Andrew M. Fribley
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Targeting Oral Cancer

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Part I

The Dynamic Epidemiology of Head and Neck Cancers and Current Treatment Modalities

1 Assessing the Changing Oral and Pharyngeal Cancer Demographic in the United States

Andrew S. Holpuch and Susan R. Mallery

Abstract

In 2015, oral and pharyngeal cancer (OPC) will be diagnosed in an estimated 45,780 people in the United States (71.3 % male – accounting for 4 % of all cancer diagnoses in men) and 8650 deaths (69.4 % male) will be attributed to this disease. While the 5-year survival rate has slowly improved over the last several decades, mirroring an overall decline in tobacco use, the incidence has increased largely due to a rise in human papillomavirus (HPV)-associated oral and pharyngeal cancers. These primary risk factors (i.e., tobacco use and HPV infection), along with alcohol consumption, dietary patterns, immunosuppression, and genetic predisposition, are introduced relative to their role in the development of OPC. Concepts for the detection (clinical tools and appearance of precancerous lesions) and prevention (behavioral modification and HPV vaccination) of OPC are also presented.

1.1 Epidemiology and Demographics

In 2015, it is estimated that 1.65 million Americans will be diagnosed with cancer (51.1 % male) and nearly 600,000 will succumb to the disease (52.9 % male) [1]. As a result of changing behavioral trends and improved preventative screening, the collective incidence of all cancers has continued to decline over the past two decades [1]. Similarly, 5-year relative survival rates have improved nearly 20 % since 1975 [1]. While these general trends portray overall improvement in the incidence and management of cancer in the United States, evaluation of race- and location-specific statistics demonstrates unique trends relative to individual cancer types.

Specifically, in 2015, oral and pharyngeal cancer (OPC) will be diagnosed in an estimated 45,780 patients in the United States (71.3 % male – accounting for 4 % of all cancer diagnoses in men) and 8650 deaths (69.4 % male) will be attributed to this disease [1]. As defined by the

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International Classification of Diseases, Tenth Division (ICD-10), OPC is classified as any malignant neoplasm of the lip, oral cavity (tongue, major salivary glands, mucosa, floor of mouth, other/unspecified parts of oral cavity), and pharynx (oropharynx, nasopharynx, and hypopharynx) [2]. Clearly, the broad classification of OPC encompasses a multitude of cancer subtypes, but roughly 90 % of these are represented by squamous cell carcinoma (SCC) [3]. Although the overall 5-year survival rates for OPC have significantly increased from 53 % in 1975 to 66 % in 2010 – a number likely skewed due to increased detection and prevention of lip cancers – disparity among racial survival rates is evident (Caucasian: 67 %; African-American: 45 %) [1]. This disparity has been attributed to lack of early detection, as 27 % of African-Americans have distant metastases at the time of diagnosis compared to only 16 % of Caucasians, i.e., the greatest disparity of all cancers presented by Siegel et al. [1]. Not surprisingly, 5-year relative survival rates vary with the stage at diagnosis: 79 % survival with localized disease, 42 % for regional disease and 19 % for distant metastases [4].

Access to high-quality healthcare due to an inequitable poverty burden is a major contributing factor to these disparities, as even in Medicare-insured patients, African-Americans are less likely to receive standard-of-care therapies than their corresponding Caucasian patients [5, 6]. Notably, patients diagnosed with late-stage OPC were also more likely to be uninsured or Medicaid recipients (OR: 1.37, 95 % CI 1.21–1.25) [7].

Interestingly, despite improved statistics regarding overall OPC incidence and mortality, a trend reversal has been observed in certain demographic groups [8]. While analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data over the past four decades (i.e., data currently available from 1975 to 2011) provides similar OPC data to that presented above (i.e., generalized improvement of observed incidence rates for all genders and races: Caucasian males, −1.21 %; Caucasian females, −0.66 %; African-American males, −1.53 %; African-American females, −1.38 %), temporal stratification of the data over the past 5 years shows that the greatest decline was observed in African-American males (−6.64 %) while the incidence in African-American females actually increased from −1.38 to +3.18 % [8]. Interestingly, mortality rates for Caucasian males have increased more rapidly over the last 10 years (30 years, −2.16 %; 10 years, −1.83 %; 5 years, −0.33 %) [8].

These trends were further clarified when broken down by geographic distribution, which showed increased mortality rates across all races in eight states (Nevada, North Carolina, Iowa, Ohio, Maine, Idaho, North Dakota, and Wyoming) [8]. Notably, within the last 5 years, Nevada, Idaho, and North Dakota showed marked increases in mortality rates in Caucasian males over the age of 50 [8]. Evaluation of the most recent Behavioral Risk Factor Surveillance System (BRFSS) data shows that five of the eight states identified with increased OPC mortality rates also had higher than average rates of alcohol and tobacco consumption patterns, i.e., primary risk factors for OPC [8]. While there appears to be a correlation with alcohol and tobacco use and oral cancer mortality rates, Kentucky and Wisconsin have the highest levels of current tobacco and alcohol consumers, but demonstrate decreasing rates of oral cancer incidence and mortality [8]. This indicates that other risk factors are involved in the development and progression of OPC in the United States (Table 1.1).

