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Chapter 1

Introductory Chapter: Head and Neck Cancer

Sivapatham Sundaresan and Paliarasu Rajapriya

Additional information is available at the end of the chapter

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1. Introduction

Cancer is the major cause of mortality in economically advanced nations, and in developing nations it is the second leading cause of death [1]. The survival rate due to the heterogeneity in treatment offered within centers across India for buccal mucosa cancer in India is 5 years ranges from 60 to 80% for stage I disease to 5 to 15% for locally progressive disease [2, 3].

Squamous cell carcinoma (HNSCC) develops in the oral cavity, larynx, or hypopharynx and oropharynx. In accordance with incidence rate, it is reported as the sixth leading cancer worldwide [4]. It is likely that approximately 600,000 cases have been established worldwide, and the 5-year survival rate is only 40–50% in patients with HNSCC [5]. In a 5-year period, estimated new cases of head and neck cancer were 300,000 and approximately 145,000 deaths in 2012 and 702,000 predominant cases [6]. It was reported that two-thirds of the global incidence of oral cancer occurs in low- and middle-income countries (LMICs). In that, half of those cases are in South Asia. In India alone, one-fifth of the population have head and neck cancer and one-fourth of all head and neck cancer demises [6]. **Figure 1** illustrates the region of all head and neck cancers.

2. Pathogenesis of head and neck cancer

There is a prolonged preclinical phase for head and neck cancer, and also it constitutes well-documented precancerous lesions. The precancerous lesions comprise leukoplakia, erythroplakia, oral submucous fibrosis (OSMF), lichen planus, and chronic traumatic ulcers. The frequency at annual rate was estimated to be in the range from 0.13 to 2.2% during the transformation of oral precancerous lesions to cancer [7, 8].

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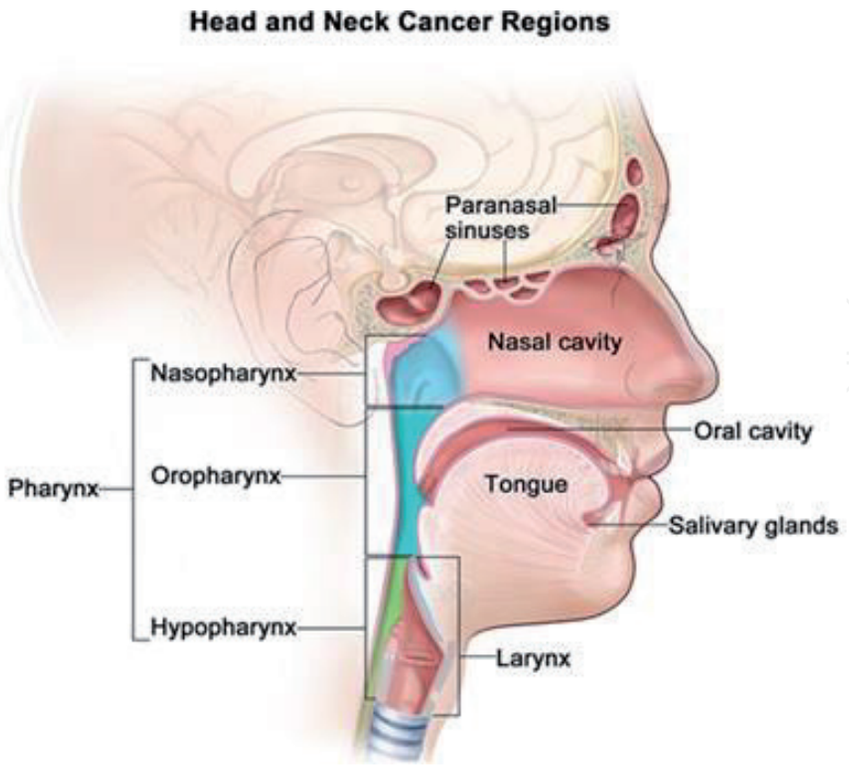


Figure 1. Head and Neck Cancer Regions.

