PATIENT EXPERIENCES WITH HIGH-RISK ORAL LESIONS FROM DETECTION TO DIAGNOSIS

by

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ABSTRACT

With <50% 5-year survival rates, oral cancer is often diagnosed at late-stage. Detection of lesions at earlier stages results in better prognosis. Continued tobacco use after cancer treatment is a risk for recurrence. However, little is known of the process from lesion identification to diagnosis, impact of smoking behavioural changes and barriers for tobacco cessation in patients with a high-risk oral lesion (HRL) diagnosis.

Two survey-type questionnaires were used to collect data on tobacco usage and patient experiences leading to HRL diagnosis. Patients attending the BC Cancer Agency diagnosed with HRLs within 12 months of interview were invited to participate in Study I. Patients who also smoked ≥100 cigarettes within 5 years of questionnaire were eligible for Study II.

Among 150 Study I patients, 61% were self-identified (SIG) and 39% were professionally screened (PSG; 88% by dental professionals). PSG identified significantly more precancerous lesions compared with SIG (54% vs. 23%, $P = 0.0003$) and was more likely to screen ever smokers ($P = 0.05$). SIG showed significantly higher rates of time delay from detection to diagnosis ≥3 months, compared with PSG (58% vs. 36%, $P = 0.007$). Frequency of dental visits strongly
correlated with identification of HRLs by healthcare professionals ($P = 0.004$).

Common symptoms for SIG were pain (77%) and non-healing ulcers (62%), which prompted patients to seek healthcare, while 71% of PSG patients were asymptomatic. Surprisingly, almost half (47%) of patients were not aware of oral cancer.

Of 58 Study II patients, main tobacco cessation barriers included stress (67%), smoking enjoyment (64%), and not being ready to quit (60%). Increased nicotine intake may be associated with increased difficulties with tobacco cessation. Knowledge of health risks from tobacco usage (71%) and tobacco cessation aids (43%) were main cessation facilitators. The HRL diagnosis was a pivotal factor for patients to stop or reduce cigarette consumption.

Oral cancer screening by healthcare professionals, particularly dental professionals, can facilitate identification of earlier oral lesions at risk of cancer progression. Promotion of oral cancer awareness and tobacco cessation for patients and healthcare professionals may facilitate earlier diagnosis of oral lesions and prevent recurrent lesions.
This dissertation is an original intellectual product of the author, Darlene Tam. The fieldwork reported in Chapters 2 and 3 were covered by UBC/BCCA Ethics Review Board Certificate numbers H07-01942 and H10-01406, respectively.

The research presented herein was performed in collaboration between Darlene Tam and her graduate supervisory committee (Drs. Catherine Poh, Miriam Rosin, Jonn Wu, and Lewei Zhang), the BC Cancer Agency Head and Neck New Patient Clinic (Drs. Eric Berthelet, John Hay, and Jonn Wu), and the Oral Oncology Clinic (Drs. Allan Hovan and Catherine Poh).

The identification and design of the research program was a joint effort between the graduate supervisor, Dr. Catherine Poh and the author, Darlene Tam. The survey questionnaire implemented for Study I: Experience to Diagnosis (ETD), as described in Chapter 2 and shown in APPENDIX A.2, is a refinement and extension of a questionnaire developed by Heather C. Biggar and Dr. Catherine Poh. The survey questionnaire implemented for Study II: Tobacco Usage and Diagnosis (TUD), as described in Chapter 3 and shown in APPENDIX A.4, is a joint development between Darlene Tam and Dr. Catherine Poh. Performance of the data collection and analysis of the research was done completely by Darlene Tam, with input from Dr. Catherine Poh regarding the data inclusion.
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<th>Definition</th>
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<tbody>
<tr>
<td>BaP</td>
<td>Benzo[α]pyrene</td>
</tr>
<tr>
<td>BCCA</td>
<td>BC Cancer Agency</td>
</tr>
<tr>
<td>BED</td>
<td>Biologically Effective Dose</td>
</tr>
<tr>
<td>cdk</td>
<td>Cyclin-dependent kinase</td>
</tr>
<tr>
<td>CIS</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>CTS</td>
<td>Continues to Smoke</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome</td>
</tr>
<tr>
<td>DD2</td>
<td>Moderate Dysplasia</td>
</tr>
<tr>
<td>DD3</td>
<td>Severe Dysplasia</td>
</tr>
<tr>
<td>DDS</td>
<td>Doctor of Dental Surgery (Dentist)</td>
</tr>
<tr>
<td>DDS Specialist</td>
<td>Dental Specialist</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DTD</td>
<td>Detection to Diagnosis</td>
</tr>
<tr>
<td>ETD</td>
<td>Experience to Diagnosis</td>
</tr>
<tr>
<td>HNNP</td>
<td>Head and Neck New Patient</td>
</tr>
<tr>
<td>HP</td>
<td>Health Professional</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papillomavirus</td>
</tr>
<tr>
<td>HRL</td>
<td>High-Risk Oral Lesion</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>ID</td>
<td>Identification</td>
</tr>
<tr>
<td>NNK</td>
<td>Nicotine-derived nitrosamine ketone</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
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<td>--------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>NNN</td>
<td>N'-nitrosonornicotine</td>
</tr>
<tr>
<td>NRT</td>
<td>Nicotine Replacement Therapy</td>
</tr>
<tr>
<td>OO</td>
<td>Oral Oncology</td>
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<tr>
<td>OPL</td>
<td>Oral Premalignant Lesion</td>
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<tr>
<td>OSCC</td>
<td>Oral Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>PAH</td>
<td>Polycyclic Aromatic Hydrocarbon</td>
</tr>
<tr>
<td>PSG</td>
<td>Professionally Screened Group</td>
</tr>
<tr>
<td>QAD</td>
<td>Quit After Diagnosis</td>
</tr>
<tr>
<td>QBD</td>
<td>Quit Before Diagnosis</td>
</tr>
<tr>
<td>RDH</td>
<td>Registered Dental Hygienist</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous Cell Carcinoma</td>
</tr>
<tr>
<td>SCCHN</td>
<td>Squamous Cell Carcinoma of the Head and Neck</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SFT</td>
<td>Second Field Tumour</td>
</tr>
<tr>
<td>SIG</td>
<td>Self-Identified Group</td>
</tr>
<tr>
<td>SPT</td>
<td>Second Primary Tumour</td>
</tr>
<tr>
<td>TSNA</td>
<td>Tobacco-specific N-nitrosamine</td>
</tr>
<tr>
<td>TTM</td>
<td>Transtheoretical Model</td>
</tr>
<tr>
<td>UADT</td>
<td>Upper Aerodigestive Tract</td>
</tr>
<tr>
<td>vs.</td>
<td>Versus</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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LIST OF SYMBOLS

Study I: Experience to Diagnosis (ETD)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>⭐</td>
<td>Dental Specialist</td>
</tr>
<tr>
<td>◊</td>
<td>Dentist</td>
</tr>
<tr>
<td>❌</td>
<td>Medical Doctor</td>
</tr>
<tr>
<td>🔖</td>
<td>Medical Specialist</td>
</tr>
<tr>
<td>⚪</td>
<td>Professionally Screened Group (PSG)</td>
</tr>
<tr>
<td>⬤</td>
<td>Registered Dental Hygienist</td>
</tr>
<tr>
<td>⬡</td>
<td>Self-Identified Group (SIG)</td>
</tr>
<tr>
<td>( T_0 )</td>
<td>Time of initial HP visit or detection</td>
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</table>

Diagnostic outcome of the high-grade HRL, as indicated above the X – axis:

<table>
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<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>⋁</td>
<td>Carcinoma \textit{in situ}/CIS</td>
</tr>
<tr>
<td>⋄</td>
<td>Squamous Cell Carcinoma/SCC</td>
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Diagnostic outcome of the dysplastic HRL, as indicated below the X – axis:

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>⋁</td>
<td>Moderate Dysplasia/DD2</td>
</tr>
<tr>
<td>⋄</td>
<td>Severe Dysplasia/DD3</td>
</tr>
</tbody>
</table>
Referral pathway for each high-grade HRL, as indicated above the X – axis:

- Carcinoma in situ/CIS
- Squamous Cell Carcinoma/SCC

Referral pathway for each dysplastic HRL, as indicated below the X – axis:

- Moderate Dysplasia/DD2
- Severe Dysplasia/DD3

Study II: Tobacco Usage and Diagnosis (TUD)

- ♦ Number of Cigarettes Smoked Before HRL Diagnosis
- ◆ Number of Cigarettes Smoked After HRL Diagnosis
- ♣ Quit Before HRL Diagnosis
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give even a fraction of what you give to the public every day.

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- The UBC Faculty of Dentistry Research Day Student Poster Competition Award
DEDICATION

I dedicate this thesis to all of the women and children who have had to endure challenges in life in order to achieve their life goals. This thesis is also dedicated to my mentor and life-long friend, Dr. Robert Cory, for always believing in me and encouraging me to be the best that I can be. I will always remember how you inspired me to never give up when I thought I was not capable of achieving a goal. As you put it, “Nothing is impossible.” I further dedicate this thesis to my beautiful best friend, SoCo, who patiently waited to go out for his walks and lovingly sat by me during those many late nights of writing. Thank you, Bob and SoCo for your loving support over the years.
1. **Introduction**

Oral squamous cell carcinoma (OSCC) is a devastating disease with high morbidity and high mortality. Globally, OSCC ranks sixth amongst all cancers (Nair and Pillai, 2005; Li and Sturgis, 2006; Giuliano, Tortolero-Luna et al., 2008; Saman, 2012) and is characterized by aggressive localized tumours with debilitating treatments (Li and Sturgis, 2006). Additionally, OSCC is associated with 50% 5-year survival rates, 30% recurrence rates, and high rates of second primary malignancies, (Szentirmay, Pólus et al., 2005; Li and Sturgis, 2006).

Ninety-five percent (95%) of oral cancers are squamous cell carcinomas (Villa, Villa et al., 2011). Oral squamous cell carcinoma (OSCC) has a global incidence of over 300,000 newly-diagnosed cases (Herrero, 2003; Tsantoulis, Kastrinakis et al., 2007; Warnakulasuriya, 2009), and 128,000 deaths every year world-wide (Jemal, Bray et al., 2011). Canada alone, had 4,000 newly-diagnosed cases and 1,150 deaths due to OSCCs in 2012 (Canadian Cancer Society’s Steering Committee on Cancer Statistics, 2012), while British Columbia had 461 newly diagnosed cases and 170 deaths as a result of OSCCs in 2009 (BC Cancer Agency, 2009). With less than 50% 5-year survival rates, OSCC has one of the lowest survival rates among the major types of human cancers (Yu, Wood et al., 2008). It affects twice as many males as females (Scully and Bedi, 2000; Silverman,
2001; Neville and Day, 2002), with over 90% of cases affecting people 45 years of age and older (Silverman, 2001; Warnakulasuriya, 2009).

Due to the impact of field cancerization with the carcinogens in tobacco, effects can be observed on large surface areas such as the entire mucosal surface of the aerodigestive tract (Day, Blot et al., 1994). Continuous tobacco consumption after surgery for high-risk oral lesions (HRLs) has been associated with a risk of local recurrence and formation of a second primary malignancy (Day, Blot et al., 1994; Khuri, Kim et al., 2001; Do, Johnson et al., 2003). Second primary cancers develop in one-third of patients with Stage III or IV OSCC, commonly at the same site within 3 years of first tumour diagnosis (recurrent lesions), or at new sites in other head and neck areas, the esophagus, and/or lung (Day, Blot et al., 1994; Khuri, Kim et al., 2001; Braakhuis, Tabor et al., 2003; Li and Sturgis, 2006). With tobacco and alcohol risk behaviours contributing to about three-quarters of cases, oral cancer is recognized as a preventable disease (Reichart, 2001; Kademani, 2007). However, little is known about the impact of smoking behavioural changes in patients with a diagnosis of HRLs or their barriers for tobacco cessation, with currently only one study reporting pre- and post-diagnosis tobacco usage (Mayne, Cartmel et al., 2009).

1.1 Early Detection – Better Outcome

Approximately 50% of high-risk oral lesions (HRLs) present as late-stage (Stage III – IV) cancers at the time of diagnosis (Kantola, Jokinen et al., 2001;
Gómez, Warnakulasuriya et al., 2010). Advanced stage (Stage III and IV) oral cancer is associated with a high mortality rate and 5-year survival rate of 20% (Stahl, Meskin et al., 2004; Yu, Wood et al., 2008). Therefore, OSCC has a poor prognosis. Patients who experience delays have a 30% higher chance of presenting with advanced stage cancers at the time of diagnosis (Gómez, Seoane et al., 2009). Detection of oral squamous cell carcinomas (OSCCs) at its early stages (Stage I – II) results in better prognosis overall, with 5-year survival improving to 80% (Silverman, 2001; Neville and Day, 2002; Stahl, Meskin et al., 2004). Treatments for late-stage oral cancer are also more aggressive, resulting in higher morbidity compared to that of early-stage oral cancer, due to increased scarring, disfigurement, dysphagia and difficulties with speaking (Vokes, Weichselbaum et al., 1993; Kantola, Jokinen et al., 2001). Detection of lesions at its earlier stages, therefore, results in decreased morbidity and mortality, as well as improved quality of life (Neville and Day, 2002; Peacock, Pogrel et al., 2008; Baykul, Yilmaz et al., 2010). Reasons for OSCC being diagnosed at its late stages are unclear, however, deficiencies in professional and public awareness may partly attribute to the late diagnosis (Silverman, 2001). Further investigation is warranted to explore the reasons for delay in diagnosis, as early detection is key in reducing morbidity and mortality for this disease.