Not surprisingly, in addition to the African-American/Caucasian disparities revealed from the analysis of the SEER and BRFSS data, there are also substantial differences for OPC incidence in other ethnic groups. Nasopharyngeal cancers (NPC) are elevated in Chinese immigrants from the Szechuan province [9]. Interestingly, nasopharyngeal cancer rates from Szechuan province immigrants are intermediate between US-born Chinese and those persons who remain in the Szechuan province, findings which imply a combination of both genetic and environmental factors in the pathogenesis of this disease [9]. NPCs are also unique from standard oropharyngeal squamous cell carcinomas via the well-recognized contribution of Epstein–Barr virus and the accompanying heavy lymphocytic infiltrate [10]. As additional SEER and BRFSS data are compiled, disparities in the incidence and mortality in diverse ethnic groups are expected.

Table 1.1 Risk factors associated with the development of OSCC

Risk factor	Unique features of associated tumor
Tobacco	OSCCs retain many molecular characteristics of tobacco-induced malignancies at other sites such as lung; features that likely reflect the robust carcinogen metabolism present in human oral epithelia
Alcohol	
Human papillomavirus	More sensitive to selective chemotherapeutics and radiation; multimodal treatment has achieved higher success rates for this OSCC variant
Diet	
Immune status	If iatrogenic immunosuppression, tumor immunity will improve with reduction/elimination of immunosuppressant drugs
Heritable conditions	With the specific molecular mutations and deficiencies identified, targeted therapy to address these issues is now feasible

Furthermore, the previous studies did not characterize demographic changes with regard to cancer type or location (e.g., oral SCC or pharyngeal SCC – i.e., as separate entities). Stratifying the data by tumor location shows an increase in pharyngeal cancers in Caucasian males, without concomitant increases in oral cavity cancers [11]. These changing trends within this specific demographic group have been associated with an increasing prevalence of human papillomavirus infections in the oropharynx [11]. These data highlight the importance of demographic-specific risk factors, of which additional studies investigating race- and geographic-related differences in OPC incidence and mortality could provide valuable insight for the education and prevention in specific populations.

1.2 Risk Factors

Identifying and understanding the contributing factors to the development of OPC will facilitate the detection and prevention of disease. Numerous behavioral and physical factors are associated with the development of OPC and, more specifically, oral and pharyngeal squamous cell carcinoma. Age is frequently considered a risk factor for OPC, as it historically occurs in persons over the age of 40, indicating a temporal component for the accumulation of cellular damage resulting in malignant transformation potential. In spite of the contribution of age to cancer development, a paradigm shift in OPC development is actively underway with increasing incidence of OPCs in nonsmokers under the age of 60 and in nontraditional anatomical locations [11].

Cancers of the anterior oral cavity (i.e., anterior of tonsillar pillars) are most commonly associated with alcohol and tobacco use, which are routinely monitored on the state level by the Centers for Disease Control's Office on Smoking and Health via the National Health Interview Survey (NHIS) and Behavioral Risk Factor Surveillance System (BRFSS). These surveys provide valuable data regarding use patterns, but do not establish associations between these patterns and cancer incidence. Furthermore, alcohol and tobacco use in the United States have decreased over the past several decades, but race and location-specific trends have developed [8]. These changes in the demographic affected by OPC are likely due to shifting risk behaviors and new, emerging risk factors. Specifically, the human papillomavirus serotypes 16 and 18 (i.e., high-risk oncogenic HPV16 and HPV18) are directly responsible for the increasing incidence of pharyngeal cancers in Caucasian males under the age of 60 [11, 12]. In addition to these prominent risk factors, dietary habits, sun/ultraviolet exposure (lip cancers), betel quid use (common in Eastern countries), immunosuppression, and genetic predisposition are all considered risk factors for the development of oral and pharyngeal squamous cell carcinoma.

1.2.1 Tobacco and Alcohol

The development of OPC is linked to numerous risk factors, representing a multifaceted etiology,

with tobacco and alcohol consumption generally considered the primary risk factors. Over the last several decades, the US government has causally linked tobacco use to the development of cancer at eight major anatomical sites, and it is related to increased mortality in several others [13]. While other risk factors play a role in OPC etiology, historically, tobacco represents the most important, yet preventable cause of OPC.

The majority of tobacco-related carcinogens are by-products of pyrolysis, of which over 4000 chemical constituents are produced [13]. Smokeless tobacco varies widely based on the production process but favors the formation of carcinogenic tobacco-specific N-nitrosamines [14–19]. In addition, studies have shown interpatient heterogeneity with regard to an individual's capacity to bioactivate carcinogens present in smokeless tobacco (e.g., N′-nitrosonornicotine and 4-(methylnitrosamino)-1-3-pyridyl-1-butanone) [16–20]. More specifically, the presence of phase I and II metabolic enzymes within the oral epithelium predisposes the individual to the production of carcinogens from compounds present in smokeless tobacco [20, 21]. Burnt tobacco releases an additional group of chemicals, i.e., the polycyclic aromatic hydrocarbons. The fate of these chemicals in the mouth is also contingent upon the smoker's oral epithelial metabolic profile [22, 23]. Cytochrome p450 enzymes 1A1, 1B1, and 1A2 which are present in human oral epithelia can bioactivate benzo(a)pyrene to the ultimate carcinogen benzo(a)pyrene diol epoxide [22]. Persons with a preponderance of phase II enzymes, such as GSH-s-transferases and UGT glucuronosyl transferases that are also present in human oral epithelia, have greater inherent protective potential [24]. These enzymes convert the reactive oxygenated polycyclic aromatic hydrocarbons to more polar compounds for excretion in the urine [23, 24]. Collectively, these data demonstrate the carcinogenic potential of both smokeless and smoked tobacco products (i.e., cigarettes, pipe, and cigars), with a greater predilection toward smoked tobacco by-products and OPC. In addition, during concurrent alcohol and tobacco use, alcohol acts as a solvent for tobacco carcinogens, enhances their penetration through the surface epithelium, and enables access to critical oral epithelial stem cell populations [25, 26].

