Risk Factors of Oral Cancer and Potentially malignant disorders (PMDs) – Developing a High / Low Risk Profiling System

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) remains a lethal and deforming disease, with a significant mortality and a rising incidence in younger and female patients. It is thus imperative to identify potential risk factors for OSCC and oral PMDs and to design an accurate data collection tool to try to identify patients at high risk of OSCC development.

14 factors consistently found to be associated with the pathogenesis of OSCC and oral PMDs. Eight of themwere identified as high risk (including tobacco, alcohol, betel quid, marijuana, genetic factors, age, diet and immunodeficiency) and 6 low risk (such as oral health, socioeconomic status, HPV, candida infection, alcoholic mouth wash and diabetes) were stratified according to severity of risk, associated carcinogenicity and clinicopathological effects, using evidence obtained from the International Agency for Research on Cancer (IARC).

This review provides understanding of the significance of various risk factors in oral carcinogenesis to help to stratify patients, especially those with potentially malignant disorders, into high and low risk groups.

Key words: Oral cancer, oral potentially malignant disorders and risk factor. (J Bagh Coll Dentistry 2016; 28(1):63-72).

INTRODUCTION

The most common oral cancer is oral squamous cell carcinoma (OSCC) [(1)]. OSCC affects significant numbers of people around the world and represents more than 90% of head and neck cancers [(2)] with 4-10% of them have been reported in patients below the age of 40 years [(3)]. Approximately two thirds of OSCCs are diagnosed at advanced stages [(4)].The late diagnosis of a significant number of OSCCs is mostly attributable to delays in patients seeking treatment, insufficient patient awareness, asymptomatic clinical states and/or inappropriate investigation [(5)]. Despite the different treatment modalities for OSCCs, such as surgery, radiotherapy, chemotherapy, chemo-radiation and immunotherapy [(6)], the five-year survival rate has not improved in recent years [(7)]. There is thus a vital need for an effective and reliable diagnostic and treatment proceduresthroughan early detection and subsequent effective and less aggressive treatment with lower morbidity and reduced cost [(8)] as well as better prognosis and better quality of life [(9)].

Oral squamous cell carcinoma may arise from Potentially Malignant Disorders (PMDs), a term that has been recently introduced by the WHO to describe a group of disorders that carry an unpredictable risk of malignant transformation (MT) [(10)].

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PMDs are mainly erythroplakia, erythroleukoplakia, leukoplakia, submucous fibrosis,lichen planus and actinic cheilitis as well as inherited cancer syndromes [(11)]. Most oral PMDs are asymptomatic or present with few symptoms; they are regarded as an intermediate stage between normal and malignant tissues [(12)] reflecting the multi-step process of oral cancer development [(13)].

One-third of oral PMDs has been estimated to progress to cancer [(14)]. Thus, it is important to identify patients at risk of developing PMDs and to detect these disorders as early as possible, avoiding MT of PMDs to oral cancer. The carcinogenesis process may be initiated by carcinogens from lifestyle habits.Risk factors for oral PMDs are generally believed to correspond to those of OSCCs [(15,16)]. In this era of globalization, many of these habits have now crossed borders and appear in various areas throughout the world.

A risk factor is a variable that might be associated with an increased risk of a disease and it either acts as a disease initiator or promoter [(17)]. Early diagnosis and treatment of oral cancer and PMDs requires assessment of potential predisposing risk factors [(18)] and necessitates a partnership between clinicians, pathologists and surgeons.

Current research efforts are aimed towards early identification of risk factor(s) associated with the process of oral carcinogenesis and to recognize those patients at increased risk [(19)].

One can understand that, patients with PMDs may be stratified as either high-risk or low-risk by considering their demography, clinicopathological features, the severity/ location of dysplasia, pre-

existing or the associated risk factors and individual genetic susceptibility.

METHODS

Study design

In this paper, we have attempted to review some of the papers published over a 30 years between 1981-2011, with particular reference to risk factors of oral cancers and PMDs. This article reviews lifestyle/habitual and social risk factors associated with OSCCs and the most common oral PMDs. Studies published in English-language journals were retrieved by searching PubMed;National Library of Medicine (NLM) journal literature search system. Review articles were also examined to identify additional studies that used biochemical, immunologic tests.

