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Oral Premalignancy: The Roles of Early Detection and Chemoprevention

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Introduction

Head and neck cancer is the fifth most common cancer worldwide (1). Males are more affected than females. The incidence is high in some regions of Europe, Hong Kong, India, and Brazil and among African Americans in the United States. In the United States, 52,000 Americans develop head and neck cancer annually and 11,500 die from the disease (2). Most premalignancy and chemoprevention studies have focused on head and neck squamous cell carcinoma (HNSCC) of the oral cavity. The primary risk factors associated with HNSCC cancer include tobacco use and alcohol consumption, with a dose-response relationship and synergistic effect (3). Betel nut chewing in Asia is an independent risk factor (4-7). A subgroup of non-smoker non-drinker (NSND) patients has been identified: i- young to middle-aged men with oropharyngeal cancer associated with human papilloma virus infection, and ii-young women with oral tongue cancer, or elderly women with gingival/buccal cancer with no clear etiologic factor (8-10).

Field cancerization and multistep carcinogenesis form the biological basis of chemoprevention. The concept of field cancerization refers to the effects of chronic exposure to tobacco and alcohol in patients with or without cancer, with progressive onset of molecular alterations in initially histologically and clinically normal epithelia (11). It is supported by the identification of similar genetic alterations in matched dysplastic and malignant lesions from the oral cavity (12). The lateral migration of genetically altered cells through the oral mucosa can form multiple lesions, a phenomenon called clonal cancerization (13). In other cases, genetic alterations found in dysplastic lesions were not found in matched cancer, providing some evidence that multifocal disease can arise from the development of several genetically altered clones from different initiating events. Finally, the frequent development of synchronous or metachronous second or multiple primaries in the head and neck and/or the lung also supports the concept of field cancerization (14). The use of molecular markers such as DNA methylation of individual genes or global gene expression changes has validated the concept of field cancerization (15-17).

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Califano et al. proposed a “Vogelgram” for HNSCC, which linked histologic changes to specific molecular alterations (18). They proposed that the accumulation of genetic events drives the transformation of squamous mucosa of the head and neck. Histologically, changes occur from normal to hyperkeratosis, hyperplasia, mild, moderate and severe dysplasia and carcinoma *in situ* before becoming invasive carcinoma. Molecular alterations in epithelial cells precede histological changes. Clinically, the mucosa may appear normal, or appear grossly abnormal with the findings of leukoplakia, erythroplakia, leukoerythroplakia, or lichen planus. Lesions appearing with these characteristics or submucous fibrosis, palatal lesions in reverse smokers, or other less common findings are referred to as potentially malignant disorders (PMDs) (19).

Primary, secondary, and tertiary prevention for oral squamous cell carcinoma (OSCC) (Table 1)

Primary prevention of HNSCC refers to the prevention of cancer by avoiding known carcinogens (20). Secondary cancer prevention includes early detection cancer through screening programs in a population at risk and asymptomatic, as well as prevention of the transformation of PMDs (21). Tertiary cancer prevention refers to the prevention and early detection of second primary tumors (SPTs) in individuals who have been treated for cancer (14). Individuals with tobacco and/or smoking history and normal appearing mucosa, patients with PMDs, and patients who have been treated for HNSCC and at risk for recurrent disease and SPT have increasing risks of developing HNSCC.

Primary cancer prevention

Quitting tobacco smoking and alcohol reduces the risk of developing HNSCC. It has been reported that the benefit of smoking cessation is great and can be realized in a relatively short period of time. For example, those who have stopped smoking for 1 to 4 years have a 30% lower risk for developing HNSCC than those who continue smoking. The risk of HNSCC decreases to that of never smokers for those who have quit smoking for 20 years or more. Cessation of alcohol is also associated with a reversal of HNSCC risk after quitting for 20 years or more (22).

Secondary cancer prevention

Diagnostic delay is a recognized challenge in the population of patients diagnosed with OSCC and includes patient delay, limited accessibility to health care system and health care provider delay (23). Diagnostic delay has been shown as a risk factor for tumor growth (24). Diagnostic delays have been associated with decreased survival in some recent studies (25). Therefore increased public awareness of early symptoms of PMDs as well as education of health care providers' about these lesions should improve early detection, increase cure rates and decrease treatment-related morbidity (23).

