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A Literature Analysis of the Risk Factors for Oral Cancer

Shih-An Liu

*National Yang-Ming University, Taichung Veterans General Hospital
Taiwan, R.O.C.*

1. Introduction

Oral cancer is one of the top ten most common cancers in men. It is estimated that 190,000 new oral cavity cancer cases were diagnosed in 2008 worldwide with 83,000 deaths (Ferlay et al., 2010). In Taiwan, oral cancer has been one of the top 10 causes of death from cancer since 1991. According to the annual report from the Department of Health of the Executive Yuan, the death toll for oral cancer in males has been increasing at a surprising rate (Liu et al., 2006). Although advances in the treatment of oral cancers have been made in the last four decades, benefits have not been reflected in mortality figures. Therefore, primary prevention such as cessation of tobacco smoking and alcohol consumption along with early detection are necessary control procedures to improve the prognosis for oral cancer (Ramadas et al., 2003). However, it is crucial to identify relevant risk factors for contracting oral cancer before implementation of prevention programs. Here, we review the relevant literature and critically appraise the risk factors for contracting oral cancer.

2. Materials and methods

Web-based exploration of electronic resources was carried out to screen published literature. We searched for relevant articles (published up to May 2011) in the Medline/PubMed database. These searches included the use of free text and index terms, such as “risk factor”, “oral cancer” and “head/neck cancer”, in order to expand the number of potentially pertinent studies retrieved. Furthermore, we checked the relevant references cited in the retrieved articles for further studies to review. The levels of evidence and grades of recommendation of the cited studies are listed in Table 1. The process of article selection is summarized in Figure 1.

3. Risk factors for contracting oral cancer

All relevant risk factors in the literature are listed in Table 1. Further description of risk factors for oral cancer are discussed below.

3.1 Lifestyle factors

The etiology of oral cancer involves multiple factors and the most important are life style factors, such as cigarette smoking, alcohol consumption and betel quid chewing.

Fig. 1. Results of literatures search. The figure illustrates the whole process of searching for articles for inclusion in this review.

3.1.1 Tobacco smoking

Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program revealed state-specific increases in oral cancer in United States. Further analysis indicated such states had comparatively higher percentages of smokers currently, as well as historically (Bunnell et al., 2010). It was estimated that a betel quid-chewing patient consumes 310,000 pieces of betel quid and a smoking patient consumes 14,000 packs of cigarettes before the diagnosis of oral cavity cancer on average. Besides, betel quid chewer and cigarette smoker were more prone to be diagnosed with oral cavity cancer at a younger age than abstainers (Tsai et al., 2009). Furthermore, heavy smoker were not only more likely to be diagnosed at a younger age but also at an advanced stage. Apart from active smoking, patients who were exposed to passive smoke were also found to have higher odds ratios (1.62 ~ 2.46) for contracting oral cavity and oropharynx cancers in a hospital-based case control study (Lee et al., 2009). The odds ratios or relative risks for contracting oral cancer among cigarette smoker, alcohol drinkers, or betel quid chewers are summarized in Table 2.

Risk factors	Grade of recommendation	Level of evidence
Lifestyle factors		
Cigarette smoking	A ~ B	1c ~ 3b
Alcoholic consumption	B	2b ~ 3b
Betel quid chewing	B	2b ~ 3b
Genetic factors	B	2b ~ 3b
Infectious factors	B	3a ~ 3b
Environmental factors	B	2b ~ 3b
Dietary factors	B	2b ~ 3b
Socio-economic factors	B	3a ~ 3b
Ethnicity and race	B	2b ~ 3b
Others	B	2b ~ 3a