The clinical conditions such as nodular lesions, painless small ulcers, or growths present in very early preclinical invasive early stage cancers culminate the disease. Changes can be easily seen and are clinically detectable through careful visual inspection, and palpation of the oral mucosa was the hallmark of processes. Highlighting the disease prognosis that localized early head and neck cancers ˂4 cm that has not spread to the regional lymph nodes can be successfully treated with either radiotherapy or surgery resulting in 80% of 5-year survival rates [9].

Leukoplakia may be clinically categorized as homogeneous or nonhomogeneous condition, in which a white snowy plaque or patch will form on the tongue. If the lesions have a thin, flat, uniform, smooth, and white appearance, it is categorized as homogeneous, and nonhomogeneous lesions may have a white and red appearance or tiny, white, pinhead-size raised nodules on a reddish background or a proliferative, warty presence. Erythroplakia exists as a red patch with a smooth or granular surface that cannot be categorized clinically or pathologically as any other definable disease [10]. Erythroplakia has a higher chance than leukoplakia to anchorage occult invasive cancer and to undergo malignant transformation.

Interweaving white lines (known as *Wickham's striae*) with a reddish border or as a mix of reddish and ulcerated areas will appear on oral lichen planus. OSMF, mostly restricted to the people of Indian subcontinent origin and in certain Pacific islands such as the Mariana Islands, presents with a blanching of the oral mucosa, burning sensation, and intolerance to spicy food. As the disease progresses, hardening and weaken of the oral and pharyngeal mucosa occur, leading to reduced mouth opening and difficulty in swallowing and speaking. Smokers who smoke with the lighted end of the tobacco product inside the mouth, known as

reverse smoking, will be acquired with palatal lesions resulting in white or mixed reddish-white lesions of the palate [10].

A higher risk of malignant alteration may be related with the factors like female gender, lesions of long period, large precancerous lesions, precancerous lesions in nonusers of tobacco, tongue, and floor of mouth lesions, nonhomogeneous lesions, and lesions showing epithelial dysplasia and aneuploidy [11]. However, during the follow-up in patients, it is impossible to predict with certainty where the precancerous lesion will become malignant. The malignant alteration of precancerous lesions can be prevented by interventions, such as avoiding the use of tobacco and consuming alcohol and by excision of the lesions in selected cases.

3. Incidence and mortality

WHO conveyed that head and neck cancer occurrence and death are high in India, Papua New Guinea, and Taiwan, China, where the habit of chewing betel quid's with tobacco or without tobacco or areca nut chewing is common, as well as in France, Eastern Europe, and parts of South America such as Brazil and Uruguay, where tobacco smoking and alcohol ingestion are high. The age-standardized incidence rates for men are, on average, twice as high as those for women. WHO reported that in selected countries where some reliable cancer registries exist, India is highest and Belarus is lowest, with incidence rates changing by more than five times in men and women. The estimated age-standardized incidence rates of head and neck cancer also fluctuate among countries in different regions [6].

In South and Southeast Asia, buccal (cheek) mucosa is the most common site for head and neck cancer; the tongue is the most prominent site in all other regions [12]. Regional differences in frequency and the site of occurrence are related to the major causes, which are betel quid and tobacco chewing in South and Southeast Asia and alcohol and smoking in Western countries [13]. The mortality rates of head and neck cancer range between 1 and 15 per 100,000 persons in different regions; mortality rates exceed 10 per 100,000 in Eastern European countries, such as the Czech Republic, Hungary, and the Slovak Republic. Head and neck cancer mortality rates are influenced by head and neck cancer incidence, access to treatment, and deviations in site distribution.