Screening for Oral Squamous Cell Carcinoma—Recommendations regarding screening for OSCC have been recently published (26). Screening by means of examination can detect PMDs and malignant lesions (27). However, clinical features alone cannot reliably distinguish between malignant and benign or premalignant lesions and the clinician cannot always accurately predict the risk of malignant transformation on the basis of routine biopsy (28-30). Only one randomized clinical trial has evaluated the effect of screening by means of visual and tactile examination on oral cancer mortality in India (31).

Between 1996 and 2004, of the 96,517 eligible participants in the intervention group, 87,655 (91%) were screened at least once, 53,312 (55%) twice, and 29,102 (30%) three times. Of the 5145 individuals who screened positive, 3218 (63%) only complied with referral. 95,356

eligible participants in the control group received standard care. The mortality rate was not significantly different in the intervention group compared with the control group when considering the overall population. Interestingly, tobacco and/or alcohol males who underwent screening had a significant mortality rate decrease (hazard ratio 0.57, 95% confidence interval: 0.35 to 0.93). This suggests that visual and tactile examination in a high-risk population may improve survival. However, this observation came from a subgroup analysis and needs further validation in a prospective study. Also, the applicability of these findings in western countries remains to be demonstrated.

Commercially available visualization devices based on tissue reflectance (ViziLite and ViziLite Plus) and autofluorescence (VELscope) have been evaluated but there is insufficient evidence that they improve the detection of PMDs beyond that of a conventional visual and tactile examination, and their use can be associated with an increased risk of false-positive findings (26). In patients with clinically suspicious lesions, the Oral CDx BrushTest can detect transepithelial cytology of disaggregated cells; however, in these cases, immediate biopsy is indicated which makes the relevance of this test questionable. The American Dental Association Council on Scientific Affairs recommends that clinicians remain alert for signs of potential malignancy when performing a routine visual and tactile examination in dental patients, especially those with a history of smoking and heavy alcohol use (26). The expert review panel also recommended that further research is needed to develop reliable, cost-effective screening tests.

Tertiary prevention

Regular posttreatment follow-up is highly recommended in patients after curative treatment of HNSCC by the National Comprehensive Cancer Network in order to detect:

1. Recurrence
2. A second primary cancer in the head and neck or lung and/or
3. Complications of treatment

Another major goal should also include smoking and alcohol cessation. In patients with a smoking history 20 pack years or more, the use of low-dose helical CT scanning of the lung can be discussed for screening of a second primary tumor in the lung (32).

Natural history and treatment of oral leukoplakia, the most frequent premalignancy disease

Oral leukoplakia is clinically defined as a white patch or plaque on the oral mucosa that cannot be removed by scraping and cannot be classified clinically or microscopically as another disease entity. It encompasses a wide variety of histologic findings from hyperkeratosis to hyperplasia and various grades of dysplasia. Three classifications have been proposed to describe the degree of dysplasia (33-35). To increase the likelihood of agreement between pathologists, a two class classification has been recently proposed) that will need to be evaluated prospectively (36):

1. no/questionable/mild: low-risk
2. moderate/severe: high-risk

Liu et al. studied the usefulness of the binary system of grading dysplasia by reviewing retrospectively 218 Chinese cases of OL with a median followup period of 5.3 years (37). High-risk OL had a hazard ratio of 4.6 (95% CI 2.36 to 8.84) to develop OSCC and was an independent risk factor of transformation. The risk was particularly high during the first 2 to 3 years of followup.

The natural history of OL remains poorly understood (28). Oral leukoplakia can remain for many years without changing, can regress spontaneously or after cessation of tobacco or alcohol use, and can transform to invasive SCC. The reported rate of malignant transformation has been low in community-based studies in developing countries (0.06% per year) and higher in observational studies in western countries involving patients followed in hospital-based academic centers (1 to 5% per year). The majority of the studies in the US found a rate of malignant transformation between 17% and 24% during periods of up to 30 years (38-40).