While numerous studies have established tobacco use and alcohol consumption as independent risk factors (i.e., increasing risk for OPC by up to 27-fold), combined use results in synergistic development of OPC [7]. A recent study (2004) evaluating 137 cases of OPC demonstrated a synergistic effect of tobacco and alcohol use [27]. The authors identified the multivariate odds ratios (OR) for developing OPC in heavy smokers (OR: 20.7), heavy drinkers (OR: 4.9), and combined use (OR: 48) [27]. A similar study separated risk by anatomical site, showing synergistically elevated risk of OPC development in the oral cavity (OR: 228) and/or pharynx (OR: 100) in individuals consuming more than 77 drinks per week and smoking more than 25 cigarettes per day [28]. Interestingly, increased alcohol consumption with stable tobacco use correlated with an increase of oral cavity, but not pharyngeal, cancer development [28]. Finally, a large case–control study (1114 OPC cases and 1268 controls) in the United States found similar synergism between tobacco and alcohol consumption (estimating that combined use accounts for roughly 75 % of OPC in the United States), with those individuals smoking more than 2 packs and consuming more than 4 drinks per day increasing their odds 35-fold for developing OPC [29]. Taken together, these studies demonstrate the substantial role of tobacco and alcohol use in the development of OPC.

1.2.2 Oncogenic Strains of Human Papillomavirus

The human papillomavirus, principally HPV subtypes 16 and 18, has been definitively associated with the development of OPC, particularly in the oropharynx, base of tongue, tonsillar pillars, and tonsils [12]. HPV is a common, sexually transmitted virus, with over 100 serotypes, which have infected an estimated 40 million Americans [11, 12]. While most Americans will be exposed to HPV in their lifetimes, by either oncogenic or non-oncogenic serotypes, an estimated 1 % lacks

the immune response to HPV16, resulting in an increased risk of developing OPC [11, 12]. Over the past several decades, changing sexual behaviors in young adults are increasing the spread of HPV and, thus, resulting in a pronounced increase of OPC incidence in the younger demographic without prominent alcohol/tobacco histories [30, 31]. These sexual behaviors include young age at first intercourse, history of genital warts, and number of sexual partners (greater than 26 for vaginal sex and greater than 6 for oral sex – indicating that oral sex is strongly associated with a risk of HPV infection and OPC development) [31, 32]. Other prominent factors associated with HPV infection include the male sex, husbands of females with a history of cervical carcinoma, a history of sexually transmitted diseases, human immunodeficiency virus infection, and immunosuppression [31–34].

In 1985, Löning et al. identified a causal relationship between HPV and OPC [35]. Since this discovery, the link between high-risk HPV subtype 16 and OPC has been elucidated (both molecularly and epidemiologically) as a significant etiological factor, accounting for up to a 15-fold increase in the development of OPC [36–38]. Unfortunately, HPV-positive OPCs often present at an advanced stage (i.e., cervical lymph node involvement), but unlike OPCs associated with traditional risk factors, HPV-positive OPCs are seemingly more sensitive to chemoradiotherapy resulting in improved progression-free survival rates (approximately 70 % greater than non-HPV OPC survival rates) [39–42]. Interestingly, studies in patients with OPC have shown a 15-fold increase of HPV-positive cancers in nonsmokers than smokers [41]. Collectively, these results demonstrate HPV as a distinct risk factor for OPC, which is shifting toward a younger demographic.

1.2.3 Dietary

Dietary factors, and a generally healthy lifestyle, play a significant role in decreasing the risk of preventing numerous cancer types, including OPC. The scientific evidence, however, does not provide the definitive association that has been shown with tobacco/alcohol and HPV, which is likely attributed to confounding variables with regard to lifestyle that diminish dietary associations.

Several studies have investigated vitamin intake relative to OPC risk; demonstrating diets low in beta-carotene, vitamin C, vitamin D, and vitamin E increased the risk of developing OPC, while diets high in these factors imparted a protective effect by reducing risk by nearly 50 % [43–49]. Specifically, vitamin C consumption greater than 745 mg/week exhibited a protective effect in two separate studies, decreasing risk of developing OPC with odds ratios of 0.39 and 0.63 [43, 50]. Similarly, regular use of vitamin D and E supplements reduced OPC risk to 0.76 and 0.5, respectively [46, 51]. In general, studies evaluating vegetable and fruit consumption have shown a protective effect against OPC [52–54]. In contrast, a case–control study in Uruguay with 4000 participants demonstrated that diets high in red meat significantly increased the odds of developing OPC (OR: 3.65) [55]. In general, these studies demonstrate that diets high in vegetable and fruit consumption exhibit a protective effect, while the converse enhance OPC risk.

1.2.4 Immunosuppression

Immunocompromised patients are at high-risk for several forms of cancer, including OPC. This group includes those infected with human immunodeficiency virus (HIV) and those recipients of iatrogenic immunosuppression (e.g., transplant recipients).

While HIV-positive patients are at an increased risk of developing oral and pharyngeal SCCs (OR: 1.4–2.6 relative to non-HIV population in the United States), they are also historically prone to the development of Kaposi's sarcoma and non-Hodgkin's lymphoma within the oral cavity [56, 57]. Studies evaluating SEER data from the 1980s, coinciding with the HIV epidemic in the United States, demonstrated a 14-fold increase of oral Kaposi's sarcoma and non-Hodgkin's lymphoma in 20–54-year-old

males in the San Francisco, California (high-density of HIV positive patients), area relative to other SEER combined sites [58]. In addition, recent studies suggest that up to 26 % of HIV-infected individuals are coinfected with the oncogenic HPV16, compared to roughly 1 % of the non-HIV population [59]. The increased incidence of HPV infection combined with the high prevalence of tobacco use in the HIV-positive population is expected to result in the increased incidence of OPC in the near future [59].