Thirty-hundredrelative published articleswere identified between the period of 1981 and 2011, from 27 countries; mainly from United states, United Kingdom, France, Germany and other countries and were comprehensively reviewed. The identifiable factors were classified into high and low risk categories dependent upon sufficientclinical, pathological and laboratory evidence.

RESULTS AND DISCUSSION

In this paper, fourteen risk factors were identified from one-hundred and twenty-one articles that were selected from 300 retrieved articles from numerous studies examining the relative risk for oral cancer and PMDs. We have tried to classify the risk factors as either high or low risk factors with the objective to stratify patients subsequentlyinto high or low risk group.

Such classification is important to guide a successful treatment plan for each particular patient, depending on patients demography, clinico-pathological presentation and pre-existing or associated risk factors.In addition this aimed elucidating the natural history of oral PMDs/oral cancer and evaluating the effectiveness of prevention and opportunistic screening in high-risk [20].

The possible carcinogenicity of the risk factors

A. High Risk Factors

Several risk factors associated with the aetiology of PMDs and OSCCs, but tobacco smoking and alcohol consumption are the two major confirmed risk factors [21]. They are independently and synergistically associated with high risk in a dose-dependent pattern [22]. Followed by six high- risk factors identified from many scientific papers with established or sufficient mechanistic events or evidence.

In the current study, the exposure profile of smoking and drinking behaviour including number of cigarettes smoked per day and the units of alcohol consumed per week, history of use were all considered. These exposure parameters were important in relation to patient demography and clinicopathological features of PMDs such as oral anatomical site, clinical appearance, size and the presence of epithelial dysplasia. In addition, local factors (intraoral dental prosthesis wear) and the presence of systemic disease such as immunodeficiency, anaemia, diabetes mellitus, hypertension, a familial cancer history and oral candida infection.

Depending on the sufficient evidence to risk of oral cancer and PMDs development, 8 high- risk factors were identified from previous studies (Table 1).

Table 1: High risk factors for oral carcinogenesis

	High risk factors
1.	Tobacco
2.	Alcohol
3.	Betel quid
4.	Marijuana
5.	Genetic factors / individual susceptibility
6.	Old age
7.	Dietary factor
8.	Immunodeficiency

1. Tobacco

- Tobacco use remains the1st most important and preventable risk factor for PMDs and oral cancer.
- Smoked tobacco releases a complicated mixture of thousands of chemicals; of these, more than 60 known chemical carcinogens, and a further 16 chemicals in unburned tobacco, have been identified by the International Agency for Research on Cancer.
- Oral leukoplakias have been shown to occur up to six times more frequently in smokers than in non-smokers [23] in a dose-response relationship; increased risk is associated with an increased number of cigarettes smoked per day [24] and epithelial dysplasia [25].
- Approximately, 60% of oral leukoplakias may disappear if patients stop smoking [26], whilst continued exposure to risk factors may result in persistent disease andincreased risk of oral epithelial dysplasia, an important key stage in oral carcinogenesis preceding MT [27] and developing carcinoma which is 50 to 100 times greater in smokers than in the general population [28].

- The carcinogenicity of tobacco smoking is related to the tobacco specific nitrosamines [29] that have direct mutagenic effect on the exposed epithelia of upper aerodigestive tract by reacting with DNA, forming DNA adducts which have subsequently mutational effect on important oncogenes and tumour suppressor genes (P53) ending with cancer development [30].
- Smokeless tobacco, such as Shammah/toombakis a complex mixture consisting of powdered tobacco leaves, slaked lime (calcium carbonate), ash, oil and other materials such as black pepper, mint and flavours [31].
- The incidence rate of leukoplakia is the highest in the tobacco habit chewers and lowest in the no habits group,with the rate of MT is the highest among leukoplakias associated with tobacco [32].
- The IARC working group on smokeless tobacco hasreported that there is sufficient evidence of the oral carcinogenicity of smokeless tobacco [33].The carcinogenesis may be due to direct contact with lower lip, lower vestibule and floor of the mouth [34].
- These carcinogens in experimental in vitro systems affect oral keratinocytes and cause alterations in cell proliferation, apoptosis and activation of inflammatory mediators [35].
- One can conclude that tobacco is the principle risk factor for oral carcinogenesis associated with a site preferential localisation and inter-individual variation in the activity of enzymes involved in the detoxification of tobacco smoke.

