Università degli Studi di Sassari
Scuola di Dottorato di ricerca in
Scienze biomediche
XXV ciclo

"DENTAL PATIENTS' KNOWLEDGE, ATTITUDES, AND BEHAVIORS RELATED TO ORAL CANCER. THE NEED OF A NATION-WIDE ORAL CANCER PREVENTION PROGRAM"

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To my mom and dad…

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CHAPTER 1: INTRODUCTION

Head and neck cancers are a heterogeneous group of cancers that arise from the mucosa of the larynx, pharynx, oral cavity, nasal cavity and paranasal sinuses. The majority of these epithelial malignancies are squamous cell carcinoma of the head and neck (HNSCC) and the histologic grade can vary from well-differentiated keratinising to undifferentiated non-keratinising. Most of head and neck cancers are attributable to the combination of cigarette smoking and alcohol drinking. Recent studies have implicated HPV infection as an independent risk factor for HNSCC(D'Souza, et al., 2007; Gillison, et al., 2000).

Almost 640,000 cases of head and neck cancer (including 262,861 oral cavity cancers, 151,219 laryngeal cancers, and 220,119 pharyngeal cancers) and 360,000 cancer deaths occur worldwide each year(Ferlay, et al., 2010). Oral pharyngeal cancer is the most common cancer in South Asia. According to the World Health Organization, approximately 37% (146,669 cases) of the newly diagnosed cases occurred in India, Pakistan, and Bangladesh. The high incidence of oral cancer in South Asia is attributed to the use of areca products, indigenous tobacco products, and chewing tobacco(Cogliano, et al., 2004; Muwonge, et al., 2008). In Europe, oral and pharyngeal cancer together is the seventh

most common cancer and is commonly diagnosed in the sixth and seventh decades of a person's life, with the highest prevalence rates occurring in patients over 65 years of age (de Camargo Cancela, et al., 2010). Though the magnitude of oral cancer is lower Europe compared to several other developing countries, the incidence rates have risen during the twentieth century, especially among young individuals (Warnakulasuriya, Mak, & Moller, 2007). The highest incidence of oral cancer was observed in France whereas the northern regions of Italy, Germany, Portugal, Spain, and Switzerland have reported intermediate rates compared with other European countries. Oral cavity cancer incidence rates for Italian men are 3.7 per 100,000 (CI 3.5-3.9) and 1.3 (CI 1.2-1.4) for women. The overall age-standardized mortality rate from oral and pharyngeal cancer in Italy is for man 4.3 per 100,000 and 1.0 per 100,000 for women(Garavello, et al., 2010).

Frequently, patients with early-stage cancer present with only vague symptoms and minimal physical findings; early identification of signs and symptoms of both oral potentially premalignant disorders and HNSCC may decrease the burden associated with this disease. Several screening methods have been proposed for early detection in the last decades (Patton, Epstein, & Kerr, 2008), but they do not seem to improve

diagnostic accuracy nor help the clinicians in the diagnostic process. Undetected potentially malignant disorders can progress to cancer and affect the quality of life of the patient. Although oral cancers are more clinically visible and accessible than most other cancers, they are detected and diagnosed at advanced clinical stages (Maryland Department of Health and Mental Hygiene, 2003). This is due to three main causes. First, there are gaps in knowledge and practices among dentists and other healthcare providers relating to oral cancer prevention and early detection (Yellowitz et al., 1998; Horowitz et al., 2000; Yellowitz et al., 2000). Second, there is no standard screening recommendation for oral cancer, as there is for other cancers such as breast, cervical, and colorectal (American Dental Association, 2010; American Cancer Society, 2008; Rethman et al., 2010). Finally, there is a lack of knowledge among the public of the risk factors for oral cancer, as well its signs and symptoms (Horowitz et al., 1998). Thus, the frequency at which patients are screened for oral cancer varies among dentists. Despite the multiple treatment options available and the continuous progress in therapy the prognosis for advanced HNSCC patients remains poor. The 5-year survival rate of late-stage disease is only 20% and that of early stage is approximately 80%(Ries LAG, 2008). The five-year survival rate varies

widely by stage at the time of diagnosis. It ranges from 81.8 percent for patients diagnosed at a localized (early) stage, to 52.1 percent for patients with regional lymph node involvement, to 26.5 percent for patients with distant metastasis (Horner et al., 2009). The majority of oral cancer cases can most likely be prevented with modification of risky health behaviors. Most cases of oral cancer are attributable to modifiable risk factors, specifically tobacco use and alcohol consumption. The combined use of alcohol and tobacco use, multiplies the risk. Also, the risk of oral cancer increases with the amount of alcohol consumed and is highest among heavy alcohol users. As such, education regarding oral cancer risk factors and behavioral modifications based of this knowledge has the potential to modify these trends.

Health educators have widely used formative research techniques to create effective interventions that target a specific community (Ayala & Elder, 2001). Formative research is research prior to implementation of a program and helps researchers to: (1) understand the target population's needs and (2) create a program specific to these needs (Bloom, Hastings & Madaus, 1971; Cronbach, 1963; Scriven, 1967; Thiagarajan, Semmel & Semmel, 1974). This type of research helps to form tailored health communication designed to reach specific segments of the population.

Since formative research is such a valuable health education research tool, it is appropriate to use for the specific task of understanding dental patients' knowledge, attitudes, perceptions, motivations, and behaviors related to the use of alcohol, tobacco, and the risk of developing oral cancer. Applying formative research methodologies in this context will allow the researcher to generate unique insights about the target population. Information provided by research participants can be used to inform the development of specifically focused messages and program strategies for prevention, early detection and treatment programs that may be effective in reducing oral cancer risk behaviors.

Problem statement

This investigation sought to assess as to investigate patients' knowledge regarding oral cancer risk factors and to explore communication and health messaging between clinicians and patients attending dental departments within Italian university hospitals. Results served as formative research to inform a health education intervention. Specifically, the study aimed to answer the following research questions:

1. What is the oral cancer knowledge among Italian dental patients?
2. Do patients know that early detection means better prognosis?
3. Are patients aware of the signs, symptoms and risk factors for

oral cancer?

4. What are the trends of alcohol and tobacco use among Italian dental patients?
5. Do dentist influences patients' risky behaviors associated with oral cancer?
6. Do dentist counsel their patients on oral cancer?

Rationale for this Project

In the past decade, Italy has made progress in its oral cancer prevention initiatives. Measures of this progress include a decrease in the oral cancer mortality rate, an increase in the number of adults age 40 and over that report having an oral cancer examination in the past year, and an increase in the number of adults age 40 and over that report ever having an oral cancer examination in their lifetime.

However, there is still more work to be done in providing oral cancer education and oral cancer screening. Dentists have the great opportunity to counsel their patients about risk factors for oral cancer and are in the best position to screen patients for oral cancer signs and symptoms because they see their patients relatively frequently and regularly. Regular screening examinations increase the chances of detecting oral cancers at early stages (Horowitz et al., 1996). Therefore this study aimed to

investigate patients' knowledge regarding oral cancer risk factors and to explore communication and health messaging between clinicians and patients attending Dental Departments within Italian University hospitals.

Definition of Terms

Oral Cancer. It is a cancer that forms in tissues of the oral cavity. The oral cavity includes the tongue, floor of mouth, the lining inside the lips and cheeks, gingiva, hard palate, and salivary glands. *The oropharynx includes the* back one-third of the tongue, the soft palate (back of the mouth), the tonsils, the back of the throat, and the walls of the pharynx (University of Maryland Medical Center, 2010).

Oral Cancer Risk Factors. The primary risk factors for oral cancer are: past and present consumption of tobacco and alcohol products; exposure to ultraviolet radiation (increases risk of lip cancer); exposure to viruses such as Human papillomavirus (increases risk of oropharyngeal cancer; no data available for oral cavity only); low consumption of fruits and vegetables; and, age older than 45 years (American Cancer Society, 2010a).

Oral Cancer Signs and Symptoms. In early stages, oral cancer does not cause pain or discomfort and it may be difficult to see. The early signs and

symptoms of oral cancer include a sore in the mouth that bleeds easily or does not heal (most common symptom) or a persistent white or red patch on the gums, tongue, tonsil, or lining of the mouth (American Cancer Society, 2010b).

Potentially premalignant disorders of the oral cavity*

Oral leukoplakia

According to the original 1978 WHO definition leukoplakia is defined as “a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer”. During the following years other definitions have been proposed, however the one of WHO is still used today.

The pooled prevalence estimated for oral leukoplakia was between 1.49% and 4.27% (Petti, 2003).

Leukoplakia may affect any site of the oral cavity. Clinical different types of leukoplakia in order of increasing severity are homogeneous, non-homogeneous and verrucous type. The homogeneous type is usually thin, flat and uniform white in color. The non-homogeneous is a both white and red lesion that may be either nodular or flat (van der Waal, 2010). Proliferative verrucous leukoplakia is defined by its progressive clinical course, changing clinical and histopathological features, and potential to

develop into cancer. Verrucous leukoplakia is a more aggressive lesion with a malignant transformation in nearly 74% of cases (Bagan, Scully, Jimenez, & Martorell, 2010). Also large size (>200 mm^2) and tongue and floor of the mouth location increases the risk of malignant transformation (Lee, et al., 2006; Roed-Petersen, 1971) (Holmstrup, Vedtofte, Reibel, & Stoltze, 2006). Patients are usually asymptomatic. Consensus on therapy approaches and management of oral leukoplakia still remain unclear. However various treatment procedures have been reported such as surgical interventions, including laser therapy and cryotherapy, vitamin A, vitamin C, retinoids beta and carotene (Lodi, Sardella, Bez, Demarosi, & Carrassi, 2006; Ribeiro, Salles, da Silva, & Mesquita, 2010).

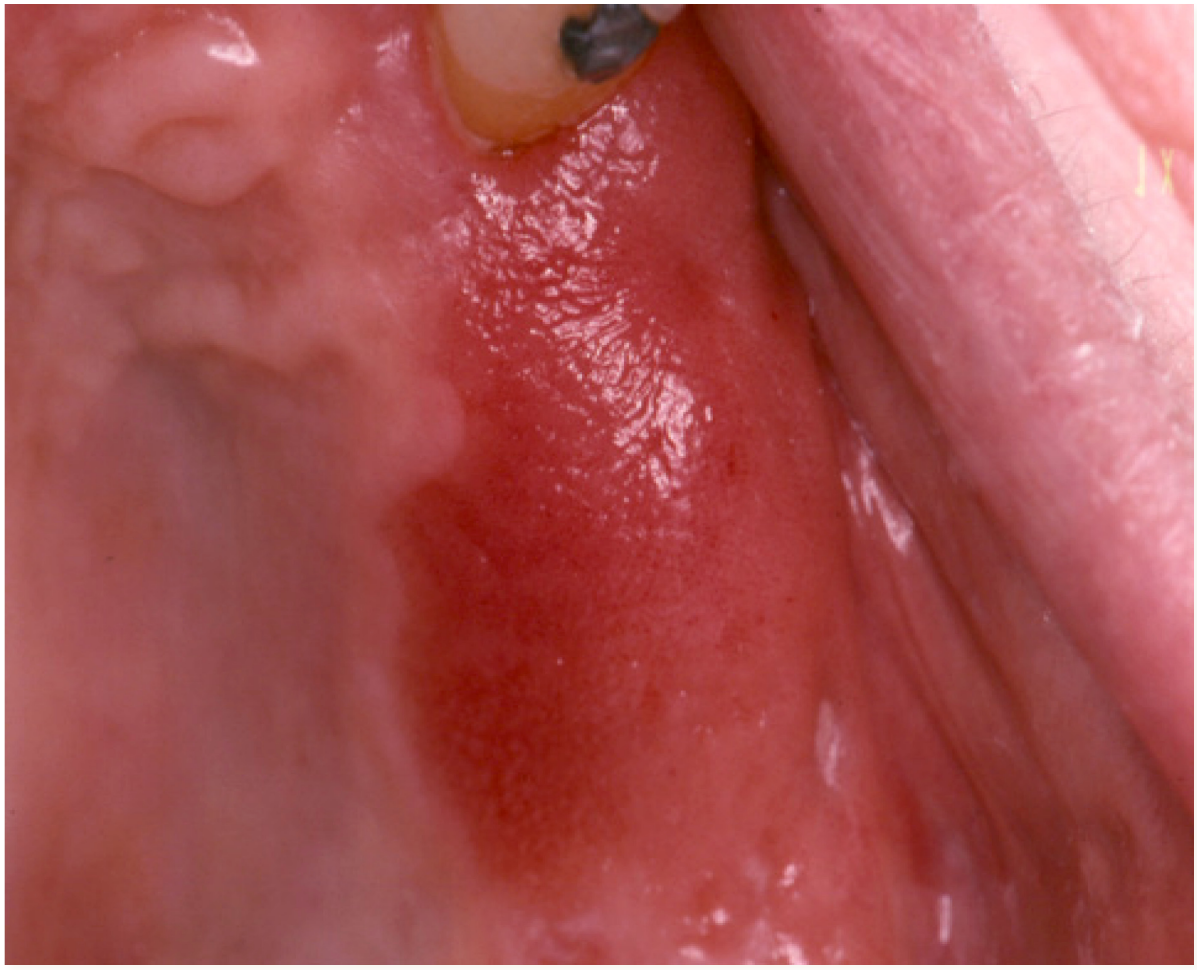
Oral leukoplakia of the ventral tongue

Oral erythroplakia

Erythroplakia is an uncommon, severe disease, defined a “any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterized clinically or pathologically as any other recognizable condition”. Reported prevalence varies between 0.02% and 0.083%.

Clinically it can be depressed or flat and predominately occurs in the floor of the mouth, the soft palate, the ventral tongue and the tonsillar fauces.

Erythroplakia is often asymptomatic, although some patients may complain of a burning sensation, sore. Alcohol and tobacco are known to be important etiological factors. Surgical excision is the treatment of choice though more studies are needed(Hashibe, et al., 2000; Reichart & Philipsen, 2005).