The trends in incidence and mortality among men and women are closely correlated with the patterns and trends in tobacco and alcohol use. Increase in tobacco and areca nut chewing and alcohol consumption causes an elevated incidence rate which has been reported in Karachi [14] and in Taiwan [15]. Head and neck cancer incidence and mortality rates have been gradually falling over the past 2 decades because of declining smoking prevalence and alcohol ingestion in the US [16]. However, because of human papillomavirus (HPV), there is an increase in cancers at the base of the tongue, which has been observed in white men in the United States [17].

It was reported that over the past 2 decades, incidence and mortality rates for head and neck cancer have been declining steadily in most European countries. The increasing rates had been observed in some Central European countries, such as Hungary and the Slovak Republic, reflecting changes in alcohol and tobacco consumption [18]. There was a steady

decrease in the mortality rate of head and neck cancer in France since reaching a peak in the early 1990s and the decline correlated with the reduction in alcohol consumption. Incidence and mortality have been stable in the Nordic countries, the Russian Federation, and the United Kingdom. Mortality rates have been steadily declining in Australia and Hong Kong SAR, China but increasing in Japan and the Republic of Korea [19].

4. Diet and head and neck cancer

The current report highlighted that about 15% of all cancer deaths are related to unhealthy diets, including high intake of red meat, processed meat, and sodium, as well as low intake of fruits and vegetables [20]. Most research is still not consistent about specific nutritional items yet for the cause of cancer geographically [21]. The most current comprehensive review of diet and cancer risks confirms an elevated risk related to red and processed meat but finds less evidence supporting the benefit of the consumption of fruits and vegetables in reducing risk [22]. When well-established risk factors are included in the estimation of cancer, the variations in the strength of the evidence in different studies over time makes the measurement of dietary intake problematic in epidemiological studies. Nearly 5% of cancer deaths worldwide (387,000) would be attributable to dietary risk factors [20]. Ingestion of red meat and processed meat increases the risk of colorectal cancer by an estimate of 43% [21]. Ingestion of red meat and processed meat is generally rising in low- and middle-income countries (LMICs), but is stable in high-income countries (HICs). Another major dietary risk factor is high salt intake, which increases the risk of stomach cancer. Globally, salt intake has declined, and

