	1.7	5	8.9	20.6	36.1	48	59	68.1	30.9

b) Females



	10 to 14	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75+
Oral cavity	0.2	0.2	0.9	3.3	7.1	10.1	18.6	25.8	46.5	56.4	80.7	137.8	147.8	58.7
Pharynx	-	-	0.3	0.6	1.5	2	2.4	3.5	6.1	8.4	10.9	11.8	12.2	7.7

Figure 1. Cancer of Oral Cavity and Pharynx, Age Specific Incidence Rates a) Males; b) Females

risk factors for cancers of the oral cavity and pharynx though several less important risk factors have also been associated. There is a strong evidence for an etiological relationship with human papilloma virus. Other etiologic factors associated with oral squamous cell carcinoma, but far less significant statistically, include syphilis, sideropenic dysphagia, low educational attainment, occupation as a farmer or manual worker and various indicators of poor oral hygiene. (Sciubba, 2001; Franceschi, 2000; Parkin, 1998)

The habit of betal chewing is of great antiquity, tobacco being added sixteenth century onwards. (Muir and Zaridze, 1986) The basic quid comprises the leaf of betal vine (Piper betle), sliced or shaved arecanut from the betal palm (Areca catechu), slaked lime paste and catechu paste. Paan masala a later addition to this family is a powdery mixture of betel nut, lime and arecanut (supari) in various proportions. Tobacco may be a component of some variants of paan masala. This 'smokeless tobacco use' has been widely publicized in the carcinogenesis of oral cancer in individuals of South-Asian origin. Case-control studies in India have attributed a combination of smoking, alcohol drinking, paan-tobacco chewing and poor oral hygiene to oral cancer. (Balaram, 2002; Dhar, 2000) The incidence in Karachi (District South) is identical to the high risk geographical zones of India, indicating that cultural and lifestyle characteristics retained by the migrants as the major determinants of the disease.

In Karachi more than 70% of members of both genders chew paan masala; this includes school children as young as 3-4 years of age. 36% of the females and 44% of the males in Karachi chew paan with or without tobacco. (Alam, 1998; Merchant, 1998) These figures correspond well with the incidence of oral cancer. As in several other regions of the sub-continent, arecanut use has been indicated as an independent risk factor for oral cavity cancer, and probably for the pharyngeal cancers, however there is no reliable study to confirm this co-relation for Pakistan. In Karachi identical risk factors are seen for oral cancer in both genders, whereas for pharynx (excuding nasopharynx), the risk factor in males is thrice that of the females. A lower oral/pharyngeal ratio in men compared to women, is observed globally. (Franceschi, 2000) The most important single risk factor for development of these cancers appears to be tobacco use. All forms of tobacco in use are considered major risk factors eg cigarette and bidi smoking, snuff or naswar. Alcohol is not a confounder in this Muslim country. In the developed countries, alcohol synergizes with tobacco as a risk factor for all upper aerodigestive tract cancers, this is super-multiplicative for the mouth.

A trend towards higher prevalence of oral cancer is observed in Karachi and no progress has been achieved concerning cancer control during the last few decades. Despite the simplicity of the oral examination, cytological and histopathological verifications, most of oral cancers are discovered at advanced stages bearing severe prognosis. Most of the patients sought medical care in the first year; however more than half of them had lesions in stage T3 and T4.(Table 2) The keys to reducing mortality are prevention and control, emphasizing cessation of tobacco use and cancer screening. The earlier any intraoral or extraoral abnormalities or lesions are detected and biopsied, more lives can be saved. Though controversy exists whether screening programs effectively reduce the mortality rate, it is largely believed that the protection offered by screening persisted up to 3 years since the last test. (Sankaranarayanan, 2002) Improved awareness of both the attendant medical team and the target population may improve the chances of prevention

There is an increasing incidence of oral cancer in the younger persons. The reasons are unclear. It has been hypothesised either to be a result of an increase in exposure to known risk factors amongst certain groups in the community, or to be due to new aetiological agents. A survey of young persons with oral cancer suggest that most are exposed to traditional risk factors of tobacco smoking, drinking alcohol and a low consumption of fruit and vegetables. (Mackenzie, 2000) The chewing habit is so deeply ingrained in the Indian culture that a high prevalence of arecanut chewing is seen amongst children (second generation) of South Asian origin living in UK and Australia (Farrand, 2001; Cox, 2000).