Oral erythroplakia of the hard palate

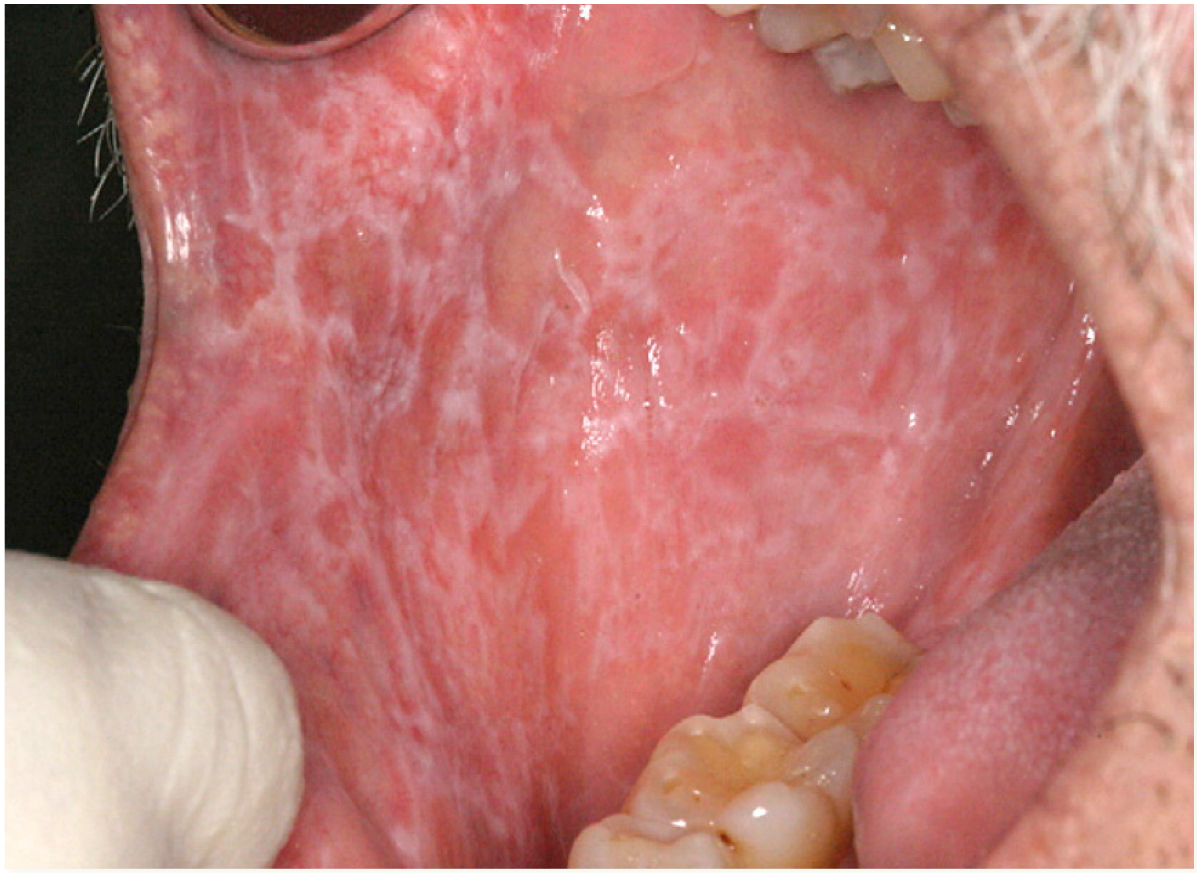
Oral lichen planus

Lichen planus is an inflammatory disease of unknown etiology that mostly affects the oral mucosa, but it may also involve other the skin or other mucosa. Its prevalence is still unknown, but it is estimated to occur in <1% of the population(Carrozzo & Thorpe, 2009). Oral lichen planus (OLP) may occur in any mucosal surface, including the lips, but most frequently affects the buccal mucosa. These lesions are often present on both right and left cheek mucosa.

OLP may manifest in one of three clinical forms: 1) reticular (keratotic configurations); 2) atrophic (keratosis is combined with erythematous changes); and 3) erosive (ulcerated or bullous)(Sousa & Rosa, 2008).

Symptoms can range from none to extremely painful lesions with difficulties in eating and thus affecting the quality of life.

Avoidance of potential precipitating drugs, tobacco, alcohol, and local trauma, as well as good oral hygiene, is essential. Topical steroids are efficacious medication to control signs and symptoms. Systemic steroids should be limited to the short-term cure of severe refractory OLP. Life-long clinical follow-up, at least annually, is fundamental(Scully & Carrozzo, 2008).



Oral lichen planus of the buccal mucosa

Oral submucous fibrosis

Oral submucous fibrosis (OSF) is an irreversible and rare premalignant disorder. The WHO definition defined OSF as " a slowly progressive disease in which fibrous bands form in the oral mucosa, ultimately leading to severe restriction of the mouth including the tongue".

It is more frequent in Southeast Asia (especially in India) and South Africa(Angadi & Rao, 2010). It may affect any site of the oral and oropharyngeal cavity and esophagus. Patients reported trismus, a burning sensation and stiffening of the oral mucosa. OSF is particularly associated with areca nut chewing, the main component of betel quid and is recognized for its malignant potential. No treatments have proven to be effective, although some surgical and conservative interventions may be beneficial. Treatment modalities of OSF are currently based on disease severity (Aziz, 2010).

Common indicators of later stages of the disease are: pain in the mouth that doesn't go away (also very common); a sore throat or a feeling that something is caught in the throat that doesn't go away; trouble chewing or swallowing; trouble moving the jaw or tongue; numbness of the tongue or other area of the mouth; swelling of the jaw that causes dentures to fit

poorly or become uncomfortable; loosening of the teeth or pain around the teeth or jaw; voice changes; a lump or mass in the neck; weight loss; and, persistent bad breath. It is important to see a physician or dentist if any of these conditions are present and lasts more than two weeks (American Cancer Society, 2010b).

Oral submucous fibrosis

Adjunctive screening techniques

A variety of diagnostic aids and adjunctive techniques used to assist in the screening of healthy patients or to assess abnormal oral lesions.

In 1951 the United States Commission of Chronic Illness defined screening as "the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures to sort out who probably have a disease from those who probably do not”("Commission on Chronic Illness. Chronic illness in the United States. Vol I. ," 1957). Cancer screening may result in the detection of both premalignant lesions as well as cancer at an early stage. Head and neck cancer screening activities aim to break the multi-step progression model that leads to cancer. The performance of screening tests is usually measured in terms of specificity, sensitivity, negative-predictive values (NPV) and positive-predictive values. A good screening test should be safe, non-invasive, have a high sensitivity and specificity and preferably detect precursor lesions(Lingen, Kalmar, Karrison, & Speight, 2008). Currently recommended screening methods are the mammogram for breast cancer, the prostate-specific antigen (PSA) test for prostate cancer, the Papanicolaou (PAP) test for cervical cancer and the fecal occult blood

testing (FOBT) for colorectal cancer(Smith, Cokkinides, Brooks, Saslow, & Brawley, 2010).

Visual and tactile examination is the most common tool available for clinicians and may result in detection of oral cancers at early stages of development (stages I and II). Other adjunctive screening aids have been described in the last decades. These include 1) vital staining, 2) brush biopsy, 3) devices based on autofluorescence, 4) devices based on chemiluminescence and 5) biomarkers assessment. Vital stainings, brush biopsy and visualization adjuncts are portable tools for the clinicians and easy to use.

Conventional oral examination

The conventional oral examination consists of a thorough head, neck and intraoral examination, with examination of the cervical lymph nodes and visual examination and palpation of the oral mucosal surfaces ("Perform a death-defying act. The 90-second oral cancer examination," 2001).

Vital Staining

Toluidine blue is a metachromatic dye that stains mitochondrial DNA, cells with greater-than-normal DNA content or altered DNA in dysplastic and malignant cells. The dye may also stain active inflammatory lesions and will be mechanically retained on the dorsum of the tongue, in dental

plaque, and in mucosal ulcerations. The staining technique involves applying a 1 percent aqueous toluidine blue dye to the suspicious lesion for approximately 30 seconds, followed by a tap water rinse. The lesion is then lightly blotted with 1 percent acetic acid to reduce the background level of staining. Only positive areas will retain stain after this decolorization process(Epstein, Sciubba, Silverman, & Sroussi, 2007).

Brush Biopsy

Oral brush biopsy was introduced in 1999. A commercially available device is a computer-assisted method of analysis of the oral brush biopsy in the detection of precancerous and cancerous lesions of the oral mucosa. The kit consists of a glass slide, fixative, and an oral brush biopsy instrument that is used to obtain a transepithelial specimen. The collected sample is spread onto the glass slide and bathed with the liquid, ethanol-based fixative. The slide is sent to laboratories where it is scanned to detect potentially abnormal cells(Sciubba, 1999).

Devices based on chemiluminescence

Chemiluminescent light is used to visualize the oral cavity after rinsing the mouth with 1% dilute acid acetic to remove debris. This highlight dysplastic lesions as acetowhite regions(McIntosh, McCullough, & Farah, 2009).

Devices based on autofluorescence

Tissue is illuminated with a light source and images of the fluorescence produced in the tissue and altered by absorption and scattering events are recorded using a camera. The presence of disease changes the concentration of the fluorophores as well as the light scattering and absorption properties of the tissue. The autofluorescence spectroscopy system consists of a light source that excites the tissue through a fiber and the fluorescence produced in the tissues is analyzed by a spectrograph. The recorded spectra can be saved to a computer, which allows mathematical spectral analysis (Drezek, et al., 2001; Perform a death-defying act. The 90-second oral cancer examination," 2001).

A recent diagnostic aid for the detection of oral precancer and cancer combines fluorescence and reflectance spectroscopy.

Screening methods-studies

Several studies have been done looking at the value of adjunctive oral cancer and pre-cancer screening methods. The majority of these studies had small sample sizes and the largest comprised 298 patients (Svirsky, et al., 2002). Sensitivity and specificity for the detection of oral potentially malignant disorders had a wide range. Reported sensitivity for brush biopsy technique ranged from 71.4% (Poate, et al., 2004) to

100.0%(Svirsky, et al., 2002), vital staining from 57.1% (Mashberg, 1980) to 100.0%(Epstein, Silverman, Epstein, Lonky, & Bride, 2008), fluorescence from 50.0%(Mehrotra, et al., 2010) to 98.0% (Lane, et al., 2006) and chemiluminescence from 0.0% (Mehrotra, et al., 2010) to 100.0% (Ram & Siar, 2005). Similarly reported specificity ranges were 32.0%(Poate, et al., 2004) and 100.0%(Sciubba, 1999) for brush biopsy, 25% (Ram & Siar, 2005) and 76.7%(Silverman, Migliorati, & Barbosa, 1984) for vital staining, 38.9% (Mehrotra, et al., 2010) and 100.0%(Lane, et al., 2006) for fluorescence and 0.0% (Farah & McCullough, 2007)-75.5%(Mehrotra, et al., 2010) for chemiluminescence.

No large randomized-controlled methods were available for the adjunctive screening techniques. Although some studies evaluated more than one screening methods (Epstein, et al., 2008; Mashberg, 1980; Mehrotra, et al., 2010; Ram & Siar, 2005), none compared all the adjunctive screening methods together. These studies were hospital-based and suffered from several biases. Problems encountered with these screening methods included a high proportion of false-negative examinations. Also, the majority of the studies used biopsy confirmed diagnosis of dysplasia or cancer; because oral lesions had been already identified by a clinical

examination, sensitivity and specificity were overestimated and verification biased was then present.

The diagnostic aids available in commerce are not yet reliable to differentiate precancerous lesions from benign lesions such as inflammatory reactions (e.g. friction keratosis, hyperplastic lesions). Indeed, the presence of inflammation in the oral mucosa may be a confounding factor in the diagnosis of oral lesions and the biopsy remains the only available tool for a differential diagnosis. Adjunctive screening techniques would eventually reduce the amount of biopsies if they were able to show oral epithelial changes over time.

One large Indian randomized controlled trial (n= 96,517) (Sankaranarayanan, et al., 2005) evaluated the effectiveness of visual inspection of the oral cavity. The investigators reported that oral visual screening could significantly reduce mortality (32% reduction) in high-risk individuals. However, the Kerala study was found to have some methodological weaknesses (Kujan, Glenny, Oliver, Thakker, & Sloan, 2006). To date there is not enough evidence to determine whether oral screening by visual examination could reduce mortality from oral cancer and whether other adjunctive screening methods could increase clinicians' ability to differentiate between benign abnormalities and

dysplastic/malignant disorders. As such, there is an urgent need of new studies to assess whether early detection of HNSCC may eventually reduce the morbidity and mortality associated with the disease.

* Specific data and tables are available in the Appendix section of the present dissertation.

CHAPTER 2: LITERATURE REVIEW

What is Oral Cancer?

Oral cancer is cancer of the lips, oral cavity and oropharynx. The oral cavity includes the tongue, floor of mouth, the lining inside the lips and cheeks, gums, hard palate, and salivary glands. The most common sites for oral cancer are: the tongue (30%), the lip (17%), and the floor of the mouth (14%) (Silverman, 2001).

In 2008, 263,861 new oral cavity cancers were diagnosed globally and about 65% of these cancers occurred in men. This accounts for approximately 2% of all new cancer diagnosed (men: 2.6%; women: 1.5%). Oral cancers cause more than 120,000 deaths each year, with a five-year survival rate of 60% (Ferlay, et al., 2010; Parkin, Bray, Ferlay, & Pisani, 2005). The mortality rate for oral cancer is higher than that of several other cancers, such as cervical cancer, Hodgkin's lymphoma, and malignant melanoma (Stahl et al., 2004). It is estimated that one American dies from oral cancer every hour (Kademani, 2007).

Historically, oral cancers were associated with men aged sixty years and older who used tobacco and alcohol products (Johnson, 2001; Blot et al., 1988). However, the epidemiological data indicates that the patient

demographic is changing. The male-to- female ratio of oral cancers has changed from 10:1 to 2:1 in the last four decades. The incidence of oral cancer in women has increased significantly, largely due to an increase in women smoking (Shiboski et al., 2000). There has been a steady increase in the incidence of oral cancers in patients younger than 40 years of age (from 0.4 to 4.0 percent) and in those without risk factors (Llewellyn et al., 2001; Schantz and Yu, 2002; Ries et al., 2006). Incidence rates are currently increasing in many places around the world, especially among younger individuals (aged less than 45 years).

Advanced Stage of Oral Cancer of the right mandibular vestibule

Early Stage of Oral Cancer of the right ventral tongue in a young adult

Risk Factors

The primary risk factors for oral cancer are: past and present use of tobacco products; excessive use of alcohol; exposure to ultraviolet radiation; low consumption of fruits and vegetables; and, age older than 45 years (American Cancer Society, 2010a). Each of these risk factors is briefly described below.

Tobacco. All forms of tobacco, including cigarettes, cigars, pipes and smokeless tobacco, have been established as causal for oral cancer. Smokers are six times more likely than non-smokers to develop oral cancer, and tobacco usage of any kind accounts for more than 75 percent of oral cancer deaths in the U.S. (Tomar, 2001). Patients who continue to smoke after diagnosis of an initial tumor have up to a six-fold greater risk of developing a second primary tumor than patients who stop smoking after diagnosis (Johnson, 2001; Blot et al., 1988). After three to five years of smoking cessation, a fifty percent reduction of risk for oral cancer risk has been observed, and within ten years of cessation, the risk returns to normal (U.S. Department of Health and Human Services, 2004; Blot et al., 1988).