Table 1. Relevant risk factors for contracting oral cancer in the literature

Variable	Odds ratios or Relative risk (95% CI ^a)	Study design	Reference
Smoking			
Cigarette smoking	8.4 (3.5 ~ 20.4)	Case-control	Ko et al., 1995
Current smoker	6.41 (3.32 ~ 12.37)	Case-control	Castellsagué et al., 2004
Habitual smoker	4.65 (2.74 ~ 7.89)	Cohort	Yen et al., 2008
> 30 pack-years	2.9 (1.8 ~ 4.5)	Case-control	Smith et al., 2010
Smoker	1.68 (1.00 ~ 2.81)	Case-control	Ihsan et al., 2011
Bidi smoking	2.6 (1.4 ~ 4.9)	Cohort	Jayalekshmi et al., 2011
> 40 pack-years ^b	8.46 (6.22 ~ 11.50)	Case-control	Lee et al., 2011
>= 60 pack-years	10.1 (6.1 ~ 16.7)	Case-control	Lubin et al., 2010
Former smoker ^b	5.49 (4.06 ~ 7.41)	Case-control	Szymanska et al., 2011
Alcohol			
Alcohol drinking	3.2 (1.8 ~ 5.6)	Case-control	Ko et al., 1995
Current drinker	3.46 (1.88 ~ 6.35)	Case-control	Castellsagué et al., 2004
Habitual drinker	0.95 (0.29 ~ 3.11)	Cohort	Yen et al., 2008
>= 30 grams per day ^c	1.92 (1.08 ~ 3.40)	Cohort	Shanmugham et al., 2010
> 21 drinks per week ^d	4.8 (2.8 ~ 8.3)	Case-control	Smith et al., 2010
Alcohol consumption	1.71 (1.20 ~ 2.44)	Case-control	Li et al., 2011
Alcohol drinker ^b	4.62 (3.39 ~ 6.28)	Case-control	Szymanska et al., 2011
Betel quid			
Betel chewing	8.5 (4.4 ~ 16.2)	Case-control	Ko et al., 1995
Habitual chewer	10.97 (3.22 ~ 37.34)	Cohort	Yen et al., 2008
Chewer	12.52 (5.45 ~ 28.77)	Cohort	Wen et al., 2010
Chewer	1.85 (1.02 ~ 3.33)	Case-control	Ihsan et al., 2011

All use abstainers as reference group
^a CI: confidence interval
^b Including oral cavity and oropharynx patients
^c Women only
^d One drink was equivalent to a 12-oz can or a bottle of beer, 4 oz glass of wine, or 1.5 oz shot of hard liquor

Table 2. The association of smoking, alcoholic consumption and betel quid chewing and the risk of contracting oral cavity cancer

Tobacco contains N-nitroso compounds which are well-known carcinogens. In addition, cigarette smoke condensate has the capacity to activate nuclear factor kappa-B in squamous cell lines. Nuclear factor kappa-B is a transcription factor and has been implicated in the regulation of many proinflammatory pathways, which might be one mechanism leading to carcinogenesis (Rohrer et al., 2010). Other tobacco-generated carcinogens include tobacco-specific nitrosamines (TSNAs, e.g. NNN, NNK, NAT and NAB), and free radicals that can inhibit antioxidant enzymes (such as, glutathione-S-transferase, glutathione reductase, superoxide dismutase, catalase, and glutathione peroxidase) (Scully, 2011). This specific antioxidant enzyme activity loss renders the oral epithelial cells more vulnerable to the harmful effects of both thiocyanate ions and hydroxyl free radicals produced by residual H_2O_2 in the presence of salivary redox-active metal ions. It has been demonstrated that thiocyanate ions and free radicals may adversely react with DNA, thus paving the way for progression of oral cancer (Reznick et al., 2003).

3.1.2 Alcohol consumption

Although alcoholic consumption is often cited as a known risk factor of oral cavity cancer (Altieri et al., 2004; Scully, 2011; Szymańska et al., 2011), some studies did find alcohol was not associated with an elevated risk of oral cavity cancer (Takács et al., 2011; Yen et al., 2008). One possible explanation for the seeming contradiction may be that different studies defined alcohol consumption differently. Also, not all studies collected quantitative data on alcoholic consumption. Furthermore, the different alcohol-drinking profiles of various regions made the comparisons among studies more complicated. On the other hand, a previous case control study found a lower risk of oral cavity cancer in postmenopausal women with moderate alcoholic consumption (Takács et al., 2011). The beneficial systemic changes, namely the increased insulin sensitivity and elevated estrogen levels may explain the protective effects in these latter groups of cases.