Prolonged iatrogenic immunosuppression, such as that following hematopoietic stem cell transplantation (HSCT), can be complicated by the development of chronic graft versus host disease (cGVHD) and the subsequent increased risk of developing solid tumors, including OPC. Common immunosuppression regimens include combination treatment with cyclosporine, tacrolimus, azathioprine, and corticosteroids [60]. In 1997, Curtis et al. conducted a multi-institute database study of 19,229 patients who had received HSCT and concluded that the male sex, cGVHD, and greater than 24-month treatment with azathioprine were strongly linked to an increased risk of developing OPC (OR: 11.1) [60, 61]. Specifically, a combination of cyclosporine, azathioprine, and corticosteroids resulted in a fivefold increased risk of developing OPC [60]. Collectively, immunosuppressed individuals and those with a history of HSCT or cGVHD are at an elevated risk for developing OPC and require periodic, thorough oral evaluations.

1.3 Heritable Conditions Associated with the Development of OSCC

While efforts to elucidate a "genetic fingerprint" indicative of the development of oral squamous cell carcinoma (OSCC) have not yet been successful, inroads into genetic and epigenetic contributing factors have been made. Identification that loss of heterozygosity at specific tumor suppressor loci heralds malignant transformation of premalignant oral epithelial lesions enhanced the predictability of OSCC development [62]. Furthermore, demonstration of the extensive heterogeneity of human oral cavity xenobiotic-metabolizing enzymes provides insights regarding the varied sensitivities of human oral mucosal epithelia to recognized carcinogens [20–22, 24]. The integral role of genetics in OSCC development, however, is most clearly manifest by two heritable conditions, i.e., Fanconi anemia (FA) and dyskeratosis congenita (DC). Both of these conditions are associated with a dramatically higher risk (1000-fold) and at a younger age for OSCC development [63, 64]. While the specific genetic perturbations of FA and DC are unique, there are also striking similarities between these diseases [63, 64]. Both FA and DC belong to the "inherited bone marrow failure syndromes" that include other heritable diseases such as Diamond–Blackfan anemia and severe congenital neutropenia [64]. Although all of these heritable syndromes carry an increased risk for acute myeloid leukemia, FA and DC are uniquely also susceptible to solid cancers [65, 66]. Marked chromosomal instability – attributable to faulty DNA repair (FA) and telomerase function (DC) – is a predominant common feature of FA and DC [65, 66]. Furthermore, both FA and DC patients experience immunosuppression attributable to bone marrow suppression, which enhances their tumor susceptibility [67, 68]. A final commonality is the nature of the tissues that undergo malignant transformation [63, 64]. Both FA and DC cancers arise in tissues with rapid cell turnover that mandates high replication rates such as bone marrow and throughout the gastrointestinal track (predominantly oral cavity) and skin [63, 64]. (Please see Table 1.2 for a summary of clinical and genetic features.) A recently published science article substantiates these clinical observations. This study employed a rigorous mathematical model to compare the estimated number of stem cell divisions at a tissue site with cancer risk [69]. Similar to these clinical observations in FA and DC patients, the authors concluded that tissues with higher rates of stem cell divisions experienced higher cancer incidence [69]. The longevity of stem cells – including mutated stem cells – and their potential

Table 1.2 Features, genetic mutations, and associated diseases in persons with Fanconi anemia and dyskeratosis congenita

Clinical manifestations	
Fanconi anemia	Developmental defects that can include short stature, cardiac and renal abnormalities, endocrinopathies, hyperpigmentation *Most consequential:* bone marrow failure or aplastic anemia at a young age
Dyskeratosis congenita	"Classic triad" which consists of dystrophic nail changes, oral leukoplakia, reticulated skin pigmentation. May also note pulmonary fibrosis, hypogonadism, alopecia, cirrhosis, canities prematura *Most consequential:* bone marrow failure at a young age
Patterns of inheritance	
Fanconi anemia	Autosomal recessive (majority) X-linked (1–2 %)
Dyskeratosis congenita	Autosomal dominant X-linked
Diagnostic criteria	
Fanconi anemia	Chromosomal instability and sensitivity to cross-linking agents. Positive results not pathognomonic as may reflect other syndromes associated with unstable DNA Conclusive tests entail screening for mutation in the known FA genes (15 distinct "complementation groups" recognized)
Dyskeratosis congenita	Genetic analyses reveal mutations in gene that codes for telomerase RNA (autosomal dominant), mutations in *DKC1* (X-linked)
Genetic mutations	
Fanconi anemia	*Genes affected: FANCA, CANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, GANCG, FANCJ (BRIP1), FANCL, FANCM/Hef* *FANC* proteins function in a myriad of roles in DNA repair that include formation of a nuclear complex necessary for ubiquitination and others that support endonuclease and helicase functions. FA proteins associate with other DNA repair complexes
Dyskeratosis congenita	*Genes affected: DKC1 (X-linked,* codes for the telomerase RNA-associated protein dyskerin*), hTR* (autosomal dominant, gene that codes for human telomerase RNA), *NOLA3* (autosomal recessive, telomerase maintenance) The associated genetic mutations cause telomerase erosion and deficiency, which ultimately result in chromatin instability
Cancer risk	
Fanconi anemia	Acute myeloid leukemia (may be preceded by myelodysplastic syndrome) *Head and neck squamous cell carcinoma (HNSCC)* Esophageal carcinomas Genitourinary cancers in women
Dyskeratosis congenita	Acute myeloid leukemia *Head and neck squamous cell carcinoma*. May experience multiple primary tumors. If multiple tumors, HNSCC almost always present Skin and gastrointestinal carcinomas, Hodgkin's and non-Hodgkin's lymphoma

to pass these mutations to daughter cells were an underlying premise for their observations [69].