2. Alcohol

- Alcohol consumption is regarded as the 2nd risk factor [36].
- Alcohol may exert direct toxic effects on the epithelial mucosa [22] through dissolving some of the lipid content of the bilayerphospho-lipid cell membrane [37] in the superficial regions of the epithelium, increasing its permeability [22] which increases the penetration of carcinogens across the oral mucosa [38].
- Alcohol can cause reduction in mean cytoplasmic area of oral epithelia for heavy drinker patients [39].
- Reduction in the endocytosis of oral cells reduces elimination of local carcinogens leading to an increase exposure time to a particular carcinogen.
- Acetaldehydes are 1st alcohol metabolite [37] are unstable substances produce free toxic radicals damaging the DNA or may covalently bonded to DNA forming DNA adducts [40]. This may interfere with DNA synthesis and repair [41] revealing the starting step of alcohol carcinogenicity.
- Alcohol interfere with diet bioavailability [42] causing nutritional deficiency [43].
- Alcohol ableto reduce immune function through inhibiting the detoxification of carcinogens [44]. In addition to ethanol, alcoholic beverage contains othercomponents, volatile and non-volatile flavour and other additives , of these components are nitrosamines, acrylamide, oxidized polyphenols which are classified as a possible carcinogenic to humans, as animal experiments have showed mutagenic activity on oral epithelial cells [45].
- A combination of tobacco smoking and alcohol drinking is a strong intensifying risk factor for PMDs,epithelial dysplasia andsubsequent malignant transformation [9].
- Tobacco smoking and excessive alcohol consumption are the major risk factors of epithelial dysplasia and OSCC [27].
- Approximately, 75% of all oral cancers arise in association with tobacco and alcohol use [46]. The possibility of strong combined effects of alcohol and tobacco may be due to high levels of acetaldehyde production from both in a synergistic and multiplicative risk effect [47]. After a dose of ethanol, salivary acetaldehyde was 2 times higher in smokers without smoking and 7-times higher with active smoking [48].

3. Betel quid

It is estimated that between 10% and 20% of the world's population use betel quid and it is regarded as the fourth most frequently consumed psychoactivesubstance after nicotine, ethanol, and caffeine [49].

- Betel quid cytotoxicity, mutagenicity, and genotoxicity toward different kinds of cells including oral epithelial cells, bone marrow cells, and peripheral blood mononuclear cells [50].This genotoxicity may change the structure of DNA, proteins and lipids resulting in antigenicity [51].
- Betel quid ingredients may induce inflammation of keratinocytes by stimulating the production of prostaglandins, tumour necrosis factor-alpha (TNF-a), interleukin-6, interleukin-8 and granulocyte-macrophage colonystimulating factor in keratinocytes which may intensify tissue inflammation, early

cell-mediated immunity and immune surveillance in the chewers [52].

- Inflammatory responses, new specific antigen, neoantigen, may be formed by the reaction of host tissues with carcinogens which can provoke malignant changes with generation of particular tumour-associated antigens which are subsequently enhance host immunity resulting in proliferation of antigen-specific lymphocytes [53].
- The carcinogenicity of betel quid may refer to nitrosation with consequent production of potentially carcinogenic nitrosamines such as, 3-methylnitrosopropionitrile and also generation of reactive oxygen species in the oral cavity due to auto-oxidation of polyphenols contained in areca nut which enhanced by the alkaline pH from slaked lime [54].

4. Marijuana (cannabis)

Due to the fact of similarity in carcinogens and co-carcinogens, between marijuana and tobacco smoke except for nicotine [55], it is more convenient to include marijuana use in the risk assessment of patients with oral cancers and precancer [56].