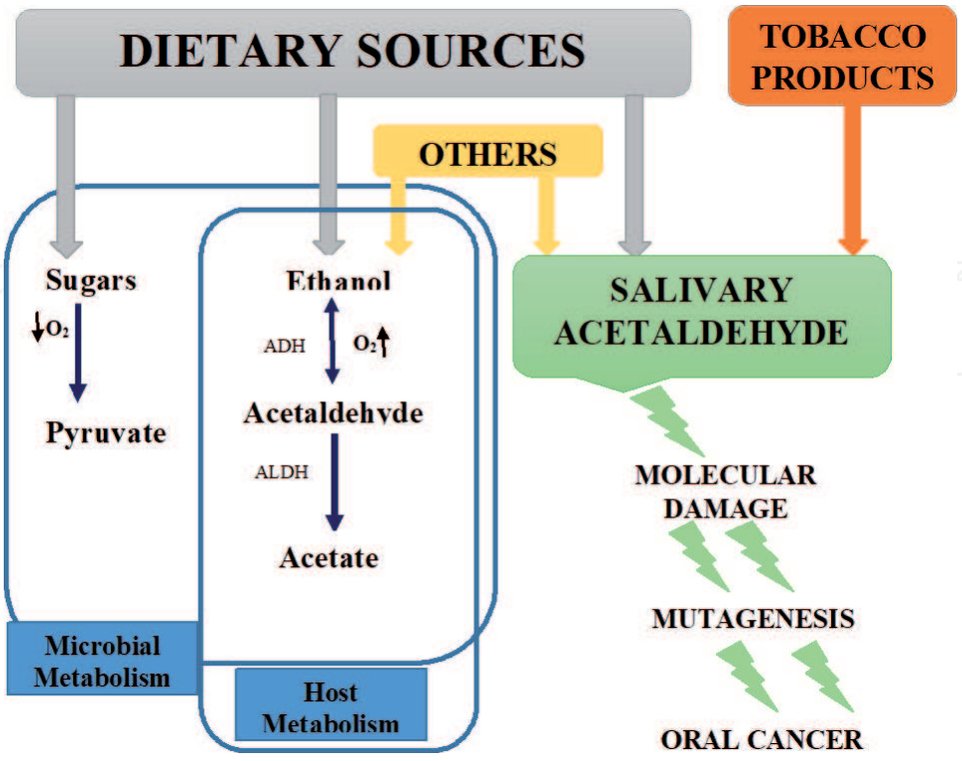


Figure 2. The mechanism of salivary involvement with diet and cancer.

the associated cancer burden has declined as a result [22]; currently, 1.5 and 2% of all cancer deaths in HICs and LMICs, respectively, are attributed to high salt intake, compared with 2.2 and 2.7%, respectively, in 1990 is highlighted by Lim and others. In the United Kingdom, 10% of new stomach cancer cases diagnosed in 2010 may be attributable to high salt intake [23].

Figure 2 describes the mechanism of salivary involvement with diet and cancer.

Over the past era, key factor in the decline in cancer incidence reported to be the better food preservation methods and reducing the salt. The levels of red meat consumption in recent decades may explain the low colorectal cancer rates in southern Asia [21], as well as the high rates in many Western European countries were reported [24, 25]. Researchers find association for obesity and overweight to cancer is firmer than the dietary evidence has been reported, indicating that 3 and 6% of cancer deaths in LMICs and HICs, respectively, can be attributed to excess weight, as quantified by the body mass index (BMI) [26, 27]. High BMI was raised as a cause of cancer deaths more substantively in LMICs, a 54% increase over the past 30 years, compared with a 26% increase in HICs over the same period [28].

5. Buccal mucosa cancer—our perspective

A buccal mucosa carcinoma is a violent form of head and neck cancer associated with the high rate of locoregional reappearance and poor existence [29]. It is the most common cancer in men and the third most common cancer in women in India [30]. National Cancer Registry Program (India) has stated approximately 13,500 cases of buccal mucosa carcinoma from various Indian cancer registries [31]. Indian Council of Medical Research guideline on buccal mucosa carcinoma management reported that there is the absence of national and international data specifically on buccal mucosa cancer, and very few randomized studies from India on various aspects of buccal mucosa cancer are available [32]. Tumor thickness and other prognostic factors were institutes to be not correct predictors of relapse and most of the studies were not adequately powered to draw a definite conclusion. Patients with head and neck cancer observed by computed tomography, magnetic resonance imaging (MRI), ultrasound-guided fine needle aspiration biopsy, and positron emission tomography (PET) have significant false positive and false negative results, invariably not capable of detecting nodal metastasis [33, 34]. Genetic alterations recognized to date have not been used clinically in the assessment of surgical margins, and no study has developed a gene signature that can accurately predict which patients with buccal cancer are at a higher risk of disease recurrence. Traditional surgical procedures may miss involved lymph nodes due to a limitation in histopathology examinations [35]. Lymph-node metastasis can be predicted by gene expression profiles of primary oral cavity squamous cell carcinomas [36]. Further, markers of prognosis will be validated by qRT-PCR technique. Gene expression profiles of primary tumor and their matched normal mucosa and comparing with different tumor stage and lymph-node status and to identify clinically significant prognostic markers is warranted.

Increase in the incidence of buccal mucosa carcinoma was observed from the hospital registry over the last 15 years [3]. The incidence and cumulative risk of buccal mucosa cancer in

Chennai were higher in both sexes among all of the states in India [37]. Currently, there are no markers that can consistently predict malignant progression in oral dysplastic lesions. Recurrent disease after surgery and radiotherapy is hard to salvage because of availability of earlier markers to predict the stage of disease [38]. It was reported that variability in the clinical course of patients remains unexplained and conventional clinicopathological parameters fail to answer all questions. Identification of novel prognostic factors may allow a rational selection of the most appropriate therapeutic options for individual patients [39].