1.1.1 Clinical Problems in Early Detection

Health professionals typically utilize tactile assessment and white light visualization as a means for clinical inspection for oral premalignant lesions (OPLs)
and oral cancer (Lingen, 2010). To the untrained professional, OPLs and some early-stage oral cancers may appear as inflammatory lesions or may be easily missed without the assistance of adjunctive screening aids, such as toluidine blue and fluorescent visualization devices (Lingen, 2010).

Patients who are referred to a specialist promptly by the health professional during their initial visit have significant reductions in professional and total diagnostic delay, when compared with patients who received no follow-up (Yu, Wood et al., 2008). Surprisingly, one study found that approximately 13% of health professionals did not recommend a referral to a specialist after initial visit (Yu, Wood et al., 2008).

### 1.1.2 Patient Factors

#### 1.1.2.1 Gender Differences

Females are associated with greater total delays from initial detection to diagnostic workup, when compared with males (Yu, Wood et al., 2008). It is unclear whether this gender difference is attributed to patient delay or professional delay.

#### 1.1.2.2 Tobacco Use

Non-smoking patients experience longer professional and total diagnostic delays as opposed to those who smoke (Yu, Wood et al., 2008). Health professionals may be more attentive at performing risk factor driven screenings for
oral cancer, rather than adopting a universal approach to oral cancer screening (Yu, Wood et al., 2008).

1.1.2.3 Frequency of Dental Visits

The absence of regular annual dental visits is a strong indicator of patient and professional diagnostic delay (Yu, Wood et al., 2008). Patients who are under the care of a dental professional have a better chance of receiving an oral cancer examination for earlier detection of a high-risk oral lesion, as opposed to those who are not seeking regular dental care.

1.2 Risk Factors

Numerous risk factors for oral squamous cell carcinoma (OSCC) are identified, including tobacco use, alcohol consumption, genetics, decreased immune function, poor diet, and infections (Neville and Day, 2002; Castellsague and Munoz, 2003; Herrero, 2003; Walker, Boey et al., 2003; Baseman and Koutsky, 2005; Döbróssy, 2005; Nair and Pillai, 2005; Syrjänen, 2005; Szentirmay, Pólus et al., 2005; Castro and Bussoloti Filho, 2006; de Visser, Eichten et al., 2006; Li and Sturgis, 2006; Gillison, 2007; Kademani, 2007; Sturgis and Cinciripini, 2007; Tsantoulis, Kastrinakis et al., 2007; Giuliano, Tortolero-Luna et al., 2008; Hennessey, Westra et al., 2009). Main risk factors include tobacco and alcohol risk behaviours, which contribute to about three-quarters of OSCC cases (Reichart, 2001; Kademani, 2007; Saman, 2012) and increasingly, human papillomavirus
With these risk behaviours modifiable by individual autonomy, oral cancer is recognized as a preventable disease.

1.2.1 Tobacco

Traditionally, tobacco and alcohol risk behaviours contribute to about three-quarters of cases (Reichart, 2001; Kademani, 2007). According to the World Health Organization (WHO), it is estimated that there are at least 1.2 billion smokers worldwide, with smoking rates on the decline at a rate of 3% per year in North America from the 1970s onwards (Guindon and Boisclair, 2003; Hecht, 2003). Despite reductions in North American smoking habits since the 1970s and a subsequent reduction of tobacco-related OSCC in the general population, there is an increasing trend of OSCC in patients of younger age (<45 years) with no history of smoking or drinking abuse (Llewellyn, Johnson et al., 2004; Fakhry and Gillison, 2006; Li and Sturgis, 2006; Sturgis and Cinciripini, 2007; Gillison, Chaturvedi et al., 2008; Giuliano, Tortolero-Luna et al., 2008; Novakova and Laco, 2008; Vidal and Gillison, 2008).

Tobacco, or *Nicotiana tabacum*, is from the *Solanaceae* family of plants (Health Canada, 2002; IARC, 2004). Tobacco can be chewed on its own or smoked in cigarettes, cigars, pipes, or bidis (where a small amount of tobacco is wrapped in a leaf of a different plant) (IARC, 2004). Smoking is now the most common method of tobacco usage in North American and European countries, while the use of bidis is a lesser known manner that is normally adopted in South Asia (IARC, 2004). The
WHO estimates about 1 billion males and 250 million females who are daily smokers around the world (Hecht, 2003). Cigarettes have been manufactured since the mid-nineteenth century, but did not gain popularity until the early twentieth century. Cigarette smoking began with increased consumption by males in North American and European countries, followed by females decades later in these nations. Consumption of cigarettes by males of developing countries such as China, did not begin until about 50 years later, during the last quarter of the twentieth century (IARC, 2004). As a result, the epidemic of tobacco-related diseases has experienced a lag for females in developed countries, as well as for males of developing nations (IARC, 2004).

Tobacco smoking is associated with cancers of multiple organ sites, including cancers of the upper respiratory tract (nasal cavities, paranasal sinuses, nasopharynx), upper aerodigestive tract (oral cavity, larynx, pharynx), esophagus, lungs, stomach, liver, kidneys, pancreas, bladder, colon, cervix, and blood or bone marrow (leukemia) (Shields, 2000; Hecht, 2003; Sarna, Cooley et al., 2003; Sasco, Secretan et al., 2004; Vineis, Alavanja et al., 2004). Tobacco is the single most preventable cause of morbidity and mortality (Hecht, 2003). Mortality is 4.9-fold higher for current smokers at the time of cancer diagnosis, as compared to never smokers during post treatment follow-up (Mayne, Cartmel et al., 2009). Heavy smoking is the consumption of 20 or more cigarettes a day, and is associated with greater risk of malignant transformation (Jaber, Porter et al., 1999). Worldwide, it causes 4 million deaths annually, with 1.8 million deaths attributed to tobacco-
related cancers (IARC, 2004; WHO, 2008). In the midst of 7.9 million total cancer deaths occurring globally every year, tobacco accounts for almost 25% of all cancer-associated fatalities (WHO, 2008).

1.2.1.1 Tobacco Carcinogens

There are over 3,500 chemicals in cigarette smoke, with at least 60 of them being known carcinogens and tumour promoters that are classified as Group 1, 2A, 2B and 3 carcinogens (Physicians for a Smoke-Free Canada, 1999; Hecht, 2003; Chi, Appleton et al., 2009; IARC, 2012). Additionally, at least 16 known carcinogens can be found in unburned tobacco (Hecht, 2003). Table 1.1 is adapted from Physicians for a Smoke-Free Canada and provides a summary of the current classification of some of the known carcinogens in tobacco smoke (Physicians for a Smoke-Free Canada, 1999; IARC, 2004; IARC, 2007; IARC, 2012).

Both smokeless (chewing) and smoking tobaccos are classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens (IARC, 2012). Group 1 carcinogens are agents that have sufficient evidence of carcinogenicity to humans (IARC, 2004). Group 2A agents have limited evidence of carcinogenicity to humans but sufficient evidence of carcinogenicity in animals, Group 2B agents have limited evidence of carcinogenicity to humans and limited to sufficient evidence of carcinogenicity in animals, Group 3 agents have insufficient evidence to classify them as carcinogenic to humans, and Group 4 agents have evidence suggesting no carcinogenicity in humans (IARC, 2004; IARC, 2007).
Some of the more potent carcinogens include polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific N-nitrosamines (TSNAs) (Hoffmann, Rivenson et al., 1991; Shields, 2000; Hecht, 2003; Hecht, Carmella et al., 2008; Chi, Appleton et al., 2009). Examples of PAHs and TSNAs include benzo[α]pyrene (BaP), nicotine-derived nitrosamino ketone (NNK), and N'-nitrosonornicotine (NNN). Table 1.2 is adapted from S. S. Hecht and summarizes some tobacco carcinogens and their related oral cancer sites (Hecht, 2003).
Table 1.1  Classification of Known Carcinogens in Tobacco Smoke

<table>
<thead>
<tr>
<th>Group 1 Carcinogenic to Humans</th>
<th>Group 2A Probably Carcinogenic to Humans</th>
<th>Group 2B Possibly Carcinogenic to Humans</th>
<th>Group 3 Carcinogenicity to Humans Not Classifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Smoking and Tobacco Smoke</td>
<td>Acrylonitrile</td>
<td>Acetaldehyde</td>
<td>Crotonaldehyde</td>
</tr>
<tr>
<td>1,3-Butadiene* Cadmium Chromium Ethylene Oxide* Formaldehyde* 2-Naphthylamine Nickel 4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butane (NNK)** N'-Nitrosouanonicotine (NNN)** ortho-Toluidine** Polonium-210 (Radon) Vinyl Chloride</td>
<td>N-Nitrosodimethylamine***</td>
<td>Dibenz[a,j]acridine</td>
<td>7H-Dibenzo[c,g]carbazole Dibenzo[a,j]pyrene 1,1-Dimethylyhydrazine Furan Hydrazine Indeno[1,2,3-cd]pyrene Isoprene Lead 5-Methylchrysene 2-Nitropropane N'-Nitrosodiethanolamine N'-Nitrosomethylethylamine N'-Nitrosomorpholine N'-Nitrosopyrrolidine Quinoline</td>
</tr>
</tbody>
</table>

*Status upgraded from Group 2A carcinogen to Group 1
**Status upgraded from Group 2B carcinogen to Group 1
***Status upgraded from Group 2B carcinogen to Group 2A
****Status upgraded from Group 3 carcinogen to Group 2B

Table 1.2  Oral Cancer Sites and Their Related Tobacco Carcinogens

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Tobacco Carcinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>PAH, NNK (in combination with human papillomavirus)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>NNN, other nitrosamines</td>
</tr>
<tr>
<td>Larynx</td>
<td>PAH</td>
</tr>
<tr>
<td>Oral cavity (smokers)</td>
<td>PAH, NNK, NNN</td>
</tr>
<tr>
<td>Oral cavity (smokeless tobacco)</td>
<td>NNK, NNN</td>
</tr>
</tbody>
</table>
1.2.1.2 Tobacco Carcinogenesis

Tobacco carcinogenesis is a multistage process that may take place over a course of 30 years due to cycles of chronic irritation, detoxification, cellular damage, DNA repair and programmed cell death (apoptosis) (Lai and Shields, 1999; Hecht, 2003). It is initiated by a biologically effective dose (BED) of carcinogen(s), which is dependent on 1) the number of cigarettes smoked every day, 2) the type of cigarette smoked (i.e., filtered/non-filtered, mentholated, length, tar and nicotine content), 3) individual smoking style (i.e., inhalation/no inhalation, duration of inhalation, interval between puffs, number of puffs taken per cigarette before it is discarded), 4) carcinogen metabolism (i.e., host cellular metabolic activation and detoxification), 5) DNA damage (i.e., availability and effectiveness of DNA repair enzymes and cell cycle efficiency), and 6) cell survival (i.e., whether cells undergo necrosis and apoptosis) (Shields, 2000). Once a BED is achieved, cellular enzymes (i.e., cytochrome P450 [CYP]) transform carcinogens into reactive intermediates, since most carcinogens are biologically inactive prior to this (Shields, 2000; Hecht, 2003). The reactive intermediates then form carcinogen-DNA-adducts that promote DNA damage or epigenetic alterations (Shields, 2000). Two types of DNA adducts formed by TSNAs (methylation and pyridoxylbutylation of nucleotides) are required for carcinogenesis (Shields, 2000). If the host is unable to inhibit, delay or reverse the damage caused by the carcinogen-DNA-adducts with its own immunity or with the help of dietary or pharmacological chemopreventive agents, subsequent mutation and genetic defects will occur in critical regions of proto-oncogenes to form oncogenes (i.e., RAS and MYC), or in tumour-suppressor genes (i.e., p53 and cdk
inhibitor 2A, which encodes p16), resulting in uncontrolled proliferation (Hong and Sporn, 1997; Hecht, 2003; Surh, 2003). Apoptosis must be induced in order to remove DNA-damaged cells, otherwise tumorigenesis will persist.

DNA adducts, protein adducts and urinary metabolites are carcinogen biomarkers, which are indicative of carcinogen uptake, metabolic activation and detoxification in people who smoke or who are exposed to second hand smoke (Hecht, 2003). Such biomarkers can be used as a measure of carcinogen metabolism. Carcinogen metabolism may differ from person to person due to interindividual variations in genetic susceptibility (Lai and Shields, 1999). This in turn translates to differences in the frequency of metabolites binding to DNA to cause mutations, and therefore cancer risk (Hecht, 2003).