Ethanol may work as a carcinogenic initiator or as a promoter that enhances permeability of cells to other environmental carcinogens, such as cigarette smoke. Ethanol is oxidized to acetaldehyde mostly through alcohol dehydrogenase and, to a lesser extent, cytochrome P450 enzymes in chronic drinkers (Lubin et al., 2009). Acetaldehyde is classified as “carcinogenic to humans” (IARC Group 1) by the International Agency for Research on Cancer (IARC) (Lachenmeier et al., 2011). Acetaldehyde not only induces DNA-protein cross-linking and DNA interstrand cross-linking, but also interferes with DNA repair mechanism by inhibiting repair enzyme. Apart from alcoholic consumption, acetaldehyde may also be produced by oral bacterial flora in patients with poor dentition or poor oral hygiene (Homann et al., 2000). A previous study found that short-term salivary acetaldehyde increased due to direct exposure to alcoholic beverages (Lachenmeier et al., 2011). This may suggest a possible mechanism to explain the greater risk for oral cavity cancer associated with alcoholic consumption.

3.1.3 Betel quid chewing

Betel quid is one of the most commonly used psychoactive substances. It has been estimated that there are 600 million betel quid chewers worldwide (Wen et al., 2010). People who chew betel quid but do not smoke cigarettes or consume alcohol were reported to have an odds ratio of 10.97 (95% confidence interval: 3.22-37.34) for contracting oral cancer (Yen et al.,

2008). Another case-control study found betel quid chewer had an odds ratio of 6.9 (95% confidence interval: 3.1-15.2) for developing oral cancer after adjustment for smoking and drinking alcohol (Ko et al., 1995).

Arecoline, the major alkaloid of areca nut, has been known to induce cytotoxicity and genotoxicity in various systems (Lin et al., 2011). It is also mutagenic in both bacteria and mammalian cells (Chang et al., 2001). Arecoline was found to inhibit P53, repress DNA repair, and trigger DNA damage response in human epithelial cells via an *in-vitro* study (Tsai et al., 2008). Chewing betel quid induces local irritation and trauma in the oral mucosa, leading to chronic inflammation, oxidative stress, and cytokine production, and the traumatic wound offers easier access to the system for carcinogens contained in betel quid (Wen et al., 2010). Betel quid chewing not only causes genomic instability, but also has a close relationship with cell-mediated immunity, which could play a role in the malignant transformation of oral mucosa (Yen et al., 2008).

3.1.4 Synergistic effect

Many studies have found that there is a synergic effect of cigarette smoking, alcoholic consumption, and betel quid chewing in carcinogenesis of oral cavity mucosa (Castellsagué et al., 2004; Chang et al., 2001; Ko et al., 1995; Szymańska et al., 2011; Wen et al., 2010; Yen et al., 2008). Patients who smoked and also consumed alcohol had an odds ratio of 9.03 for contracting oral cavity cancers, whereas patients who only smoke or only consumed alcohol had odds ratios of 4.65 and 0.95, respectively when compared with abstainers (Yen et al., 2008). *In vitro*, the addition of extracellular nicotine worked synergistically on the arecoline-induced cytotoxicity and this may partially explain why those who chew betel quid and smoke cigarette are at great risk of contracting oral cancer (Chang et al., 2001).

3.2 Genetic factors

Genetic instability, either spontaneous or mutagen induced, has been regarded as a predisposing factor for neoplastic transformation (Patel et al., 2010). Cancer is the result of DNA mutations occurring spontaneously and from the action of different mutagens. A sequence of genetic changes leads finally to loss of growth control and immortality (Scully, 2011). Together with these changes are mechanisms that metabolise carcinogens, repair DNA damage, control growth, and defend the human body against cancer. The development from an ordinary healthy cell to a pre-malignant or a potentially malignant cell is called oncogenesis (carcinogenesis). The level of chromatin breaks induced by a mutagen challenge may serve as an indicator of an individual's capacity to repair damaged DNA. A previous study showed that mean level of chromosomal aberrations was higher in oral cancer patients when compared with that of healthy controls (Patel et al., 2010). A dose relationship between lifetime tobacco exposure and chromosomal aberrations was also found in aforementioned study. Apart from healthy tissues, genomic imbalances in premalignant lesion tissues also had a strong association with malignant transformation (Garnis et al., 2009).

3.2.1 Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR) is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands. Increased or

aberrant expression of the EGFR or its ligands may lead to many processes important for tumor growth, including cell proliferation, survival, angiogenesis, invasion, and metastasis (Janmaat & Giaccone, 2003). A previous study investigating EGFR gene in oral premalignant lesion specimens found that increased EGFR gene copy number was associated with higher risk of oral cancer (Taoudi Benchekroun et al., 2010). Other studies found significant increases in EGFR copy number and EGFR immuno-reactivity in oral squamous cell carcinoma patients when compared with long-term betel quid chewers, or compared with matched adjacent oral mucosa (Chiang et al., 2008).

