In the Name of God

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Title:

Epidemiological study of oral and pharyngeal cancers in Kermanshah province from March 1993 to March 2006

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To:

I specially thank my dear wife and my dear daughter for giving me his love and respect during this procedure.

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Chapter 1

Introduction

1. Introduction

Cancers of the oral cavity and pharynx (OCP) include tumors of the lip, tongue, gingiva (gums), floor of the mouth, soft and hard palate, tonsils, salivary glands, oropharynx, nasopharynx, hypopharynx and other less frequent sites (1, 2).

1.1. Epidemiology

Oral cancer is one of the 10 most frequent cancers worldwide (3,4). The majority of oral cancer is squamous cell carcinoma (1, 2, 3, 4, 5, 6).Cancers of the oral cavity and pharynx combined account worldwide after the exclusion of nosopharynx, for approximately 220,000 new cases, per year in men (5% of all cancers) and 90,000 in women (2% of all cancers) (7).

Variation of oral and pharynx cancer per geographic region around the world is large. Incidence rate are higher in developed countries than in developing countries. However, in countries of southern Asia, such as India, oral cancer is the most common cancer affecting males and the third one affecting females, after breast and cervix uteri tumors (8).

Other geographic areas with high incidences are eastern, western and southern Europe, Australia and New Zealand and Melanesia.

France reports the highest level (12.4 per 100,000 inhabitants per annum in Bas-Rhin), whereas the Nordic countries show relatively low figures (1.1, 1.7 per 100,000 per annum) (9).

Latin America and the Caribbean have intermediate incidence rates for oral cancer; however, the rate among countries of the region varies widely (1,7,8,9,12).

In most European countries, oral cancer mortality for men has been rising appreciably between the 1950s and the late 1980s and also for women-whose rates are substantially lower-some steady up ward trend was observed. The rise for men was about 4-fold in Germany and Hungary, and over 2-fold in Czechoslovakia, Poland, Romania or Spain. Thus, the rises in oral cancer mortality were among the largest registered for any common neoplasm. Upward trends in oral cancer mortality until the early 1990s, were registered also in the USA, Thailand and India (2, 8, 9, 10, 11, 22, 23).

1.2. Age and Sex

The incidence for oral cancer is clearly age related, which may reflect declining immune surveillance with age, time for the accumulation of genetic changes and duration of exposure to initiators and promoters (these include chemical and decreased immunologic surveillance (4).

Oral cancer, like most cancers, is a disease of older age. About 95% of all oral cancers occurs in persons over 40 years old and the

average age at the time of diagnosis 65 (1, 2, 6, 13). The older age of cancer patients suggests that a time factor may operate, involving predetermined change in the biochemical – biophysical processes (nuclear, enzymatic, metabolic, immunologic) of aging cells-changes that may be influenced by chemicals, viruses, hormones, nutrients, or physical irritants (6, 14, 16, 20).

Younger patients (arbitrarily defined as aged less than 45 years) account for approximately 6% of all oral cancers in the UK (6, 17).

Recently the incidence of oral cancer amongst young adults is increasing is many European and high incidence countries (17, 18, 19, 21).

Oral cancer occurs more frequently in males, but the male to female ratio, which in 1950 exceeded 6 to 1, is now slightly less than 2 to 1 (6).

1.3. Race & Genetics

Ethnic background is known to influence type of cancer. Cancer in blacks is increasing at a faster rate than in whites; oral and pharyngeal cancer is the fourth leading cancer site in black men and the seventh leading site of cancer in non-Hispanic white men in the United State.

Oral cancers in men and women occur less frequently in Asians and Hispanics compared to white and blacks. As another example, cancer of the nasopharynx is 20 to 30 times more prevalent in Chine's than in whites (6, 24, 25).

Studies of human cancer of specific types have shown aggregation in some families, implying a genetic influence. Carcinogenesis is a genetic process that leads to a change in morphology and in cellular behavior. The assessment of changes at the molecular level may become the primary means of diagnosis and may guide management. Major genes involved in head and neck squamous cell carcinoma (HNSCC) include proto-oncogene and tumor-suppressor genes (TSGs). Other factors that play a role in the progression of disease may include allelic loss at other chromosome regions, mutations to proto-oncogenes and TSGs, or epigenetic changes such as deoxyribonucleic acid (DNA methylation or histone deacetylation (4, 8, 26, 27).

1.4. Etiology & Risk Factors

The exact cause of oral cancer is unknown and may remain a mystery because of the multifactorial nature of carcinogenesis.

Evidence indicates that although inherited genes do influence cancer risk, heredity alone explains only a fraction of all cancer.

Variation in incidence rates among different groups or populations may be influenced by difference in exposure to carcinogenic initiators or promoters. For example, the use of tobacco or alcohol significantly increases the risk of cancer, indicating an etiologic role. The role of other factors in promoting human cancer remains important but unclear. For example, immunologic susceptibility, gene mutations,

epithelial cell growth, suppressor proteins, and enzyme action all influence cell stability and health (4, 6, 7, 8, 14, 24).