- smoking a few marijuana cigarettes per day has been described to have similar histopathological effects that observed on tracheobronchial epithelium with daily smoking of more than 20 tobacco cigarettes [57].
- Cannabinoids have been shown to induce cytogenic changes in vivo and in vitro mammalian cells, such as chromosomal breaks, deletions, translocations, error in chromosomal separation, and hypoploidy [58].
- Delta-9-tetrahydrocannabioid (THC) the principle psychoactive chemical substance in Cannabinoids, promotes the growth of tumours in mice with lung cancer by modulation of immune-system responses to the tumour [59].
- Within the oral cavity, cannabis smoking and/or chewing is associated with changes in the oral epithelia forming ‘’cannabis stomatitis’’ such as leukoedema and hyperkeratosis [60]. With chronic use this stomatitis may present as chronic inflammation of the oral epithelium and leukoplakia, which may progress to neoplasia [61].
- The higher prevalence of PMDs in marijuana users necessitates periodic oral examination of such patients for early identification of PMDs.
- The synergistic effect between tobacco and marijuana smoke has been observed, suggesting that tobacco and cannabis smoking may enhance the inflammatory responses possibly promoting their carcinogenicities [62].

5. Individual susceptibility/ Genetic factors/ family history

According to Ho *et al*. [63] not all individuals who smoke or drink develop OSCC; individual genetic susceptibility, differences in carcinogen-metabolizing enzyme function, mutagen sensitivity, apoptosis, and chromosomal aberrations either alone or in combination have been hypothesized to modify the risk of OSCC.

Nearly all carcinogens and pro-carcinogens require activation by metabolizing enzymes. Similarly, detoxifying enzymes exist and deactivate carcinogens as well as their intermediate by-products; together these enzymes are termed xenobiotic-metabolizing enzymes. Genetic polymorphisms of these enzymes can modify an individual’s response to carcinogens and hence the carcinogenic potential of such exposures [63].

- Several genetic events altering the normal functions of oncogenes and tumour suppressor genes leading to cellular phenotypic changes that can increase cell proliferation, loss of cell cohesion [64].
- polymorphisms of carcinogen-metabolizing enzymes may affect an individual’s susceptibility to risk factors and subsequent occurrence of oral cancer [40].
- There is growing evidence from case control studies that consider family history as a risk factor for oral cancer [65]. The evidence is mainly based on the fact that more than 50% of oral cancer patients have not been exposed to the major identifiable carcinogens alcohol, tobacco or betel quid [64]. Also young age onset with unusual high incidence of familial oral cancer cases are more likely to support the general acceptance of genetic individual variations [66] in the development of oral cancer [67].
- Risk assessment requires an accurate and comprehensive family history “genetic pedigree” which is useful in the management plan including prevention, risk reduction and cancer screening.

6. Old age

- The majority of OSSCs and premalignant disorders are seen in patients between the age of 50 and 80 year [68] and peaks in the 70s [69], whereas it is less common in patients under the age of 50s [70].
- Telomeres; ”'DNA protein complexes that cap the chromosomal ends promoting

chromosomal stability" [71] may help to understand and explain the relation between ageing and risk of tumour development [72].Telomere length decreases may contribute to neoplastic transformation, replicative senescence or apoptosis resulting in early onset of diseases such as oral cancer [73].

- The relation between cancer and age may be explained as a result of long periods of carcinogenic exposure with mixed genetic and environmental components [74]. Thus periodic screening for all adult patients over 40 should be conducted every 6 months to exclude any abnormal oral changes related to the aging process.

7. Dietary factors

According to Popkin [75], deficiencies in fruit, non-starchy vegetable and carotenoid food is associated with 10-15% of oral cancer cases. Whereas, in a previous study higher percentages of oral cancers of 65% with low vegetable and low fruit intake has been reported [76]. Boccia *et al*. [77] found that higher intake of fruit and vegetable, even with alcohol drinking and tobacco smoking could prevent the development of head and neck SCCs by approximately 1/4. Regarding the risk of oral premalignant lesions, Maserejian and co-workers [78] showed that increase consumption of fruits, particularly citrus fruit in men reduce the risk of oral premalignant even with presence of tobacco smoking which is a well-known risk factor for oral PMDs.