Oral tumor thickness and other prognostic factors were found to be not correct predictors of relapse, and most of the study was not adequately powered to drought a definite conclusion. Clinicopathological parameters such as the TNM system, which are generally used as a basis for therapeutic decisions, frequently fail to predict the biologic behavior of the tumors or the patients' outcome [40]. ICMR guideline on buccal mucosa carcinoma highlights that new prognostic factors for buccal mucosa cancer are the very important need to manage it.

6. Buccal mucosa cancer and molecular markers

Estimates based on weighted averages of data from Bangalore, Mumbai, Bhopal, Chennai, and Delhi show that buccal mucosa carcinoma has an incidence of 4.0% of all malignancies in males and 3.5% of all malignancies in females. Buccal mucosa cancer is a dissimilar disease biologically, as compared to rest of head and neck cancer, and requires great care [41]. The buccal tumor was reported to differ from other tumors by early stage less often and arises from premalignant tissue with abnormal clinical appearances, which may prevent earlier diagnosis and referral from primary care [42].

Van't Veer et al. showed the ability of gene expression profiles to classify tumors into clinically appropriate groups and to predict the outcome by using supervised statistical analyses [43]. Individuals whose primary tumors bore the metastases-related gene expression program had significantly shorter survival times compared with individuals whose tumors needed it [44].

Importantly, candidate-gene approach study had reported genetic alterations in surgical resection margins in head and neck squamous cell carcinoma (HNSCC) from different disease sites, e.g., oral cavity, pharynx/hypopharynx, and larynx [45–47]. Markedly genetic alterations identified in HNSCC encompassed over-expression of eIF4E [48], TP53, and CDKN2A/P16 proteins [49].

A prognostic value with disease-free and overall survival was shown in a study of gene expression profile of three genes (GLUT3, HSAL2, and PACE4) were correlated with different clinical parameters [39]. A 4-gene signature (MMP1, COL4A1, THBS2, and P4HA2) for calculation of recurrence in OSCC had been studied in whole-genome expression profiling experiment and a meta-analysis of five microarray datasets developed [35].

Known risk factors like areca nut and betel quid reported to contain genotoxic, cytotoxic, and ability to stimulate human buccal mucosal fibroblast proliferation [50]. It was conveyed to act synergistically in the pathogenesis of oral submucous fibrosis and head and neck cancer [51].

Other risk factors such as arecoline, safrole, and nicotine, which are released in saliva during betel quid chewing plus cigarette smoking, inhibit collagen phagocytosis by fibroblast [52].

Majority of head and neck cancers are preceded by a period during which the affected epithelium shows evidence of epithelial dysplasia, although this may not always be clinically apparent [8]. Several studies have exposed great inter- and intra-examiner variability in the assessment of the presence or absence and the grade of oral epithelial dysplasia [53–56], the kappa values, in general, showing poor to a moderate bargain among examiners.

Five-year survival with single modality treatment of 19–20% was observed in patients with T3 and T4 stages [57]. Diaz and others had shown that the relapse amount was up to 45% in patients with early stage disease [58], and relapse rate in patients with nodes demanding some form of adjuvant treatment in early disease and high-risk tumors.

Mishra et al. had reported the relation between treatment failure and tumor thickness in a series of 176 patients with early buccal mucosa cancer [59]. Tumor thickness of more than 4 mm was found to be connected with lymph-node metastasis. In another study, tumor thickness of more than 5 mm was linked with nodal metastasis [60]. There are few studies described in the literature that associate the prognostic factors linked with clinical result of buccal cancer.

The molecular changes between the tumor subtypes are often accompanied by differences in clinical features, such as statistically robust differences in relapse-free and overall survival [61], and many studies found handfuls of specific genes whose expression is linked with prognosis [62].