1.4.1. Tobacco

Tobacco use is the leading preventable cause of premature death worldwide. It was estimated that 4.9 million people died of tobacco-related illness in the year 2000 and by 2020s that figure will rise to 10 million deaths per year, 70% of which will be in developing countries. Tobacco is a major independent risk factor for the development of oral and pharyngeal cancer and other malignancies of the upper aerodigestive tract (3, 4, 5, 6, 25, 27, 28, 29).

Tobacco is consumed in a variety of different ways though smoking of manufactured cigarettes is the most prevalent form of its use. Smokers know that tobacco is harmful to health, though they underestimate their personal risk, but the public in general are unaware of the full spectrum of health risks.

1.4.2. Epidemiology of Tobacco use and oral cancer

In the US some 25% of the population smoke, while in the UK the adult smoking rates are currently around 27%. Many other countries have high rates of smoking, but the highest reported rates are from China; a national study in 1996 reporting that 63% of males were current smokers. About half of all regular cigarette smokers will eventually be killed prematurely by their habit (30).

Oral and pharyngeal cancers have striking geographic and ethnic variations around the globe largely dependent on the pattern of tobacco and alcohol use (30, 31, 32).

1.4.3. Reveres Smoking

The habit of reverse smoking is strongly associated with palatal lesions that carry a high risk of developing to an oral cancer. This habit of smoking by holding the burning end of cigarette or cigars within the oral cavity is reported mainly is parts of India and south America and in the Philippines (31).

1.4.4. Bidi smoking

Smoking of bidi(s) made of hand-rolled tobacco wrapped in tendu leaf is a known risk factor for oral and pharyngeal cancer. Bidi is the cheapest substitute for a cigarette and is generally available in filterless form it is a crude form of smoking, smaller than a cigarette in size, home-made, and consists of about 0.5g of raw, dried and crushed tobacco flakes, hand-rolled in a dried leaf of tendu or white paper (31, 32, 33).

1.4.5. Smokeless tobacco

Worldwide oral use of smokeless tobacco (ST) takes many form and the risks appear different depending on the processing of the product which can markedly affect nitrosamine content (34).

In the west ST is available as oral snuff or in moist pouches. ST is a well recognized risk factor for oral cancer in the US (with a RR approaching 50) and "snuff dipper's cancer" is particularly prevalent in

the southern states. But there is a controversy as to the carcinogenicity of Swedish snuff ("snus") as claimed by Axell based on the reported low incidence of mouth cancer in Swedish snuff dippers in recent decades. Retrospective studies however, have shown that Swedish snuff users are indeed at high risk of cancer at the site of placement (31, 35, 36).

Most information about ST use is among Asians, where it is typically taken with betel/ areca quid. Addition of ST to the areca quid raises the relative risk of the product by nearly 15 times. Other ST products which carry significant mutagenicity are toombak (used in the Sudan), shamma (used in the Jizan province in Saudi Arabia), powdered tobacco and alkali mixtures such as nass/naswar (used in northern and central Asia and in Pakistan), khaini a mixture of ST and lime (used in Bihar state of India and Nepal) and boiled/ Sweetened ST called zarda (mostly used by people from Bangladesh). All these forms of tobacco are associated in an increased risk of oral cancer (31, 34, 37, 38).

1.4.6. Carcinogenicity of tobacco to oral tissues

Tobacco smoke contains many carcinogenic combustion products of which polynuclear aromatic hydrocarbons (PAH) predominate which are primarily contact carcinogens. In most target tissues, the principle PAH carcinogen is benzo(a) pyrene, which is activated by P450 isoenzymes to the carcinogen metabolite banzo (a) pyrene-dihydrodihydroxy epoxide. Such metabolites react with DNA to form predominantly guanosine adducts. If not detoxified by glutathione S-

transferases (GSTs), the resulting DNA adducts can lead to initiation of carcinogenesis (31, 39, 40, 53).

1.4.7. Alcohol

Alcohol, particularly in association with tobacco, has been recognized as an important risk factor for mouth cancer for almost half a century (41, 42).

Indeed, during the past 50 years, the number of liters of pure ethanol consumed per capita each year within the United Kingdom has doubled, from 4 to 8 liters (The Academy of Medical Sciences 2004; Partanen and Simpura, 2001). It is estimated that 2.9 million individuals (7% of the adult population in the United Kingdom) are dependent on alcohol (41).

The role of ethanol in alcoholic beverages can be considered to be rather similar to that of nicotine in tobacco, when it comes to causing cancer. In addition, there is convincing evidence of synergy between alcohol and tobacco in the etiology of oral squamous cell carcinoma (4, 5, 6, 8, 27, 41, 42, 43, 44, 54).