1.2.1.3 **p53 Tumour Suppressor Protein**

p53 tumour suppressor protein regulates the cell cycle by controlling p16, p21, MDM2, GADD45, bax, c-Myc, and bcl-2 genes (Li and Sturgis, 2006). Consequently, p53 is involved in maintenance of genomic stability, regulation of the cell cycle, DNA repair, and apoptosis (Shields, 2000; van Oijen and Slootweg, 2000; Hsieh, Huang et al., 2005). p53 plays a key role in DNA repair by stopping the synthesis of p21 cell cycle inhibitor at the Gap 1 phase, therefore preventing the formation of cyclin-cdk complexes that are needed for Gap 1 to proceed to the Synthesis phase (Ramet, Castren et al., 1995; Bunz, Dutriaux et al., 1998). When epigenetic alterations occur, cell cycle arrest at Gap 1 inhibits DNA replication and
mitosis (Bunz, Dutriaux et al., 1998). However, mutations in p53 can result in uncontrolled proliferation due to an inability to arrest the cell cycle at the Gap 1 checkpoint to promote DNA repair and apoptosis.

Approximately 50% of all cancers and 90% of SCCHNs exhibit p53 gene mutations, making them the most common alteration associated with human cancers (Ramet, Castren et al., 1995; Husgafvel-Pursiainen, Boffetta et al., 2000; van Oijen and Slootweg, 2000; Zienolddiny, Ryberg et al., 2001; Pfeifer, Denissenko et al., 2002; Hsieh, Huang et al., 2005). Evidence shows that benzo[a]pyrene (a PAH tobacco carcinogen), promotes DNA damage of p53 and results in its genetic mutation (Ramet, Castren et al., 1995; Shields, 2000). Additionally, smokers have a 3-fold increased risk of p53 mutations as compared with never smokers, with increased frequency of mutant p53 expression as a lesion progresses from normal cells to cancerous (Husgafvel-Pursiainen, Boffetta et al., 2000; van Oijen and Slootweg, 2000).

1.2.1.4 Field Cancerization

An index or primary tumour is defined as the first tumour that is diagnosed, and a second tumour is any malignancy that arises after the primary cancer (Leon, del Prado Venegas et al., 2009). Some scientists define second primary tumours (SPTs) as cancers that develop independently from the primary tumour, and characterize locally recurrent lesions or second field tumours (SFTs) as cancers occurring due to tumour cells from the original field remaining after surgery.
for a primary tumour (Braakhuis, Tabor et al., 2003). However, many other scientists consider SPTs, SFTs, recurrent lesions and multiple primary tumours to be analogous with one another (Bedi, Westra et al., 1996; van Oijen and Slootweg, 2000; Ha and Califano, 2003; Leon, del Prado Venegas et al., 2009). A SPT is classified as “synchronous” if it is diagnosed within 6 months of the primary tumour, or “metachronous” if it is discovered more than 6 months from the date of diagnosis of the primary tumour (Bedi, Westra et al., 1996; Leon, del Prado Venegas et al., 2009). Second and multiple primary cancers have been found to be associated with the oral cavity, pharynx, larynx, esophagus, upper aerodigestive tract (UADT), lungs, breast, skin, colon, bladder, vulva and cervix (Day, Blot et al., 1994; Wang, Christiani et al., 1999; Braakhuis, Tabor et al., 2003). Recurrent lesions occur in 10-30% of patients with late-stage (Stage III and IV) squamous cell carcinomas of the head and neck (SCCHNs), while 2-3% of patients with respiratory system and upper aerodigestive tract cancers experience second primary tumours (SPTs) (van Oijen and Slootweg, 2000; Braakhuis, Brakenhoff et al., 2005). Additionally, 4-7% of tobacco-induced upper aerodigestive tract cancers result in recurrent cancers or SPTs (Do, Johnson et al., 2003), which is evidence of tobacco’s role in increasing the risk of second cancers, making second cancers an important treatment consideration (Thomson, 2002).

In 1953, while investigating OSCCs, Slaughter et al. proposed the concept of “field cancerization” to explain the development of widespread recurrent lesions, second cancers and multiple primary tumours (Bedi, Westra et al., 1996; van Oijen
and Slootweg, 2000; Wiencke and Kelsey, 2002; Braakhuis, Tabor et al., 2003).
Tobacco or alcohol use, long-term effects of cancer treatment, host susceptibility, environmental factors, and genetic interactions can all contribute to the development of second or multiple cancers (Ng and Travis, 2008; Leon, del Prado Venegas et al., 2009). Slaughter et al. theorized that primary field cancers develop as independent multiple transforming events when exposure to a carcinogen “preconditions” a widespread span of normal epithelium, making it more susceptible to multiple genetic alterations (van Oijen and Slootweg, 2000; Wiencke and Kelsey, 2002). “Patches” of genetically unrelated (multiclonal) units of transformed daughter cells form along the field (Braakhuis, Tabor et al., 2003). Through normal processes of cancerization, the patches develop into multiple tumours, beginning with a BED of carcinogen that is activated by cellular enzymes (i.e., CYP) into reactive molecules (Shields, 2000; Hecht, 2003). This results in DNA damage or epigenetic alterations and subsequent cellular proliferation (Shields, 2000; Braakhuis, Tabor et al., 2003; Hecht, 2003). Fields exist as widespread lesions and can be more than 7 cm in diameter (Braakhuis, Tabor et al., 2003; Braakhuis, Brakenhoff et al., 2005).

An alternate theory of field cancerization proposed during the 1990s involves widespread migration of rare transformed cells that can follow one of two different pathways (Bedi, Westra et al., 1996; Califano, van der Riet et al., 1996; Partridge, Emilion et al., 1997; van Oijen and Slootweg, 2000; Thomson, 2002). In the first pathway, tumour cell migration occurs from one location to another when a single tumour cell hitch-hikes onto saliva and establishes itself within a new site.
along the affected epithelium (i.e., UADT) (van Oijen and Slootweg, 2000; Braakhuis, Tabor et al., 2003). In the second pathway, tumour cell migration takes place intraepithelially by way of blood or lymph from the original patch location to another (van Oijen and Slootweg, 2000; Braakhuis, Tabor et al., 2003). A single migrating progenitor tumour cell establishes itself in the lung or lymph nodes, rather than the mucosal lining of the affected epithelium (i.e. UADT) (van Oijen and Slootweg, 2000; Braakhuis, Tabor et al., 2003). As such, the two pathways explain the difference in presentation of migrating tumours that may appear on the mucosal surface of an affected epithelium, or within the lungs or lymph. Since the tumours arise from migration of a single transformed cell, they are genetically related and are monoclonal in origin.

1.2.1.5 Evidence for Tobacco-Related Field Cancerization

In patients with second and multiple cancers, certain characteristics were more frequently found in smokers and ex-smokers as compared to non-smokers, suggesting evidence for tobacco-induced field effects. These characteristics include loss of chromosome Y, abnormal expression of cytokeratins 7 and 8, increased proliferation of epithelial cells, which could provide for “fertile soil” to facilitate genetic alterations, p53 mutations, and reduction in cytoplasmic area (van Oijen and Slootweg, 2000). Additionally, evidence suggests that genetic polymorphisms for glutathione S-transferase enzymes, which metabolize tobacco smoke products, can predict an individual’s vulnerability to tobacco-related second and multiple cancers (Tomek and McGuirt, 2003).
Due to the impact of field cancerization with the carcinogens in tobacco, effects can be observed on large surface areas such as the entire mucosal surface of the aerodigestive tract (Day, Blot et al., 1994). Continuous tobacco smoking after surgery for primary cancer has been associated with a risk of local recurrence and formation of SPTs (Day, Blot et al., 1994; Khuri, Kim et al., 2001; Do, Johnson et al., 2003). Second primary cancers develop in up to one-third of patients with Stage III or IV OSCCs, commonly at the same site within 3 years of the first tumour diagnosis (recurrent lesions), or at new sites in other head and neck areas, the esophagus, and/or lung (Khuri, Kim et al., 2001; Do, Johnson et al., 2003; Braakhuis, Brakenhoff et al., 2005). Figure 1.1 shows an example of second primary cancers as a result of the effects of field cancerization due to continued tobacco use in a patient previously treated for OSCC.
Figure 1.1  Example of the Development of Multiple Oral Lesions Over Time of a Smoker

A 63-year-old male smoker with a history of oral cancer at the right anterior tonsillar pillar (first tumour).  A. A 1-cm polypoid lesion (SCC) developed at the left ventral tongue (arrow, 2nd tumour) 11 years after initial treatment of the first tumour at the right tonsillar pillar.  B. A small SCC developed on the lingual frenum 10 months after treatment of the second tumour (arrow, 3rd tumour).

1.2.2  Tobacco Cessation

With 3,500 chemicals in cigarette smoke, and at least 60 of these chemicals being known carcinogens, there is strong evidence for the relationship between tobacco use and initiation of multiple organ cancers (Physicians for a Smoke-Free Canada, 1999; Shields, 2000; Hecht, 2003; Sarna, Cooley et al., 2003; Sasco, Secretan et al., 2004; Vineis, Alavanja et al., 2004; Chi, Appleton et al., 2009; IARC, 2012).  A biologically effective dose of tobacco carcinogen(s) is needed before DNA damage and epigenetic alterations occur (Shields, 2000; Hecht, 2003). However, since few studies exist that investigate the association between a biologically effective dose and cancer risk, it is difficult to say what this dosage may
be (Shields, 2000). Further studies, whether retrospective or prospective observational study designs, are needed to investigate this dose-dependent to cancer risk relationship.

Continued tobacco use after treatment for cancers is a risk for local recurrence, second primary cancers, and multiple primary tumours (van Oijen and Slootweg, 2000; Thomson, 2002; Do, Johnson et al., 2003; Braakhuis, Brakenhoff et al., 2005). As initially proposed by Slaughter et al., these second cancers can be explained through the theory of field cancerization. There is limited research relating specifically to tobacco use and the development of second or multiple cancers. However, some evidence for tobacco-related field effects exist for recurrent and second or multiple primary tumours, as is supported by characteristics that were more frequently found in smokers and ex-smokers as compared to non-smokers (van Oijen and Slootweg, 2000; Tomek and McGuirt, 2003). The risk for second or multiple cancers is reduced with smoking cessation if individuals quit successfully for a period of 5 years at first diagnosis (Day, Blot et al., 1994; Do, Johnson et al., 2003). Therefore, cessation strategies are needed to decrease risk of second or multiple primary cancers and recurrent lesions. A combined therapy of support programs and nicotine replacement therapy (NRT) in varying dosages in relation to nicotine dependence has been shown to be effective for tobacco cessation (Tang, Law et al., 1994; Silagy, Mant et al., 2000).
1.2.2.1 Behavioural Approach to Tobacco Cessation

The behavioural approach to tobacco cessation addresses psychological habit through self-help educational resources, group or individual counselling support, and community primary prevention programmes (Cahill, Lancaster et al., 2010; Stanton and Grimshaw, 2013), with a cessation success rate of up to 26% (Hudmon, Corelli et al., 2010). One commonly applied approach to tobacco use behavioural modification is the Transtheoretical Model (TTM) developed by Prochaska et al, which considers ‘Stages of Change’ and ‘Processes of Change’ toward promoting healthier behaviours (DiClemente, Prochaska et al., 1991; Aveyard, Massey et al., 2009; Cahill, Lancaster et al., 2010). TTM theorizes that smokers experience a sequence of motivational stages, and suggests that tailoring interventions to a stage of change improves the likelihood of tobacco use behavioural modification (Aveyard, Massey et al., 2009; Cahill, Lancaster et al., 2010). The motivational stages include: 1) Precontemplation – the individual has no intention of quitting over the next 6 months, 2) Contemplation – the individual is thinking about quitting in the next 6 months, but has not made a commitment to quit, 3) Preparation – intent to quit within the next 30 days and experience with an unsuccessful cessation attempt in the last 12 months, 4) Action – successful tobacco cessation for 6 months or less and actively engaging in tobacco use behavioural modifications, and 5) Maintenance – successful tobacco cessation for more than 6 months, with conscious efforts to maintain a tobacco-free lifestyle (Aveyard, Massey et al., 2009; Cahill, Lancaster et al., 2010). Individuals may undergo different ‘Processes of Change’ in that their thoughts and actions may differ due to their
current stage of motivation for change (DiClemente, Prochaska et al., 1991). Therefore, stage-specific interventions may assist in moving individuals through each stage of change more efficiently than non-stage interventions, as they address distinctive attitudes and behaviours (Cahill, Lancaster et al., 2010). With at least 80% of smokers in the first two motivational stages, TTM-centred interventions are directed towards advancing individuals from precontemplation and contemplation to more advanced stages of tobacco cessation (Aveyard, Massey et al., 2009). TTM acknowledges that due to smoking being an addictive behaviour, relapse in tobacco use and cycling through the stages of change may occur before complete success with tobacco cessation (DiClemente, Prochaska et al., 1991; Cahill, Lancaster et al., 2010). Although the efficacy of the approach over conventional behavioural interventions remains unclear, TTM is shown to be effective in motivating smoking behavioural change (Aveyard, Massey et al., 2009; Cahill, Lancaster et al., 2010). However, studies suggest that conventional behavioural interventions that include preparatory information on smoking cessation targeted to individuals in the preparation stage are at least as effective at facilitating tobacco cessation (Aveyard, Massey et al., 2009; Cahill, Lancaster et al., 2010).

