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Oral Cancer and Pathogenesis

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Abstract

Introduction Oral cancer is one of the most common cancer. it constitutes a major health problem mainly in developing countries. The habit of chewing betel nut leaves rolled with lime and tobacco, a mixture known as pan, results in extended contact of the carcinogen with the buccal mucosa, which is thought to be the principal cause of Oral cancer (OC) in India. ***Materials and methods*** The literature search was carried out in NCBI Pubmed database using keywords ‘‘oral squamous cell carcinoma’’, ‘‘risk factors’’, ‘‘pathogenesis’’ and ‘‘genetic alterations*’’. Some elementary information also obtained from textbook and medical university websites. ***Results*** There are Some risk factors have been well defined which is related with oral squamous cell carcinoma with substantial evidences. The enhancement of oral cancer is a multistep process including the accumulation and consideration of genetic and epigenetic alterations in key regulatory genes. Tentative pathological studies of oral cancer in animal models and direct molecular genetic analysis of oral cancer subjects in recent times have exposed a significant amount of knowledge of some specific genetic alterations or other genetic mechanisms involved in beginning and subsequent progression.***Conclusion*** Considering known risk factors, oral cancer appears to be to a certain level, a preventable disease. Recentgrowth of molecular picture of patho-progression and molecular genetic tools opens the path for easier diagnosis, better prognostication and efficient therapeutic management.

Keywords- OSCC, Epidemiology, risk factors, Genetic Alterations.

Introduction

Oral squamous cell cancer (OSCC) is the cancer which occurs frequent in India, accounting for 50–70% of total cancer accounts for highest incidence among Asian countries [1]. OSCC is the sixth common cancer worldwide [2]. It affects buccal mucosa, cheek, floor of mouth, gingiva or the other a part of the oral cavity. Worldwide, there's an excellent difference within the incidence of cancer of the oral cavity. It accounts for fewer than 5% of all cancers in united State, Western Europe and Australia. India, rare in France, Brazil, and eastern Europe have few of the very greatest rates of cancer of the oral cavity within the world. The habit of chewing edible seed leaves rolled with lime and tobacco, a mix referred to as pan, leads to extended contact of the carcinogen with the buccal mucosa, which is assumed to be the reason behind OC in India. The incidence of OC is directly related to age, gender, affected site, and tumour stage of subjects. OC is more common in men than women, and liable on its location within the oral cavity, males are two to 6 times more likely to be valuable than females, largely because of their higher intake of alcohol, tobacco and pan-masala. If current trends continue, by 2030 tobacco will kill quite 8 million people worldwide every year, most of which can occur in developing countries with lower incomes (3). Although many people are aware thattobacco harms their health, most still accept smoking as a part of their everyday life, unaware that quite 60 toxic chemicals including carcinogens and cancer promoting substances (5,6,)in tobacco can invade the body’s various systems (6). Each cigarette is created of the many ingredients, and a few tobacco companies may use certain flavour additives to create their tobacco products more attractive, which can even be harmful to health. Not only

can these original components cause harm, but the intermediate metabolites play an unavoidable role within the process during smoking.Oral epithelial cell carcinoma (OSCC) could be a pathological sort of carcinoma, accounting for over 90% of oral cancers9. carcinoma ranks eighth among the foremost common causes of cancer-related deaths worldwide10. Oral and oropharyngeal cancers are reported to account for about 220000 new cases annually (5% of all cancers) worldwide (4). with the recent epidemiology of OSCC, the incidence in lower/middle income countries or developing countries tends to be more than that of developed countries (5). the information show that the chance factors that attribute to OSCC are age, sex, race, gender, tobacco, alcohol, betel nut, diet and nutrition (6). Among them the foremost common is tobacco. Many epidemiological studies have demonstrated a transparent dose-response relationship between tobacco use and also the risk of carcinoma or potentially malignant oral disease. Early in 1994, a study(7) analysed 454 patients with oral carcinoma and located that 60% of these with oral carcinoma smoked and over 95% of neoplasms were epithelial cell carcinoma, while another study(8)in 1999 stressed the importance of tobacco within the progress of oral epithelial dysplasia (OED) during a sizable amount of European patients. potential carcinogens that may increase the relative risk of cancer through different mechanisms, including oxidative stress on tissues, persistent reactive oxygen species, lipids, carbohydrates and DNA to disrupt cell cycle-regulated mutations or through effects on the system (9). it's widely accepted that tobacco is one most important carcinogenicfactor of OSCC, and its carcinogenic pathways and its regulators could also be multifaceted. the aim of this review is to summarize the possible mechanisms of tobacco that promote the event of OSCC, on the premise of relevant research, so on provide directions and ideas for future related research.

Methods and Materials

The eligibility criteria for studies were: Research Articles that studied the pathogenesis of oral squamous cell carcinoma (SCC) caused by some carcinogenic substances or chemicals which may present in tobacco, alcohol, cigarettes etc.