***Alcohol*.** Alcohol is the second greatest risk factor for developing oral cancer (Altieri et al., 2004; Goldstein et al., 2010). Oral cancers are six times more common in drinkers than in non-drinkers and 75-80 percent of all oral cancer patients consume alcohol frequently (American Cancer Society, 2006). Studies have shown that excessive alcohol use (defined as more than twenty-one standard drinks in a week) is associated with nutrient deficiency, which is an independent risk factor for oral cancer (Blot et al., 1988). When you combine tobacco with excessive alcohol use, the risk for developing oral cancer increases by 15-fold (Tomar, 2001). This increased risk is due to the synergistic effect of alcohol and tobacco (alcohol increases the permeability of mouth tissues to tobacco carcinogens). It has been difficult to distinguish the separate effects of tobacco and alcohol because people who consume alcohol tend to use tobacco and vice versa (Blot et al., 1988). Research shows that the risk of developing oral cancer increases with both the dosage and the length of time that tobacco and alcohol products are used (Franchesi et al., 2000; Tomar, 2001).

***Hpv*.** Approximately 20-25 percent of all oral cancers occur in people who do not smoke and who only drink alcohol occasionally (Llewellyn et al.,

2003). Research suggests that the pathogenesis of oral cancer has two distinct etiologies: one through tobacco and alcohol, and another through HPV (Blot et al., 1988; D'Souza et al., 2007; Frish et al., 2000). There is a growing recognition that HPV, HPV-16 in particular, plays a role in the etiology of a subset of oral cancers called oropharyngeal cancers (D'Souza et al., 2007; Falkry and Gillison, 2006; Gillison, 2007; Frish et al., 2000). Oropharyngeal cancers appear on the tonsillar area, the base of the tongue, and the oropharynx (Falkry and Gillison, 2006). While incidence rates for most cancer sites in the oral cavity declined or remained constant in the past three decades, those for tonsillar and base-of- tongue cancers increased significantly, predominantly for Caucasian men under the age of 65 years (Frisch et al., 2000). Although the trends in incidence rates for oral cancers have mainly been attributed to population fluctuations in the use of alcohol and tobacco, the use of alcohol and tobacco in the US has largely declined since 1964, and thus cannot explain the recent increase in the incidence of tonsillar and base-of-tongue cancers (Sturgis and Cinciripini, 2007).

A recent review of the literature found that approximately 35 percent of all oral cancers are positive for HPV DNA and 90 percent of HPV positive cancers were positive for HPV-16 (Kreimer et al., 2005). Current data

indicate that oral HPV-16 infection is primarily sexually acquired and is a strong risk factor for oral cancer (Gillison, 2007; Gillison, 2008). In a recently reported case–control study, after adjustment for age, gender, alcohol, tobacco, oral hygiene, and family history of head and neck cancers, individuals seropositive for HPV-16 had a 15-fold increase in risk for oropharyngeal cancer when compared with seronegative individuals (D'Souza et al., 2007).

HPV infection may be altering the demographics of oral cancer patients, as these patients tend to be younger, nonsmokers, and nondrinkers. Patients with HPV-positive tumors appear to have an improved prognosis, at least half the risk of death, when compared with patients with HPV-negative tumors (Falkry et al., 2008). The HPV etiology of these tumors may have future clinical implications for the diagnosis, therapy, screening, and prevention of oral cancers (Falkry and Gillison, 2006). A prophylactic vaccine capable of preventing oral HPV-16 infection could likely prevent HPV- associated oral cancers. However, for vaccination against oncogenic HPV infection to have the greatest benefit it should be administered prior to the onset of sexual behavior (Gillison, 2008). Currently, vaccines targeted against oncogenic HPV infection have been indicated for use in women only. Vaccinating males against oncogenic

HPV infection may be an important approach for the prevention of oral cancer, given the incidence is higher in men (Falkry and Gillison, 2006). There are ongoing clinical trials to determine the efficacy of such vaccines in preventing genital oncogenic HPV infection in men and clinical trials to evaluate the potential for vaccines to prevent oral HPV -16 and HPV -18 infections (Falkry and Gillison, 2006).

Ultraviolet Radiation. Exposure to sunlight is the major risk factor for lip cancer.

Other factors that increase risk for lip cancer include smoking, smokeless tobacco products, and excessive alcohol use (Perea-Milla et al., 2003). The vast majority of lip cancers occur on the lower lip. Those at greater risk for lip cancer are: men (two to three times more likely to be diagnosed with lip cancer than women), fair-skinned individuals, and individuals with viruses such as HPV, herpes simplex, and acquired immunodeficiency syndrome (AIDS) (Perea-Milla et al., 2003). Vitamin deficiency may also be a contributing factor to lip cancer. Studies indicate that the vitamins found in fruits and vegetables, particularly carotene, seem to play a role in decreasing the risk for lip cancer (Pavia et al., 2006).

Low consumption of fruits and vegetables. Poor dietary practices and nutritional deficiencies have been linked to a risk of developing oral cancer, while diets rich in fruits, vegetables, and vegetable fats are inversely related to oral cancer risk (Edefonti et al., 2010; Winn, 1995). Pavia et al. (2006) conducted a meta-analysis of sixteen studies examining the effect of fruit and vegetable consumption on oral cancer and concluded that the consumption of fruits and vegetables is associated with a reduced risk of oral cancer. They found that each portion of fruit consumed per day significantly reduced the risk of oral cancer by 49 percent and that vegetable consumption showed a significant reduction in the overall risk of oral cancer by 50 percent. A second recent meta-analysis of forty case-control studies, by Lucenteforte and colleagues (2009) found that fruits and vegetables, beta-carotene, vitamin C, selected flavonoids, and whole grains were inversely related to the risk of oral cancer. The relationship between diet and risk of oral cancer is among the strongest for any malignancy. Strong and consistent inverse associations between risk of oral cancer and consumption of fruits and vegetables have been observed, after controlling for the effects of alcohol and tobacco. Oral cancer risk declined significantly as intake of raw vegetables, citrus and noncitrus fruits increased in the majority of studies. In the IARC multinational case-control study of 1670

oral cancer cases, adjustments were made for age, sex, country, education, tobacco smoking and chewing, alcohol drinking, body mass index, and caloric intake. Patients with the highest quartile of intake of fruit and vegetables had significantly lower oral cancer risk (OR 0.4, 95% CI, 0.4–0.8) than those in the lowest quartile of intake. (Kreimer AR, et al. 2006). Elevated but inconsistent oral cancer risks were observed for diets high in eggs and butter and for certain types of meats. Diets high in meat and dairy products and low in fruit and vegetables jointly increased risk for oral cancers (OR 12, 95% CI, 4.1–34.6), after consideration of alcohol and tobacco use. Specific micronutrients correlated with a diet high in fruits and vegetables, such as the antioxidant Vitamins C and E and carotenoids, were associated with decreased risk. Importantly, risk of subsequent oral cancer in- creased as serum carotenoid levels declined in a nested, case-control study. Associations with folic acid intake are less consistent. The effect of diet on oral cancer risk may be modified by other risk factors. The benefits of a diet high in fruits and vegetables was independent of primary site of the tumor, age (stratified at 60 years), and sex. Other studies that claimed the protective effect of diet extended to the non- smoker nondrinker, included former smokers and light to moderate drinkers (1–6 drinks per day) in the analysis with never-smokers and non- drinkers.

Therefore, there is currently no data to suggest that diet is associated with risk of oral cancer in the absence of alcohol and tobacco consumption. Chronic nutritional deficiency may contribute to oral cancer risk. The risk of oral cancer increased as body mass index (BMI) declined both at diagnosis, and two years prior to diagnosis. However, the influence of decreasing BMI on risk was observed predominantly among current and former smokers and drinkers. Furthermore, low BMI several years before diagnosis was associated only with risk among smokers. These data suggest that low BMI may be a biomarker of chronic nutritional deficiencies secondary to chronic alcohol and tobacco use, at least in developed countries (Gillison, ML, 2007).

Age*.* Age is a risk factor for oral cancer. Ninety-five percent of oral cancers are diagnosed in people older than 45 years, with the average age at diagnosis 60 years (Llewellyn et al., 2003).

While age is not a modifiable risk factor, the previously described risk factors are all adjustable lifestyle factors. Studies report that up to 75 percent of oral cancers could be prevented by modifying behaviors (Blot et al., 1988). Quitting tobacco and limiting alcohol use significantly lowers the risk of developing oral cancers, even after many years of use.

Avoiding unprotected sun exposure, as well as pipe and cigar tobacco can prevent lip cancers. Lastly, research shows that eating a healthy, balanced diet with at least five servings of fruits and vegetables every day may provide some protection against oral cancer (Pavia et al., 2006; Lucenteforte et al., 2009).

Incidence Rates, Mortality Rates and Trends

In Europe, oral and pharyngeal cancer together is the seventh most common cancer and is commonly diagnosed in the sixth and seventh decades of a person's life, with the highest prevalence rates occurring in patients over 65 years of age (de Camargo Cancela, et al., 2010). Though the magnitude of oral cancer is lower Europe compared to several other developing countries, the incidence rates have risen during the twentieth century, especially among young individuals(Warnakulasuriya, et al., 2007). The highest incidence of oral cancer was observed in France whereas the northern regions of Italy, Germany, Portugal, Spain, and Switzerland have reported intermediate rates compared with other European countries. Oral cavity cancer incidence rates for Italian men are 3.7 per 100,000 (CI 3.5-3.9) and 1.3 (CI 1.2-1.4) for women. The overall age-standardized mortality rate from oral and pharyngeal cancer in Italy is

for man 4.3 per 100,000 and 1.0 per 100,000 for women(Garavello, et al., 2010).

Estimated new cases and deaths from oral cancer in the United States in 2012 are: new cases (40,250 and deaths: 7,850. From 2005-2009, the median age at diagnosis for cancer of the oral cavity and pharynx was 62 years of age. Approximately 0.6% were diagnosed under age 20; 2.2% between 20 and 34; 6.1% between 35 and 44; 20.4% between 45 and 54; 28.5% between 55 and 64; 21.1% between 65 and 74; 15.1% between 75 and 84; and 6.0% 85+ years of age. The rate in men was 2.5 times greater than that in women (13.2 vs. 5.3) (National Cancer Institute, 2012). For the period 2004-2006, the oral cancer mortality rate in the U.S. was 2.5 percent, with the rate in men more than twice that in women (3.8 vs. 1.4) (Horner et al., 2006). Oral cancer incidence rates and mortality rates have declined over the past three decades in the U.S. Recent studies have shown statistically significant differences in oral cancer incidence rates and mortality rates among population subgroups, including minorities, various age groups, and between genders (Swango, 1996). For example, a study by Shiboski et al. (2000) demonstrated that although incidence rates of oral cancer have been steadily decreasing among white males, incidence rates among older black males (65 years

and older) have been increasing. This study also found that oral cancer rates among females have increased.

Kingsley et al. (2008) examined incidence and mortality data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, for each year between 1975 and 2004, to identify specific populations within the U.S. that may be at greater risk for oral cancer, as well as trends over the past three decades. They found an overall declining trend in oral cancer incidence rates over the past 30 years, with the most significant declines observed over the past ten years. Short-term trend analysis of the past five years indicates a reversal of this decline, which may signify an important development in the epidemiology of this disease. Over the past 30 years, oral cancer incidence has declined among white males (-1.21 percent), white females (-0.66 percent), black males (-1.53 percent) and black females (-1.38 percent), although these observed declines have not been uniform across time. For example, while the incidence of oral cancer among black males declined over the past 30 years, temporal stratification of these data revealed that this decline was greatest over the past five years (-6.64 percent). This stratification also revealed the incidence of oral cancer among black females rose from - 1.38 percent over the entire 30 year period, to +3.18

percent during the most recent five- year period. Their analysis showed that incidence rates are continuing to decline in all states, except four (Nevada, Idaho, North Dakota and North Carolina) in which the rates are increasing.

Mortality rates also declined over the past 30 years for all groups. The rates of decline were: white males (-2.16 percent), white females (-1.62 percent), black males (-1.92 percent) and black females (-1.71 percent). More specific temporal analysis of the data revealed two distinct trends. First, decreases in mortality rates were greatest over the last ten-year period compared to the last 30 years, and the decreases were much less pronounced over the more recent five-year period. The second trend, found only among white males, revealed that mortality rates, although still declining, were declining by ever-smaller amounts over each time period: 30 years (-2.16 percent), 10 years (-1.83 percent), and five years (-0.33 percent).

The five-year survival rate is another important measure of the burden of oral cancer. Overall, 60 percent of people with oral cancer survive for five years after diagnosis, an increase of approximately 15 percent since the 1960's (Reis et al., 2006). While the increase in the five-year survival rate is measurable progress against this disease, this rate is still very low and

significant disparities remain between some population groups. See Section 2.5 for a discussion of disparities among different groups.

There are a few other epidemiological trends to note. From 1973 through 1996, white men and women showed an overall decrease in age-adjusted incidence rates of cancer of the lip and floor of the mouth (Shiboski et al., 2000). This is likely due to the increased awareness of the damaging effects of prolonged exposure to sunlight and the use of sunscreens for protection (Reis et al., 2000). However, there was a significant increase in age-adjusted incidence rate of tongue cancer over the same period, especially among whites aged 35 to 39 years (Shiboski et al., 2000).

Stage at Diagnosis

Like most other cancers, the prognosis for those diagnosed with oral cancer depends largely on the clinical stage of the tumor at diagnosis. The American Joint Committee on Cancer (2010) describes cancers according to tumor size, cancer location, and cancer extent (how far it has spread). Oral cancers are categorized as follows:

- *Stage I.* The cancer is less than two centimeters in size, and has not spread to lymph

  nodes in the area.

- *Stage II***.** The cancer is more than two centimeters in size, but less than four

centimeters, and has not spread to lymph nodes in the area.

- *Stage III*. Either of the following may be true: The cancer is more than four

centimeters in size, or the cancer is any size but has spread to only one lymph node on the same side of the neck as the cancer. The lymph node that contains cancer measures no more than three centimeters.

- *Stage IV*. Any of the following may be true: The cancer has spread to tissues around the lip and oral cavity. The lymph nodes in the area may or may not contain cancer. The cancer is any size and has spread to more than one lymph node on the same side of the neck as the cancer, to lymph nodes on one or both sides of the neck, or to any lymph node that measures more than six centimeters. The cancer has spread to other parts of the body.

Stage I and Stage II cancers are at a localized stage, Stage III cancers are classified as tumors with regional metastasis and Stage IV cancers are classified as tumors with distant metastasis.