No consensus is available for the treatment of OL (41). Various surgical techniques including scalpel excision, cryosurgery and laser surgery have been reported; however, no prospective studies are available to compare the efficacy and morbidities of treatments, or to test whether excision versus observation decreases the risk of recurrence or the risk of malignant transformation (42). Kuribayashi et al. reported an OL recurrence rate of 15.1% with 2% of the patients developing OSCC after scalpel excision (43). Recurrence occurs more often in patients with positive or close resection margins, and in patients with gingival leukoplakia. When a complete excision of OL is not feasible, cryosurgery is an option (44). Laser obliteration has been proposed as an alternative to scalpel excision of premalignant lesions (45). The duration of the interval that the lesion has been present and the size of the lesion are two additional factors associated with recurrence and transformation (46). Recurrence and malignant transformation rates of 29.3% and 1.2% respectively have been reported after laser surgery (47). Laser treatment provides good hemostasis, preservation of oral function, satisfactory wound healing, and can be done repeatedly under local anesthesia but it is associated with delayed epithelial healing. It is important to note that the main disadvantage of cryosurgery and laser surgery is that obliteration of the lesion by these means precludes histologic evaluation of entire specimen as opposed to a true excision. Therefore, in the case of laser obliteration, the pre-treatment biopsy provides only a representative sample of the entire lesion.

The main challenge of surgical excision remains the multifocal nature of “field cancerization” and the notion that normal appearing mucosa may also have the potential for malignant transformation. To reduce the rate of margins positive for dysplasia and the risk of recurrence and malignant transformation, the use of vital tissue staining is suggested by some authors (47). In patients with multiple malignant and premalignant lesions, the use of photodynamic therapy has also been proposed. Grant et al. pioneered the method in a small series of patients (48). In a large series of patients with oral dysplasia from the UK, a complete response was observed in 81% patients, a partial response or stable disease was observed in 8% and 3.4% patients respectively, and malignant transformation was observed in 7.5% with a mean followup of 7.3 years (49). Zhang et al suggested the use of biomarkers (loss of heterozygosity - LOH) to guide surgical resection of low-grade dysplasia and reduce the risk of transformation (50), and some authors propose an association of resection and chemoprevention (51). Several studies have shown tobacco cessation was associated with decreased incidence and resolution of OLs (52-54). Although it is tempting to believe that alcohol and/or tobacco cessation is associated with a decreased risk of malignant transformation, no evidence is available. Patient followup strategies are discussed elsewhere but have not been prospectively evaluated (41). A clinician survey has indicated followup regimens of 6 monthly for lesions without dysplasia, 3 monthly for mild/moderate dysplasia, and monthly for severe dysplasia/carcinoma *in situ* (42, 55). The degree of dysplasia and the anatomical site were the two factors influencing the followup schema.

Clinical, pathological and molecular markers for risk assessment (Table 2)

Most of the work in predictive biomarkers has been done in patients with PMDs of the oral cavity, the most frequent being oral leukoplakia (19, 28, 36, 41). Clinical factors associated with malignant transformation of OL are: (28)

- female gender
- long duration of leukoplakia
- patient age
- never smokers
- size greater than 200 mm²
- non-homogeneous type
- location on the lateral and ventral tongue, floor of mouth, and retromolar trigone and soft palate sites

However, the presence of dysplasia is often the criterion that influences clinical management of OLs. The challenges are that OL without dysplasia may still progress to cancer, that a high inter- and intra-observer discordance rate has been reported in the evaluation of dysplasia, that the degree of dysplasia has not always been associated with increased cancer risk, and that OL may be reversible even when dysplasia is identified, irrespective of environmental factors (36).

Inconsistencies in the value of clinical and pathological factors to predict the risk of malignant transformation of OL led to the development of biomarkers. However there have been several challenges to biomarker development including the low prevalence of OL in Western countries, the fact that many lesions are not biopsied, and the rate of malignant transformation per year is generally low, which requires long followup periods to be able to derive any conclusion (55). Chemoprevention studies with retinoids allowed unique prospective collections of biospecimens that led to biomarker development (56).