1.2.2.2 **Pharmacotherapy Approach to Tobacco Cessation**

The pharmacotherapy approach to tobacco cessation addresses physical addiction to nicotine and includes nicotine replacement therapies (NRTs), as well as non-nicotine pharmacotherapies. Nicotine withdrawal symptoms may occur within a few hours of tobacco cessation, causing discomfort that can be alleviated by
smoking another cigarette (Frishman, 2009). NRTs facilitate tobacco cessation by penetrating the central nervous system more slowly and in smaller concentrations than nicotine inhaled through tobacco smoking, which decreases the addictive side effects of nicotine and helps to alleviate nicotine withdrawal symptoms (Hudmon, Corelli et al., 2010). NRTs also facilitate tobacco reduction by substituting for some of the nicotine that may otherwise be introduced to the body via tobacco inhalation (Kralikova, Kozak et al., 2009). Most NRTs are available without a prescription in Canada and include: 1) 15 mg 16-hour transdermal nicotine patches, and 7, 14, or 21 mg 24-hour transdermal nicotine patches (i.e., Nicoderm®, Habitrol®) that deliver a continuous low dose of nicotine through the skin to minimize withdrawal symptoms for up to 16 to 24 hours, 2) 2 or 4 mg nicotine gum (i.e., Nicorette®) facilitates absorption of nicotine through the buccal mucosa, with peak nicotine blood levels after 30 minutes of intermittent chewing using the ‘chew and park’ technique, 3) 2 or 4 mg nicotine lozenges (i.e., Thrive®, Commit®) that deliver nicotine to the body in a similar fashion as that of nicotine gum, with peak blood nicotine levels after 60 minutes of dissolving the lozenge intraorally, 4) 10 mg nicotine inhalers (i.e., Nicorette®) which deliver nicotine mainly via absorption through the buccal mucosa and simulate the ‘hand-to-mouth’ ritual that is familiar with cigarette smoking, with peak nicotine blood levels after 30 minutes, and 5) 0.5 mg nicotine nasal sprays (i.e., Nicotrol®, Nicorette®) which are not currently available in Canada and deliver nicotine via absorption through the nasal mucosa, with peak nicotine blood levels after 5-10 minutes (Frishman, 2009; Hudmon, Corelli et al., 2010; Tobacco Free RNAO, 2011; QuitNow.ca, 2013). NRTs can be used alone to
facilitate tobacco reduction and cessation rates of up to 33%, or they may be used in combination with cigarette smoking, other NRTs, and non-nicotine pharmacotherapies to increase tobacco reduction and quit rates up to 45% (Baska, Madar et al., 2001; Frishman, 2009; Hudmon, Corelli et al., 2010).

Non-nicotine pharmacotherapies have tobacco abstinence rates of up to 38%, and include first-line prescription medications, such as Bupropion hydrochloride and Varenicline tartrate and second-line prescription medications, such as Clonidine and Nortriptyline (Frishman, 2009; Hudmon, Corelli et al., 2010). Sustained-release Bupropion hydrochloride (Zyban®, Wellbutrin®) was originally marketed as an antidepressant, but was found to also alleviate nicotine withdrawal (Frishman, 2009; Hudmon, Corelli et al., 2010; Johnson, 2010; Tobacco Free RNAO, 2011). Bupropion acts as a dopamine and norepinephrine reuptake inhibitor to increase the amount of dopamine in the brain, and a nicotinic acetylcholine-receptor antagonist to block the addictive effects of nicotine, thereby reducing withdrawal symptoms and cravings (Frishman, 2009; Hudmon, Corelli et al., 2010; Johnson, 2010; Tobacco Free RNAO, 2011). Treatment with Bupropion lasts for 7-12 weeks and begins 1 week prior to a pre-set quit date, with an initial 150 mg dose titrated up to 150 mg twice daily after 3-5 days (Frishman, 2009). Varenicline tartrate (Champix®) was designed specifically for tobacco cessation (Johnson, 2010). Varenicline is a nicotine receptor partial agonist, which stimulates the release of dopamine and blocks binding of nicotine to its receptors, resulting in reduced nicotine withdrawal symptoms, cravings and satisfaction from smoking (Frishman,
Treatment with Varenicline lasts for a minimum of 12 weeks and begins 1 week prior to a pre-set quit date, with an initial 0.5 mg once daily dose titrated up to 0.5 mg twice daily after 3 days, and 1 mg twice daily after 7 days (Frishman, 2009; Johnson, 2010; Tobacco Free RNAO, 2011).

Due to an increased chance of adverse effects such as orthostatic hypotension, xerostomia, dysgeusia, gastrointestinal disturbances, blurred vision, fatigue, dizziness, sedation and toxicity, Clonidine and Nortriptyline are reserved as second-line prescription non-nicotine pharmacotherapies for individuals who are unsuccessful with or unable to take first-line medications (Frishman, 2009; Hudmon, Corelli et al., 2010; Tobacco Free RNAO, 2011). Clonidine is an α2 adrenergic agonist, which was originally developed as an antihypertensive, but has many other medical applications, including minimizing the acute symptoms of nicotine withdrawal and cravings (Frishman, 2009). Treatment with Clonidine lasts for a maximum duration of 3-4 weeks and begins prior to a pre-set quit date, with an initial 100 µg twice daily dose titrated up to 400 µg twice daily as needed (Frishman, 2009). Nortriptyline is a noradrenergic tricyclic antidepressant that has the ability to reduce symptoms of nicotine withdrawal at daily doses between 75-100 mg for 4-12 weeks (Frishman, 2009; Dhippayom, Chaiyakunapruk et al., 2011). Nortriptyline is indicated for long-term tobacco cessation in individuals with a history of depression (Aubin, Karila et al., 2011).
1.2.2.3 Tobacco Cessation Programs

Programs funded by the B.C. Ministry of Health are available to British Columbia (B.C.) residents to assist with tobacco cessation. These include the B.C. Smoking Cessation Program (BC MOH, 2012) and QuitNow (QuitNow.ca, 2013). Together, these two programs address physical addiction and psychological habit relating to tobacco usage through a combination of medications and counselling or support services, which promote increased tobacco cessation success to 35 percent (Mallin, 2002; QuitNow.ca, 2013).

The B.C. Smoking Cessation Program (BCSCP) is a new program that was implemented on September 30, 2011 (HealthLink BC, 2013). It provides assistance with the cost of smoking cessation aids to B.C. residents with active Medical Services Plan (MSP) coverage, whether they require prescription drugs or non-prescription nicotine replacement therapy (NRT) products to address physical addiction to tobacco products (BC MOH, 2012). Eligible B.C. residents are covered for four weeks of medications, which can be refilled up to three times consecutively (up to 12 consecutive weeks of benefits) per calendar year for prescription or non-prescription smoking cessation aids (BC MOH, 2011).

Prescription drugs covered by the BCSCP as benefits under PharmaCare include bupropion (brand name Zyban®) and varenicline (brand name Champix®) (BC MOH, 2012). PharmaCare coverage for prescription drugs depends on the type of plan that an individual may be registered under (BC MOH, 2011). Individuals
covered by PharmaCare under the Permanent Residents of Licensed Residential Care Facilities (Plan B), Recipients of B.C. Income Assistance plan (Plan C), and No-Charge Psychiatric Medication plan (Plan G) are covered for prescription smoking cessation drugs at 100%. Individuals registered for the Fair PharmaCare plan have variable coverage ranging from 0% to 70-75% and 100% of the eligible cost, depending on whether or not they have met their family's annual deductible and their family maximum for eligible prescription costs. Those who prefer to use prescription smoking cessation aids are not required to register through HealthLink BC, and are advised to contact PharmaCare for eligibility information on low-cost prescription Champix® or Zyban® prior to visiting their physician for a prescription that can be filled at a local pharmacy (HealthLink BC, 2013).

Non-prescription NRT products covered under the BCSCP include two strengths of Thrive™ nicotine chewing gum and three strengths of Habitrol® nicotine patches (BC MOH, 2012). The BCSCP covers 100% of the cost for these non-prescription NRT products. Individuals who prefer NRT products must register through HealthLink BC by dialling 8-1-1 in British Columbia (HealthLink BC, 2013).

QuitNow Services are offered to B.C. residents free of charge to address psychosocial habits and cessation difficulties relating to tobacco usage. Telephone, text, and online Live Chat counselling services are available 24/7 by trained quit coaches to provide support before, during and after a tobacco cessation attempt (QuitNow, 2013; QuitNow.ca, 2013). For those who opt-in to text messaging, a free 3-month QuitNow By TEXT program is available that delivers motivational text
messages tailored to a quit date (QuitNow, 2013; QuitNow.ca, 2013). Community support from individuals who are experiencing tobacco cessation, is also available through the QuitNow-hosted Forum on www.QuitNow.ca and social media sites, such as Facebook (QuitNowBC) and Twitter (@QuitNowBC) (QuitNow, 2013; QuitNow.ca, 2013).

QuitNow offers many resources for tobacco cessation to individuals and healthcare professionals. In addition to an addictions quiz and a cost savings calculator, information on quitting, smoking cessation aids, tips on overcoming cravings or managing withdrawal symptoms, and creating a personalized quit plan can be found on their website (QuitNow.ca, 2013). Healthcare professionals can order general information or information tailored specifically by ethnicity, age and/or gender, or to individuals who are undergoing surgery to assist in tobacco cessation (QuitNow, 2013; QuitNow, 2013; QuitNow, 2013; QuitNow.ca, 2013). Printed and downloaded brochures, booklets, cost calculator tools, magnets, bookmarks, posters, and referral forms to QuitNow Services are all available at no cost to healthcare providers (QuitNow.ca, 2013).

1.2.3 Alcohol

Alcohol is an independent risk factor for oral cancer and its use alone accounts for 52% of the oral and pharyngeal cancer cases (Rodriguez, Altieri et al., 2004). Alcoholic beverages are comprised of ethanol, water, and glucose as ingredients (Reidy, McHugh et al., 2011). While ethanol does not directly cause
carcinogenic effects on the oral mucosal tissues, its metabolite, acetaldehyde, is a known carcinogen (Reidy, McHugh et al., 2011). Consumption of 6 or more alcoholic drinks a day is associated with greater risk of oral cancer (Rodriguez, Altieri et al., 2004). Exact oral squamous cell carcinoma (OSCC) pathogenesis by alcohol is unknown, however alcohol has been shown to work synergistically with tobacco to increase the carcinogenicity of tobacco nitrosamines on mucosal tissues (van Oijen and Slootweg, 2000; Do, Johnson et al., 2003; Kademani, 2007; Reidy, McHugh et al., 2011). Combined heavy use of alcohol and tobacco increases the risk of oral and pharyngeal cancers to 83%, compared with risk of 52% and 77% respectively for their usage independently, due to multiplicative effects (Rodriguez, Altieri et al., 2004). Alcohol is theorized to facilitate increased infiltration of tobacco carcinogens by improving carcinogen solubility, increasing the permeability of the mucosa to tobacco nitrosamines, causing epithelial atrophy and subsequently damaging DNA (Reidy, McHugh et al., 2011). As a result of long-term use, heavy alcohol drinkers may also suffer from systemic effects, such as malnutrition and immunosuppression, which may impact on host resistance to malignant transformation (Reidy, McHugh et al., 2011). For heavy smokers and drinkers who consume more than 100 g of alcohol per day, the risk of oral malignant transformation is more than 100 times greater (Kademani, 2007). Additionally, it has been shown that the risk of oral and pharyngeal cancers is increased by 29% for every 10 g increment of daily alcohol consumed (Guo, Zhang et al., 2012). With 80% of heavy alcohol drinkers reporting that they are also current smokers, alcohol plays an important role in oral carcinogenesis (Zygogianni, Kyrgias et al., 2011).
1.2.4 Others