1.3.1 Fanconi Anemia

FA is a rare (approximately 1 in 200,000–400,000 live births) heritable condition that exhibits both autosomal recessive (majority ~98 %) and X-linked patterns of inheritance [70, 71]. Sophisticated genetic analyses have revealed up to 15 unique "complementation groups" or genetic subtypes in FA: FA-A, FA-B, FA-C, FA-D1, FA-D2, FA-E, FA-F, FA-G, FA-I, FA-J, FA-L, FA-M, FA-N, FA-O, and FA-P [72–74]. In 2002 Howlett et al. discovered that *FANCD1* is *BRCA2* and determined that mono-allelic mutations resulted in breast cancer whereas bi-allelic mutations were associated with FA [75]. Despite the diversity of genetic subtypes, chromosomal

instability is the hallmark feature of all FA complementation groups. In health, FA proteins form multi-protein nuclear complexes that collectively form the FA pathway [76]. Healthy FA proteins perform a variety of roles in DNA repair including homologous recombination and contribute to ubiquitin ligase function [63]. Of note, FA proteins also interact in a cooperative fashion with other DNA repair pathways [63]. In addition, a role for FA proteins in monitoring oxidative stress and initiating protective responses has been identified [77]. Provided the oral cavity's high levels of exposure to xenobiotics, inflammation, and associated reactive species, the need for timely cytoprotective responses to reduce reactive oxygen species-mediated genetic damage is readily apparent.

While development of aplastic anemia between the ages of 5 and 10 is the most common FA presentation, FA-attributable developmental anomalies such as small stature could prompt an earlier diagnosis [63]. The "chromosomal breakage test," which entails challenge of suspected FA patients' peripheral blood lymphocytes with DNA clastogenic agents, remains the most common test to evaluate for FA [78]. Formerly, FA chromosomal fragility was formerly attributed exclusively to FA cells' loss of "caretaking genes" needed for DNA repair. A retrospective analysis, however, that questioned which evolutionary pressures might mandate protection from completely man-made reagents, has revised this assessment [79]. The evolved concept combines reduced DNA repair capacity with susceptibility to the redox stress that arises from metabolism of DNA interstrand cross-linking agents [79]. These authors have concluded that a prooxidant state exists in at least three FA subtypes, A, C, and G [79]. Other investigators have confirmed mitochondrial dysfunction and impaired ROS degradation [80]. Provided the oncogenic potential of reactive species-mediated nuclear and mitochondrial and DNA damage and inappropriately sustained intracellular signaling, the prooxidant cancer-permissive phenotype is understandable [81].

As a result of early diagnosis, successes of allogenic bone marrow transplantations, and improvements in graft versus host management, many FA patients now live into adulthood [82]. This enhanced life span – combined with the inherent cancer susceptibility – has redirected the focus to early detection and management of solid tumors [82]. While only 6 % of all worldwide malignancies are head and neck squamous cell carcinomas (HNSCC), HNSCCs represent the predominant solid cancers found in FA patients [83]. Approximately 50 % of nontransplanted FA patients will develop HNSCC by age 45 while 100 % of FA transplant recipients will develop HNSCC by 45 [84]. Furthermore while the majority of FA head and neck squamous cell carcinomas occur in the oral cavity, about 33 % develop in non-visibly detectable sites including oropharynx, nasopharynx, and larynx, which create challenges for early detection [85].

The etiology of FA OSCCs is distinct from the general population. While tobacco and alcohol use are the primary initiators of OSCC, FA patients' tumors most frequently arise in very young patients with negative social histories [86]. Oncogenic human papillomavirus (HPV) subtypes have more recent been implicated in some FA OSCCs [83]. Oncogenic HPV infection initiates the FA pathway in normal epithelial cells while genomic instability becomes accentuated in FA keratinocytes [83]. Furthermore, the absence of an intact FA pathway increases the susceptibility of FA cells to oncogenic HPV infections [83]. Notably, conflicting data regarding the contribution of oncogenic HPV in FA OSCCs has arisen from the European (HPV absence) and US (HPV presence) FA patient cohorts [83, 85]. Evaluations of US patients' FA OSCC tumors demonstrated the presence of oncogenic HPV in 84 % (21 of 25 tumors) evaluated [85]. In contrast European FA OSCCs did not reveal any high-risk HPV subtypes [24]. As both studies employed comparable HPV detection methodology, these clinical differences were thought to reflect geographic variations in the prevalence of HPV infections [83, 85]. The European studies also assessed surrogate HPV markers, i.e., elevation of p16, *p53* silencing as a result of HPV E6 protein, and evaluated *p53* mutations [83]. Interestingly, the data revealed that non-HPV-containing FA OSCC tumors

demonstrated comparable *TP53* allelic losses as seen in sporadic OSCCs [83]. Current guidelines for FA patients recommend close clinical follow-up, with oral cavity evaluations to be conducted by a health professional every 3 months beginning at 10 years of age [83].