1.4.8. Infections

1.4.8.1. Human Papilloma Virus

The (HPV) DNA frequency in tumors of the head and neck varies widely according to the anatomic site and the geographic region (8).

Verrucous carcinomas have the squamous histology with the strongest association with HPV, as HPV genomic material is found in 30 to 100 percent of these tumors. For squamous cell cancer in

general, the proportion of cancers with evidence of HPV genomic material appears to vary, depending upon the upper aerodigestive tract site analyzed (6, 24).

As reviewed and compiled by Steinberg, the tumor site most often revealing HPV infection is tonsil (74%), with lesser evidence of HPV in larynx (30%), tongue (22%), nasopharynx (21%) and floor of mouth (5%) carcinomas (6).

The principle high-risk genotypes (HPV-16, -18, -31, -33, -35) are associated with premalignant and malignant epithelial disease (6, 7, 8, 24, 45).

1.4.8.2. Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) has shown an emerging association with head and neck squamous cell carcinoma. Patients with HIV were younger than non-HIV patients and HIV infection was present in over 20 percent of head and neck cancer patients who were under 45 years of age (24).

1.4.8.3. Herpes Simplex Virus

Herpes simplex virus (HSV) has been associated with cancer of the oral cavity. In a study utilizing patient questionnaires for data collection, a history of proven HSV-1 infection was associated with oral cancer (24).

1.4.8.4. Esptein-Barr Virus

Eptein-Barr virus (EBV) has been associated with nasopharyngeal carcinoma. The association appears strongest with World Health

Organization (WHO) types II and III while a minority of WHO type I carcinomas have revealed EBV (24).

1.4.8.5. Syphilis

Little evidence currently supports an association between syphilis and oral cancer. Oral syphilitic lesions (chancres and gummas) may clinically resemble carcinoma (6).

1.4.9. Diet and Nutrition

Convincing evidence exists that diets high in fruits and vegetables decrease the risk for cancers of the oral cavity and pharynx. A diet that includes fresh fruit and vegetables rich in beta carotene, vitamin C, and vitamin E has been associated with a reduced risk of oral cavity and pharynx cancers.

In addition, nutritional deficiencies of Iron, riboflavin and other vitamins have been implicated in Plummer Vinson Syndrome, a condition seen particularly among Swedish women that predisposed them to some forms of pharyngeal cancer (1, 6, 43, 44, 47).

Significant reduction in risk of oral, pharyngeal and esophageal cancers has been associated with high intake of tomatoes, an important source of vitamin C in some parts of the world (24).

1.4.10. Hygiene

Poor oral hygiene is associated with oral cancer, but no causal relationship has been established (24).

Mouthwash use was considered as an oral cancer risk factor. The only significant risk elevations were among the most recent users of mouthwash.

Total duration of mouthwash use did not add to risk (44).

The association of poor dentition, poor oral hygiene and denture sores with oral cancer have been reported previously (48).

In Turkey, poorer oral hygiene and less teeth were reported in cancer patients (49).

Other studies have supported the relationship between poor oral hygiene and increased risk of oral cancer (44, 50).

1.5. Clinical presentation

Oral squamous cell carcinoma has a varied clinical presentation, including:

- Ulcer
- Exophytic (mass-forming: Fungating, papillary, verruciform)
- Endophytic (invasive, burrowing, ulcerated)
- White patch (leukoplakia)
- Red patch (Erythroplakia)
- Mixed (white and red lesion)

Cancers often present as a palpable mass that increase in size over time. Preceding the development of the tumor are subtle changes that are dependent on the anatomic site involved and the cell type of origin. Initial features can include a change in surface color (5, 6, 51, 52, 56).

Neglected tumors progress to form the classical fixed ulcer with raised and rolled edges. There is progressive invasion of surrounding soft tissue and bone, and spread to regional lymph nodes.

Destruction of underlying bone, when present, may be painful or completely painless, and it appears on radiography as a "moth-eaten" radiolucency with ill-defined or ragged margins. Carcinoma also can extend for many centimeters along a here without breaking a way to form a true metastasis (5, 6, 14, 55).

1.6. Histopathology

Squamous cell carcinoma arises from dysplastic surface epithelium and is characterized histopathologically by invasion island and cords of malignant squamous epithelial cells (5).

Squamous cell carcinoma (SCC) of the oral cavity spreads primarily by local extension and by lymphatic permeation (6).

SCC can be categorized into three classic differentiations. Well differentiated disease shows greater than 75% keratinization; moderately differentiated disease contributes to the bulk of squamous cell carcinoma and is characterized by 25% to 75% keratinization and poorly differentiated disease demonstrates less than 25% keratinization. Other variant histological subtypes of (SCC) include verrucous carcinoma, Sarcomatoid squamous cell carcinoma, lymphoepithelioma, carcinoma cuniculatum, papillary squamous cell carcinoma, Adenoid (acantholytic) squamous cell carcinoma,