Biomarkers: Loss of heterozygosity

The most robust and validated biomarkers were described in loss of heterozygosity (LOH) studies performed by Mao et al in 1996 (57). Oral leukoplakia harboring LOH at 3p14 and/or 9p21 were associated with a risk of developing invasive cancer in 37%, compared with only 6% in lesions without LOH at 3p14 and/or 9p21. These findings were subsequently validated by larger retrospective studies from two independent groups (58-60). OLs at former cancer sites with LOH at 3p and/or 9p were associated with a higher risk of development of invasive cancer (72% at 5 years) compared with leukoplakias without LOH (6% at 5 years) (61). The presence of LOH at the histologically negative margins of resection in patients with surgically treated HNSCC was a marker of risk of recurrence (62). Lee et al. have shown that the most predictive factors of risk of cancer are: (40)

- Degree of dysplasia
- Previous cancer history
- and 3 of the 5 biomarkers assessed:
 1. chromosomal polysomy
 2. p53 protein expression
 3. LOH at 3p or 9p

A recent study has prospectively validated LOH profiles as risk predictors of progression in a prospective cohort of 296 patients with primary mild/moderate oral dysplasia. High-risk lesions (3p and/or 9p LOH) had a 22.6 fold increase in risk compared with low-risk lesions (3p and/or 9p retention). Addition of another 2 markers (loci on 4q/17p) further improved risk prediction, with five-year progression rates of 3.1%, 16.3%, and 63.1% for the low-, intermediate-, and high-risk lesions, respectively (63).

Biomarkers beyond LOH

TP63 is involved in the stem cell biology of stratified squamous epithelium, and is a marker of SCC commonly used in clinical practice; the deltaNp63 isoform has oncogenic properties (64). Podoplanin was shown to promote invasion in different cancer types, and was shown to be associated with poor prognosis in OSCC (65). We reported that overexpression of podoplanin and deltaNp63 were prevalent in OL and associated with a higher risk to develop OSCC (64, 66). We have also reported increased *EGFR* gene copy number in 41% of OLs, and have shown a strong association with the risk of developing OSCC in patients with OLs overexpressing EGFR (67). In the same cohort of patients, we have shown that the vast majority of the genes associated with a high risk or low-risk to develop OSCC are upregulated or downregulated in HNSCC versus normal mucosa respectively (68). A 25-gene signature improved our prediction of OSCC development over clinical and pathological biomarkers, including the degree of dysplasia and the expression of deltaNp63 and podoplanin. Validation of those biomarkers in other cohorts of patients are pending (55). Other markers such as DNA content and DNA instability have shown some potential for risk assessment as well and are reviewed elsewhere (55, 69, 70).

Molecular Epidemiology: Genetic Polymorphisms

Molecular epidemiologic studies have identified genetic polymorphisms associated with the risk of HNSCC. Most of studied genes are related to single nucleotide polymorphisms (SNPs) in genes involved in cell cycle control and alcohol and more general metabolism (71). Recent genome-wide association studies (GWAS) have identified variants in the nicotinic acetylcholine receptor associated with nicotine dependence and lung cancer risk (72-74). Interestingly, one variant was shown to be associated with the risk of HNSCC and esophagus cancer in women but not in men (75). This finding was replicated in the INHANCE consortium cohorts (76). A particular situation is Fanconi anemia that represents a population at higher risk of developing HNSCC in the absence of other risk factors (77). Wu X et al identified 6 chromosomal SNPs and 7 mitochondrial SNPs significantly associated with risk of SPT/recurrence from a panel of 9,645 SNPs representing 998 cancer-related genes with risk of SPT/recurrence (78). These studies underscore the potential of incorporating germ-line genetic variation data with clinical and risk factor data in constructing prediction models for clinical outcomes but will require further validation in independent cohort of patients.