Although oral cancers are more clinically visible and accessible than most other cancers, they are detected and diagnosed at advanced clinical

stages (Stages III and IV)(Maryland Department of Health & Mental Hygiene, 2003). In the U.S., only one third of oral cancers are diagnosed at a localized stage (Reis et al., 2009). For 2000-2007, 34.7 percent of oral cancers were diagnosed at a localized stage, 44 percent were diagnosed at a regional stage, 13.9 percent were diagnosed at a distant stage, and 7.4 percent were diagnosed at an unknown stage (Altekruse et al., 2010).

When oral cancers are found in early stages, the survival rate is greater than 80 percent, while cancers found in late stages have five- and ten-year survival rates of 60 percent and 49 percent, respectively (American Cancer Society, 2009). These long-term survival rates have not changed significantly in the last three decades (Reis et al., 2009). The five-year survival rate varies widely by stage at the time of diagnosis. It ranges from 81.8 percent for patients diagnosed at a localized stage, to 52.1 percent for patients with regional lymph node involvement, to 26.5 percent for patients with distant metastasis (Horner et al., 2009).

The location of oral cancers also affects the five-year survival rates. In the U.S., for 1988-2006, the relative five-year survival rate by oral cancer site is as follows: lip (93.9 percent), tongue (74.6 percent), salivary gland (74.6 percent), floor of mouth (53.2 percent), gingiva/other Mouth (60.3

percent), and oropharynx and tonsil (54.2 percent). The ten-year survival rate is significantly lower for cancers of the tongue, floor of mouth and oropharynx and tonsil: lip (88.0 percent), tongue (46.6 percent), salivary gland (70.5 percent), floor of mouth (38.7 percent), gum and other mouth (49.0 percent), and oropharynx and tonsil (44.2 percent) (Fast Stats, 2010).

Treatment

Early stages of oral cancer (stage I and stage II) are highly curable by surgery and/or by radiation therapy, and the choice of treatment is dictated by the anticipated functional and cosmetic results of treatment and by the availability of the particular expertise required of the surgeon or radiation oncologist for the individual patient (Cummings CW, 1998; Wang CC, 1997). The presence of a positive margin or a tumor depth of more than 5 mm significantly increases the risk of local recurrence and suggests that combined modality treatment may be beneficial. Advanced cancers (stage III and stage IV) of the lip and oral cavity represent a wide spectrum of challenges for the surgeon and radiation oncologist. Except for patients with small T3 lesions and no regional lymph node and no distant metastases or who have no lymph nodes larger than 2 cm in

diameter, for whom treatment by radiation therapy alone or surgery alone might be appropriate, most patients with stage III or stage IV tumors are candidates for treatment by a combination of surgery and radiation therapy. Moreover, because local recurrence and/or distant metastases are common in this group of patients, they should be considered for clinical trials. Such trials evaluate the potential role of radiation modifiers or combination chemotherapy combined with surgery and/or radiation therapy. Patients with head and neck cancers have an increased chance of developing a second primary tumor of the upper aerodigestive tract. A recent study has shown that daily treatment of these patients with moderate doses of isotretinoin (13-cis-retinoic acid) for 1 year can significantly reduce the incidence of second tumors. No survival advantage has yet been demonstrated, however, in part due to recurrence and death from the primary malignancy (Papadimitrakopoulou VA, 2008; Van der Tol IG, 1999). An additional trial has shown no benefit of retinyl palmitate or retinyl palmitate plus beta-carotene when compared to retinoic acid alone. The rate of curability of cancers of the lip and oral cavity varies depending on the stage and specific site. Most patients present with early cancers of the lip, which are highly curable by surgery or by radiation therapy with cure rates of 90% to 100%. Small cancers of

the retromolar trigone, hard palate, and upper gingiva are highly curable by either radiation therapy or surgery with survival rates of as much as 100%. Local control rates of as much as 90% can be achieved with either radiation therapy or surgery in small cancers of the anterior tongue, the floor of the mouth, and buccal mucosa. Moderately advanced and advanced cancers of the lip also can be controlled effectively by surgery or radiation therapy or a combination of these. The choice of treatment is generally dictated by the anticipated functional and cosmetic results of the treatment. Moderately advanced lesions of the retromolar trigone without evidence of spread to cervical lymph nodes are usually curable and have shown local control rates of as much as 90%; such lesions of the hard palate, upper gingiva, and buccal mucosa have a local control rate of as much as 80%. In the absence of clinical evidence of spread to cervical lymph nodes, moderately advanced lesions of the floor of the mouth and anterior tongue are generally curable with survival rates of as much as 70% and 65%, respectively (www.cancer.gov).

Prevention and Early Detection

A comprehensive oral cancer examination is the primary method used to detect oral cancer. During the examination, which can be completed in

less than five minutes, the healthcare provider inspects and palpates the head, neck and oral cavity (American Cancer Society, 2008). The American Cancer Society (2008) recommends that primary care doctors and dentists examine the mouth and throat as part of a routine cancer-related checkup. Routine checkups provide the opportunity to see abnormal tissue changes and to detect cancer at a localized stage. A recent editorial published on Lancet (Mignogna et al., 2005) claimed the clinical oral examination to be an effective tool to 'save life' from oral cancer.

Only one third of all oral cancers are detected and diagnosed at a localized stage (Altekruse et al., 2010). There are three principal reasons for this low rate of early diagnosis. First, there are gaps in knowledge and practices among dentists and other healthcare providers relating to oral cancer prevention and early detection (Yellowitz et al., 1998; Horowitz et al., 2000; Yellowitz et al., 2000). Second, there is no standard screening recommendation for oral cancer, as there is for other cancers such as breast, cervical, and colorectal (American Cancer Society, 2008; American Dental Association, 2010; Rethman et al., 2010). And third, there is a lack of knowledge among the public of the risk factors for oral cancer, as well its signs and symptoms. The public also lacks knowledge

that an oral cancer exam exists, and therefore they do not even know to ask for one (Horowitz et al., 1998).

Screening

Screening In 1951 the United States Commission of Chronic Illness defined screening as "the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures to sort out who probably have a disease from those who probably do not". Cancer screening may result in the detection of both premalignant lesions as well as cancer at an early stage. Head and neck cancer screening activities aim to break the multi-step progression model that leads to cancer. The performance of screening tests is usually measured in terms of specificity, sensitivity, negative-predictive values (NPV) and positive-predictive values. A good screening test should be safe, non-invasive, have a high sensitivity and specificity and preferably detect precursor lesions. Currently recommended screening methods are the mammogram for breast cancer, the prostate-specific antigen (PSA) test for prostate cancer, the Papanicolaou (PAP) test for cervical cancer and the fecal occult blood testing (FOBT) for colorectal cancer. Visual and tactile examination is the most common tool available for clinicians and

may result in detection of oral cancers at early stages of development (stages I and II). Other adjunctive screening aids have been described in the last decades. These include 1) vital staining, 2) brush biopsy, 3) devices based on autofluorescence, 4) devices based on chemiluminescence and 5) biomarkers assessment. Vital stainings, brush biopsy and visualization adjuncts are portable tools for the clinicians and easy to use. Conventional oral examination The conventional oral examination consists of a thorough head, neck and intraoral examination, with examination of the cervical lymph nodes and visual examination and palpation of the oral mucosal surfaces. Vital Staining Toluidine blue is a metachromatic dye that stains mitochondrial DNA, cells with greater-than-normal DNA content or altered DNA in dysplastic and malignant cells. The dye may also stain active inflammatory lesions and will be mechanically retained on the dorsum of the tongue, in dental plaque, and in mucosal ulcerations. The staining technique involves applying a 1 percent aqueous toluidine blue dye to the suspicious lesion for approximately 30 seconds, followed by a tap water rinse. The lesion is then lightly blotted with 1 percent acetic acid to reduce the background level of staining. Only positive areas will retain stain after this decolorization process63. Brush Biopsy Oral brush biopsy was introduced in 1999. A commercially

available device is a computer-assisted method of analysis of the oral brush biopsy in the detection of precancerous and cancerous lesions of the oral mucosa. The kit consists of a glass slide, fixative, and an oral brush biopsy instrument that is used to obtain a transepithelial specimen. The collected sample is spread onto the glass slide and bathed with the liquid, ethanol-based fixative. The slide is sent to laboratories where it is scanned to detect potentially abnormal cells. Devices based on chemiluminescence Chemiluminescent light is used to visualize the oral cavity after rinsing the mouth with 1% dilute acid acetic to remove debris. This highlight dysplastic lesions as acetowhite regions65. Devices based on autofluorescence Tissue is illuminated with a light source and images of the fluorescence produced in the tissue and altered by absorption and scattering events are recorded using a camera. The presence of disease changes the concentration of the fluorophores as well as the light scattering and absorption properties of the tissue. The autofluorescence spectroscopy system consists of a light source that excites the tissue through a fiber and the fluorescence produced in the tissues is analyzed by a spectrograph. The recorded spectra can be saved to a computer, which allows mathematical spectral analysis. A recent diagnostic aid for the detection of oral precancer and cancer combines fluorescence and

reflectance spectroscopy. Screening methods-studies Several studies have been done looking at the value of adjunctive oral cancer and pre-cancer screening methods. The majority of these studies had small sample sizes and the largest comprised 298 patients. Sensitivity and specificity for the detection of oral potentially malignant disorders had a wide range. Reported sensitivity for brush biopsy technique ranged from 71.4%68 to 100.0%, vital staining from 57.1% to 100.0%, fluorescence from 50.0% to 98.0% and chemiluminescence from 0.0% to 100.0%. Similarly reported specificity ranges were 32.0%68 and 100.0%64 for brush biopsy, 25% and 76.7% for vital staining, 38.9% and 100.0% for fluorescence and 0.0%-75.5% for chemiluminescence. No large randomized-controlled methods were available for the adjunctive screening techniques. Although some studies evaluated more than one screening methods, none compared all the adjunctive screening methods together. These studies were hospital-based and suffered from several biases. Problems encountered with these screening methods included a high proportion of false-negative examinations. Also, the majority of the studies used biopsy confirmed diagnosis of dysplasia or cancer; because oral lesions had been already identified by a clinical examination, sensitivity and specificity were overestimated and verification biased was

then present. The diagnostic aids available in commerce are not yet reliable to differentiate precancerous lesions from benign lesions such as inflammatory reactions (e.g. friction keratosis, hyperplastic lesions). Indeed, the presence of inflammation in the oral mucosa may be a confounding factor in the diagnosis of oral lesions and the biopsy remains the only available tool for a differential diagnosis. Adjunctive screening techniques would eventually reduce the amount of biopsies if they were able to show oral epithelial changes over time. One large Indian randomized controlled trial (n= 96,517) evaluated the effectiveness of visual inspection of the oral cavity. The investigators reported that oral visual screening could significantly reduce mortality (32% reduction) in high-risk individuals. However, the Kerala study was found to have some methodological weaknesses. To date there is not enough evidence to determine whether oral screening by visual examination could reduce mortality from oral cancer and whether other adjunctive screening methods could increase clinicians' ability to differentiate between benign abnormalities and dysplastic/malignant disorders. As such, there is an urgent need of new studies to assess whether early detection of HNSCC may eventually reduce the morbidity and mortality associated with the disease.

Dentists' Knowledge, Opinions & Practices Relating to Oral Cancer

Knowledge

To conduct comprehensive oral cancer screening examinations and provide patients with appropriate information about oral cancer risk factors, dentists' knowledge must be accurate and current. Previous studies indicate that there are gaps in dentists' knowledge of the risk factors and signs and symptoms of oral cancer (Yellowitz et al., 1998; Horowitz et al., 2000; Yellowitz et al., 2000). A national study by Yellowitz et al. (2000) found that almost all dentists correctly identified patients' tobacco use (99.7 percent), having a prior oral cancer lesion (96.4 percent) and alcohol use (92.7 percent) as risk factors for oral cancer. However, only one-third of the dentists knew that oral cancers are most often diagnosed in patients 60 years of age or older and that low consumption of fruits and vegetables is a risk factor. Their assessment of dentists' knowledge of oral cancer diagnostic procedures found that 83 percent of dentists knew that squamous cell carcinoma is the most common type of cancer, 81 percent identified all of the procedures for examining the tongue for oral cancers, and 80 percent recognized that an early oral cancer lesion usually is a small, painless red area. But, only 54 percent knew the two most common sites of intraoral cancer are the

tongue and floor of the mouth, and only 37 percent knew that the two lesions most likely to be associated with oral cancer are erythroplakia and leukoplakia. If dentists do not know what to look for or where to look, their ability to detect and diagnose oral cancers at an early stage is diminished (Horowitz et al., 2000).

To measure dentists' knowledge, the researchers created two indices (Horowitz et al., 2000; Yellowitz et al., 2000); one measured knowledge of oral cancer risk factors and the other measured knowledge of oral cancer diagnostic procedures (Horowitz et al., 2000). Based on the number of correct responses to survey questions, dentists were categorized into one of three categories: high score, medium score or low score. To identify patterns of knowledge of oral cancer risks and diagnostic procedures, they cross- classified dentists on each of these two indices. They found that only 12 percent of dentists had a high score on both indices. With only 12 percent of dentists having a high knowledge of both oral cancer risk factors and diagnostic procedures, it is possible that a significant percentage of dentists may not recognize or find potentially cancerous lesions (Horowitz et al., 2000).

The authors also evaluated the effects of four background characteristics on dentists' levels of knowledge about oral cancer risk factors and

diagnostic procedures. The four background characteristics were: gender, type of practice, year of dental school graduation and the interval since their last oral cancer Continuing Education (CE) course. Many of their findings are not surprising. Recency of graduation had a consistent effect on the likelihood of getting a high score on each knowledge index. Compared with dentists who graduated before 1970, each of the three younger graduate cohorts was increasingly more likely to get a high score on each knowledge index. Dentists who had never taken an oral cancer CE course were two times less likely to get a high score on both knowledge indices than were dentists who had taken an oral cancer CE course within the past 12 months. Increased emphasis on oral cancer in dental school curricula, an outcome of this early research, may be in part responsible for this increased knowledge of oral cancer among more recent graduates (Horowitz et al., 1998; Horowitz et al., 2000; Maryland Department of Health & Mental Hygiene, 2003). The authors concluded that the correlation between the recency of graduation and dentists' levels of knowledge of risk factors and diagnostic procedures for oral cancer suggested that dental schools provide adequate coverage of oral cancer. However, they suggested CE courses were needed to help earlier graduates update their knowledge of oral cancer risk factors and

diagnostic procedures.