Figure 3 demonstrates the etiopathogenesis of OSCC.

Using high-throughput analysis of multiple surgical margins and matched oral squamous cell carcinoma to classify deregulated genes with prognostic value for recurrence need to be carried out. Presence of epithelial dysplasia or tumor cells in the surgical resection margins is linked with significant risk (66%) of local recurrence [63]. However, even with histologically normal surgical margins, 10–30% of OSCC patients will still have local recurrence [64]. Gene expression profiling by high-throughput technologies has proven to be valuable tools for prediction of outcome and progression in human malignancies including head and neck cancer [65].

To impact the survival of buccal cancer patients, molecular markers must be identified, which will help target tumors with a propensity for metastatic spread. There are numerous reports on the request of molecular biological markers for the valuation of cancer risk [66]. Molecular changes in oral pre-malignancy and head and neck cancer are influenced by differences in the ethnic and etiologic characteristics in different parts of the world [67].

Despite having poor clinical risk factors, patients who need chemotherapy will have enormous potential for better individualization of treatment options in breast cancer therapy where the clinical utility of gene signatures are playing a important contribution and proved to reliably identify patients in whom adjuvant chemotherapy is certainly not indicated [68].

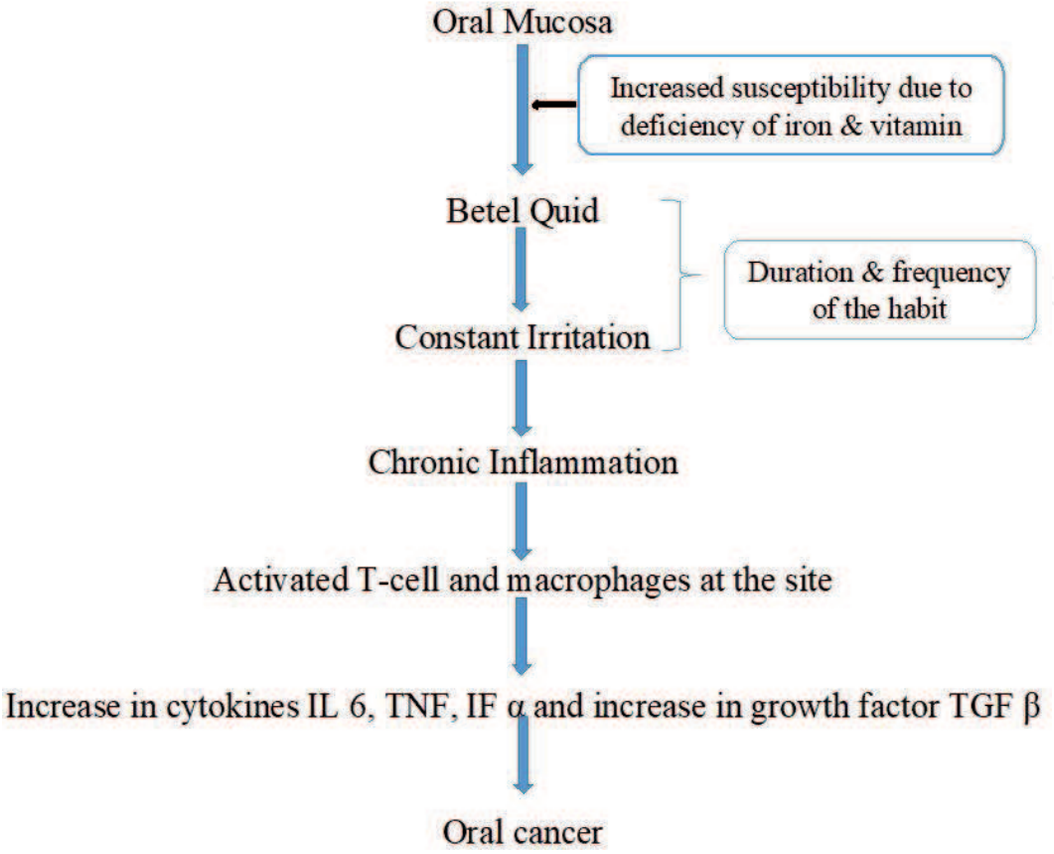


Figure 3. The etiopathogenesis of OSCC.