Chemoprevention: rationale and results

Chemoprevention refers to the use of natural or synthetic products to arrest or reverse the process of malignant transformation. The rationale that led to the development of chemoprevention is the failure of conventional therapies including surgery, radiation and chemotherapy to prevent recurrence in a significant number of patients, and the risk of SPT. Systemic administration of chemopreventive agents aims to address the challenge associated with the field cancerization. Different classes of agents have been evaluated so far, including natural products that may act through various mechanisms (green tea), and more targeted agents such as retinoid receptors ligands, selective cyclooxygenase inhibitors, p53-targeted agents, peroxisome activator receptor gamma (PPAR γ) agonists, and EGFR inhibitors.

Retinoids

Retinoids are naturally occurring and synthetic vitamin A (retinol) metabolites and analogues which bind to retinoid receptors of the RAR and RXR types, and which promote cell differentiation and decrease proliferation and apoptosis. The loss of nuclear RAR β has been described as an early event observed in premalignant dysplastic lesions (79), which suggested that targeting the retinoid signaling pathway could have merit as a chemopreventive strategy. This led to the extensive evaluation of retinoids in chemoprevention that helped to prove the principal of chemoprevention of oral cancer. However, the toxicity of the retinoids and the rapid reversal of their beneficial effects after stopping these agents prevented them from being considered as a standard of care. However, significant advances in cancer risk assessment were achieved from correlative studies of clinical specimens obtained through these efforts (56).

Retinoids for oral leukoplakia (secondary prevention)

Limitations of most of the studies of retinoids for OL is that the primary endpoint focused on OL clinical and/or histological response, which only marginally correlates with long-term oral cancer-free survival (80), and molecular abnormalities may still persist despite disappearance of the lesion with the chemopreventive agent (81).

In 1986, Hong et al reported the first double-blind, placebo-controlled trial of high dose 13-cis retinoic acid (13cRA) (1 to 2 mg/kg/day for 3 months) in this setting. The clinical response rate and rate of histologic improvement were 67% and 54% respectively in the retinoid arm and 10% in the placebo arm. However, mucocutaneous adverse events and hypertriglyceridemia were frequent and severe, requiring dose reductions in half of patients, and more than half of the patients experienced a relapse within 3 months of treatment cessation (82).

Lippman et al conducted a phase IIb maintenance trial following induction retinoid therapy (83). In this study, patients with OL were treated with 13cRA 1.5 mg/kg/day for 3 months (induction phase), followed by either low-dose 13cRA (0.5 mg/kg/day) or beta-carotene for 9 months in individuals not experiencing progression of the lesion (maintenance phase). Consistent with the previous trials, 55% and 43% of the patients had a clinical and pathological response respectively to the induction therapy. After the maintenance phase, further clinical response was observed. Severity of adverse events was lower during the maintenance phase, with a more favorable toxicity profile in the beta-carotene arm. However, on long-term follow-up, the incidence of *in situ* or invasive carcinoma was not different between the 13cRA and beta-carotene groups (38).

The follow-up trial consisted of 13cRA (0.5 mg/kg/day for 1 year followed by 0.25 mg/kg/day orally for 2 years) versus vitamin A (retinyl palmitate 25,000 IU/day) plus beta-carotene (50 mg/day) for 3 years (80). During the conduct of the study, data became available as regards to the increased lung cancer incidence and mortality associated with beta-carotene in other ongoing chemoprevention studies (84, 85). As a result, the experimental arm was modified to vitamin A single agent. Vitamin A single agent was associated with a lower 3-month clinical response rate (20%) compared to beta-carotene plus vitamin A (32.5%), and 13cRA (48.1%). The 5-year oral cancer-free survival was similar across the treatment groups (78% to 84%), and clinical response at 3-months was only marginally correlated with long-term oral cancer-free survival. This was one of the largest and longest-term studies in OL ever conducted, and it brought into question whether the use of clinical response is a valid endpoint in trials of PMDs oral premalignant lesions. Prevention of OSCC development has been recently considered as a more meaningful endpoint than clinical or histological response of the oral premalignant lesions (86).