Practices

This same national survey also evaluated dentists' practices relating to screening for risk factors when taking a medical history and the provision of oral cancer examinations (Horowitz et al., 2000; Yellowitz et al., 2000). The researchers found that when assessing a patients' risk for oral cancer, 91 percent of dentists asked about the patients' cancer history, and 65 percent asked about the patient's family history of cancer. Ninety percent asked about present tobacco use, 77 percent asked about past tobacco use and 72 percent asked about the types and amount of tobacco products used. With regard to alcohol, 60 percent of dentists asked about present alcohol use, 50 percent asked about past alcohol use, but only 33 percent asked about the types and amounts of alcohol used. On average, dentists assessed about five of the eight heath history factors.

With regard to the provision of oral cancer screening examinations, 81 percent reported that they provided an oral cancer examination for 100 percent of their patients 40 years of age and older at their initial appointment, and 78 percent said they provided this examination at recall appointments. Only 35 percent reported that they palpated lymph nodes of patients 18 years of age or older 80 percent or more of the time. Even

fewer dentists (14 percent) reported providing oral cancer examinations for edentulous patients 18 years of age and older. The low numbers of dentists palpating lymph nodes in patients is troubling because palpation is a crucial component of the oral cancer examination. If dentists are not performing this step, they are not providing the best possible care to their patients and they may miss detecting some oral cancers. It is also disturbing that so few dentists report providing exams for edentulous patients because these patients have many of the characteristics (older age, being a current or former tobacco user) that may place that at high risk for developing oral cancer (Horowitz et al., 2000).

To measure dentists' oral cancer screening practices, the authors created two indices (Horowitz et al., 2000; Yellowitz et al., 2000); one measured the number of risk factors screened when taking a medical history and the other measured provision of oral cancer examinations (Horowitz et al., 2000). Based on the number of correct responses, dentists were categorized into one of three categories: high score, medium score or low score. To examine the associations between dentists' screening practices and provision of examinations, they cross-classified dentists on each of these two indices. They found that only 15 percent of dentists had a high score on both indices. If only 15 percent of dentists are performing the

recommended screening practices, many patients are not receiving oral cancer examinations, which may lead to cancers being detected and diagnosed at later stages (Horowitz et al., 2000). In addition, if dentists do not assess their patients' risks for oral cancer, they may miss the opportunity to identify high-risk patients, such as those who smoke or drink, who should be screened regularly for oral cancer. The authors (Horowitz et al., 2000; Yellowitz et al., 2000) evaluated the effects of the four background characteristics on key aspects of oral cancer screening practices. Dentists who were graduated from 1980-1989 or 1990-1995 were 1.5 to 2.0 times, respectively, more likely to get a high score for their screening practices. Dentists who had never taken an oral cancer CE course or who had not taken one in the past five years were 2.6 or 1.7 times, respectively, less likely to get a high score. Dentists who were graduated between 1980 and 1995 were 1.5 times more likely to score high on the index measuring provision of oral cancer examinations, while dentists who had never taken an oral cancer CE course or had not take one within the past five years were 2.2 and 1.5 times, respectively, were less likely to get a high score.

Oral Cancer Screening Recommendations

To date, there are no standard screening recommendations for oral cancer, as there is for other cancers such as breast, cervical, and colorectal (American Cancer Society, 2008; American Dental Association, 2010; Rethman et al., 2010). The leading medical, professional and governmental organizations make different recommendations about the need for and frequency of oral cancer screening examinations. For example, the Healthy People 2010 recommendation is for adults 40 years and older and those at high risk to have an annual oral cancer screening (U.S. Department of Health & Human Services, n.d.). Unfortunately, only 29.4 percent of U.S. adults 18 years and older reported ever having an oral cancer examination (Pleis et al., 2009). In Maryland, 50 percent of adults 40 years and older report ever having an oral cancer screening exam, and 40 percent report they had an exam in the past twelve months (Maryland Department of Health & Mental Hygiene, 2009). While the percent of Maryland adults who report having had an oral cancer examination is significantly greater than the percent of adults in the U.S., overall these numbers are very low.

The American Dental Association (2010) states that an oral cancer screening is a routine part of the dental examination, but it does not

specify a frequency for the examinations. Many dental and health organizations recommend twice-yearly visits to the dentist for preventive checkups, but exam rates vary by healthcare provider. A third recommendation, by the American Cancer Society (2008), is for people aged 20 or older to have periodic health exams, and depending on a person's age and gender, exams for cancers of the thyroid, *oral cavity*, skin, lymph nodes, testes, and ovaries, as well as for some non-malignant (non-cancerous) diseases. The American Cancer Society's recommendation is a cause for concern in the fight against oral cancer because the oral cancer screening recommendation is buried in a paragraph that describes other cancer- related checkups, or it is a footnote in a table (Smith et al., 2010).

A fourth organization, the U.S. Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to recommend for or against routinely screening adults for oral cancer (USPSTF, 1996). In 2004, the USPSTF revised its criteria to rate the strength of the evidence and thus revised their recommendation for oral cancer examinations to the following:

> "*The USPSTF found no new good-quality evidence that screening for oral cancer leads to improved health outcomes for either high-risk*

adults (i.e., those over the age of 50 who use tobacco) or for average-risk adults in the general population. It is unlikely that controlled trials of screening for oral cancer will ever be conducted in the general population because of the very low incidence of oral cancer in the United States. There is also no new evidence for the harms of screening. As a result, the USPSTF could not determine the balance between benefits and harms of screening for oral cancer."

The current USPSTF (2004) recommendation statement regarding oral cancer is as follows:

· *Direct inspection and palpation of the oral cavity is the most commonly*

recommended method of screening for oral cancer, although there are little data on the sensitivity and specificity of this method. Screening techniques other than inspection and palpation are being evaluated but are still experimental.

· *Tobacco use in all forms is the biggest risk factor for oral cancer. Alcohol abuse combined with tobacco use increases risk.*

· *Clinicians should be alert to the possibility of oral cancer when treating patients who use tobacco or alcohol.*

· *Patients should be encouraged to not use tobacco and to limit alcohol*

use in order to decrease their risk for oral cancer as well as heart disease, stroke, lung cancer, and cirrhosis.

More recently, the American Dental Association Council on Scientific Affairs, with support from the Centers for Disease Control and Prevention, convened a panel to address the benefits and limitations of oral cancer screening and the use of adjunctive screening aids to visualize and detect malignant and potentially malignant oral lesions (Rethman et al., 2010, pg. 514). The Council's key conclusions are:

1) *While stage of cancer at diagnosis has an impact on treatment decisions and resultant health outcomes, community-based screening by means of visual and tactile examination in the general adult population intended to detect early and advanced oral cancers may not alter disease-specific mortality.*
2) *Community-based screening by means of visual and tactile examination may decrease oral cancer–specific mortality among people who use tobacco, alcohol or both.*
3) *Screening by means of visual and tactile examination may result in detection of oral cancers at early stages of development (Stages I and II).*
4) *In asymptomatic patients seeking dental care, there is insufficient*

evidence to determine whether screening by means of visual and tactile examination to detect potentially malignant and malignant lesions alters disease-specific mortality.

5) There is insufficient evidence that commercial devices based on autofluorescence or tissue reflectance enhance visual detection of potentially malignant lesions beyond that achieved through a conventional visual and tactile examination.

The authors note that it is important to remember that a conclusion of "insufficient evidence" does not necessarily mean that the intervention is or is not effective, but means that the panel did not find sufficient evidence to support a recommendation for screening (Rethman et al., 2010, pg. 514). Differing recommendations regarding the need for and frequency of oral cancer screening examinations, along with the absence of a recommendation to screen asymptomatic patients for oral cancer by both the USPSTF and the American Dental Association Council on Scientific Affairs, may result in some dentists not screening all of their patients for oral cancer. This in turn may result in oral cancers being detected at more advanced stages. It may also result in patients not asking their dentist or healthcare provider about the need for an oral cancer examination (Macek et al., 2003).

The Public's Knowledge of Oral Cancer

The third reason that oral cancer is diagnosed at advanced stages is a lack of knowledge among the public of the risk factors for and signs and symptoms of oral cancer. The public also lacks knowledge that an oral cancer exam exists, and therefore they do not even know to ask for one (Horowitz et al., 1998). In the past 20 years, studies conducted at both the national and state levels have investigated the public's knowledge of oral cancer. The annual National Health Interview Survey (NHIS) first included questions about oral cancer in 1990 (Dental, Oral, and Craniofacial Data Resource Center, n.d.). Questions assessed knowledge of risk factors for and signs and symptoms of oral cancer, as well as oral cancer exams. Follow-on studies conducted in states such as Maryland included questions about oral cancer similar to those on the NHIS, which allows for comparison of state and national data.

In the first study of the public's knowledge of oral cancer, Horowitz and colleagues (1995) analyzed the data from the 1990 NHIS. They found that only 25 percent of adults surveyed correctly identified one early sign of oral cancer, while 44 percent responded that they did not know one early sign of oral cancer. Sixty-seven percent of respondents knew that tobacco

use was a risk factor for oral cancer, but only 13 percent knew that alcohol use was associated with an increased risk for oral cancer. Respondents were also misinformed about risk factors for oral cancer, incorrectly believing that hot spicy foods or frequently biting the cheek or lip causes cancer. The authors concluded that the public was not well informed about oral cancer.

As part of an overall needs assessment for use in developing a state model of oral cancer education, prevention and early detection, Horowitz and colleagues (1998) investigated Maryland adults' knowledge of oral cancer. Similar to the NHIS, they assessed knowledge of oral cancer risk factors, signs and symptoms, and factors associated with having an oral cancer exam. Their results were similar to those of the 1990 NHIS study. Eighty-five percent of those surveyed said they had heard of oral cancer. However, only 23 percent could correctly indentify one early sign of oral cancer, and 39 percent replied that they did not know of an early sign of oral cancer. Individuals that were more likely to know one early sign of oral cancer were 40 to 64 years of age and had 12 years of education. Individuals who used smokeless tobacco were 4.6 times more likely to know one sign of oral cancer than nonusers. Individuals with the highest level of knowledge of oral cancer risk factors were females, with some

college education, and a belief that personal behaviors cause more cancers.

Only 21 percent of respondents had ever heard of an examination for oral cancer. However, when the oral cancer examination was described to these respondents, 28 percent said they had heard of an oral cancer examination. Likewise, other studies have shown an increase in the number of respondents that say they have ever had an oral cancer examination once it is described to them. This may indicate that dentists are providing oral cancer examinations without telling their patients that they are doing so (Horowitz et al., 2001; Macek et al., 2003). Those more likely to have ever had an oral cancer exam were 40-64 years of age, white, having 12 years of education or more, and a higher level of knowledge about oral cancer risk factors.

These early studies, as well as more recent studies, indicate that the public is not appropriately aware of the risk factors for oral cancer, the existence of examinations, and the importance of early detection (Stahl et al., 2004). Without accurate knowledge about oral cancer, people cannot make informed decisions about their health (Horowitz et al., 1995). Many of the risk factors for oral cancer, such as tobacco and alcohol use, are behaviors that can be modified. Therefore the dissemination of

information about oral cancer through health education and health promotion efforts may lead to a reduction of risk factors associated with the disease, as well as early detection. Interventions should be directed at individuals that are less educated, young adults, the elderly and tobacco and alcohol users (Horowitz et al., 1998). Dentists and family physicians are positioned to lead the effort to raise awareness about oral cancer because they see their patients relatively frequently. Therefore, they should ask all patients about their high-risk behaviors, educate patients about oral cancer prevention, and provide oral cancer examinations on a regular basis (Horowitz et al., 1998).

3. HEALTH LITERACY

Definition

One definition of health literacy is "*the ability to access, understand, appraise and communicate information to engage with the demands of health contexts to promote health*" (Rootman et al., 2005). Health literacy encompasses a number of skills, including reading, writing, numeracy, listening, oral communication, computer literacy, media literacy, and navigating the health care system (Schwartzberg et al., 2005; pg 3- 14). As such, it is a complex interaction between social and individual factors including: communication skills of consumers and providers; consumers and providers knowledge of health topics; culture and societal impact; demands of the healthcare system; and demands of the situation or context of the encounter (IOM, 2004; pg 3-16).

Healthcare Providers

Health literacy is typically defined and discussed in terms of an individual's ability to read, understand, and use healthcare information to make decisions and follow instructions for treatment (IOM, 2004, pgs 3-16).

However, healthcare providers also play a pivotal role in health literacy. Clear health communication is increasingly recognized as essential for patient safety, but communication problems among health care providers, patients, and families are common and a leading root cause of adverse outcomes (The Joint Commission, 2007). Much of the scientific literature related to healthcare providers focuses on provider communication skills and how to assess patients' health literacy in order to communicate more effectively (Rudd et al., 2003; Castro et al., 2007; Schwartzberg et al., 2007; Apter et al., 2008; Horowitz and Kleinman, 2008).

Provider knowledge is also a critical aspect of health literacy (Horowitz et al. 2000; Yellowitz et al, 2000). Providers must keep current with the latest scientific research and incorporate this knowledge into their practice in a timely manner for prevention, diagnosis, risk assessment and treatment of diseases (U.S. Department of Health & Human Services, n.d.). If they do not have the knowledge and skills to properly screen for and treat a health condition, they cannot provide accurate information and evidence-based care to their patients, which can result in poorer patient health outcomes (Horowitz et al., 2000; Yellowitz et al., 2000). For example, if a dentist is not aware that tobacco is a risk factor for oral cancer, they would probably not assess this risk factor when taking a medical history, would not

counsel the patient about reducing tobacco smoking. Understanding existing deficiencies in provider knowledge and skills is essential for developing interventions to minimize the deficiencies.

Oral Health Literacy

Oral health literacy is defined as “the degree to which individuals have the capacity to obtain, process and understand basic oral health information and services needed to make appropriate health decisions” (U.S. Department of Health and Human Services, 2000). Oral health literacy, like health literacy, is a function of the individual patient’s skills, the provider’s knowledge, skills and ability to communicate effectively, and the demands placed on patients by the healthcare system (IOM, 2004; pg 3-16; Jones et al., 2007). As with health literacy, effective communication is essential to delivery of quality care and it can contribute to successful oral health outcomes (Horowitz and Kleinman, 2008).

Low literacy and low health literacy present several barriers that must be overcome to achieve optimal oral healthcare. The main barriers, described in the report *The Invisible Barrier: Literacy and Its Relationship with Oral Health,* are: 1) many health-care providers are not trained to assess and address the literacy needs of their patients, so they present information without making sure the patient understands what has been

communicated; 2) many healthcare providers use readily available materials that are difficult to understand; 3) patients are reluctant to admit they do not understand something a healthcare provider says or are reluctant to ask questions for more information; and 4) many low literacy patients either do not perceive that they have a problem or 5) they recognize they have a problem and work to conceal it due to shame or embarrassment (U.S. Department of Health and Human Services, 2005). To overcome these barriers, dental professionals must become more knowledgeable about literacy, work to assess the abilities of their patients, and learn to use plain-language approaches when communicating health information to their with patients (Horowitz and Kleinman, 2008). Further research should be conducted to understand the prevalence of oral health literacy and how it might be addressed in oral/dental settings.