- Raw fruit and vegetable provide mechanical cleansing effect for oral cavity with the benefit of many properties in planted food such as dilution action, anti– oxidant and anti-carcinogenic properties of micronutrients such as vitamins A,C, E, carotenoid, flavoniod, phytosterol, folates and fibres which are crucial for neutralizing the carcinogenic effects of tobacco, alcohol, and betel quid [79].
- Fast, fermented, canned processed food having high fat content that generates polycyclic aromatic hydrocarbon during high temperature cooking and this hydrocarbon can cause cancer in laboratory animals [80].
- Heterocyclic amines such as benzopyrene generated from burned amino acids and other substance in meat found to be association the risk of oral cancer [80].

1. Oral hygiene

- Poor oral hygiene associated with increased number of microorganisms from supragingival dental plaque, may display the association between poor oral hygiene and oral cancer, as an independent risk factor due to increase acetaldehyde concentration in saliva after alcohol drinks [87].

8. Immunodeficiency

Genetic immunodeficiency has been implicated in the aetiology of oral cancer and PMDs in young individuals. Inherited cancer syndromes such as xerodermapigmentosum, Fanconi's anaemia and Bloom's syndrome are associated with an increased incidence of oral cancer [81].

Acquired, induced immunodeficiency such as in organ transplant patients where the drugs are used to prevent organ rejection; several studies have shown increased incidence of post- organ transplantation cancer involving head and neck cancers and oral PMDs. It has been reported that post-transplantation tumours increased by 2 to 4-fold compared with non-transplanted population [82]. In kidney transplantation patients, lip and skin cancers are found to be increased by 35-fold and head and neck cancer increased by 4 folds [83].

- Oral leukoplakia has been found to be the third most commonly diagnosed lesions in patients underwent sold organ transplantation with a prevalence of 10.7% [84]. The presence of leukoplakia in normal control increases the risk of oral cancer development by 5-fold compared with a 50-fold higher in immunosuppressed transplant patients [85].
- Impaired immunosurveillance due to prolonged immunosuppression therapy which may continue for several years treating chronic graft versus host disease, emerges as a major factor in the elevated incidence of tumours in transplanted patients [86].

B. Low Risk Factors

Table 2 however, showssixlow- risk factors have been identified from many studies with the majority of their results have shown inconsistency/controversy or with limited evidencefor the oral carcinogenesis. Accordingly, these factors have been considered as low risk for the development of oral cancer and PMDs.

Table 2: Low risk factors for oral carcinogenesis

Low risk factors
1. Oral health
2. Socioeconomic status
3. HPV
4. Candida albicans
5. Alcoholic mouth wash
6. Diabetes mellitus

- Acetaldehyde may cause point mutations in human lymphocytes, sister chromatid exchanges and cross chromosomal aberration or even interference with the DNA-repair machine [88]. Furthermore, acetaldehyde may interact with DNA forming adducts which may lead to mutations [41].
- Routine dental care with regular dental visits as an indicator of a good oral health may reduce or prevent the exposure to some carcinogens, in addition to regular screening programs for prevention [89] and treatment as a part of the long-term standardised care [90].

Oral hygiene status should be involved among the strategies of oral PMDs preventive and control programmes.

2. Socioeconomic status

- Low socioeconomic standard patients having low income are almost under stress which needs coping mechanisms such as tobaccosmoking/ chewing and alcohol consumption [91],which are established risk factors.
- As preventive measures, all the socioeconomic factors that can be identified as real risks for oral cancer and PMDs need to be improved by effective measures to reduce inequalities between people in society through either local or national authorities or the WHO commission.

3. Human papilloma virus

- It is well documented that HPVs are implicated in the pathogenesis of cervical cancer and although more than 95% of human cervical cancers are associated with HPV 16 and 18 [92]; the association with the head and neck cancer remains controversial.
- The carcinogenicity of the high- risk HPVs is believed to be mostly through two viral oncogenes E6 and E7 which are regarded as an indicator of HPV positive cancers, changing apoptosis that is essential for HPV-infection, to avoid the immunological response [93]. These two proteins have no intrinsic activities of enzymes, but they are able to interact directly and indirectly with two- key tumour suppresser proteins p53 and retinoblastoma. This may affect their ability to stimulate DNA repair or apoptosis interfering with the cell cycle control and promote carcinogenic processes [94].