Fenretinide is a synthetic retinoid with a more favorable toxicity profile (87-90). In a randomized study including 170 patients with resected oral premalignant lesions, Chiesa et al demonstrated that, compared to observation, treatment with fenretinide for 12 months was associated with a significant reduction in the risk of relapse 19 months after randomization. The drug was well tolerated. Unfortunately, the trial had to be stopped prematurely due to slow accrual (91).

Retinoids to prevent SPTs (tertiary prevention)

In 1990, Hong et al reported the results of a randomized trial of 13cRA (50 to 100 mg/m²/day) versus placebo for 12 months in patients with stage I to IV HNSCC who completed definitive therapy showing a lower incidence of SPT compared to placebo (92, 93). Unfortunately, a large, multicenter, phase III, placebo-controlled trial of 13cRA for 3 years that enrolled 1190 patients with stage I or II HNSCC who completed definitive treatment failed to confirm the results originally reported by Hong et al (94). Subsequent analysis of single nucleotide polymorphisms (SNPs) in the RXRA gene in 450 patients from this trial (95) revealed that more than 70% of patients had the rs3118570 allele and this SNP was associated a 3.33-fold increased risk of developing a second primary. Interestingly, this locus also identified individuals who received benefit from chemoprevention with a significant 38% reduced risk (95% CI, 0.43 to 0.90), suggesting that a pharmacogenetic approach could help select patients for 13-cRA chemoprevention.

The European Study on Chemoprevention with Vitamin A and N-Acetylcysteine (EUROSCAN) randomized 2592 patients with treated lung (40%) or head and neck (60%) malignancies to receive no intervention, retinyl palmitate, N-acetylcysteine, or both in a two-by-two factorial design. Unfortunately, the EUROSCAN failed to show a benefit from either N-acetylcysteine or retinyl palmitate in terms of survival, event-free survival or second primary tumor rates (96). Bairati et al. randomized 540 patients with stage I or II HNSCC treated with radiation therapy to receive alpha-tocopherol plus beta-carotene versus placebo for 3 years (97). After enrollment of 156 patients, beta-carotene supplementation was discontinued given the increased risk of lung cancers observed in other ongoing chemoprevention studies (84, 85). The remaining of the patients received alpha-tocopherol or placebo. After a median follow up of 52 months, there was a higher rate of SPTs during the alpha-tocopherol supplementation period, but a lower rate after supplementation was discontinued. After 8 years of follow up, the proportion of patients free of SPTs was similar between the groups (97).

Cyclooxygenase inhibitors

Cyclooxygenase-2 (COX2) has been shown to be frequently overexpressed in oral dysplasias and HNSCC (98, 99). Preclinical evidence suggests that COX2 inhibitors may have chemopreventive activity (100, 101).

Mulshine et al randomized 57 patients with oral premalignant lesions to receive placebo or a 0.1% oral rinse solution of ketorolac for 30 days. There were no significant differences in either in either clinical or histological response (102). Papadimitrakopoulou et al. conducted a pilot, randomized study of celecoxib in individuals with OL. Patients were treated with placebo, celecoxib 100 mg twice daily or 200 mg twice daily for 12 weeks during the blinded phase of the study. Celecoxib was well tolerated, but there were no differences in the response rates between the groups (103). Those disappointing results and the cardiovascular toxicities observed with COX-2 inhibitors in chemoprevention studies of colonic polyps (104) have decreased the enthusiasm for further evaluation of these drugs for HNSCC prevention.

Green tea polyphenols

The polyphenol (–)-epigallocatechin-3-gallate (EGCG) is the most abundant antioxidant present in green tea extract. Multiple signaling pathways are modulated by EGCG, including inhibition of receptor tyrosine kinases and their downstream pathways, inhibition of NF- κ -B, and activation of the p53 pathway (105). Studies evaluating EGCG in the prevention setting have used different preparations with varying amounts of EGCG and other potentially active ingredients. Therefore, results from these studies should be interpreted carefully.