1.2.4.1 Human Papillomavirus (HPV)

HPV is one of the most common sexually transmitted diseases in the general population (Giuliano, 2007). This may be due to increasing sexual promiscuity, oral sex practices and HPV infection among teenagers and young adults (Li and Sturgis, 2006; Sturgis and Cinciripini, 2007; Chaturvedi, Engels et al., 2008; Psyrri and DiMaio, 2008). By 50 years of age, it is estimated that more than 80% of all sexually active females will have HPV (Kahn, 2005; Conner and Collins, 2008; Huang, 2008). Many oral premalignant and malignant lesions, particularly of the oropharynx, are associated with oncogenic HPV (Ha and Califano, 2004; Hobbs, Sterne et al., 2006). It is estimated that 20% to 30% of all SCCHN are HPV-related (Kreimer, Clifford et al., 2005; Vidal and Gillison, 2008; zur Hausen, 2008). HPV is commonly found in oropharyngeal cancers affecting Waldeyer's tonsillar ring, owing to the fact that the basal mucosal cells of the tonsillar crypts are easily accessible (Campisi, Panzarella et al., 2007; Novakova and Laco, 2008; Termine, Panzarella et al., 2008). Up to 85% of oral premalignant lesions contain HPV deoxyribonucleic acid (DNA) (Ha and Califano, 2004; Campisi, Panzarella et al., 2007), which is evidence of a possible causal association between HPV and oral carcinogenesis progressing from normal epithelium to dysplasia and finally squamous cell carcinoma.
HPV-16 and to a lesser extent HPV-18, is shown to be strongly associated with oral cancer, with approximately 50% of squamous cell carcinomas of the oropharynx being associated with one of these two types (Campo, 2002; Syrjanen, 2003; Ha and Califano, 2004; Kreimer, Clifford et al., 2005; de Visser, Eichten et al., 2006; Campisi, Panzarella et al., 2007; Sturgis and Cinciripini, 2007; Warnakulasuriya, 2009). HPV-16 is also found in a high percentage (up to 90%) of non-smokers diagnosed with SCCHN (Fakhry and Gillison, 2006; Li and Sturgis, 2006; Gillison, 2008; Psyrri and DiMaio, 2008). HPV-16 seropositivity has an adjusted odds ratio for SCCHN development of 2.2, while oropharyngeal cancer and base-of-tongue tumours are 14.4 and 20.7 respectively (Ha and Califano, 2004). Although this is not as significant as the adjusted odds ratio of 74 for cervical squamous cell carcinoma (Ha and Califano, 2004), the link between HPV seropositivity and SCCHN cannot be ignored. Furthermore, despite the decline in HPV DNA over time, the average time between HPV blood serum conversion and cancer diagnosis is demonstrated to be 9.4 yrs, which supports an early role of HPV in malignant transformation (Ha and Califano, 2004).

Interestingly, there are reports of possibly better prognosis associated with HPV 16-positive SCCHN than SCCHN that are HPV-negative (Syrmänen, 2005; Li and Sturgis, 2006; Sturgis and Cinciripini, 2007; Psyrri and DiMaio, 2008). It is uncertain whether HPV 16-positivity alone is responsible for the improved survival, or if it is due to the stronger immune systems of the more youthful patients it affects, as well as improvements in treatment modalities (Li and Sturgis, 2006; Sturgis and
In addition, HPV 16-positive SCCHN is demonstrated to have better response to radiotherapy than non-HPV SCCHN (Szentirmai, Pólus et al., 2005; Chaturvedi, Engels et al., 2008).

HPVs are small, non-enveloped, iso-exahedric capsid-coated, and double-stranded circular DNA viruses that belong to the Papillomaviridae family (Ha and Califano, 2004; Castro and Bussolot Filho, 2006; Li and Sturgis, 2006; Zheng and Baker, 2006; Campisi, Panzarella et al., 2007; Hennessey, Westra et al., 2009). They are host-specific and have an affinity for keratinocytes of squamous epithelial cells (Gillison and Shah, 2003; Nair and Pillai, 2005; Fakhry and Gillison, 2006; Li and Sturgis, 2006; Zheng and Baker, 2006; Campisi, Panzarella et al., 2007; Termine, Panzarella et al., 2008; Hennessey, Westra et al., 2009). Areas where HPV can be found include the cervix, anogenital tract, urethra, skin, oropharynx, larynx, trachea-bronchial and oral mucosa (Campisi, Panzarella et al., 2007). HPVs are considered carcinogenic in the sites that they infect, especially in cases of persistent infection (Nair and Pillai, 2005; Huang, 2008). HPV-related OSCC and cervical cancer demonstrate similarities in their oncogenesis (Sturgis and Cinciripini, 2007). As such, it seems reasonable to extrapolate the HPV carcinogenesis model for cervical cancers to OSCCs (Sturgis and Cinciripini, 2007). While the mode of transmission to the upper aerodigestive tract is still being explored, HPV has been shown to be transmitted through sexual contact (more frequently from male to female), vertical spread during maternal delivery, and self-inoculation (Cason and Mant, 2005; Szentirmai, Pólus et al., 2005; Li and Sturgis, 2006; Campisi,
Panzarella et al., 2007; Giuliano, 2007; Sturgis and Cinciripini, 2007; Giuliano, Tortolero-Luna et al., 2008). Risk factors for infection include young age at first intercourse, multiple sexual partners and oral-genital or oral-anal sex (Gillison and Shah, 2003; Baseman and Koutsky, 2005; Szentirmay, Pólus et al., 2005; Li and Sturgis, 2006; Stanley, 2007; Conner and Collins, 2008; Gillison, 2008).

There are more than 100 different types of HPVs (Syrjanen, 2003; Cason and Mant, 2005; Szentirmay, Pólus et al., 2005; Castro and Bussoloti Filho, 2006; Li and Sturgis, 2006; Campisi, Panzarella et al., 2007; Conner and Collins, 2008; Vidal and Gillison, 2008) that fall into one of two categories based on their association with malignant lesions: low-risk (i.e., HPV-6 and HPV-11) or high-risk (i.e., HPV-16 and HPV-18) (Ha and Califano, 2004; Cason and Mant, 2005; Nair and Pillai, 2005; Szentirmay, Pólus et al., 2005; Li and Sturgis, 2006; Campisi, Panzarella et al., 2007; Tsantoulis, Kastrinakis et al., 2007; Hennessey, Westra et al., 2009). (Table 1.3 summarizes some of the common HPV types.) Low-risk HPVs involve the presence of HPV DNA as a nuclear plasmid and cause benign lesions such as warts and respiratory papillomas, while high-risk HPVs feature DNA integration into the host genome and are associated with high-grade squamous cell neoplasias and carcinomas (Gillison and Shah, 2003; Syrjanen, 2003; Syrjänen, 2005; Li and Sturgis, 2006; Campisi, Panzarella et al., 2007). HPVs can lie in a dormant or latent state for long periods of time in mucosal epithelia before appearing clinically and developing into malignant lesions, which may explain why both types have been found in clinically normal oral mucosa (Campo, 2002; Ha and Califano, 2004; Li and
Sturgis, 2006; Campisi, Panzarella et al., 2007). Its circular genome codes for 6 early-phase genes, 2 late-phase genes, and a long local control region (the regulatory region) (Ha and Califano, 2004; Nair and Pillai, 2005; Li and Sturgis, 2006; Campisi, Panzarella et al., 2007). Early genes regulate DNA replication, transcription, and cellular transformation, while late genes encode for proteins involved in viral proliferation (i.e., viral capsid proteins) and help transfer viral DNA into the cell (Ha and Califano, 2004; Nair and Pillai, 2005; Li and Sturgis, 2006; Campisi, Panzarella et al., 2007). In an HPV-infected state, epithelial cells can appear histologically as acanthosis, dyskeratosis, keratinocyte multinucleation and koilocytosis (Campisi, Panzarella et al., 2007).

Table 1.3 Low-Risk and High-Risk HPV Types

<table>
<thead>
<tr>
<th>Low-Risk HPV</th>
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<tr>
<td>74</td>
<td>53</td>
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*The most important types involved in oral and genital lesions are highlighted in BOLD.*
1.2.4.2 *Mechanisms of HPV-Related Oral Carcinogenesis*

HPV oral carcinogenesis depends on the immune system’s ability to destroy and remove the virus through innate and adaptive immune responses (de Visser, Eichten et al., 2006). Innate immune cells form the first line of defence during acute infection and inflammation, and control adaptive immune response activity (de Visser, Eichten et al., 2006). However, the roles of the two immune responses reverse if inflammation or infection is chronic, whereby adaptive immune cells can cause persistent activation of innate immune cells (de Visser, Eichten et al., 2006). Full activation of adaptive immune cells in response to premalignant or malignant growths can destroy cancer cells, while constant activation of innate immune cells may encourage malignancies by causing chronic tissue damage through inflammatory processes (de Visser, Eichten et al., 2006). More than 15% of all cancers are the result of infection and chronic inflammation (de Visser, Eichten et al., 2006). Immune status is therefore an important factor in oral oncogenesis.

As mentioned previously, HPV has a specificity for keratinocytes of squamous epithelial cells (Nair and Pillai, 2005; Li and Sturgis, 2006; Campisi, Panzarella et al., 2007). However, in order for HPV to infect, it must be able to penetrate the superficial epithelial layers and reach the basal layer, where keratinocytes originate (Campisi, Panzarella et al., 2007). Viral invasion into the basal epithelium is normally through wounds or abrasions (Psyrri and DiMaio, 2008). HPV infection is associated with cytologic changes, such as absence of keratin formation (Ha and Califano, 2004). This lack of keratin facilitates cell replication.
inside maturing keratinocytes, and subsequent proliferative cell growth (Campisi, Panzarella et al., 2007). Prolonged infection may take place over months or years without clinical presentation due to minimal viral antigen presentation by antigen-presenting cells (APCs) (Campisi, Panzarella et al., 2007).

Cell cycle control is important for maintaining normal cell growth, differentiation, genome function, and lysis, therefore compromises in cell cycle control may result in genetic instability and carcinogenesis (Li and Sturgis, 2006). The nucleus of infected cells contains HPV genomes as episomes, which consists of three genomic regions: an early region (E), a late region (L), and a long control region (LCR) (Ha and Califano, 2004; Nair and Pillai, 2005; Li and Sturgis, 2006; Zheng and Baker, 2006; Campisi, Panzarella et al., 2007). HPV episome integration into the host genome is demonstrated in oral premalignant and malignant lesions (Nair and Pillai, 2005), resulting in genetic alteration of normal cells. HPV-related LCR mutation within oral epithelial cells may cause increased expression of HPV-transforming proteins (Nair and Pillai, 2005) that could take over cell cycle control and initiate cell proliferation. (Table 1.4 provides a summary of the genomes important for malignant transformation.)

E1 and E2 proteins of the early region are engaged in viral DNA replication, transcription regulation, and papilloma formation (Campo, 2002; Ha and Califano, 2004; Nair and Pillai, 2005; Zheng and Baker, 2006; Psyrri and DiMaio, 2008). While both E1 and E2 are needed cooperatively to initiate viral replication, E2 plays a bigger role in oncogenesis (Psyrri and DiMaio, 2008; Vidal and Gillison,
E2 transcripts influence E6 and E7 viral reproduction (Li and Sturgis, 2006), as well as improve plasmid DNA packaging into pseudovirions (Campo, 2002). This in turn may localize promyelocytic leukemia (PML) oncogenic domain (POD) via L2, a minor capsid protein (Campo, 2002; Ching, Dellaire et al., 2005; Torok, Ching et al., 2009). POD is involved in numerous nuclear processes, such as regulation of the cell cycle, DNA repair, transcription, proteolysis, apoptosis, and tumour suppression (Ching, Dellaire et al., 2005; Torok, Ching et al., 2009). Therefore, localization of POD indirectly by E2 affects the aforementioned nuclear processes (Campo, 2002).

E6 and E7 are viral oncogenes that contribute primarily to malignant transformation and tumour progression (Nair and Pillai, 2005; Li and Sturgis, 2006; Zheng and Baker, 2006). They encode for main transforming proteins that are capable of altering primary human keratinocytes, resulting in cell cycle interference and oral epithelial cell immortalization (Ha and Califano, 2004; Nair and Pillai, 2005; Li and Sturgis, 2006; Zheng and Baker, 2006; Campisi, Panzarella et al., 2007). There are over 40 variants of these oncogenes (Nair and Pillai, 2005). E6 and E7 interrupt cell cycle regulation and apoptosis by influencing p53 and retinoblastoma (Rb), which are critical tumour suppressor proteins (Ha and Califano, 2004; Nair and Pillai, 2005; Li and Sturgis, 2006; Shillitoe, 2006; Sturgis and Cinciripini, 2007; Vidal and Gillison, 2008). Rb protein causes Gap 1-phase cell cycle arrest, and p53 regulates the cell cycle by controlling p16, p21, MDM2, GADD45, bax, c-Myc, and bcl-2 genes, thereby promoting obstruction of the Gap 1 cell-cycle and apoptosis (Li
and Sturgis, 2006; Psyrri and DiMaio, 2008). (Overexpression of p16 tumour suppressor gene due to upregulation of p16 by Rb is associated with HPV-related OSCC, while loss of p16 expression due to downregulation of p16 and p53 by Rb is associated with tobacco and alcohol-related OSCC (Psyrri and DiMaio, 2008).) E6 activates telomerase and promotes p53 tumour suppressor gene product degradation through a ubiquitin-dependant proteolysis system, and E7 functions in tumour promotion by binding with, transforming and inactivating pRb, then impeding transforming growth factor beta 2 (TGF-β2) action (Ha and Califano, 2004; Nair and Pillai, 2005; Li and Sturgis, 2006; Campisi, Panzarella et al., 2007; Tsantoulis, Kastrinakis et al., 2007; Psyrri and DiMaio, 2008; Hennessey, Westra et al., 2009). (TGF-βs influence cell growth, tissue repair, immunity, inflammation, and carcinogenesis (Govinden and Bhoola, 2003; Buck and Knabbe, 2006).) E7 action on pRb results in degradation by ubiquitination and ensuing E2F activation, leading to transcriptional activation and cell proliferation (Ha and Califano, 2004; Nair and Pillai, 2005; Tsantoulis, Kastrinakis et al., 2007; Cahill, Stead et al., 2011). Interference with either p53 or Rb causes disruption of cell cycle regulation and uncontrolled cell proliferation due to loss of checkpoint integrity at Gap 1 (Ha and Califano, 2004; Li and Sturgis, 2006; Campisi, Panzarella et al., 2007). E6 influence is weak in the early phase but strong during tumorigenesis (Li and Sturgis, 2006). E1-E2 disruption is necessary during integration of the HPV genome into the host DNA (Ha and Califano, 2004; Nair and Pillai, 2005; Li and Sturgis, 2006). This leads to viral DNA interruption, increased expression and stability of E6 and E7 proteins,
inactivation of many early or late genes, as well as unchecked transcription (Ha and Califano, 2004; Nair and Pillai, 2005; Li and Sturgis, 2006).