4. EPIDEMIOLOGICAL STUDY

Background information

In 2008, 263,861 new oral cavity cancers were diagnosed globally and about 65% of these cancers occurred in men. This accounts for approximately 2% of all new cancer diagnosed (men: 2.6%; women: 1.5%). Oral cancers cause more than 120,000 deaths each year, with a five-year survival rate of 60% (Ferlay, et al., 2010; Parkin, Bray, Ferlay, & Pisani, 2005). Further, incidence rates are currently increasing in many places around the world, especially among younger individuals (aged less than 45 years) (Llewellyn, Johnson, & Warnakulasuriya, 2001; Llewellyn, Linklater, Bell, Johnson, & Warnakulasuriya, 2004; S. Warnakulasuriya, Mak, & Moller, 2007). Most cases of oral cancer are attributable to modifiable risk factors, specifically tobacco use and alcohol consumption (Pelucchi, Gallus, Garavello, Bosetti, & La Vecchia, 2006). As such, education regarding oral cancer risk factors and behavioral modifications based of this knowledge has the potential to modify these trends. Previous studies evaluated whether or not dentists and primary physicians are aware of oral cancer risk factors and if they educated patients about cancer prevention (Colella, Gaeta, Moscariello, & Angelillo, 2008;

Greenwood & Lowry, 2001; Lopez-Jornet, Camacho-Alonso, & Molina-Minano, 2010). In 2008 Colella et al. (Colella, et al., 2008) investigated Italian dentists' (N=1000) knowledge, attitudes, and behaviors regarding oral cancer: the majority of dentists identified tobacco (94%) and alcohol usage (79%) as oral cancer risk factors. Further, more than half of these dentists queried their patients about their tobacco (56%) and alcohol (60%) use. In Spain (Seoane, et al., 2010) dentists (N=440) reported that they provided systematic counseling on alcohol (55%) and tobacco smoking (88%) cessation. Education promoting awareness of oral cancer in patients may help in preventing high-risk behaviors such as tobacco and alcohol consumption (Tromp, Brouha, Hordijk, Winnubst, & de Leeuw, 2005; K. A. Warnakulasuriya, et al., 1999). While studies have investigated oral cancer knowledge among oral health care providers, little is available about the knowledge of dental patients. As dentists we wanted a better understanding of the knowledge of our patient population. Therefore, the purpose of the present analysis was to investigate patients' knowledge regarding oral cancer risk factors and to explore communication and health messaging between clinicians and patients attending Dental Departments within Italian University hospitals.

Methods

This study was a collaboration between: 1) the Dental Clinic, Department of Oral and Maxillo-Facial Science, Sapienza University of Rome, 2) the Dental Clinic, Department of Medicine, Surgery and Dentistry, University of Milan, 3) the Department of Dentistry, University of Messina, and 4) the Department of Dentistry, Vita-Salute San Raffaele University. This study was funded by a grant from the Italian Ministry of Health (Ministero del Lavoro, della salute e delle politiche sociali-CCM). Study population and recruitment In December 2009, questionnaires were sent to the Dental Departments the four public Italian university hospitals (550 per hospital): two in the north of Italy (San Paolo Hospital - University of Milano [MilanoSP] and San Raffaele Hospital–University Vita e Salute [Milano SR]), one in the center of Italy (Umberto I Hospital - University La Sapienza [Roma]) and one in the south (University of Messina [Messina]). These hospitals were chosen because they were geographically diverse and because they had a high patient load. This population was targeted in order to improve the level of clinician's knowledge about patients referred to specialized clinics. Patients were selected sequentially based on the following inclusion criteria 1) age 18 or older, and 2) ability to read, understand and answer the questionnaire. The Italian Ministry of Health

approved this study. Each participant gave written consent. The questionnaire All patients received the same questionnaire in the waiting room of the dental clinic; the questionnaires were self-administered, yet a dental student was available if any question arose. The questionnaire assessed: socio-demographic information including country of birth, age, gender and education level; self-reported medical history; family history of oral cancer; tobacco and alcohol habits; and diet (do you eat meat? Fish? Fruit? Vegetables? Milk/cheese?); oral hygiene habits and oral symptoms; height, weight and drug intake.

Response categories for these questions were “never”, “seldom”, “once a week”, “2-3 times/week” and “daily”. Participants were queried as to their knowledge regarding oral cancer and oral cancer risks factors using the following questions: “Is it possible to have a malignant tumor of oral cavity?” “Is oral cancer treatable?” and “Is a white or red patch in the mouth a possible initial sign of cancer?”. Smoking status was assessed by the following questions: 1) Do you smoke tobacco now ?; 2) if not a current smoker, did you smoke in the past?; 3) Have you ever smoked a total of 100 cigarettes or more over your lifetime?. The responses to these questions were used to build our smoking status variable. Alcohol intake was evaluated as number of glasses per day; heavy alcohol consumption

was defined as consuming an average of more than 2 glasses per day. Finally participants were asked whether dentists/physicians provided counseling or education on oral cancer and its risk factors. Response categories for all questions were "Yes" and "No". After a twelve-week period for the data collection, the responsible people at each hospital were contacted and requested to return the questionnaires. Four more weeks were allowed for the return of the questionnaires. Questionnaires were returned by mail to the research team for the analysis. No compensation was offered for participation.

Validity and Reliability

Validity. Content validity of the present questionnaire instrument was determined by comparing our questionnaire with previous validated instruments from the National Institutes of Health in the United States and from the National Health and Nutrition Examination Surveys.

Reliability. Reliability has been established over the years, with similar results obtained in the many studies that have used the National Oral Cancer Survey of Dentists and Patients (Clovis et al., 2002; Cruz et al., 2002; Patton et al., 2005; LeHew et al., 2007; Applebaum et al., 2009).

Statistical Analysis

Of the 2200 mailed questionnaires (4 hospitals * 550 questionnaires per hospital), 1201 were returned (54.6%). The response rates were 96.5% from Roma, 63.8% from Milano SP, 42.9% from Milano SR and 15.1% from Messina. Participants were given the option of refusing to answer each of the questions on the questionnaire, and these refusals were treated as missing observations. We described the distribution of participant characteristics, including demographics, smoking status, and heavy alcohol consumption. Oral cancer (OC) knowledge was evaluated overall; we also assessed whether the hospital, education level, oral hygiene (brushing teeth with a fluoride toothpaste daily), smoking status, heavy alcohol consumption and oral cancer family history modified OC knowledge. Similarly, oral cancer education was described overall; then, we assessed whether the hospital, education level, oral hygiene, smoking status, heavy alcohol consumption and oral cancer family history modified OC education. Associations between exposures of interest such as positive OC family history, hospital, education level, oral hygiene and our outcomes (OC knowledge and OC education) were evaluated by the use of logistic regression models to estimate odds ratios (ORs) and 95%

confidence intervals (CIs). Moreover, we evaluated whether positive OC family history impacted smoking and drinking status. Associations were assessed by use of the $\chi 2$ test. All p-values reported were considered statistically significant at $p<0.05$.

Results

A total of 1201 questionnaires were collected from 459 males and 735 females. Overall, subjects ranged in age from 18 to 98; the median age was 46 years (interquartile range 37-54 years). The majority of the study participants were Italian (89.7%). Around 25% of patients completed University, 52.0% completed high school and 22.7% reported less than nine years of education. Positive family history of oral cancer was present in 17.1% of participants. Approximately 36% of the population reported current smoking, although the proportion of smokers was higher in subjects from Messina (48.8%) compared to Milano SP and Milano SR (26.6% and 31.6%, respectively). Heavy alcohol consumption was reported by 65.6% of subjects and the highest rate was found in the North of Italy (76.7% in Milano SR, 72.0% in Milano SP, 57.7% in Roma, and 54.2% in Messina) (Table 1).

Oral cancer knowledge

Overall, 93.6 % of the sample reported that early detection was related to better prognosis of oral cancer (Table 2). 65.2% and 79.5% of individuals reported that a white/red patch and mass/ulcer in the mouth, respectively, were possible signs of oral cancer. The majority of participants correctly

identified cigarette smoking as a risk factor for oral cancer (87.8%) and vegetable consumption (73.7%) and good oral hygiene (79.4%) as possible protective factors. However heavy alcohol consumption (59.2%) and pipe smoking (20.7%) were less frequently reported as oral cancer risk factors. Also, 69.1% of current smokers did not receive counseling to quit smoking from dentists.

88.9% of the study participants ate meat 2-3 times per week and 35% of the individuals had fish 2-3 times weekly. 72.2% of the patients and 67.3% had fruit and vegetables respectively. Milk and dairy products were taken by 34.2% of the study population. Sugary products were consumed daily by 48.5% of the subjects (Figures 1-6).

Fig. 1. Meat consumption

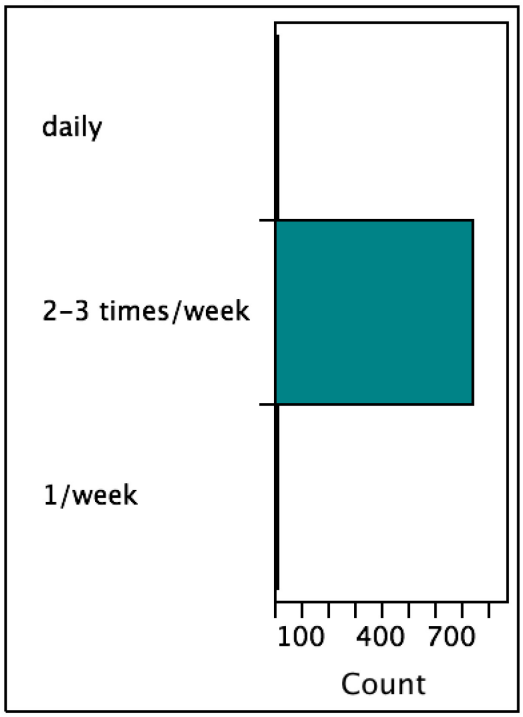


Fig. 2. Fish consumption

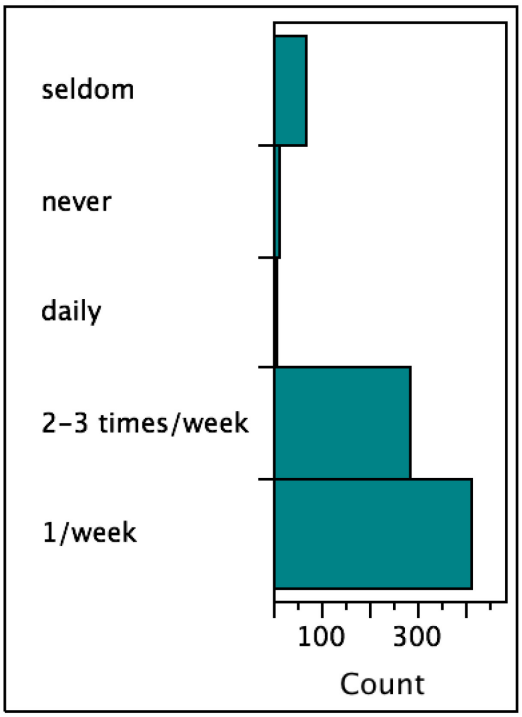


Fig. 3. Fruit consumption

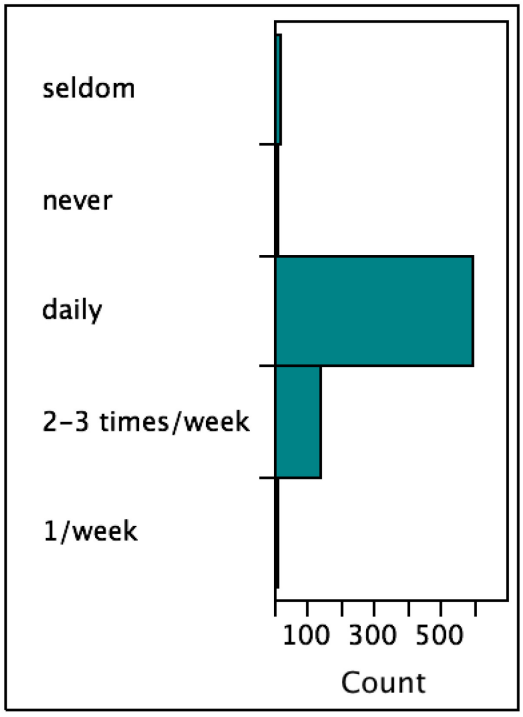


Fig. 4. Vegetables consumption

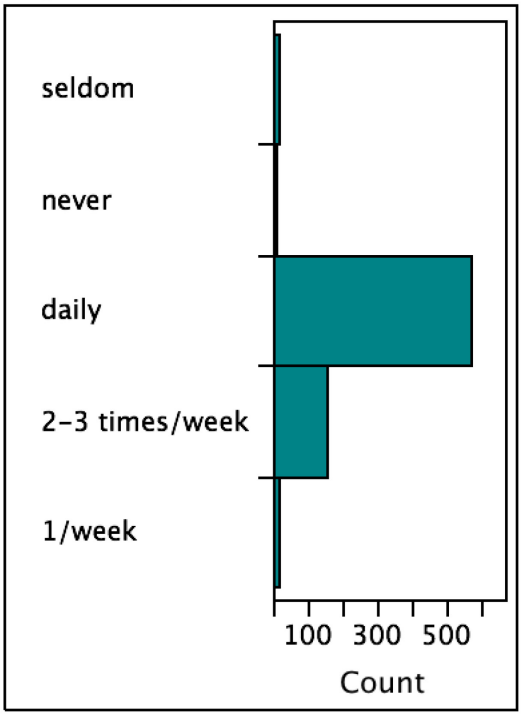


Fig. 5. Milk & Dairy products

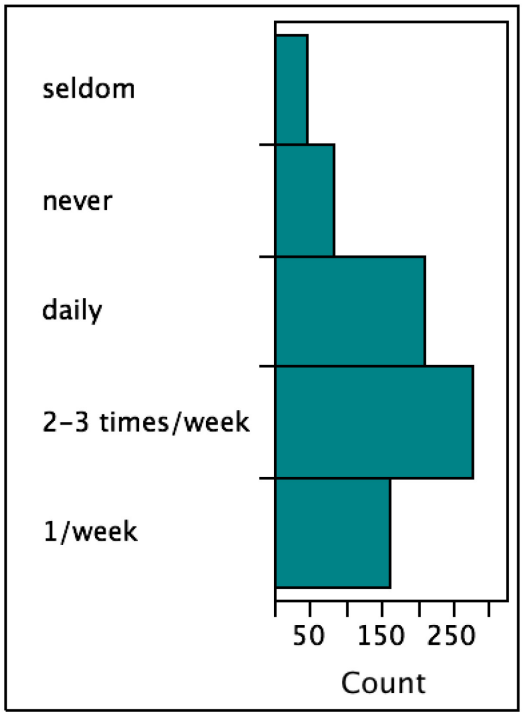
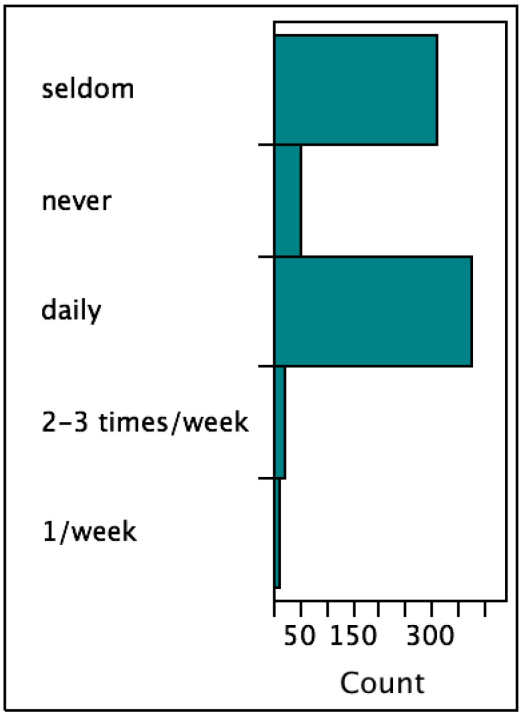