3.2.2 P53

P53 is one of the most important tumor suppressor genes. Tumor suppressor genes work normally in cellular growth control by regulating the cell cycle, apoptosis, cell adhesion, and DNA repair. Silencing of tumor suppressor genes occurs in carcinogenesis. P53 mutation was also found to have an association with tobacco smoking and alcohol drinking. Inactivation of P53 by mutations is a critical molecular event in the upper aero-digestive tract carcinogenesis (Szymańska et al., 2010). Alteration of P53 expression is related to increased genomic instability in oral intraepithelial neoplasia and may accelerate the genetic modifications during oral tumorigenesis (Lippman et al., 2005). P53 codon72 polymorphism was found to be associated with a higher risk for contracting oral cancer (Kuroda et al., 2007).

3.2.3 Gene polymorphisms

Single nucleotide polymorphisms (SNPs) are genes areas that have altered DNA sequences which may not induce an aminoacid modification, or misrepresented DNA sequences that do not seem to have the potential for any unfavorable consequence in healthy people but may be markers for tendency to contract diseases (Scully & Petti, 2010). Certain genetic polymorphisms associated with enzymes for alcohol metabolism, such as, alcohol dehydrogenase genes and cytochrome P450 genes, are related to a greater risk of contracting oral squamous cell carcinoma. Besides, this risk is proportional to the amount of alcohol consumption (Marichalar-Mendia et al., 2010). Previous studies found hypoxia inducible factor-1 alpha gene polymorphisms C1722T and G1790A were associated with an increased risk of contracting oral cancer (Chen et al., 2009; Shieh et al., 2010). SNPs of the vascular endothelial growth factor gene were reported to have an association with development of oral cancer. The +936 T allele and the -2578 C/A SNP were expressed significantly more often in peripheral blood samples from oral squamous cell carcinoma patients when compared with those from healthy controls (Kämmerer et al., 2010). In a meta-analysis of case-control study, Arg194Trp polymorphism in the X-ray repair cross-complementing group 1 gene was significantly associated with oral cancer in an Asian population (Zhou et al., 2009).

3.2.4 Others

Promoter methylation of human MutL homolog1 (hMLH1) was found in 76% of oral squamous cell carcinoma patients but in none of the healthy control samples. The hMLH1 gene belongs to the human DNA mismatch repair system and is essential in reducing the accumulation of mutations and maintaining genomic stability (González-Ramírez et al., 2011).

3.3 Infectious factors

Infection can be induced by bacteria, fungus, and virus. Periodontal disease has been shown to increase the risk of oral cancer. This chronic infection and resultant low-grade systemic inflammatory response along with oxidative stress may be one possible pathway of carcinogenesis (Gasche et al., 2011). Also, the oral ecological shifts accompanying periodontal disease are characterized by proliferation of ketone-producing and nitrate-reducing microorganisms, which may contribute to increases in carcinogen concentrations (Divaris et al., 2010). Furthermore, several oral microorganisms can produce carcinogenic acetaldehyde from alcohol (Homann et al., 2000). This may explain why poor oral hygiene is associated with oral cancer. A case-control study conducted in Japan found that frequent toothbrushing could reduce the risk of upper aerodigestive tract cancer, especially in those who are heavy smokers and drinkers (Sato et al., 2011).

Candida albicans is the yeast most commonly isolated from the oral cavity. *Candida* may invade oral epithelium and may be causally involved in dysplastic change. Nitrosamines produced by *Candida* may activate specific proto-oncogens. *Candida* can also efficiently convert ethanol into carcinogenic acetaldehyde (Scully, 2011).