Most sporadic tumors are the result of a multi-step process of accumulated genetic alterations. These alterations affect epithelial cell behavior by way of loss of chromosomal heterozygosity, which in turn leads to a series of events progressing to the ultimate stage of invasive squamous cell carcinoma. (Sciubba, 2001) Alterations in p53 tumour suppressor gene and its expression; GSTM1 null genotype, homozygous deletion of the GSTM1 gene are all implicated in the pathogenesis of betel quid and tobacco-related oral cancer. The risk increases further when these individuals are exposed to environmental toxicants such as chemicals in cigarette smoke, alcohol, and betel quid. (Buch, 2002; Kietthubthew, 2001) Human papilloma virus types and its association with P53 codon 72 polymorphism in tobacco addicted oral squamous cell carcinoma (OSCC) patients has also been observed in Eastern India. (Nagpal, 2002) Deficient CYP2A6 activity due to genetic polymorphism reduces oral cancer risk in betel quid chewers. (Topcu, 2002) Regular consumption of green tea is also considered beneficial in the prevention of oral cancer, in individuals that ingest alcohol in combination with the use of tobacco products. The mechanism involving a p57 mediated survival pathway. (Hsu, 2002)

Oral and oropharyngeal cancers represent 3% of all cancers in the United States annually, with nearly 50% of people diagnosed with oral and oropharyngeal cancers dying as a result of the disease. (Weinberg, 2002; Sciubba, 2000) There was little change in early detection of oral cancer or in 5-year relative survival rates between 1973-84 and 1985-96 in nine SEER regions. (Shiboski, 2000) Sixty percent of oral cancers are well advanced by the time they are detected, even though physicians and dentists frequently examine the oral cavity. Because the dental practitioner is in an ideal position for recognizing any abnormality of the oral mucosa,

he or she is involved in the battle against oral cancer by helping establish the diagnosis at an early stage. (Sciubba, 2000) This suggests a deficiency in professional and public education regarding early diagnosis of oral cancer.

Conclusion

The demographic, site, stage, and histologic data available for this large number of cases at the Karachi Cancer Registry allowed an accurate characterization of the contemporary status of oral cancer in the Karachi. The incidence of cancer oral cavity and pharynx in Karachi is comparable to high incidence regions of the world. As distinct from other geographical areas oral cancer is as common in females as in males, which may reflect the pattern of exposure to known risk factors such as betal quid, arecanut and tobacco and the absence of alcohol as a risk factor in both genders. Aspergillus contamination of arecanut could also be a risk factor but no confirmation studies or quantification is available. Despite the common risk factors incidence of pharyngeal cancer is three times higher in men as compared with women. Further research needs to be focused on the etiological aspects of these cancers. The keys to reducing the incidence and mortality due to oral and pharyngeal cancers are prevention and control, emphasizing cessation of tobacco use and cancer screening. A targeted cancer and tobacco control program is presently non-existent in Pakistan.

References

Alam SE (1998). Prevalence and pattern of smoking in Pakistan. *J Pak Med Assoc*, **48**, 64-6.

Balaram P, Sridhar H, Rajkumar T, et al (2002). Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. *Int J Cancer*, **98**, 440-5.

Boucher BJ (2001). Paan without tobacco: an independent risk factor for oral cancer. *Int J Cancer*, **91**, 592-3.

Buch SC, Notani PN, Bhisey RA (2002). Polymorphism at GSTM1, GSTM3 and GSTT1 gene loci and susceptibility to oral cancer in an Indian population. *Carcinogenesis*, **23**, 803-7.

Census Bulletin-1 (1998). Population and Housing Census of Pakistan, Population Census Organisation Statistics division, Federal Bureau of Statistics, Government of Pakistan.

Cox S (2000). Oral cancer in Australia-risk factors and disease distribution. *Ann R Australas Coll Dent Surg*, **15**, 261-3.

Dhar PK, Rao TR, Sreekumaran-Nair N, et al (2000). Identification of risk factors for specific subsites within the oral and oropharyngeal region - a study of 647 cancer patients. *Indian J Cancer*, **37**, 114-22.