Li et al reported the first placebo-controlled, randomized study of green tea in 59 patients with oral premalignant lesions. Patients assigned to the experimental arm received 760 mg of mixed tea capsules orally four times per day and 10% of mixed tea ointment topically (EGCG content not known). There was a favorable clinical response rate in the experimental arm (37.9%) compared to placebo (10%) (106).

Recently, Tsao et al conducted a placebo-controlled, phase II study of three different doses of green tea extract for 12 weeks in 41 patients with OL. Each 350 mg green tea extract capsule contained 13.2% of EGCG. The dose levels were 500 mg/m² versus 750 mg/m² versus 1000 mg/m² three times per day. The higher doses of the drug were associated with insomnia and nervousness. The response rates in the two higher-dose arms combined (58.8%) were significantly better than in the 500mg/m² arm (36.4%), and placebo (18.2%), suggesting a dose-response effect, however no differences in oral cancer-free survival was observed. This study supports the evaluation of green tea extracts in longer-term trials (107). Different formulations of green tea extracts (108) and combination with other agents (e.g., EGFR inhibitors) (109) are being developed.

p53-targeted agents

TP53 inactivating mutations are seen in 47 to 62% HNSCC and are the most frequent somatic mutations (110, 111). Attempts at restoring p53 function in pre-malignant lesions, or targeting p53 mutant pre-malignant cells have been described. ONYX-015 is an attenuated adenovirus cytotoxic to cells with dysfunctional p53-dependant signaling pathways.

Rudin et al enrolled 22 patients with dysplastic lesions of the oral mucosa in a study of a mouthwash of ONYX-015. Histologic resolution of dysplasia occurred in 37% of the patients, but the majority of the responses were short-lived and baseline p53 expression did not predict for response to ONYX-015 (112).

Li et al evaluated the effects of multipoint intraepithelial injections of a recombinant human adenovirus-p53 in 22 patients with dysplastic OL. After treatment, 100% of the lesions demonstrated a positive staining for p53 protein expression, mainly located in the basal and spinous layer of the epithelium. After 24 months of follow-up, 22.7% of the patients had a complete response, 50% of the patients had a 20 to 70% reduction in the size of the OL, 18.2% had stable lesions and 9.1% developed invasive cancer (113). Although those results are encouraging, the topical delivery of these agents may not address the remaining of the mucosa at risk.

Thiazolidinediones

Following binding of the ligand to the receptor, PPAR γ heterodimerize with RXR and the complex binds to response elements of target genes. PPAR γ agonists have been shown to promote terminal differentiation, inhibition of proliferation, and stimulation of apoptosis in

cancer cell lines *in vitro*. In pre-clinical animal models, the thiazolidinediones pioglitazone (114) or troglitazone (115) decreased the tongue carcinoma multiplicity and incidence, respectively, compared to placebo. Diabetic patients treated with thiazolidinediones had a reduced incidence of lung (116) and head and neck (117) cancers in retrospective epidemiologic studies, when compared to diabetic patients receiving alternative oral hypoglycemic agents. In a randomized, placebo-controlled, phase II study including 43 patients with OL, treatment with pioglitazone daily for 3 months led to a higher clinical and/or histological response rate compared to placebo (68% versus 0, respectively) (118). This trial formed the basis for a larger, ongoing, multicenter, phase IIb study of pioglitazone versus placebo in patients with oral pre-malignant lesions.