1.3.2 Dyskeratosis Congenita

As previously mentioned dyskeratosis congenita (DC) and FA are unique among the bone marrow failure syndromes by virtue of their increased susceptibility to solid tumors. Like FA, DC is also heritable by an X-linked recessive pattern, an autosomal recessive pattern, and unlike FA also an autosomal dominant pattern of inheritance [64]. In addition, sporadic cases, presumed to reflect dominant de novo gene mutations, are also fairly frequent [66]. The incidence of solid cancer susceptibility in DC patients is only surpassed by persons with FA [64]. Comparable to FA, the majority of DC patients with multiple tumors develop at least one HNSCC [64]. The actuarial cancer risk for persons with DC is ~40 % by age 50 and over 60 % by age 68 [64]. DC, like FA, is a rare condition, with a prevalence of approximately 1 in 1,000,000 births [66]. While bone marrow failure may be the presenting manifestation, early in life persons with DC often develop "dyskeratotic" features that entail dystrophic nails, reticular skin pigmentation, and precancerous oral epithelial lesions [66, 87]. A diagnosis of DC can be made of the basis of two of three of the "diagnostic triad" [66]. In addition, clinical presentations of DC can vary in accordance with the extent of expression, a feature that is most notable in patients with the autosomal dominant form [64].

The underlying deficit in DC patients' cells is defective telomerase activity [66]. The specific proteins affected, however, are unique depending upon the inheritance patterns [66]. The *DKC1* gene, which is responsible for production of dyskerin, is mutated in persons with X-linked DC [64]. Major functions of dyskerin include RNA processing, conversion of rRNA uridine residues to pseudouridine, and maintenance of the telomerase enzyme complex through RNA binding [64–66]. Nonfunctional dyskerin has appreciable consequences, most notably faulty telomerase function and premature telomere shortening [64]. Similarly, autosomal dominant DC also perturbs telomerase function via mutations in the telomerase RNA component [64]. The genetic perturbation that occurs in autosomal DC was elusive and more recently identified as a homozygous mutation in *NOLA3* (also known as *NOP10*), which also functions in telomere maintenance [88]. Many cancers "preserve" cellular life spans by increasing telomere length. DC's premature telomerase shortening that is accompanied by a cancer-promoting phenotype is somewhat paradoxical. Telomere erosion and instabilities are permissive for end-to-end chromosomal fusion, a feature that could dramatically perturb cell replenishment [89]. Healthy human oral epithelia self-renew approximately every 28 days. The dramatic predilection for oral cancers in DC likely reflects the telomerase dependency of tissues that require constant cell turnover and the cancer-enabling consequences of growth-promoting chromosomal fusions [64].

Management strategies for persons with DC are complicated by the varying degrees of disease expression and the specific tissues affected [66]. Unlike FA, bone marrow transplantation has not uniformly increased survival in persons with DC [64]. Alternate therapies such as anabolic steroids with reduced androgenizing effects and selective bone marrow donors and recipients, i.e., siblings for patients with no existing pulmonary disease, have proven more successful. With regard to patients' oral lesions, the current recommendations include monthly self-examinations and three evaluations by healthcare professionals a year (two with the patient's dentist, one with an otolaryngologist) [66].

1.4 Detection

Factors affecting incidence would presumably also affect mortality rates; however, some factors (e.g., stage at diagnosis, access to care, and treatment success) influence mortality but not incidence. Since 1973, the SEER data have not shown any improvement in the proportion of

OPCs diagnosed at earlier stages (i.e., more localized). This suggests a failure by healthcare professionals to screen for lesions at early stages, a lack of effective screening methods, or lack of patient access to screening exams.

Precursor lesions for OSCC frequently present clinically as white (leukoplakia), red (erythroplakia), or mixed (erythroleukoplakia) well-defined lesions [90]. These lesions are commonly found in "pooling areas" of the oral cavity, such as the floor of mouth, ventrolateral tongue, and retromolar trigone where carcinogen-laden saliva bathes the local mucosa. With the exception of erythroplakia (lesions severe dysplasia or worse – microscopically), clinical presentation of a lesion does not convey the extent of maturational disturbances that range from relatively benign (atypia) to intraepithelial cancer (carcinoma in situ). In addition, as premalignant oral epithelial lesions are dynamic, clinical appearances can vary to extremely subtle to readily visible in a matter of days [91]. This phenotype can complicate early diagnosis for even experienced clinicians.

The oral epithelium is composed of several layers of keratinocytes, but in normal epithelium, only the deepest layer adjacent to the basement membrane (i.e., stratum basale) undergoes cell division to repopulate the superficial layers (i.e., stratum spinosum, granulosum, and corneum). In oral dysplasia and carcinoma in situ, however, this homeostatic process is disrupted and the aberrant keratinocytes inappropriately replicate DNA and proliferate throughout the full-thickness epithelium. Studies have shown that up to 36 % of histologically confirmed premalignant lesions transform to overt OSCC, acquiring the capacity to invade the basement membrane and metastasize to distant sites [92]. Also, proliferative verrucous leukoplakia represents a unique spectrum of changes that entail multifocal oral premalignant lesions that have a markedly elevated propensity (over 70 %) of undergoing malignant transformation [93].

Currently, the two best predictive indicators that an oral epithelial dysplastic lesion will progress to OSCC are lesional histologic grade and loss of heterozygosity (LOH) at putative tumor suppressor gene loci [94, 95]. Once the basement membrane has been violated by tumor cells, both lesional microscopic appearance (histologic grade) and extent of disease [clinical extent staged per standard T (size of primary tumor), M (present of distant disease), N (lymph node involvement) protocol] are employed to determine the overall prognosis and optimal treatment strategy [90].