In addition to effects on p53 and Rb, E6 and E7 can impede Nuclear Factor kappa B (NFκB) activity (Nair and Pillai, 2005). NFκB is a transcription factor involved in immune response regulation, maturation of immune cells, development of secondary lymphoid organs and osteoclastogenesis (Wong and Tergaonkar, 2009). NFκB binds to HPV-16 LCR and can act as a transcriptional repressor (Nair and Pillai, 2005). Persistent HPV infection of keratinocytes interferes with NFκB and alters critical cytokine expression (Nair and Pillai, 2005). Tumour necrosis factor α (TNFα) is a cytokine that stimulates apoptosis and is used by cytotoxic T-cells to destroy cells infected by viruses (Nair and Pillai, 2005). E6 transforms the NFκB signal pathway, while E7 impairs nuclear translocation of NFκB by TNFα, thereby preventing NFκB and its associated DNA from binding which results in uncontrolled cell proliferation (Nair and Pillai, 2005).

Features of HPV-positive SCCHNs include expression of E6 and E7, fewer p53 and Rb mutations, oropharyngeal origin, poor differentiation, aneuploidy, higher staging of lesions, reduced Rb expression, and less frequent occurrence in those who smoke and drink alcohol (Gillison and Shah, 2003; Fakhry and Gillison, 2006; Li and Sturgis, 2006). HPV-16 positive lesions can be classified into two groups: lesions that express E6 and do not have p53 mutation, or lesions that do not express E6 but have p53 mutations (Nair and Pillai, 2005). Mutations in p53 may occur early on in oral cancer development (Nair and Pillai, 2005). Presence of either
HPV E6 or E7 antibodies is associated with a risk of 9.2 for oropharyngeal cancer and 2.9 for OSCC, while presence of both increases the risk to 67.1 for oropharyngeal cancer and 4.3 for OSCC (Li and Sturgis, 2006).

E5 is another protein that is important in HPV-mediated cell transformation (Campo, 2002; Campisi, Panzarella et al., 2007). E5 plays an important part in immune surveillance by facilitating antigenic peptide presentation to effector T-cells (Campo, 2002). It modulates growth factor receptors and various kinases (i.e., cdk), as well as down-regulates major histocompatibility complex class I (MHC I) expression (Campo, 2002). MHC molecules bind and present short fragments of antigenic peptide on the surface of APCs to T-cell receptors to activate the T-cells (Apostolopoulos, Lazoura et al., 2008). The activated T-cells either destroy or help to destroy the APC (Apostolopoulos, Lazoura et al., 2008). Down-regulation of MHC I helps HPV escape host immune surveillance and establish infections (Campo, 2002). E5 proteins also prevent MHC I transport to the cell surface and confines MHC I to the Golgi cisternae (Campo, 2002). Therefore, E5 aids in both cell proliferation and evasion of immune responses (Campo, 2002).
Table 1.4 HPV Genomes in Malignant Transformation and Their Functions

<table>
<thead>
<tr>
<th>HPV Protein</th>
<th>Function</th>
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| E1          | • Viral DNA replication and transcription regulation  
              • Needed to initiate viral replication in cooperation with E2 |
| E2          | • Viral DNA replication and transcription regulation  
              • Needed to initiate viral replication in cooperation with E1  
              • Transcripts influence E6 and E7 viral reproduction  
              • Improves plasmid DNA packaging into pseudovirions |
| E5          | • Immune surveillance, cell proliferation and evasion of immune responses  
              • Facilitates antigenic peptide presentation to effector T-cells  
              • Modulates growth factor receptors and various kinases  
              • Down-regulates MHC I  
              • Prevents MHC I transport to the cell surface  
              • Confines MHC I to the Golgi cisternae |
| E6          | • Malignant transformation and tumor progression  
              • Activates telomerase and promotes p53 degradation through a ubiquitin-dependant proteolysis system  
              • Transforms NFκB signal pathway |
| E7          | • Malignant transformation and tumor progression  
              • Binds with, transforms and inactivates Rb proteins  
              • Impedes TGF-β2 action  
              • Prevents NFκB from binding with its associated DNA |
| L1          | • Minor capsid protein |
| L2          | • Minor capsid protein |

1.2.4.3 Prevention or Therapeutic Treatment of HPV

Studies support the effectiveness of HPV vaccination both prophylactically for preventing viral infection and transmission, as well as therapeutically for the regression of early or late-stage infections (Campo, 2002; Satyaprakash, Creed et
al., 2009). Prophylactic vaccines target L1 and L2 viral capsid proteins and prevent primary HPV infection by inducing humoral immune responses to produce antibodies against HPV (Kahn, 2005; Barr and Sings, 2008; zur Hausen, 2008). Therapeutic vaccines elicit a cell-mediated cytotoxic T-cell response, resulting in removal of virus-infected cells (Kahn, 2005). Therapeutic vaccines prevent HPV infection progression of early-stage and late-stage squamous epithelial lesions and promote their regression (Kahn, 2005). While prophylactic vaccine use in humans show benefits against HPV infection and transmission, therapeutic use of vaccines for HPV have not yet been proven to be efficacious (Campo, 2002; Satyaprakash, Creed et al., 2009). Difficulties with studies for therapeutic HPV vaccination include a limited sample size of early and late-stage HPV infections, and ethical considerations relating to the non-treatment of precancerous lesions (Satyaprakash, Creed et al., 2009). Despite this, vaccines with a therapeutic role in fighting HPV infection and potential malignant transformation may have some use in the future, with potential targets being E2, E5, or E6 and E7 (Li and Sturgis, 2006; Satyaprakash, Creed et al., 2009).

HPV-16 and 18 vaccines can offer effective protection against HPV infection and HPV-related cancers for up to 4.5 years (Tsantoulis, Kastrinakis et al., 2007). Recent studies show cross-protection against HPV 16-related type HPV-31, and HPV 18-related type HPV 45, which further increases the efficacy of HPV vaccines against viral transmission and malignant transformation (zur Hausen, 2008). The primary objective of widespread vaccination programs is to prevent
HPV-16 and 18 transmission and reduce cervical cancer incidence rates, while the secondary goal is to reduce the risk of HPV-related cancers such as SCCHN (Li and Sturgis, 2006; Tsantoulis, Kastrinakis et al., 2007; Gillison, Chaturvedi et al., 2008). HPV vaccines are effective only in previously non-exposed subjects and appear to offer little therapeutic effect in already HPV-infected subjects (zur Hausen, 2008). Although the data supports the efficacy of HPV vaccines for the prevention of viral infection and transmission, as well as reduction of cervical cancer incidence, there is currently no data that shows its role in the prevention of SCCHN (Tsantoulis, Kastrinakis et al., 2007; Gillison, 2008).

Gardasil®, a quadrivalent vaccine against HPV-6, 11, 16 and 18, is developed from non-infectious virus-like particles and has recently been approved by the FDA for use in Canada and the US (Giuliano, 2007; Sturgis and Cinciripini, 2007; Barr and Sings, 2008; Conner and Collins, 2008; Satyaprakash, Creed et al., 2009). Gardasil® is indicated for females and males between the ages of 9 and 26 years, with recommendations for a 3-dose vaccination regimen currently directed at 11-12 year-old females and “catch-up” vaccinations administered to 13-26 year-old females who have not yet been vaccinated (Giuliano, 2007; Stanley, 2007; Sturgis and Cinciripini, 2007; Conner and Collins, 2008; Huang, 2008; Satyaprakash, Creed et al., 2009; Public Health Agency of Canada, 2011). Additional research is required to determine the exact duration of protection and the need for boosters (Huang, 2008). A bivalent HPV vaccine (Cervarix®) has also been developed and recently approved by the FDA for use in Canada and the US to
protect against HPV-16 and 18 (Stanley, 2007; Conner and Collins, 2008; Public Health Agency of Canada, 2011). Cervarix® is approved for females only between the ages of 10 and 25 years, with recommendations for a 3-dose vaccination regimen currently directed at 9-13 year-old females over a 6 month period (Public Health Agency of Canada, 2011). While Gardasil® offers protection against both warts as well as cancers, Cervarix® would exclusively protect against cancer. Both vaccines have shown to be safe, immunogenic and effective for the prevention of HPV infection (Stanley, 2007; Barr and Sings, 2008; Gillison, Chaturvedi et al., 2008). (Table 1.5 provides a summary of the HPV vaccines.)

OSCC incidence continues to be higher for males than for females (Gillison, 2008; Gillison, Chaturvedi et al., 2008). Since the HPV vaccines are currently targeted mainly at females, males may only experience secondary indirect benefits from widespread vaccination after the reduction of HPV incidence among females (Sturgis and Cinciripini, 2007). Limiting HPV vaccination programs to females would therefore postpone any potential prevention and reduction of HPV-related SCCHN for males (Sturgis and Cinciripini, 2007). The potential bi-directional positive impact for both genders in the prevention of warts and cancers is promising and available data support vaccination programs that target both males and females (Giuliano, 2007; Conner and Collins, 2008; Gillison, Chaturvedi et al., 2008). However, in terms of the cost-benefits for widespread vaccination programs, a female-only vaccination program appears to be more cost effective than vaccination of both males and females (Marra, Cloutier et al., 2009).
Other methods of preventing HPV transmission and SCCHN include health promotion initiatives that encourage safe sex practices (Walker, Boey et al., 2003; Cason and Mant, 2005). In addition, new proposed preventative measures involving topical microbicides to provide a chemical, biological, and physical barrier against infections (Howett and Kuhl, 2005), could play a prophylactic or adjuvant role in preventing HPV transmission. Sexual abstinence, monogamy with an uninfected person, and reduction in the number of sex partners are effective ways to control HPV infection (Stanley, 2007; Conner and Collins, 2008). The efficacy of condom use for the prevention of HPV transmission remains controversial, as some studies demonstrate condom use in reducing HPV transmission by 70%, while other studies have found no evidence to support its role in the prevention of HPV infection (Holmes, Levine et al., 2004; Conner and Collins, 2008). However, the data shows condom use is associated with accelerated regression of HPV-related lesions and quicker HPV infection clearance by females (Holmes, Levine et al., 2004). This supports condom use for its therapeutic value in promoting the efficient clearance of HPV from an infected individual.

Table 1.5  HPV Vaccines and the HPV Types They Cover

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>HPV-6</th>
<th>HPV-11</th>
<th>HPV-16</th>
<th>HPV-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardasil®</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cervarix®</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.3 Oral Premalignant Lesions

Oral premalignant lesions (OPLs) are lesions of the oral cavity that have not histologically progressed to oral cancers, however due to its pathological changes in morphology of tissues, OPLs have increased risk for cancer progression (Warnakulasuriya, Johnson et al., 2007). OPLs clinically present as leukoplakia, erythroplakia, lichen planus, and oral submucous fibrosis, and histologically as dysplasias and carcinoma in situ (Epstein, Gorsky et al., 2008). Colour, contour, texture, location, and degree of dysplastic change of an OPL are often indicators of its risk for malignant transformation (Epstein, Gorsky et al., 2008; Mehanna, Rattay et al., 2009). As some OPLs will develop into malignancies, it is important to understand what they are, as well as their risk for developing cancers.