Presently, more than 100 types of human papilloma viruses (HPV) have been identified. HPV-16 and HPV-18 are the most common virus types identified in oral carcinoma. Two meta-analyses found HPV is an independent risk factor for oral and oropharyngeal carcinoma (Dayyani et al., 2010; Hobbs et al., 2006). Two proteins of HPV, E6 and E7, are thought to be involved in the carcinogenesis of oral cancer. The E6 protein can bind to the cellular P53 protein and this leads to the breakdown and reduction in concentration of P53 in the cancer cell. As a consequence, the damaged cancer cells lose their ability to repair DNA and cannot undergo apoptosis. The E7 protein has the ability to bind the cellular RB protein, releasing transcription factors, which are then free to transactivate the expression of other cellular proteins (Shillitoe, 2009). A previous study has showed a combination of herpes simplex virus seropositivity and a history of smoking was associated with a higher risk of oral cancer than would be expected from a purely additive effect (Starr et al., 2001). However, the nature of the herpes simplex virus genome makes it difficult to generate specific probes and the possible sequences that were detected have not been identified (Shillitoe, 2009).

3.4 Environmental factors

3.4.1 Sunlight

In Denmark, a population-based case-control study found that individuals who were employed in outdoor work for more than 10 years had a 1.67-fold (95% confidence interval 1.38 ~ 2.03) increased risk of contracting lip cancer (Kenborg et al., 2010). The lower lip receives more direct sunlight than the upper lip. Therefore, lip cancer tends to develop in lower lip. However, it is interesting to note that the basal cell cancer and cutaneous malignant melanoma were less prevalent in outdoor workers in aforementioned study.

3.4.2 Heavy metals

Heavy metals are extremely persistent in the environment and can induce unfavorable consequences on human body. Heavy metals are incorporated into food crops grown in the

soils, and subsequently find their way into the human body following the consumption of such contaminated food items. The IARC classifies many heavy metals, such as arsenic (As), chromium (Cr), and nickel (Ni), as human carcinogens (Chiang et al., 2010). In an observational study conducted in Taiwan, the incidence of oral cancer was geographically associated with the concentrations of As and Ni in the patients' residential areas (Su et al., 2010). Blood levels of Ni and Cr in oral cancer patients were 1.6 and 1.4 times higher, respectively, than those of healthy controls in a case-control study. Individuals with high Ni blood level had a 16-fold higher relative risk of contracting oral cancer than those with low Ni blood level. Also, people with high Cr blood level had a 7-fold higher relative risk of contracting oral cancer than those with low Cr blood level (Yuan et al., 2011). The role of heavy metals in the mechanism of development of oral cancer warrants further investigation.

3.5 Dietary factors

It is interesting to find that caffeinated coffee drinking was inversely related with the risk of oral cavity cancer (odds ratio: 0.96, 95% confidence interval: 0.94 ~ 0.98) in a pooled case-control study (Galeone et al., 2010). In addition, people who had a dietary pattern of animal product consumption had a greater risk of developing oral cancer (odds ratio: 1.56, 95% confidence interval: 1.13-2.15) (Edefonti et al., 2010). Moreover, women with low folate intake had a higher risk of developing oral cancer if they also consumed a high amount of alcohol (Shanmugham et al., 2010). On the other hand, a traditional Mediterranean diet was found to reduce the risk of upper aerodigestive tract cancers in a case-control study conducted in Greece (Samoli et al., 2010). Intake of citrus fruit was also reported to lower the risk of developing oral cancer (Foschi et al., 2010). Although some studies showed that the Mediterranean-type diet and vegetable rich diet could reduce the risk of oral cancer, the evidence is still weak. The effect of individual food components and trace elements on carcinogenesis remains unclear (Meurman, 2010).

3.6 Socio-economic factors

There was a significant increase in the incidence of head and neck cancer including oral cancer in people with low level of education (odds ratios: 1.85 ~ 5.3) and lower income patients (odds ratios: 1.7 ~ 2.41) (Boing et al., 2011; Conway et al., 2008; Johnson et al., 2010; Madani et al., 2010; Swaminathan et al., 2009). Although there was a strong association between smoking/alcohol consumption and socioeconomic status, individuals with lower education level, lower income, lower occupational status/social class, and those performing manual labor still had a higher risk of contracting head and neck cancer including oral cancer after adjusting for smoking and alcohol consumption (Boing et al., 2011; Conway et al., 2008). Possible explanations includes, limited access to health care and health information, exposure to harmful physical environments and agents, and stresses caused by job insecurity or unemployment, and so on (Conway et al., 2008).