As alluded to above, a host of logical biomarkers to predict malignant transformation potential, e.g., chromosomal polysomy, loss of E-cadherin accompanied by nuclear translocation of beta-catenin, and aberrant *p*53 expression, have been helpful [92, 96]. To date, only microscopic appearance and LOH have shown predictive benefit [92, 95, 96]. Due to the vast intra-tumor and interpatient heterogeneity of protein expression and signaling profiles in OSCC, a collective panel of numerous biomarkers is likely a more viable option for routine histopathological screening of potential disease progression to invasive OSCC.

Field cancerization is a theory in which one or more areas of epithelium, including the transient amplifying population and epithelial stem cells, have acquired pro-tumorigenic genetic modifications (e.g., loss of tumor suppressor genes) [97]. A field lesion does not demonstrate invasion of the basement membrane, a trademark of overt carcinoma; however the accumulation of genetic aberrations in cell progeny leads to progressive pro-tumorigenic traits (e.g., uncontrolled proliferation and invasion) [97]. Aspects of the recognized high-risk disease proliferative verrucous leukoplakia are an excellent clinical example of multifocal oral epithelial "initiation." This concept presents a challenge for patient management as excision of an entire lesion with clean microscopic margins will inevitably leave "field cancerized" epithelium behind leading to local recurrence.

1.5 Strategies to Enhance Detection of Premalignant and Early Malignant Oral Epithelial Lesions

While thorough examination by well-trained clinicians employing good lighting remains an effective means for early detection of most

premalignant lesions and early OSCCs [98], a variety of adjunct detection methods have been developed. One of the first methods to be developed and thoroughly investigated was vital tissue staining via application of the metachromatic dye, toluidine blue, to high-risk sites to facilitate in the detection of suspicious oral lesions [99–101]. As toluidine blue stains nuclear and mitochondrial DNA, its use was logical, especially for the identification of high-grade dysplasia and early malignant disease that has an abundance of cells with hyperdiploid nuclei [102]. These studies demonstrate the benefits of toluidine blue application by well-trained clinicians for the identification of suspicious lesions and selection of biopsy sites. Generalized toluidine blue application by less experienced healthcare providers, however, is not recommended. Instead, patients should be referred to a head and neck specialist for more extensive assessment.

While beneficial, toluidine blue has not proven to be a useful diagnostic aid for most nonspecialized clinicians. To fill this void, a variety of commercial products have entered the oral diagnosis field. One of the best-recognized commercialized ventures was OralCDX, distributed by OralCDx Laboratories Suffern, NY. The OralCDx kit includes a stiff brush, which is used by the clinician to obtain a cytological preparation that should, if performed correctly, include the all-important basal layer keratinocytes. The submitted cytological preparation is then assessed via computer analyses for a variety of features including cytomorphometry, DNA cytometry, and selected immunocytochemical parameters [103]. This technology that was marketed to general dental practitioners as a "brush biopsy" unfortunately has a fatal flaw, i.e., false negatives [104]. False positives lead to additional costs, e.g., blade biopsy and pathology fees and anxiety for patients. False negatives, however, provide a deceptive sense of security and enable significant lesions such as OSCCs to escape detection and treatment. This significant issue has reduced confidence in the usefulness of OralCDx for identification of premalignant and early malignant disease.

A variety of spectroscopy-based devices, which employ fluorescent, light scattering, and Raman spectroscopic techniques, to facilitate detection of preneoplastic and early OSCC have also been developed [105]. The underlying basis for all these technologies is predicated upon "unique spectral patterns" that are created as oral epithelia transitions from health to a preneoplastic–neoplastic state [105]. Some of the most aggressively marketed techniques entailed used of a fluorescent light-emitting source, e.g., VELscope (Visually Enhanced Lesion Scope, LED Dental, White Rock, British Columbia) and Vizilite (DenMat, Lompoc, CA). While conceptually feasible, this technology has encountered several challenges that have restricted its applicability. As presented by the manufacturers, fluorescence attenuation, i.e., quenching, correlates with premalignant or malignant epithelial changes. In addition, the manufacturers acknowledged a variety of clinical confounders such as physiologic pigmentation that would perturb interpretation. More extensive confounding factors that attenuated fluorescence including a large spectrum of nonneoplastic conditions as chronic mucositis, common variations of normal, e.g., geographic tongue, traumatic ulceration, lymphoid aggregates, and physiologic melanin pigmentation were identified in an IRB-approved VELscope study (Fig. 1.1) [106]. In addition, certain healthy anatomical sites, i.e., attached gingiva and tonsillar pillars, also functioned as effective "fluorescence quenchers" [106]. More issues were encountered with varying degrees of fluorescence attenuation that complicated interpretation regarding whether or not the loss of fluorescence was adequate to deem the lesion "suspicious" [106]. Collectively, these extensive confounding variables, reported incidents of false-negative findings, increased cost and stress to patients who receive false-positive imaging, and cost of the equipment – coupled with the concern that clinicians may rely extensively on fluorescence technology and overlook premalignant or malignant lesions – have markedly reduced enthusiasm for use of fluorescent spectroscopy for reliable diagnosis of preneoplastic and neoplastic oral lesions [107].