1.3.1 Leukoplakia

According to the World Health Organization, a leukoplakia is any oral white lesion that is not clinically or histologically defined as any other disease (Neville and Day, 2002; Warnakulasuriya, Johnson et al., 2007), and it is a clinical term rather than a pathological term (Neville and Day, 2002). However, after histological investigation, lesions left uncharacterized by any disease, are referred to as leukoplakias with or without dysplasia (Warnakulasuriya, Johnson et al., 2007). Leukoplakias can be categorized as homogeneous or non-homogeneous lesions, based on their colour and texture (Warnakulasuriya, Johnson et al., 2007). Homogeneous lesions display a uniform colour and texture, and are thin in
thickness, while non-homogeneous lesions are heterogeneous in colour (white with red speckled colour), and in texture, with often a rugged or uneven, thick consistency (Warnakulasuriya, Johnson et al., 2007). Leukoplakias have a higher association with middle-aged males (Neville and Day, 2002). Interestingly, those found in non-smokers have a greater chance of progressing to cancer than leukoplakias found in smokers (Neville and Day, 2002).

### 1.3.2 Risk of Cancer Progression

The progression rate of OPLs varies from study to study. Studies show that oral leukoplakia is associated with a 0.9 – 17% chance of malignant transformation within 10 years of first noticing signs and/or symptoms, with non-homogeneous lesions having a higher chance of progressing to cancers (Warnakulasuriya, Johnson et al., 2007; Epstein, Gorsky et al., 2008; Grajewski, Quarcoo et al., 2010). For oral erythroplakia, the risk of malignant transformation is as high as 14 – 50% within 10 years of initial detection (Grajewski, Quarcoo et al., 2010). Lesions of the floor of mouth, lateral tongue and lower lip are associated with more changes that are dysplastic or malignant (Silverman, 2001; Neville and Day, 2002), and are therefore sites at increased risk of cancer progression.

Differences in transformation rates are evident between high-risk oral lesions (HRLs) of varying histological grades. One study reported a 10.3% of mild to moderate oral dysplasias progress to oral cancers, while 24.1% of severe oral dysplasia and carcinoma *in situ* advance to malignant lesions (Mehanna, Rattay et
al., 2009). There is no consensus on how to treat OPLs. Some studies reported that surgical removal improves prognosis but some others disagree. In one study, surgical excision of lesions has been shown to improve prognosis of HRLs, with only 5.4% of patients who had surgical excision progressing to oral cancers, while 14.6% of patients who did not have any treatment experienced malignant transformation (Mehanna, Rattay et al., 2009).

1.4 Survey Design

Due to the complexities of obtaining opinions and understanding patient experiences, a qualitative and quantitative mixed-methods or ‘triangulation’ survey design was required (Jackson and Furnham, 2000; Cowan, 2009). This increased the probability of obtaining a higher response rate, since participants are more likely to identify with the study goals and have an interest in the study results (Jackson and Furnham, 2000). Descriptive surveys that incorporated a combination of retrospective and cross-sectional questions were utilized, in order to collect both current and recalled quantitative and qualitative data (Bowling, 2002; Cowan, 2009) relating to patient experiences with HRLs and tobacco use. A phenomenological approach was employed to interpret the qualitative data (Cowan, 2009). Descriptive studies facilitate understanding of changes to health services, and any facilitators or barriers to better oral health (Bowling, 2002). In particular, retrospective, cross-sectional surveys are an economical and efficient way of collecting data from a large group of patients in a small amount of time (Bowling, 2002). Although the cause cannot be established, retrospective, cross-sectional surveys can identify
associations between variables, which can be used for recommendations of future directions in research or healthcare (Bowling, 2002).

For the pilot study phase, a structured, in-depth direct (face-to-face) interview survey was utilized, along with non-probability convenience sampling (Jackson and Furnham, 2000; Cowan, 2009). This type of sampling was adopted, since it was not possible to select a large random sample from the population of patients currently registered with the Vancouver location of the BC Cancer Agency (BCCA), who would meet the selection criteria described in Sections 2.2.1 and 3.2.1. Patients were opportunistically invited and recruited as they presented to the BCCA Oral Oncology or Head and Neck New Patient clinics, based on the selection criteria. Although it requires a greater number of person-hours, direct survey methods facilitate the collection of a representative sample expediently due to higher response rates and allows for more flexibility in terms of questionnaire construction and design (Jackson and Furnham, 2000; Bowling, 2002). A structured interview survey follows a fixed order of pre-selected standardized questions, which is initially more difficult to design, but results in more ease of data analysis and interpretation (Jackson and Furnham, 2000). Questions can be adapted and open-ended questions can be elaborated or clarified during the interviews, which assists in refining the questionnaire survey for use in a larger-scale study (Jackson and Furnham, 2000; Bowling, 2002).

In preparation for the larger-scale study, a structured questionnaire survey was selected for: 1) flexibility of the environmental setting that the questionnaire
could be administered in, whether in a laboratory, clinic, or at home, 2) flexibility of the level of interaction when collecting data, whether face-to-face or self-completed by participants, 3) its relatively quick participation time, which increases response rate and is more efficient use of resources available in terms of data generated per person-hours, as well as 4) its effectiveness in collecting easy to code, quantitative data for analysis (Bowling, 2002; Cowan, 2009). With the goal of taking the survey to a larger-scale study that would be self-administered, the questionnaire was limited to 20 minutes and followed a sequence, which included more general questions relating to demographic and personal details first, sensitive questions towards the middle or the end of the survey, and simple, easy to answer questions towards the end (Jackson and Furnham, 2000). Both closed and open-ended questions were utilized for the survey. The closed questions involved ‘Yes’/’No’ responses, a checklist or nominal scale, and category scales as forced choices, which enable easy coding of the data and avoids under-reporting (Jackson and Furnham, 2000; Bowling, 2002). Although sometimes difficult to analyze, open-ended questions were included to probe for additional valuable insights into patient experiences with their HRL diagnosis, and to get a sense of the words and phrases that the patient population may use for developing a survey that would be utilized for a larger-scale study (Jackson and Furnham, 2000; Bowling, 2002). Closed questions were presented before the open-ended questions, and a ‘funnel’ approach to question sequence was employed to filter out questions that do not apply to some patients (Jackson and Furnham, 2000; Bowling, 2002). Data collected by the surveys were supplemented by information obtained from the BC Cancer Agency database.
1.5 Statement of the Problem

Lack of awareness and late diagnosis of oral cancer have shown poor prognosis (Elwood and Gallagher, 1985; Elwood and Gallagher, 1986). However, there is little known of the process from lesion identification to the initiation of treatment for these patients. Moreover, continuous smoking after treatment for oral cancer has been associated with a 6-fold increased risk of a second cancer, with a 10 – 30% increased risk of recurrence and 4-7% increased risk of formation of a second primary oral malignancy (Day, Blot et al., 1994; van Oijen and Slootweg, 2000; Do, Johnson et al., 2003; Kademani, 2007). Little is known about the impact of smoking behavioural changes in patients with an HRL diagnosis or their barriers for tobacco cessation, if any.
1.6 **Research Questions**

To address these problems, we have designed 2 studies.

For Study I, the research questions include:

1) In B.C., how are these lesions at risk identified?

2) What is the experience from lesion identification to lesion diagnosis, from patients’ prospective?

3) If identifiable, what factors impact on diagnostic time delay, according to patient experiences?

For Study II, the research questions are:

1) Does a diagnosis of an HRL result in changes in smoking habits?

2) Are there any facilitators or barriers for tobacco cessation in patients diagnosed with HRLs?

1.7 **Hypothesis**

The hypothesis for Study I is, self-identified HRLs are often found at more advanced stages and are more prone to having longer time delays to diagnosis as opposed to health professional-identified HRLs, and for Study II, an HRL diagnosis motivates patients who smoke to change their smoking behaviours.
1.8 Objectives

The overall goal of my thesis is to develop a survey that we can use in a population-based, province-wide data collection and to understand the experience from patients, of their journey from lesion identification to diagnosis, so that eventually, we can design appropriate strategies to better control this disease.

To better address the specific objective of each study in the thesis, the objectives will be stated under each study.
2. Study I: Experience to Diagnosis (ETD)

Figure 2.1 Flowchart to Illustrate Study Design and Relationship between the 2 Studies

2.1 Objectives

The objectives of Study I are: 1) To examine the clinic-pathological features of high-risk oral lesions (HRLs) at varying initial diagnostic stages, 2) To characterize the time delay of HRLs from initial lesion identification to diagnostic workup, and 3) To determine the factors that impact on time delay, according to patient experiences.

2.2 Method

2.2.1 Clinics and Patients

From 2007 to 2011, individuals attending the BC Cancer Agency (BCCA) in Vancouver, British Columbia were invited to participate in this study. The BCCA is part of the Provincial Health Services Authority of British Columbia. It provides access to assessment and diagnostic services, and cancer control care to patients residing in British Columbia and Yukon (BC Cancer Agency, 2012). The study population includes patients from the Oral Oncology (OO) Clinic, as well as patients from the BCCA Radiation Oncology Department’s Head and Neck New Patient (HNNP) Clinic, which are two divisions of the BCCA that address its mandates in the context of oral cancers (Figure 2.1). Together, these two clinics access 75% of the potentially surgical patients diagnosed with HRLs in British Columbia. The majority of patients recruited from the Oral Oncology (OO) Clinic were diagnosed with moderate to severe oral dysplasias and early-stage oral cancers as part of a Surgery
Trial (Poh, Zhang et al., 2006), and 50% of patients from the HNNP Clinic were Stage III-IV patients undergoing radiation or combined chemo-radiation therapy.

Individuals who were 19 years and older, can read English, and had a diagnosis of HRL within 12 months were eligible for the study. Diagnosis of an HRL was confirmed through biopsy. Prior to participating in the survey, patients were provided with a written description of the study background, objectives and methods. This study has been approved by the UBC/BCCA Ethics Review Board (H07-01942). Written informed consent was then obtained before proceeding with the survey (see APPENDIX A.1).

Between February 2009 and August 2011, among 135 screened patients, 110 (81%) patients were identified to be eligible for the study and consented to complete questionnaires. The data from the 110 patients were pooled with the results from the pilot study (N = 40) conducted by Heather C. Biggar (Biggar, 2009) for analysis.

2.2.2 Questionnaire

The survey questionnaire used in Study I was refined from the one developed and used in the pilot study by Heather C. Biggar (Biggar, 2009). The questionnaire (see APPENDIX A.2) included 18 questions with a selection of categorical check boxes for 15 questions and fill-in-the-blanks for 3 questions to collect both quantitative and qualitative data that could easily be completed by an individual without the assistance of an interviewer. Socio-demographic data collected included information
on gender, date of birth, ethnicity, ever-smoking status, current smoking status, and date of smoking cessation (if applicable). Questions on the frequency of Health Professional (HP) visits included: *Which of the following healthcare professionals do you see regularly?* (Check boxes included: Dental Practitioner, Medical Practitioner, or Other, and the frequency of visits.) Questions relating to the initial detection of the HRL included: *Who first detected the change (lesion) in your mouth? What date was the change (lesion) noticed? What were the first symptoms you noticed? What was your initial feeling to discovering your symptoms? What was the first thing that you did after noticing your symptoms?* Questions regarding the initial examination of the HRL included: *Which health practitioner first examined the change (lesion) in your mouth? (If your lesion was first identified by a healthcare practitioner, select the next health practitioner that you were referred to.) What was the date of your first visit to this health practitioner? What did the health practitioner recommend you to do?* Questions about the biopsy of the HRL included: *Who performed the first biopsy? What was the date of your first biopsy?* An open-ended question relating to the patient’s knowledge of oral cancer prior to noticing initial symptoms included: *Before noticing your first symptoms, which types of cancer would you say you had heard of?* Open-ended questions regarding the impact of the HRL and experiences leading to a diagnosis for the patient included: *When you received the diagnosis of your oral lesion, how did it make you feel? Did the diagnosis impact your day-to-day activities in any way? Do you have any further comments regarding your experiences leading to the diagnosis of an oral lesion?* The final question related to further contact: *May we contact you if we need clarification of any of the answers in*
this questionnaire? Additional data relating to the date of biopsy, pathological diagnosis, and anatomical site of the lesion was obtained through data collection via the BC Cancer Agency database.

2.2.3 Definitions of Terminologies Used in the Study

High-Risk Oral Lesion (HRL) means an oral lesion with a diagnosis of moderate dysplasia (DD2), severe dysplasia (DD3), carcinoma in situ (CIS) or squamous cell carcinoma (SCC). Non-invasive HRLs include HRLs that have a diagnosis of DD2, DD3, and CIS, and invasive HRLs are SCCs. Early-stage cancers are Stage I or Stage II SCC with no lymphadenopathy and late-stage cancers are Stage III or Stage IV SCC, according to the American Joint Committee on Cancer (Edge and Compton, 2010; Farasat, Yu et al., 2011; Clark, Rumcheva et al., 2012).