3.7 Ethnicity and race

The incidence rates of oral cancer vary considerably across racial/ethnic groups worldwide (Warnakulasuriya, 2009a). South Asians have higher incidence rates of oral cancer than people from most other countries. Black males in the United States have higher rates of

oropharyngeal cancer than white males (Warnakulasuriya, 2009b). However, such results could be confounded by nutritional difference, smoking pattern, differences in the amounts of cigarettes smoked or alcohol consumed, and interaction among smoking, alcohol consumption, and betel quid chewing.

3.8 Others

A previous study about the development of secondary solid tumors after allogeneic hematopoietic bone marrow transplant in Japan found that the risk for developing oral cavity cancer among those who had received such a transplant was 35.25-fold (95% confidence interval: 17.59 ~ 63.06) higher than that of the age- and sex-adjusted general population (Yokota et al., 2011). Body mass index gain was inversely associated with upper aero-digestive tract cancers including oral cancer in a large scale, prospective, multi-center study in European countries. It was speculated that this phenomenon might be due to other confounding factors, including interactions of body fat distribution with smoking and/or drinking, biological mechanisms, indication of early tumor development or other related carcinogenic mechanisms (Lubin et al., 2010; Park et al., 2011). A retrospective study found a significant association between chronic trauma of oral mucosa and oral cancer after adjusting for confounding factors, such as smoking and alcohol consumption (Piemonte et al., 2010). Sexual behaviors, such as more frequent sexual partners and oral sex were also reported to be associated with increased risk of oral cancer (Heck et al., 2010). However, such results may be confounded by HPV infection status.

3.9 Controversial risk factors

Although some studies found that heredity/familial risk, marijuana (cannabis) smoking, khat (qat) chewing, nicotine replacement therapy, human immunodeficiency virus infection, and alcohol in mouthwashes were linked with higher risk of developing oral cancer, these results are controversial and further investigation is still needed to elucidate the relationship between aforementioned factors and oral cancer (Warnakulasuriya, 2009b).

4. Prevention of oral cancer

A majority of people are at greater risks of developing oral cancer as a result of exposure to tobacco and/or alcohol or betel quid. It is estimated that a billion men and 250 million women smoke cigarettes, 2 billion people consume alcohol, and 600-1,200 million people chew betel quid worldwide (Scully, 2011). Therefore, oral cancer is largely preventable by lifestyle modification. A previous study found at least three-quarters of oral cancers could be avoided by the elimination of unsafe lifestyles such as cigarette smoking and alcoholic consumption. Smoking cessation contributes to decreased risk of oral cancers, with 35% decrease in risk within 1-4 years and 80% decrease of risk by 20 years, reaching the level of those who have never smoked lifelong non-smokers (Marron et al., 2010).

The most frequently used screening method for oral cancer is visual and physical examination of oral mucosa. Many studies have demonstrated that such screening programs could detect potentially malignant and malignant lesions at very early stages. However, there is still not enough concrete evidence to conclude if screening alters disease-specific mortality in asymptomatic person seeking dental care (Rethman, et al., 2010).

Although the use of non-steroid anti-inflammatory drugs (NSAID) has been associated with a reduced risk of developing several types of cancer, no definite conclusion or consensus has been reached on the effect of NSAIDs on head and neck cancer risk. Further large-scale studies are mandatory to elucidate possible relationships between NSAIDs and head and neck cancer (Wilson et al., 2011).

5. Conclusion

Recognition of relevant risk factors for oral cancer can help physician to identify those patients at greater risk of developing oral cancer. Besides, it can help health authorities to implement effective programs to prevent oral cancer. Furthermore, it is important to educate the public about the relevant risk factors of contracting oral cancer so that those with unhealthy habits can modify their lifestyles.

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Oral cancer is a significant public health challenge globally. Although the oral cavity is easily accessible, early diagnosis remains slow compared to the enhanced detection of cancers of the breast, colon, prostate, and melanoma. As a result, the mortality rate from oral cancer for the past four decades has remained high at over 50% in spite of advances in treatment modalities. This contrasts with considerable decrease in mortality rates for cancers of the breast, colon, prostate, and melanoma during the same period. This book attempts to provide a reference-friendly update on the etiologic/risk factors, current clinical diagnostic tools, management philosophies, molecular biomarkers, and progression indicators of oral cancer.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

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Unit 405, Office Block, Hotel Equatorial Shanghai
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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