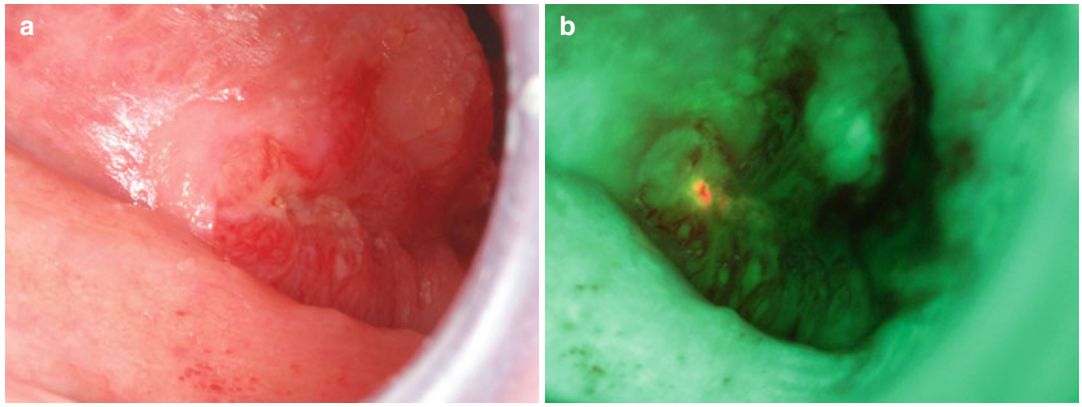

Fig. 1.1 (**a**) The clinical photograph (left image) depicts an ulcerated lesion with indurated borders of the left lateral–ventral tongue. The biopsied specimen was microscopically diagnosed as moderately differentiated squamous cell carcinoma. (**b**) The right photograph demonstrates its corresponding VELscope image. A focus of bright orange fluorescence, consistent with bacterial colonization of portions of the ulcer's fibrinous pseudomembrane, is apparent. The squamous cell carcinoma demonstrates a loss of fluorescence relative to the uniform apple-green birefringence of the surrounding normal tissues. Fluorescence reduction, however, is not uniform throughout the specimen. Notably, only a portion of the carcinoma demonstrates complete fluorescence quenching (Clinical photograph and VELscope image compliments of Dr. Kristin McNamara, Division of Oral Maxillofacial Pathology and Radiology, College of Dentistry, the Ohio State University)

1.6 Risk Reduction Strategies

Efforts to prevent the development of OPC involve a combined approach of early detection, behavior modification, and therapeutic intervention and require active participation from both the patient and clinician. As discussed above, early detection, monitoring, and surgical management via blade excision or laser ablation of premalignant lesions represent the primary methods of OPC prevention and management. In addition, tobacco cessation programs and the advent of readily available oncogenic HPV vaccinations provide preventive avenues for minimizing the risk associated with OPC development.

Tobacco use is the leading cause of preventable diseases worldwide; not surprisingly, tobacco and alcohol cessation programs also represent the primary behavioral modification for preventing OPCs. Studies have demonstrated that tobacco cessation is currently the most effective means of inducing stable, long-term regression and decreases the risk of developing second primary cancers in OSCC survivors [108, 109]. Efforts to prevent tobacco and alcohol use in adolescents are optimal, as individuals lacking a smoking/alcohol history have a significantly reduced risk of developing OPC and other diseases. Community- and state-based initiatives include the enforcement of advertising and sales restrictions and promotion of abstinence from tobacco/alcohol use through school-based programs. For those individuals who have tobacco-use histories, cessation advice provided by physicians, dentists, and other primary care personnel (i.e., office-based cessation programs) can significantly impact decisions regarding tobacco discontinuation. The National Cancer Institute (NCI) has published two manuals specifically designed to guide the physician or dentist through the advising process of tobacco cessation [110, 111]. In addition to these manuals, the NCI has also published a summary of the effectiveness and obstacles encountered through office-based cessation programs [112]. On a larger scale, hospital-based programs funded by the NCI, the American Lung Association, the CDC, and most notably the National Tobacco Prevention and Control Program's Initiatives to Mobilize for the Prevention and Control of Tobacco Use (IMPACT) are also available for community-based cessation.

In addition to tobacco-related prevention of OPCs, HPV-positive OPCs are optimal candidates

for targeted prevention as they continue to increase in prevalence [113, 114]. Two US Food and Drug Administration-approved vaccines are currently available (i.e., HPV bivalent, types 16 and 18; and HPV quadrivalent, types 6, 11, 16, and 18) and have been shown to be highly effective at preventing HPV-related cancers [115–117]. While evidence showing that vaccination protects against HPV-positive OPCs has yet to be established (several clinical trials are currently underway), herd immunity to the oncogenic HPV subtypes is expected to decrease the incidence of HPV-positive OPC [114]. Unfortunately, recent data from 2012 show that only 53.8 % girls and 6.8 % of boys ages 13–17 had received the full course of HPV vaccinations, of which vaccination must be done prior to first sexual intercourse to prevent possible infection [114]. Furthermore, carriers of oral HPV can be identified and educated regarding their individual risk of progression to OPC and the risk of infecting others.

1.7 Summary

The oral and pharyngeal cancer demographic has been shifting toward male Caucasians under the age of 60. This shift is the result of increasing oncogenic HPV infections in the oral cavity, resulting in the development of OPC. Additionally, the common risk factors, i.e., alcohol/tobacco and poor diet, still remain as prominent contributors to the progression of oral and pharyngeal cancers. Efforts to detect these lesions at an early stage through screenings provided by healthcare professionals (i.e., with or without diagnostic aids) prevent their development (HPV vaccination) or progression (surgical/pharmacologic management, tobacco cessation, diet modification) and are anticipated to curtail the rising rate of cancers in the oral cavity and pharynx.

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