Risk Factors Causing Oral Squamous Cell Carcinoma

Many risk factors or possible contributing agents for OC have been described. Chemical factors like tobacco and alcohol, biological factors like human papillomavirus (HPV), syphilis, and viruses have been shown to be significantly related with stages of OC (9).

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Chemical Factors

Tobacco

There are efficientlydescriptions suggesting that tobacco in different forms, including smoking, masticating and in betel quid etc., have carcinogenic impact in oral cavity. The commonest form of tobacco use is cigarette smoking. several forms in which tobacco is utilized as smoke are- cigarettes, cigars, pipe and bidi etc. Hookah or chillum (a clay pipe used to keep the burning tobacco) are other mutual forms of smoking in some countries of Asia including India. In some part of India like Mizoram, tobacco smoke is dissolved in dihydrogen monoxide (‘‘smoke on the water’’) which is another peculiar form of tobacco use10).

Alcohol

Various studies have suggested alcohol to be a major risk factor for OC. There is a certain degree of disagreement whether alcohol alone may have carcinogenic impact. This is due to simultaneous tobacco and alcohol intake of study subjects in sundry epidemiological studies. Studies have shown that individuals consuming more than 180g of whisky daily have ten times higher risk of OC than the light imbibers (11). Alcohol may have improver effect and it has been suggested that it facilitates the opening of carcinogens into the exposed cells, altering the metabolism of oral mucosal cells (12).

Betel Quids

The recommended terminology is that Quids are yare from areca nut, remedied or sun-dried, and chopped, then customarily placed on a leaf of the Piper betel vine, although influorescence is utilized by some, for example, in Papua Incipient Guinea. Slaked lime is an essential ingredient. It lowers pH and expedites relinquishment of alkaloids from both tobacco and nut, with enhanced pharmacological effect. Daftary etal.(19) set out the evidence for the carcinogenicity of betel quid and the consequential role of tobacco in considerable detail.

Smokeless Tobacco

Much of the tobacco in the world is consumed without combustion. Rather, it is placed in contact with mucous membranes, through which nicotine is absorbed to provide the harmful effect. Utilization of nasal stuff, popular in the last century, is returning. Other forms of snuff, loose or packeted and placed in the oral vestibule, are ordinary in Scandinavia and the Coalesced States. Tobacco is withal prepared in blocks or flakes for masticating. In developing countries, tobacco is mostly consumed commixed with other ingredients (Table 2). The very extensive evidence for carcinogenicity of these coalescences is covered exhaustively(20,21).Toombak, the form utilized in Sudan, contains very high calibers of tobacco concrete nitrosamines (TSNs), and users show significantly incremented risks of oral squamous cell carcinoma.

Areca Nut

Though the IARC29 concluded that there was inadequate evidence that the masticating of betel quid without tobacco was carcinogenic to man, this is a probability. In Guam, where areca nut is masticated alone or with leaf only, there is apparently no incrementation in oral cancer.(21)Conversely in Taiwan, most heftily ponderous chewers of betel quids do not include tobacco, yet oral cancer is associated.(23) Importantly, the synergistic role of alcohol has not been evaluated in these studies.(24) As evaluate the hazards of these intricate amalgamations, it is consequential to recollect that betel leaf is protective,(25)and at least two compounds have been identified: carotene and hydroxychavicol, an astringent antiseptic.

Biological Factors

Viruses

Role of oncogenic viruses in human cancer is an emerging area of research. Viruses are capable of capture host cellular apparatus and modifying DNA and the chromosomal structures and inducing proliferative variations in the cells. HPV [26] and Herpes simplex virus (HSV) have been established in recent years as causative agents of OC. HPV has been identified in approximately 23.5% of OC cases [27]. The most commonly detected HPV in head and neck squamous cell carcinoma (HNSCC) is HPV-16, which has been demonstrated in 90–95% of all HPV positive HNSCC cases, followed by HPV-18, HPV-31, and HPV33. The prognostic significance of HPV in pre-cancerous oral lesion is not pellucid. However, few studies have found upgraded disease-specific survival and better prognosis for HPV positive OC. HSV-1 or ‘‘oral herpes’’ is commonly associated with sores around the mouth and lip and has been suggested to be a causative agent of OC (28). Epidemiological studies showed higher caliber of IgG and IgM antibodies to OC patients compared to control subjects (29). Kassim et al (30) reported oncogenic relationship between HSV-1 and oral squamous cell carcinoma (OSCC). A population predicated study showed HSV-1 to enhance development of OSCC in HPV infected patients and individuals with history of cigarette smoking(30). Risk of oral cavity and pharyngeal cancer is two-fold higher among human immunodeficiency virus (HIV) patients labeling a link between HIV and OSCC (31, 32). Epstein Barr Virus (EBV), human herpesvirus-8 (HHV-8) and cytomegalovirus have additionally been reported as risk factors of OSCC in different studies(33, 34).

Nutritional Factors

Dietary deficiencies are also suggested to play a role in the development of OC. This, however, requires more clinical and experimental evidence for establishment of causal association with the development of OC. Some workers have reported lower risk of OC with higher intake of fruits and vegetables (35).