Fig. 6. Sugar consumption



In stratified analysis, individuals with a positive family history for oral cancer were three times more likely to identify risk factors for oral cancer correctly such as cigarette smoking (OR: 2.9, 95%CI 1.5-6.3) and twice more likely to identify possible signs of oral cancer such as a mass/ulcer (OR: 1.9, 95%CI 1.2-3.2) (Table 2). Family history of oral cancer did not affect current smoking status (OR: 1.1, 95%CI 0.9-1.3) or heavy alcohol consumption (OR: 1.1, 95%CI 0.8-1.5).

Current (34%), former (11%) and never smokers (50%) reported similar OC knowledge ($p>0.05$). The only exception was that current smokers were significantly more knowledgeable about the initial signs of oral malignancy compared to former and never smokers ($p<0.05$; data not shown). Knowledge that heavy alcohol consumption is a risk factor for oral cancer was similar among individuals who did and did not consume heavy alcohol (38.8% vs. 27.5%, $p=0.47$; data not shown). No associations were observed between level of education, gender, or age and oral cancer knowledge.

Oral cancer education

The majority of the individuals did not receive counseling on oral cancer by dentists, physicians or other health care providers (86.1%, 92.3% and 88.9% respectively).

Individuals with a positive family history for oral cancer had a significant increase in the odds of receiving oral cancer counseling by physicians (OR: 2.1, 95%CI 1.4-3.9), dentists (OR: 2.5, 95%CI 1.6-3.6) or other health care personnel (OR: 4.3, 95%CI 2.8-6.4) compared to those with negative family history for oral cancer (Table 3). Counseling and education on oral cancer provided by physicians (p=0.14), dentists (p=0.39) or other health care personnel (p=0.80) was similar among never, former and current smokers (data not shown).

We additionally evaluated OC knowledge and education by hospital, education level and oral hygiene status. No differences were observed.

Table 1. Characteristics of study participants by hospital

	Roma (*N*=531)	Milano SP (*N*=351)	Milano SR (*N*=236)	Messina (*N*=83)	Total (*N*=1201)
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Gender					
Female	399 (75.7)	172 (49.4)	121 (51.3)	43 (51.8)	735 (61.6)
Male	128 (24.3)	176 (50.6)	115 (48.7)	40 (48.2)	459 (38.4)
Country of birth[a]					
Italy	466 (92.1)	298 (85.4)	228 (96.6)	83 (100.0)	1075 (89.7)
Europe	40 (7.9)	14 (4.0)	2 (0.9)	0 (0.0)	56 (4.7)
Other	0 (0.0)	37 (10.6)	6 (2.5)	0 (0.0)	68 (5.6)
Age category					
18-29	23 (4.4)	91 (25.9)	41 (17.4)	15 (18.0)	170 (14.1)
30-39	99 (18.6)	50 (14.2)	41 (17.4)	19 (22.9)	209 (17.4)
40-49	211 (39.7)	69 (19.7)	68 (28.8)	14 (16.9)	362 (30.2)
50-59	124 (23.4)	67 (19.1)	56 (23.8)	14 (16.9)	261 (21.7)
60-69	41 (7.7)	36 (10.3)	15 (6.3)	14 (16.9)	106 (8.8)
70+	33 (6.2)	38 (10.8)	15 (6.3)	7 (8.4)	93 (7.8)
Median [IQR]	*46* [40-54]	*45* [30-55]	*46* [36-53]	*46* [34-60]	*46* [37-54]
Education (years)					
Less than 10	110 (21.0)	77 (22.3)	57 (24.2)	26 (31.3)	270 (22.7)
9 to 14	274 (52.4)	170 (49.1)	132 (55.9)	42 (50.6)	618 (52.0)
15 or more	139 (26.6)	99 (28.6)	47 (19.9)	15 (18.1)	300 (25.3)
Family history of oral cancer					
No	418 (81.6)	287 (82.0)	208 (88.1)	66 (79.5)	979 (82.9)
Yes	94 (18.4)	63 (18.0)	28 (11.9)	17 (20.5)	202 (17.1)
Smoking status					
Never	267 (56.8)[b]	180 (52.0)[b]	108 (46.8)	39 (47.6)	594 (52.6)
Former	0 (0.0)	74 (21.4)	50 (21.6)	3 (3.7)	127 (11.2)
Current	203 (43.2)	92 (26.6)	73 (31.6)	40 (48.8)	408 (36.1)
Lifetime smoking quantity					
<100 cigarettes	0 (0.0)	44 (23.7)	7 (6.1)	0 (0.0)	51 (10.6)
≥100 cigarettes	137 (100.0)	142 (76.3)	107 (93.9)	43 (100.0)	429 (89.4)
Alcohol consumption					
Never	199 (42.3)[b]	92 (28.0)	54 (23.3)	38 (45.8)	383 (34.4)
Ever	271 (57.7)	236 (72.0)	178 (76.7)	45 (54.2)	730 (65.6)

Abbreviation IQR Intra-quartile range

[a] Due to small sample size America, Asia and Australia were collapsed into “Other” category.

[b] Indicate that more than 10% data were missing.

Table 2. Oral cancer knowledge overall and by family history

	Total	Family history of oral cancer	
	n (%)[a]	*Yes (N=202)*	*Odds Ratio (95%CI)*
Does early detection of oral cancer means better prognosis?			
No	60 (5.1)	5 (8.3)	1.0
Yes	1124 (94.9)	197 (17.5)	2.4 (0.9-7.7)
Is a white/red patch in the mouth a possible initial sign of cancer?			
No	364 (34.8)[b]	44 (12.1)	1.0
Yes	682 (65.2)[b]	157 (23.0)	0.9 (0.6-1.4)
Is a mass/ulcer in the mouth a possible sign of cancer?			
No	225 (20.5)	23 (10.2)	1.0
Yes	873 (79.5)	167 (19.1)	1.9 (1.2-3.2)
Is oral cancer more frequent in people 40+?			
No	390 (35.9)	64 (16.4)	1.0
Yes	697 (64.1)	131 (18.8)	1.1 (0.8-1.6)
Does cigarette smoking increase risk of oral cancer?			
No	144 (12.2)	10 (6.9)	1.0
Yes	1033 (87.8)	190 (18.4)	2.9 (1.5-6.3)
Does eating vegetables decrease risk of oral cancer?			
	255 (22.4)	21 (8.2)	
Yes	885 (77.6)	174 (19.7)	2.7 (1.6-4.5)
Does pipe smoking increase risk of oral cancer?			
No	876 (79.3)	37 (4.2)	1.0
Yes	228 (20.7)	156 (68.4)	1.1 (0.7-1.7)
Does heavy beer/wine drinking increase risk of oral cancer?			
No	457 (40.8)	89 (19.5)	1.0
Yes	662 (59.2)	111 (16.8)	0.9 (0.6-1.2)
Does good oral hygiene decrease risk of oral cancer?			
No	239 (20.6)	44 (18.4)	1.0
Yes	919 (79.4)	157 (17.1)	0.9 (0.6-1.4)
Heavy alcohol consumption			
No	457 (41.4)	62 (16.2)	1.0
Yes	648 (58.6)	125 (17.1)	1.1 (0.8-1.5)
Smoking status			
Never	594 (52.6)	96 (16.2)	1.0
Former	127 (11.2)	23 (18.1)	1.1 (0.8-1.3)
Current	408 (36.1)	67 (16.4)	1.1 (0.9-1.3)

[a] Indicate the total percentage of responders
[b] Indicate that more than 10% data were missing

Table 3. Oral cancer education overall and by family history

	Total	Family history of oral cancer	
	n (%)[a]	*Yes (N=202)*	*Odds Ratio (95%CI)*
Have you been counseled on oral tumor by your physician?			
No	1086 (92.3)	162 (14.9)	1.0
Yes	91 (7.7)	27 (29.7)	2.1 (1.4-3.9)
Have you been counseled on oral tumor by your dentist?			
No	1020 (86.1)	145 (14.2)	1.0
Yes	164 (13.9)	48 (29.3)	2.5 (1.6-3.6)
Have you been counseled on oral tumor by any other health care provider?			
No	1049 (88.9)	146 (13.9)	1.0
Yes	131 (11.1)	54 (41.2)	4.3 (2.8-6.4)
Has the dentist counseled to quit smoking?			
No	307 (68.2)[b]	45 (14.7)	1.0
Yes	143 (31.8)[b]	29 (20.3)	1.5 (0.9-2.6)

[a] Indicate the total percentage of responders
[b] Indicate that more than 10% data were missing

Discussion

We conducted a large multicentric study to examine patients' knowledge regarding oral cancer risk factors and to explore communication and health messaging between clinicians and dental patients in Italy; few studies have addressed questions on patients' oral cancer knowledge. Our findings show that the majority (94%) of individuals are knowledgeable regarding what clinical signs are associated with oral cancer (such as red/white patch and/or mass/ulcer in the mouth). Further, this knowledge was modified by the personal experience of having a positive family history for oral cancer: these individuals identified the risk factors and possible signs of oral cancer significantly more frequently compared to individuals with no family history. While knowledge of oral cancer was high overall, it did not appear that this information was being provided by clinicians: less than 15% of participants reported receiving counseling about oral cancer from their physicians or dentists. From this incongruency, it appears as if individuals are seeking information from alternative sources, perhaps Web-based resources, magazines, or books(Chen & Siu, 2001; James, James, Davies, Harvey, & Tweddle, 1999). In our work, only one-third of dentists in Italy regularly promoted

tobacco-smoking cessation to current smokers despite the fact that patients are both comfortable receiving tobacco cessation advice and expect their dentists to provide such counseling (Campbell, Sletten, & Petty, 1999). Further, most smokers in our study knew that smoking was a risk factor for oral cancer (87%) and yet continued to smoke. Similarly, two-thirds of smoking adults from a US study (N= 803) (Hay, et al., 2002) and more than half of smoking adults from Kuwait (N=1012) (Al-Shammari, Moussa, Al-Ansari, Al-Duwairy, & Honkala, 2006) were aware of the correlation between heavy smoking and oral cancer but, nevertheless, continued to smoke. Data from large-scale randomized clinical trials provide evidence that counseling by health professionals modestly improves smoking cessation rates (Lancaster & Stead, 2004; Lemmens, Oenema, Knut, & Brug, 2008) and therefore highlights the importance of continued efforts on the part of clinicians. A dedicated curriculum content might improve upon deficiencies in counseling skills and conveying tobacco-use cessation information (Gordon, Albert, Crews, & Fried, 2009). Patients knew that smoking and heavy alcohol consumption were risk factors for oral cancer, but did not change behavior. These findings suggest that health professionals may need to

focus on changing their patients' behavior, in addition to educating patients about oral cancer risk factors. As in all work, our results must be interpreted in the context of the limitations of the study. First, the response rate for the questionnaire was slightly greater than 50%. As such, a systematic bias may have been introduced if the non-responders were different and not representative of those who answered our questionnaire. Because demographic information was not available for non-responders, the magnitude of this bias could not be assessed. Second, our results may not be generalizable to the population at large, as the proportion of oral cancer family history was high (17%). It may be that participants with positive oral cancer family history were more likely to participate in this study. Also, response rates differed by hospital (96.5% from Roma, 63.8% from Milano SP, 42.9% from Milano SR and 15.1% form Messina). Thus, data from centers with lower response rates may be less generalizable for the general population. In addition, our study population was recruited from dental clinics nested within tertiary referral centers. As such, the results of this study likely represent an overestimate of knowledge about oral cancer risk factors, signs and symptoms. Finally, in attempting to assess the participants knowledge by use of the

questionnaire, many of the questions could have been considered 'leading questions' in that the questions were typically asked so that 'yes' was the correct answer. For example, we asked "Does cigarette smoking increase risk of oral cancer?" and then "Does good oral hygiene decrease risk of oral cancer?" Since the appropriate answer was embedded in the question, some respondents probably tended to agree with statements rather than disagree (Edwards, 2010), which would artificially inflate the apparent knowledge of our study population. Health promotion messaging to patients is an essential component of preventive medicine; prevention/cessation of tobacco and alcohol use contributes to good general and oral health (Dyer & Robinson, 2006). While dentists and physicians have the great opportunity to counsel their patients about risk factors for oral cancer, according to this survey, health professionals infrequently provided this information. Yet, our population was reasonably informed about oral cancer, and its risk factors, signs, and symptoms. Additional communication between patients and health care personnel could increase oral cancer knowledge and potentially motivate individuals towards improved well-being. To reduce the morbidity and mortality associated with oral cancer, dentists must have accurate knowledge and

proficient skills to detect and diagnose oral cancers at early stages. Additionally, they should perform routine oral cancer screening examinations and counsel patients to modify behaviors that increase the risk for oral cancer. Our findings indicate that deficiencies exist in dentists' practices relating to oral cancer prevention and early detection. There are also inconsistencies between patients' knowledge and screening practices. Accurate and current knowledge and skills are the foundation of optimal patient care, and are essential for improving oral cancer prevention and early detection efforts in Italy. Existing oral cancer course materials should be evaluated to identify strengths and deficiencies, and a comprehensive program should be designed. These programs should emphasize screening for risk factors; performing oral cancer examinations and self-examination; and counseling to modify behaviors associated with increased risk for oral cancer. To ensure that dental professionals have oral cancer screening competencies, the Italian Ministry of Health should require applicants to perform oral cancer screening examinations for licensure. This greater emphasis on oral cancer knowledge and skills, may lead to detection of cancers at earlier stages. Lastly, dental school curricula should be modified to place greater emphasis on oral cancer

prevention and early detection. Schools should require students to perform oral cancer examinations as part of the curricula, emphasize risk assessment and counseling to reduce risk.