A specific tumor marker is not clinically available for the discovery of cancer at an early and possibly curative stage. Lymph-node metastasis is the main step in tumor progression and a risk factor for reappearance subsequent to surgery. Cluster analysis, part of data analysis of microarray, clearly parted cases with lymph-node metastasis from those without metastasis. Data indicated that sorting of patients into high- and low-risk subgroups on the basis of the prognosis summary may be useful means of guiding adjuvant therapy in patients with lymph-node positive breast cancer.

Figure 4 shows the mechanism of oral squamous carcinoma.

Patients who needed adjuvant chemotherapy but also those who did not need adjuvant chemotherapy, leading to a reduction in the number of women who would otherwise receive chemotherapy without compromising long-term clinical outcome was done using the 70-gene signature [69].

Netherlands Cancer Institute in Amsterdam (NKI) calculated expression of 70 genes was found to be statistically significantly linked with disease outcome, as defined by the presence of distant metastasis within 5 years. Metastases have also been found in the absence of clinically obvious primary tumors [70]. Ability to form distant metastases is a concern of particular method of transformation as contrasting to a selection process auxiliary the metastatic phenotype per se.

Determination of any signature genes are most important in the cascade of events driving metastasis along with tumor behavior is warranted. Bieche and others reported a 3-gene expression profile, which distinguished subgroups of patients with good, intermediate, and poor outcomes [71].