Molecular Pathogenesis of Oral Cancer

Oral carcinogenesis like any other cancer is a progressive disease and ordinary epithelium passes through stages starting from dysplasia to finally transforming into invasive phenotypes. Although all types of carcinomas are visually perceived in oral cavity, the most ordinary form of OC is squamous cell carcinoma. Utilization of genetic and proteomic approach in recent years have revealed the molecular pathological picture of OC. There is active search to identify genetic alterations in oncogenes or tumour suppressor genes, role of genomic instability and epigenetic modifications and to engender a gene expression profile in oral oncogenesis (36). Understanding these genetic changes and gene expression patterns are keys to the construal of molecular pathogenesis of OC. Though, there are some significant leads achieved, the excellent understanding of molecular pathology of OC and its sodality with causative agent will require another decennium of intensive research.

Role of Proto-Oncogenes, Oncogenes and Genetic Alterations:

Genetic alterations define molecular substructure of carcinogenesis which includes point mutations, amplifications, rearrangements, and expunctions. Several oncogenes have withal been implicated in oral carcinogenesis (37). Aberrant expression of epidermal magnification factor receptor (EGFR), K-ras, c-myc, int-2, Parathyroid adenomatosis 1 (PRAD-1) and B-cell lymphoma (bcl) like oncogenes have been reported in OC development (38). Over expression and amplification of cellular oncogene EGFR have been reported in a 7,12-Dimethylbenz(a)anthracene (DMBA) induced hamster cheek pouch malignant OC model (39). Transforming magnification factor-alpha (TGF-a) is kenned to promote neovascularization and mitogenesis. It has been shown to be aberrantly expressed in human OC and in hamster oral tumor (40).

Tumor Suppressor Genes

The major epigenetic modification over 50% of all primary HNSCC p53 mutation (41). Inactivation of p53 represents the most prevalent genetic instability altogether human cancers (42). the most commonly removed region in HNSCC is found at chromosome 9p21–22 (43). Loss of chromosome 9p21 occurs within the majority of invasive tumors in head and neck cancer (44). Homozygous expunctions during this region are frequent and represent one amongst the foremost mundane genetic changes identified. p16 (CDKN2) present during this effaced region, could be a potent inhibitor of cyclin D1 (45). Loss of p16 protein has been visually examined in most advanced pre-malignant lesions additionally (46). Mayo et al. (47) have identified an alternate RNA transcript for p16 termed as Alternative Rating Frame (ARF; or p16b). Prelude of p16 or p16ARF into HNC cell lines end in potent magnification suppression [48]. Loss of chromosome 17p is withal frequent in most human cancer including OC. it's visually perceived in approximately 60% of invasive lesions. Though p53 inactivation correlates proximately with loss of 17p in invasive lesions, p53 mutations are quite infrequent in early lesions that contain 17p loss. Loss of chromosome arm 10 and 13q are additionally noted in primary tumors [49].

Epigenetic Alterations

Transmutations within the methylation patterns can play a paramount role in tumorigenesis. Epigenetic modifications are frequently connected with the loss of genetic expression and consequential for the multiple indispensable genetic events during carcinogenesis. Malignant progression takes place because these alterations can inactivate DNA rehabilitating genes. Methylation patterns of p16, methylguanine-DNA methyltransferase (MGMT) and Death-associated protein kinase (DAP-K) genes in smears of

patients affected by head and neck cancer showed aberrant hypermethylation patterns by a methylation specific polymerase chain reaction (PCR)

Molecular Epidemiology

The pattern of specific point mutation in OC patient may provides a clue to the aetiology of that exact tumor. Brennan et al. (48) analyzed the pattern of p53 mutation in HNSCC. They found that the incidence of p53 mutation was much higher in patients who were exposed to both tobacco and alcohol versus non-users. it's been suggested that alcohol appears to enhance the effect of smoking thanks to an incrementation within the absorbance of carcinogens contained within the cigarette smoke. Several epidemiologic evidences suggest that abstinence from cigarette smoking may decrease the incidence of HNSCC (49). HPV positive oral and oro-pharyngeal cancer comprise a definite clinico-pathological entity. they're less susceptible to occur among heftily ponderous smokers and imbibers, have lesser likelihood of p53 mutation and have better cancer-specific survival. it's been suggested that HPV positive tumours may have better prognosis by inactivating retinoblastoma (Rb)(50).

Conclusions

It has been confirmed that the utilization of tobacco is related to the event of OSCC. These finding is predicated on existing research, tobacco can source of epigenetic alteration of oral epithelial cells, inhibit multiple systemic immune functions of the host, and through its toxic metabolites cause oxidative stress on tissues to induce OSCC. Moreover some specific viruses like EBV and HPV are thought to play a task within the development of OSCC. to substantiate these findings, further studies are needed comprising larger sample sizes. Meanwhile, with the event of research on this subject, more probable mechanisms remain to be studied. because the treatment of OSCC is tough and also the prognosis is poor, further research on this subject are going to be helpful for early diagnosis or prevention of tobacco-related oral carcinoma through efforts for cessation of tobacco consumption.

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