Farrand P, Rowe RM, Johnston A, Murdoch H (2001). Prevalence, age of onset and demographic relationships of different arecanut habits amongst children in Tower Hamlets, London. *Br Dent J*, **190**, 150-4.

Ferlay J, Bray F, Pisani P, Parkin DM (2001). Globocan 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC Cancer Base No. 5, Lyon.

Franceschi S, Bidoli E, Herrero R, Munoz N (2000). Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues. *Oral-Oncol*, **36**, 106-15.

Hsu Stephen D, Singh Baldev B, Lewis Jill B, et al (2002). Chemoprevention of oral cancer by green tea. *Gen Dent*, **50**, 140-6.

Kietthubthew S, Sriplung H, Au WW (2001). Genetic and environmental interactions on oral cancer in Southern Thailand. *Environ Mol Mutagen*, **37**, 111-6.

Mackenzie J, Ah-See K, Thakker N, et al (2000). Increasing incidence of oral cancer amongst young persons: what is the aetiology? *Oral Oncol*, **36**, 387-9.

Merchant AT, Luby SP, Perveen G (1998). Smoking in Pakistan: more than cancer and heart disease. *J Pak Med Assoc*, **43**, 77-9.

Muir CS and Zaridaze DG (1986). Smokeless Tobacco and Cancer: an overview. In Tobacco a Major International Health Hazard Zaridze DG and Peto R. (eds) pp35-44 IARC Scientific Publications No.74, Lyon

Nagpal JK, Patnaik S, Das BR (2002). Prevalence of high-risk human papilloma virus types and its association with P53 codon 72 polymorphism in tobacco addicted oral squamous cell carcinoma (OSCC) patients of Eastern India. *Int J Cancer*, **97**, 649-53.

Parkin DM (1998). The Global Burden of Cancer. *Cancer Biology* **8**, 219-35.

Parkin DM, Chen VW and Ferley J (eds.) (1994). Comparability and Quality Control in Cancer Registration, IARC Technical Report No.19, Lyon.

Parkin DM, Whelan SL, Ferley J, Raymond L, Young J (eds.) (1997). Cancer Incidence in the Five Continents Volume VII, IARC Technical Report No.143, Lyon.

Sankaranarayanan R, Fernandez-Garrote L, Lence-Anta J, Pisani P, Rodriguez-Salva A (2002). Visual inspection in oral cancer screening in Cuba: a case-control study. *Oral Oncol*, **38**, 131-6.

Sciubba JJ (2000). Oral precancer and cancer: etiology, clinical presentation, diagnosis and management. *Compend Contin Educ Dent*, **21**, 892-8.

Sciubba JJ (2001). Oral cancer. The importance of early diagnosis and treatment. *Am J Clin Dermatol*, **2**, 239-51.

Segi M (1960). Cancer Mortality in Selected Sites -in 24 Countries (1950-57), Sendai, Tohoku University School of Public Health.

Shiboski CH, Shiboski SC, Silverman S Jr (2000). Trends in oral cancer rates in the United States, 1973-1996. *Community Dent Oral Epidemiol*, **28**, 249-56.

Skeet RC (1991). Comparability and Quality Control. In Cancer Registration: Principles and Methods, Jensen OM, Parkin DM, MacLennan R, Muir CS and Skeet RG (eds); IARC Scientific Publications No. 95, Lyon.

Topcu Zeki, Chiba Itsuo, Fujieda Masaki, et al (2002). CYP2A6 gene deletion reduces oral cancer risk in betel quid chewers in Sri Lanka. *Carcinogenesis*, **23**, 595-8.

Warnakulasuriya S, Trivedy C, Peters TJ (2002). Arecanut use: an independent risk factor for oral cancer. *BMJ*, **324**, 799-800.

WHO (1990). International Classification of Diseases for Oncology, Ed. 2, Geneva, World Health Organisation.

WHO (1992). International Statistical Classification of Diseases and Health Related Problems 10th Revision, Geneva, World Health Organisation.

Weinberg Mea A, Estefan Denise J (2002). Assessing oral malignancies. *Am Fam Physician*, **65**, 1379-84.