Dental professionals are in a unique role to provide risk factor counseling regarding the prevention of oral cancer, particularly, counseling related to tobacco and alcohol use. In addition, patients visiting the dental offices for problem-oriented appointments may be streamlined into a regular preventive recall schedule where they are seen for preventive services on a regular basis. Oral cancer risk factor counseling can be added to these preventive services, and can potentially be a life saving element of care (Davis JM, 2005).

It is important to begin addressing barriers related to oral cancer screenings and risk factor counseling. Improved educational models in dental and medical schools as well as continuing education courses can address some of these barriers as well as move the profession forward in making a paradigm shift where providing these services is no longer just an additional benefit, but instead, the expectation of oral health professionals and their patients. Despite the amount of research related to cancer prevention and information regarding risk reduction lifestyle behaviors, a substantial

number of people continue to engage in behaviors that increase their chance of acquiring oral and other cancers in their lifetime (Thacker, 1997). A combination of alcohol and tobacco use is shown to be the most lethal in the development of oral cancer (Zhang, Morgenstern, et al., 1999). It is therefore necessary for oral health researchers to use the information gathered in the previous studies regarding the knowledge, attitudes, motivations, social influences, perceptions and behaviors of the Italian community in order to inform development of preventative programs that reduce risky behaviors and increase the effectiveness of health promotion and oral cancer prevention.

A paper by Speight and colleagues (Speight, Palmer, et al., 2006) and the FDI World Dental Federation recently stressed the importance of all oral health care professionals in the prevention of oral cancer. Specifically:

- Prevention interventions need to address factors that influence users to engage in risky behaviors, incorporate factors that are protective for nonusers, and incorporate factors that could influence users not to start or to discontinue use. The factors that discriminate user status can then be used to inform prevention programming at any or all of three levels, primary, secondary and tertiary.

- Health personnel working with risky populations may be able to impact the oral cancer attitudes, motivations and perceptions, and behaviors related to alcohol, tobacco use, and diet with interventions designed to address each of these categories.
- Patients should be encouraged to speak with their doctors and dentists about their oral cancer related behaviors. Additionally, doctors and dentists should be encouraged to implement aggressive multi level prevention interventions with their patients.
- Health educators must improve teaching methods related to health promoting behaviors related to oral cancer prevention by identifying specific barriers to knowledge, attitudes, motivations, of the individuals related to their behaviors of alcohol, tobacco, and marijuana use.
- Health education advocacy must address secondary audiences such as legislators to increase cost of alcohol and tobacco taxes to dissuade purchasing.
- Future funding for oral cancer prevention program development and research must be attained to create successful formative evaluation initiatives and decrease oral cancer risk behaviors.
- Implementation of reliable and valid diagnostic technologies and

appropriate training is necessary for the identification, assessment and referral of patients for definitive oral cancer diagnosis and treatment, and for post- treatment management.

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5. APPENDIX

Table 1a. Studies on leukoplakia and malignant progression

STUDY	YEAR	COUNTRY	METHOD AND SETTING	POP	DATE	MEAN FU, Y	MIN. FU, Y	MEAN OR MEDIAN AGE, Y	RISK FACTORS	DIAGN	LESION	SURGICA EXCISIO PATIENT
Hsue	2007	Taiwan	Prosp H	1458	1991-2001	3.6		47.5	tob-alc	bio	dyspl lesi	166
Holmstrup	2006	Denmark	Retro H	236	1977-1997	6.0	1.0	60.8	tob	clin and then bio	leu and erythro	67
Saito	2001	Japan	Retro H	142	1976-1997	4.0	0.6	54.0	tob-alc	clin and then bio	leu	50
Cowan	2001	Northern Ireland	Retro pop	1347	1975-1994				tob-alc	bio	dyspl lesi + OSCC	0
Lee	2000	USA	Pros H	70	1988-1998	7.0			tob-alc	bio	PL	0
Schepman	1998	Netherlands	Retro H	263	1973-1997	2.5	0.5	67.1	tob-alc	clin &bio	leu	37
Lumerman	1995	USA	Retro lab		1974-1982	1.5	0.5	59.3		bio	dyspl	0
Hogewind	1989	Netherlands	Retro H	46	1969-1984	2.5	1.0		tob	bio	leu	13
Lind	1987	Norway	Retro H		1970-1980	9.3		57.7		bio		0
Silverman	1984	USA	Pros H	257	<1968-?	7.2	0.5	54.0	tob	clin	leu	0
Gupta	1980	India	Pros pop		1966-?	8.5						0
Banoczy	1976	Hungary	Retro H	500	Not clear	6.3				bio	dyspl	45
Silverman	1976	India	Pros pop	6718	1967-1971	2.0		>35	tob	bio	leu	0
Mincer	1972	USA	Pros H	67	1963-1971	8.0	1.0		tob	bio		0

Table 1b. Studies on leukoplakia and malignant progression

STUDY	YEAR	TOT DYSPL (N)	MILD	MOD	SEVERE	CIS	MT (N)	MTR	MILD (N)	MILD (%)	MOD (N)	MOD (%)	SEV (N)	SEV (%)	CIS (N)	CIS (%)
Hsue	2007	166	138	15	13	0	8	4,8%	6	4,3%	2	13,3%	0	0,0%		
Holmstrup	2006	88	42	26	14	6	12	11,4%	5	11,9%	2	7,7%	1	7,1%	4	66,7%
Saito	2001	91	48	36	7	0	7	7,7%	6	12,5%	1	2,8%	0	0,0%	-	-
Cowan	2001	165	-	-	-	-	17	14,5%	-	-	-	-	-	-	-	-
Lee	2000	70	61	-	9	-	20	31,4%	16	12,5%	-	-	6	66,7%	-	-
Schepman	1998	65	20	26	19	-	12	21,8%	-	0,0%	-	-		-	-	-
Lumerman	1995	44	19	18	6	1	7	16,3%	3	15,8%	3	16,7%	1	16,7%	1	100,0%
Hogewind	1989	13	5	3	5	-	1	7,7%	0	0,0%	1	33,3%	0	0,0%	-	-
Lind	1987	47	16	24	7	-	8	17,0 %	1	6,3%	4	16,7%	3	42,9%	-	-
Silverman	1984	22	-	-	-	-	8	36,4%	-	-	-	-	-	-	-	-
Gupta	1980	90	-	-	-	-	6	6,7%	-	-	-	-	-	-	-	-
Banoczy	1976	68	13	43	12	-	9	13,2%	1	7,7%	3	7,0%	5	41,7%	-	-
Silverman	1976	35	-	-	-	-	6	17,1%	-	-	-	-	-	-	-	-
Mincer	1972	45	-	32	13	-	5	11,1%	-	-	2	6,3%	3	23,1%	-	-
Total		1009	362	223	105	7	126	12.5%	38	10,5%	18	8,1%	19	18,1%	5	71,4%

Table 1c. Studies on leukoplakia and malignant progression

STUDY	YEAR	TOTAL DYSPLASIA	MILD (N)	MILD (%)	MODERATE (N)	MODERATE (%)	SEVERE (N)	SEVERE (%)	MALE	FEMALE	MALE T	FEMALE T	AGE (MEAN)
Hsue	2007	166	138	83.1	15	9.1	13	7.8					47.5
Holmstrup	2006	88	42	47.7	26	29.5	14	15.9					
Saito	2001	91	48	52.7	36	39.6	7	7.7	80	62	5	4	54
Cowan	2001	165	-		-		-				25	16	59
Lee	2000	70	61	87.1	-		9	12.9	37	33			
Schepman	1998	65	20	30.8	26	40.0	19	29.2	76	90			57
Lumerman	1995	44	19	43.2	18	40.9	6	13.6	20	24			59.3
Hogewind	1989	13	5	38.5	3	23.1	5	38.5	50	34	0	1	
Lind	1987	47	16	34.0	24	51.1	7	14.9					57.5
Silverman	1984	22	-		-		-						54
Gupta	1980	90	-		-		-						
Banoczy	1976	68	13	19.1	43	63.2	12	17.6	47	21			
Silverman	1976	35	-		-		-				5	1	
Mincer	1972	45	-		32	71.1	13	28.9					61.2

Table 2. Studies on oral lichen planus and malignant progression

STUDY	YEAR	COUNTRY	POP	DATE	FU (Y)	DIAGN	OLP	CANCER	MTR (%)
Bermejo-Fenoli	2009	Spain	550	1991-2007		clin	550	5	0.9
Fang	2009	China	2119	1951-2006	-		2119	23	1.1
Thongprasom	2009	Thailand	350	1997-2007		bio	350	1	0.3
Carbone	2009	Italy	808	1987-2004	6 months - 17 years	bio	808	15	1.9
Van der Meij	2007	The Netherlands	192	1996-2004	5	bio	192	4	2.1
Hsue	2007	China	1458		10	clin-bio	143	3	2.10
Mignogna	2006	Italy	700		16		700	45	6.43
Ingafou	2006	UK	690		–		690	13	1.9
Bornstein	2006	Sweden	141	1995-2001	–		141	4	2.84
Laeijendecker	2005	The Netherlands	200	1991-2003	4.3		200	3	1.5
Xue	2005	China	674	1963-2003	3–21	bio	674	4	0.6
Lanfranchi-Tizeira	2003	Argentina	10244	1991-1997	–	bio	719	32	4.5
van der Meij	2003	The Netherlands	173		–	bio	173	3	1.7
Eisen	2002	USA	723		–	bio	723	6	0.8
Rode	2002	Slovenia	55		25	bio	55	0	0
Chainani-Wu N	2001	USA	229	1996-2000		Bio	229	4	1.7
Mignogna	2001	Italy	502		–	bio	502	24	4.7
Rajentheran	1999	UK	832	1983-1996	–	bio	832	7	0.8
Markopoulos	1997	Greece	326		6 months–10 years		326	4	1.3
Gorsky	1996	Israel	157		3 months–15 years	bio	157	2	1.3
Brown	1993	USA	193		8.0		193	0	0
Voute	1992	The Netherlands	727		7.8	bio	113	3	2.7
Silverman	1991	USA	570		7.5		214	5	2.3
Sigurgeirsson	1991	Sweden			9.9		2071	8	0.4
Salem	1989	Saudi Arabia	4277	1982-1987	3.2		72	4	5.6
Holmstrup	1988	Denmark	611		1–24		611	9	1.5

Silverman	1985	USA	570		6 months–10 years	570	7	1.2
Kaugars	1982	USA	30920	1953-1979	–	71	71	0.23
Fulling	1973	Denmark	327		3.6	225	1	0.4

Table 3. Studies on submucous fibrosis and malignant progression

STUDY	YEAR	ETHNICITY	COUNTRY	METH AND SETTING	RISK FACTOR	POP	DATE	MEAN FU, Y	DIAGN	LESION	MT (N)	MTR (%)
Aziz	2008			Case-report	Betel	1			bio	1		
Hsue	2007	Tawainese	Taiwan			1458			bio	402	8	1.9
Reichart	2006	India	Germany	Case-report	Gutka	1			bio	1		
Vilmer	1986	India	France	Case-report		1				1		
Murti	1985	India	India	Pros	Chilli areca-nut	66		10		66	5	7.6
McGurk	1984	India-Pak	UK			3				3	2	66.6
Pindborg	1984	India	India			66		8		66	3	4.5
Laskaris	1981	Greece	Russia	Case-report		1			bio	1	1	100.0

Table 4. Studies on erythroplakia and malignant progression

STUDY	YEAR	COUNTRY	METHOD	POP	DATE	DIAGN	PATIENTS ERYTH (N)	PREVALENCE ERYTH (%)	MTR (N)	MTR (%)	MAN	WOM
Lapthanasupkul	2007	Thailand	Retro	7177	1973-2004	bio	9	0,13	6	66,7	6	3
Hashibe	2000	India		47773		clin	100	0,2			51	49
Lumerman	1995	USA	retro lab	50000	1974-1982	clin-bio	7	0,01	1	14,3	-	-
Vedtofte	1987	Denmark					14		5	35,7	0	10
Amagasa	1985	Japan					12		6	50	8	4
Silverman	1984	USA	pros H	257 leu	<1968-?	clin	22		8	36	-	-
Lay	1982	Burma		6000			5	0,08				
Shafer	1975	USA		64345	1950-1974	bio	58	0,09	33	56,9	30	64
Mincer	1972	USA	pros H	67	1963-1971		16		3	18,8		
Metha	1971	India		50915	1966-1969		9	0,02				

Table 5. Oral screening methods in biopsy-proven oral premalignant disorders

STUDY	# PT	# LESIONS BIOPSIED	POP	SITE	SCREENING METHOD	HISTOLOGY/COMPARISON	SENS	SPEC	PPV	NPV
Mashberg, 1980	178	235	MC	Ns	COE	**Ca**	96.5			
Mashberg, 1980	178	235	MC	Ns	COE	**Cis**	91.7			
Zheng, 2004	49	118	MC	Ns	Fluorescence	**Benign vs. Ca**	98.0	96.0		
Onizawa, 1999	130	130	DC	Ns	Fluorescence	**Ca**	91.1	84.3	90.0	86.0
Onizawa, 1996	30	32	DC	Ns	Fluorescence	**Ca**	88.0	94.0	93.0	88.0
Betz, 2002	50	137	ENT	Ns	Fluorescence	**Ca**	87.8	56.4		
Muller, 2003	15	91	MC	Ns for biopsy	Fluorescence	**Dysplastic vs. Ca**	64.0	90.0	90.0	64.0
Zheng, 2004	49	118	MC	Ns	Fluorescence	**Dysplastic vs. Ca**	98.0	92.0		
Mashberg, 1980	178	235	MC	Ns	TB	**Ca**	94.3			
Mashberg, 1980	178	235	MC	Ns	TB	**Cis**	91.7			
Mashberg, 1981	105	105	MC	Ns	TB application	**Ca**	98.2	91.1		
Mashberg, 1981	105	105	MC	Ns	TB rinse	**Ca**	94.7	92.7		
Warnakulasuriya, 1996	102	145	DC	Ns	TB rinse	**Ca**	100.0			

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