EGFR inhibitors

The concept of reverse migration, that is, importing agents, targets and study designs to personalize interventions, and concepts developed in advanced cancer to the setting of cancer prevention, has been recently proposed (119). The evaluation of EGFR inhibitors for chemoprevention is a good example of the reverse migration concept given the efficacy of cetuximab-based therapies in locally advanced and metastatic disease (120). EGFR is overexpressed in malignant, premalignant and normal-appearing tissues from HNSCC patients. EGFR expression increases progressively with increasing degree of dysplasia and is markedly elevated in more than 90% HNSCC (121, 122). We have reported that increased EGFR gene copy number in OLs was frequent and associated with an increased risk of developing OSCC (67). Erlotinib has been shown to decrease the incidence of OSCC in a chemically-induced mouse model (123). The use of EGFR tyrosine kinase inhibitor (TKI) in the chemoprevention setting is currently being evaluated in the multi-center, Erlotinib for Prevention of Oral Cancer (EPOC) activated in 2006 and that has completed accrual recently. Patients with OL (with or without a prior history of OSCC) are first evaluated for the presence of LOH that have been shown to be associated with a high risk to develop OSCC (57, 58, 61). All patients are followed for development of OSCC, but only the molecularly-defined high risk patients are randomized to receive placebo or erlotinib 150 mg orally daily for one year. Unlike most previous studies in oral premalignant lesions, the primary endpoint of this trial is incidence of OSCC. EPOC is an example of more efficient clinical trial designs for cancer prevention. Because it focuses on a high-risk population based on a molecular profile, it allows for a smaller trial (N=150 total patients) which is sufficiently powered to detect a possible effect of erlotinib in preventing the development of invasive cancer. Results are eagerly awaited.

Conclusions

The mutational etiology of HNSCC is diverse and few targetable mutations have been identified, further emphasizing the need to improve prevention strategies (110, 111). Studies of chemopreventive agents have not resulted in the development of an intervention that can be considered as standard of care, but have allowed for the identification of LOH as a biomarker of risk of disease progression. More work is needed to improve our understanding of the natural history of PMDs and to identify key molecular changes that render transformation irreversible. We are entering a new era of chemoprevention employing novel trial designs and agents, focusing on molecularly-defined high risk cohorts, and supported by improved pre-clinical models (124). This will hopefully lead to effective strategies to reduce the incidence, morbidity and mortality from head and neck cancers in the near future.

Abbreviations: Oral Premalignancy

COX2	Cyclooxygenase-2
EGCG	epigallocatevhin-3-gallate
EPOC	Erlotinib for Prevention of Oral Cancer
EUROSCAN	The European Study on Chemoprevention with Vitamin A and N-Acetylcysteine
GWAS	genome-wide association studies
HNSCC	head and neck squamous cell carcinoma
LOH	loss of heterozygosity
NSND	non-smoker non-drinker
OL	oral leukoplakia
OSCC	oral squamous cell carcinoma
PMDs	potentially malignant disorders
SNPs	single nucleotide polymorphisms
SPTs	second primary tumors (
TKI	t/yrosine kinase inhibitor

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Key points

- Premalignancy and chemoprevention studies in head and neck cancer typically focus on the oral cavity
- Avoiding or cessation of alcohol and smoking, early detection of potentially malignant disorders (PMD) or cancer, and early detection of recurrent and/or second primary tumor form the basis of prevention of oral cancer.
- Oral leukoplakia represents the most frequent PMD.
- Clinical and pathological parameters are poor predictors of oral cancer development.
- Despite disappointing results of extensive evaluation of retinoids for chemoprevention in the secondary or tertiary prevention setting, analysis of the tissue prospectively collected in those trials allowed identification of molecular biomarkers of risk to develop oral cancer, loss of heterozygosity being the most validated one.
- Improving risk assessment and identification of new targets for chemoprevention represent the main challenges in this field.

Table 1

Approaches for primary, secondary and tertiary prevention of oral cancer

Definition	
Primary prevention	Avoiding known carcinogens
Secondary prevention	Early detection of cancer
	Prevention of the transformation of PMDs
Tertiary prevention	Prevention of second primary tumors or recurrence
	Early detection of second primary tumors or recurrence

Table 2

Clinical, pathological and molecular markers of risk to develop oral cancer in patients with oral leukoplakia. Loss of heterozygosity at various sites is the only molecular marker that has been validated prospectively and appears in bold

Clinical	Pathological	Biomarkers
Female gender Long duration of leukoplakia Older patients Never smokers Size > 200 mm ² Non-homogeneous type Lateral and ventral tongue floor of mouth, and retromolar /soft palate sites	Degree of dysplasia	LOH Chromosomal instability or aneuploidy DeltaNp63 expression Podoplanin EGFR expression and gene copy number Gene expression profiles Constitutional genetic variations