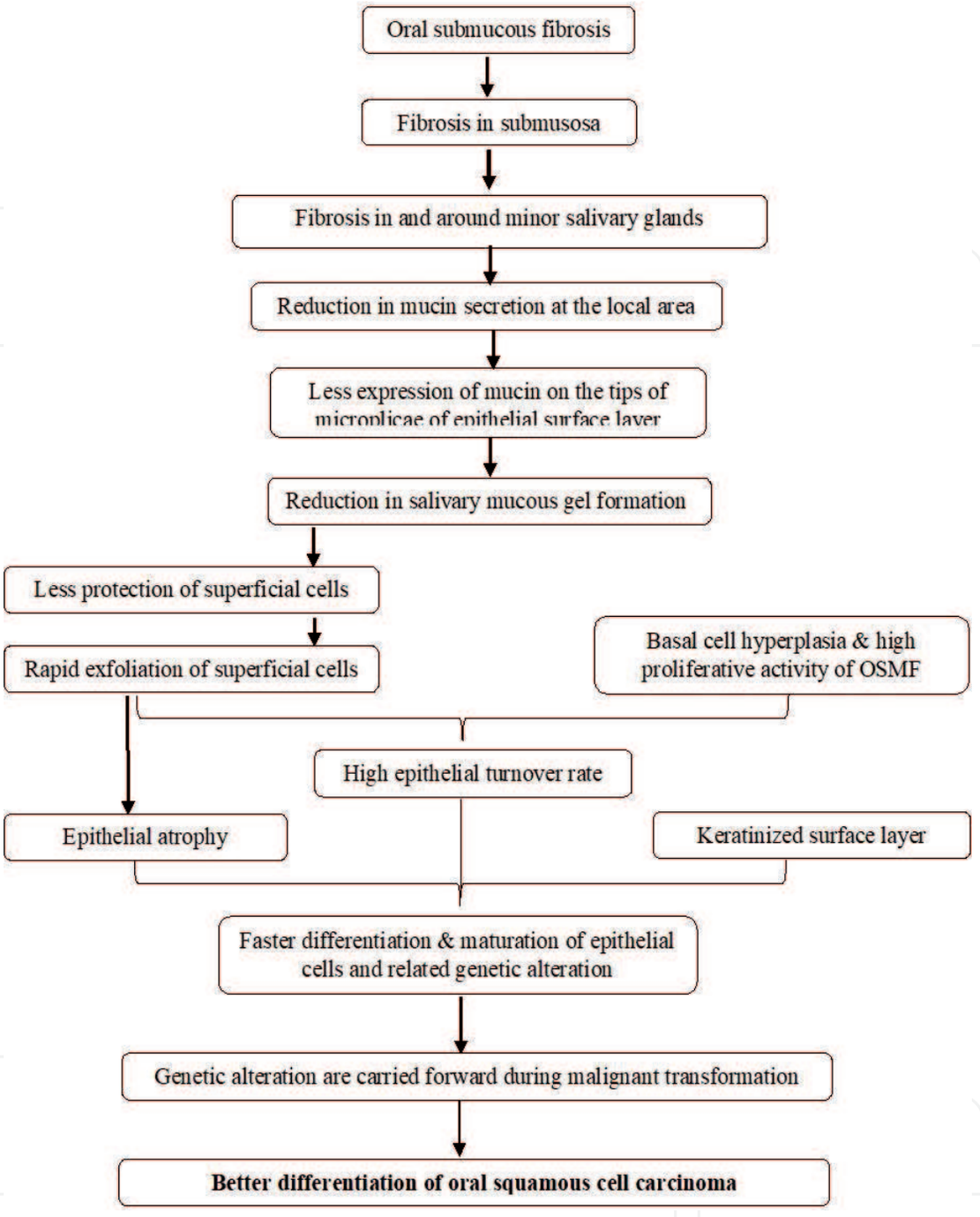


Figure 4. The mechanism of oral squamous carcinoma.

7. Head and neck cancer and research hypothesis

As the tools to categorize precancerous lesions in the mouth remain to improve, fewer men will die needlessly from head and neck cancer. Researchers are now harnessing the power of nanotechnology science to engineer strategies to investigate human fluids and tissues for abnormal molecules that are suggestive of a developing oral tumor. To detect abnormal cells and proteins in saliva that are associated with a developing oral tumor in-office diagnostic devices are being developed by investigators.

Treatment will improve, as targeted molecular therapy and personalized medicine become a truth. Predictable to guide treatment decisions for the individual patient on the basis of tumor HPV status is an evolving research, and evidence-based clinical trials are on the go. An inquiry is also defining the signaling pathways and networks that determine the development of head and neck cancer cells had been drawn, which will result in novel anticancer drugs that goals the particular molecular absences in each individual head and neck cancer patient.

Head and neck cancers are readily accessible, unlike tumors of the prostate, pancreas, or other internal organs. Rapid growth of valuable information for developing improved cure rates for both oral and other cancers is attained, and becomes more effortlessly studied cancers which may allow to accomplish the goal.

Locoregional control and overall patient survival potentially may improve the development of novel chemotherapy regimens and targeted therapeutic agents. Groups, like the Eastern Cooperative Oncology Group (ECOG), Radiation Therapy Oncology Group (RTOG), Southwest Oncology Group (SWOG), and European Organization for the Research and Treatment of Cancer (EORTC), facilitate patient enrollment into multi-institutional prospective randomized trials, which have delivered us with the necessary data to define current and future standards of care. Measures to identify biomarkers that predict disease behavior will carry on as individualized therapy evolves. Endorsed quality-of-life index measures additional define treatment results, and escalation of combined treatment likely will necessitate significant attention regarding treatment-induced toxicities is to be looked upon [72, 73]. The use of tobacco-related foodstuffs remains important worldwide, but further etiologic factors such as HPV similarly affect HNSCC presentation, behavior, and treatment [74]. Though improvement has been made throughout the past 60 years, a boundless deal remains to be consummate in head and neck cancer prevention.

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