4. Candida albicans

- Nitrosamine compounds produced by candida species may directly or with other carcinogens, activate specific proto-oncogenes initiating the development of development of oral neoplasia [95].
- In spite of the general acceptance of an association between Candida infection and the occurrence of oral epithelial dysplasia, the possible role of yeast in oral carcinogenesis is still unclear and further studies in this area of research are warranted.

5. Alcoholic mouth wash

- The majority of studies have shown inconsistent results or negative relations due to difficulties in separating the independent effects of mouthwash from smoking, drinking effects and also to the exact effects of other mouthwash constituents [96]. Furthermore, these studies suffer from limitations such as underreporting of mouthwash use by individuals and the use of different mouthwash types, varying alcohol content, duration of use and time retained in the mouth leading to inaccurate results.
- The potential mechanisms are;ethanol altering the cell surfaces of oral mucosa leading to increase their susceptibility to the effects of carcinogens by increasing their permeability, or alcohol may dissolves carcinogens and increases their absorption by tissue enhancing the carcinogenic mechanism subsequently [97].

6. Diabetes mellitus

- Diabetic patients may develop a progressive atrophy of oral mucosa due to decreased salivary secretion and lower salivary pH [98]. This may increase oral disorders, such as glossitis and cheilitis [99] and also can increase the permeability of the oral mucosa to different carcinogens as a result of loss of normal protective barrier [100].
- Tumorogenisity may be directly mediated by insulin receptors in target cells or might be due to related changes in endogenous hormone metabolism [100].
- Insulin deficiency results in reduction of insulin receptor substrate-1 [101] and changes in cytoskeleton leading to reduction in cell adhesion by affecting focal adhesion kinase pathways [102]. This is probably a starting step towards neoplasia and subsequent oral cancer development [101].
- Further, insulin can stimulate the synthesis and biologic activity of insulin-like growth factor-1 which promotes cell proliferation and inhibit apoptosis [103]. It has been indicated that the effect of insulin-like growth factor-1 might

be connected to p53 mutations, which are frequently seen in head and neck tumours [104].

- Elevate blood glucose levels and protein breakdown may lead to excessive formation of free radical [99] causes imbalance between production of free toxic radicals and biological system due to reduction of antioxidant activity of enzymes [100]. This may cause DNA damage and subsequent promotion of carcinogenesis [105].
- To explain the exact associated mechanisms, future studies should take in consideration information such as the type of diabetes, type of treatment, age of onset of diabetes, duration between the onset of diabetes and the development of PMDs [104]; to determine if the association is related to characteristics of the diabetic state or to the treatment agents or to other associated risk factors.

As conclusions

1. The identifiable risk factors are either high or low risk categories depending upon sufficient or limited (controversial) evidence for oral carcinogenesis.
2. High risk patients should be identified by taking very details medical, lifestyle history and family history.This is throughdetailed risk factor data collection sheet designed to stratify patients into high or low risk group to aid future management; figure 1.
3. Assessment of the risk factors in PMDs patients may help to identify patients at higher risk of unfavourable clinical outcomes who require more extended care and surveillance.

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Data Collection Sheet
Patient hospital No.
Patient study No.
First presentation time
Sex Female ☐ Male ☐
Date of Birth
Occupation
Civil status Married ☐ Divorced ☐ Single ☐ Widowed ☐
Medical history
1) Immunodeficiency 2) Diabetes 3) Hypertension 4) Anaemia 5) Candidal infection 6)Human papilloma virus
Other Medical Conditions
Risk factors
Tobacco smoking 1) Current smoking ☐ 2) Ex-smoking ☐ 3) Non-smoker ☐ History of smoking (years) ☐ Cigarettes per day ☐
Alcohol Drinking 1) Current drinker ☐ 2) Ex-drinker ☐ 3) Non-drinker ☐ History of drinking ☐ Units per week ☐
Diet Prepared food ☐ Fresh food/vegetables ☐
Familial cancer history Father ☐ Mother ☐ 1st relative ☐ 2nd relative ☐
Oral hygiene Good ☐ Bad ☐
Mouth wash use User ☐ Non-user ☐ Type of mouth wash ☐
Oral prosthesis None ☐ Upper or lower denture ☐ Full denture ☐ Crown and bridge ☐

Figure 1: Recommended risk factor assessment case sheet