Time of Detection to Diagnosis (DTD) means the time from initial detection of an HRL to definitive pathological diagnosis, as determined by biopsy. Time Delay is defined as the time from initial detection to definitive pathological diagnosis, as determined by biopsy, which is greater than or equal to 3 months. Patient-related Delay (Patient Delay) means the time between the patient first noticing a sign or symptom of an HRL and their first consultation with an HP concerning that sign or symptom, which is equal to or greater than 3 months. Health Professional-related Delay (Professional Delay) means the time from a patient’s first consultation with an
HP for an HRL to the definitive pathological diagnosis. Overall Time Delay to diagnosis is equal to Patient Delay and Professional Delay combined.

Self-Identified Group (SIG) includes patients with HRLs that are initially identified by patients themselves. Professionally Screened Group (PSG) includes patients with HRLs that are identified by an HP through screening activities. Health Professional (HP) in the context of this study means a Dental or Medical Professional, including Dentists, Registered Dental Hygienists, Dental Specialists, Medical Doctor, and Medical Specialists.

2.2.4 Data Analysis

The data was analyzed using unpaired Student’s $t$– test or ANOVA for means analysis of continuous parametric data. Contingency tables with Fisher’s Exact or Chi-squared test were used for analyzing non-parametric or categorical data.

2.3 Results

2.3.1 Demographics and Lesion Characteristics

Of a total of 150 patients, the majority were male ($N = 90, 60\%$), Caucasian ethnicity ($N=126, 84\%$), ever smoker ($N=95, 63\%$) and middle-aged (mean age $\pm$ SD, $61.3 \pm 12.7$ years; ranging 19-90 years; Table 2.1). About half of the patients ($47\%$) had never heard of oral cancer.
At the time of diagnosis, anatomical sites of the HRLs were found to include the tongue (85, 57%), floor of mouth (24, 16%), the soft palate (5, 3%), and other intraoral sites (36, 24%) (see Table 2.1). Fifty-three (35%) of the patients were diagnosed with non-invasive HRLs, whereas 97 (65%) patients were diagnosed as invasive HRLs, including 67 (45%) early-stage cancers and 30 (20%) late-stage cancers.

2.3.2 Characteristics of Patients and Diseases among Varying Diagnostic Stages

When we examined the disease stages, there were no differences in demographics in age, gender, ethnicity, smoking habit and oral cancer awareness. However, there was a difference in the lesional site (Table 2.1).

The mean time (± SD) from detection to diagnosis was 13.1 ± 34.7 months with an equal distribution of patients who are less than 3 months and greater than or equal to 3 months (51% vs. 49%; see Table 2.1). There was no significant difference in mean time and number of patients experiencing time lag of 3 months or longer from non-invasive HRL, early-stage cancer to late-stage cancer ($P = 0.83$ and 0.14, respectively; Table 2.1).

Among these patients, 94% (N = 141) patients saw an HP at least once a year (see Table 2.1). Interestingly, the frequency of HP visit had no impact in disease staging ($P = 0.12$); however, patients who saw dental professionals at least once a year had more non-invasive HRL, early-stage cancer than late-stage cancer
\( P = 0.001 \). There was no difference in the frequency of medical professional visits in disease staging (Table 2.1). There were significant differences in diagnostic staging for those whose initial lesion detection was by patients themselves; patients were more likely than an HP to identify late-stage SCCs \( P = 0.0003 \); see Table 2.1.)
Table 2.1  Patient and Lesion Characteristics and Disease Stages

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Non-invasive (Dysplasia, CIS)</th>
<th>Early-stage Cancer</th>
<th>Late-stage Cancer</th>
<th>P-Value*</th>
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</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 150 (100%)</td>
<td>N = 53 (35%)</td>
<td>N = 67 (45%)</td>
<td>N = 30 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>90 (60)</td>
<td>33 (62)</td>
<td>38 (57)</td>
<td>19 (63)</td>
<td>0.76</td>
</tr>
<tr>
<td>Female</td>
<td>60 (40)</td>
<td>20 (38)</td>
<td>29 (43)</td>
<td>11 (37)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age ± SD</td>
<td>61.6 ± 12.7</td>
<td>59.3 ± 13.0</td>
<td>62.9 ± 10.8</td>
<td>61.0 ± 15.7</td>
<td>0.30</td>
</tr>
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<td><strong>Ethnicity</strong></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>126 (84)</td>
<td>48 (91)</td>
<td>55 (82)</td>
<td>23 (77)</td>
<td>0.21</td>
</tr>
<tr>
<td>Other</td>
<td>24 (16)</td>
<td>5 (9)</td>
<td>12 (18)</td>
<td>7 (23)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-Smoker</td>
<td>55 (37)</td>
<td>14 (26)</td>
<td>28 (42)</td>
<td>13 (43)</td>
<td></td>
</tr>
<tr>
<td>Ever-Smoker</td>
<td>95 (63)</td>
<td>39 (74)</td>
<td>39 (58)</td>
<td>17 (57)</td>
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</tr>
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<td>Smoker</td>
<td>41 (43)</td>
<td>17 (44)</td>
<td>16 (41)</td>
<td>8 (47)</td>
<td>0.91(2)</td>
</tr>
<tr>
<td>Former Smoker ≥ 1 yr</td>
<td>54 (57)</td>
<td>22 (56)</td>
<td>23 (59)</td>
<td>9 (53)</td>
<td></td>
</tr>
<tr>
<td><strong>Oral Cancer Awareness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79 (53)</td>
<td>31 (58)</td>
<td>30 (45)</td>
<td>18 (60)</td>
<td>0.22</td>
</tr>
<tr>
<td>No</td>
<td>71 (47)</td>
<td>22 (42)</td>
<td>37 (55)</td>
<td>12 (40)</td>
<td></td>
</tr>
<tr>
<td><strong>Lesion Site</strong></td>
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<td></td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Tongue</td>
<td>85 (57)</td>
<td>31 (58)</td>
<td>44 (66)</td>
<td>10 (33)</td>
<td></td>
</tr>
<tr>
<td>Floor of Mouth</td>
<td>24 (16)</td>
<td>12 (23)</td>
<td>8 (12)</td>
<td>4 (13)</td>
<td></td>
</tr>
<tr>
<td>Soft Palate</td>
<td>5 (3)</td>
<td>3 (6)</td>
<td>1 (1)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>36 (24)</td>
<td>7 (13)</td>
<td>14 (21)</td>
<td>15 (50)</td>
<td></td>
</tr>
<tr>
<td><strong>Time from Detection to Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Mean Time ± SD (Months)</td>
<td>13.1 ± 34.7</td>
<td>12.3 ± 35.4</td>
<td>15.0 ± 35.4</td>
<td>10.5 ± 32.4</td>
<td></td>
</tr>
<tr>
<td>&lt; 3 Months (Counts)</td>
<td>76 (51)</td>
<td>30 (57)</td>
<td>28 (42)</td>
<td>18 (60)</td>
<td>0.14</td>
</tr>
<tr>
<td>≥ 3 Months (Counts)</td>
<td>74 (49)</td>
<td>23 (43)</td>
<td>39 (58)</td>
<td>12 (40)</td>
<td></td>
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*P-Value compares Non-invasive vs. Early-stage Cancer vs. Late-stage Cancer for variables listed within each grouping.
Table 2.2  Patient and Lesion Characteristics and Time Delay ≥ 3 Months

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<td>Age</td>
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</tr>
<tr>
<td>Mean Age ± SD</td>
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<td>Lesion Site</td>
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<td>Tongue</td>
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<td>Soft Palate</td>
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<td>Other</td>
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<tr>
<td>Initial Identification of Lesion</td>
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<td>0.007</td>
</tr>
<tr>
<td>Self</td>
<td>91 (61)</td>
<td>38 (50)</td>
<td>53 (72)</td>
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<tr>
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<td>59 (39)</td>
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<td>21 (28)</td>
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<tr>
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<tr>
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<td>43 (58)</td>
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<tr>
<td>Medical Professional</td>
<td>71 (47)</td>
<td>40 (53)</td>
<td>31 (42)</td>
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</tr>
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</table>

(1)Ever-Smoker vs. Never-Smoker (2)Smoker vs. Former Smoker vs. Never-Smoker

*P-Value compares < 3 months vs. ≥ 3 months for variables listed within each grouping


2.3.3 Time Delay in HRL Detection to Diagnosis

When examining Time Delay, there was no difference in patient demographics, oral cancer awareness, lesional sites, and disease staging between those diagnosed less than 3 months and those diagnosed greater than or equal to 3 months (Table 2.2). There was no difference in the frequency of health professional visits. Interestingly, there were significant differences in time delay for those whose initial lesion detection was by patients themselves (SIG; \( P = 0.007 \)) and mean number of HP visits prior to diagnosis (Table 2.2).

2.3.4 SIG versus PSG Patients

Of the 150 patients in this study, 91 (61%) of the HRLs belong to the SIG (patients self-identified the HRL) and 59 (39%) belong to the PSG (HPs identified the HRL) (Table 2.3). For those in the PSG, 88% were first screened and detected by dental professionals (58% by dentist, 36.5% by dental hygienist).

Since there were significant differences between the SIG and the PSG in time delay, and patients seemed to have different experiences, we would like to describe them separately and compare the experiences between the 2 groups. The detailed differences will be described in the following sections.

2.3.4.1 Demographics and Lesional Characteristics of the SIG and the PSG

There was no significant difference in mean age, gender, ethnicity and the awareness of oral cancer between the SIG and the PSG patients (see Table 2.3).
Interestingly, there were more smokers in PSG (73% vs. 57%, $P = 0.05$; see Table 2.3). There were significant differences in disease staging and time delay ($\geq 3$ months from detection to diagnosis) between the SIG and PSG ($P = 0.0003$ and $P = 0.007$, respectively). Early and late-stage lesions are more likely to be diagnosed by patients themselves than by an HP, and the SIG have more incidences of time delay as compared to PSG. Although there was no difference in the frequency of HP visits, there was a significant difference in the frequency of dental professional visits between the 2 groups (SIG vs. PSG = 65% vs. 86%, $P = 0.004$). On the other hand, 69% of the SIG saw medical professionals first, compared to 14% in the PSG ($P < 0.0001$).

2.3.4.2 **HP involvement from Detection to Diagnosis of the SIG and the PSG**

On detection of the HRL, 79 (53%) of the 150 patients were first seen by a dental professional. Seventy-one (47%) of the patients were first seen by a medical professional. Comparing dental professionals and medical professionals, dental professionals were first seen for more premalignant lesions (68%), while medical professionals were seen for more late-stage invasive squamous cell carcinomas (77%, $P = 0.0002$; Table 2.1). However, there was no difference in mean time from detection to diagnosis and the mean number of HP visits prior to diagnosis of patients between the SIG and PSG (Table 2.3), but there were significant differences in disease staging and time delay. Therefore, it would be interesting to identify other factors contributing to time delay.
In Table 2.3, a series of time intervals from initial lesion detection to diagnosis is presented. For the SIG, the mean time (± SD) from initial self-detection to see the first HP for further investigation was 6.2 ± 15.6 months and the first HP seen were mainly medical professionals (69%). The mean time (± SD) from the first HP seen to diagnosis was shorter in the SIG than those in the PSG (5.7 ± 17.2 vs. 15.0 ± 42.6 months), but despite the large variation, the difference was of no significance (P = 0.07). The delay in time can be due to the patient and/or HPs.
Table 2.3  Patient and Lesion Characteristics of SIG and PSG

<table>
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<tr>
<th>Demographics</th>
<th>All N = 150 (100%)</th>
<th>SIG N = 91 (61%)</th>
<th>PSG N = 59 (39%)</th>
<th>P-Value*</th>
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<td>75 (82)</td>
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<td>47 (52)</td>
<td>32 (54)</td>
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<td>Tongue</td>
<td>85 (57)</td>
<td>54 (59)</td>
<td>31 (52)</td>
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<td>11 (19)</td>
<td>0.23</td>
</tr>
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<td>Soft Palate</td>
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<td>21 (36)</td>
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<td>11.9 ± 38.9</td>
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(1)Ever-Smoker vs. Never-Smoker  (2)Smoker vs. Former Smoker vs. Never-Smoker
*P-Value compares SIG vs. PSG for variables listed within each grouping
**Detection to Diagnosis  ***P-value uses 1st HP to 2nd HP for PSG and compares to 1st Detection to 1st HP for SIG
****P-value compares 1st HP to Diagnosis for SIG and DTD for PSG
Table 2.4  Factors Contributing to Diagnostic Delay of SIG and PSG

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<td>0.0001</td>
</tr>
<tr>
<td>DDS</td>
<td>5 (3)</td>
<td>0 (0)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>DDS Specialist</td>
<td>65 (44)</td>
<td>29 (32)</td>
<td>36 (61)</td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>6 (4)</td>
<td>6 (6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>MD Specialist</td>
<td>74 (49)</td>
<td>56 (62)</td>
<td>18 (31)</td>
<td></td>
</tr>
</tbody>
</table>

*\(P\)-Value compares SIG vs. PSG for variables listed within each grouping
2.3.5 **Timeline from Initial HRL Detection to Diagnosis for SIG and PSG**

The following sections include five figures (Figures 2.2 – 2.6) which are event calendar charts that illustrate: the category of the individual involved with the initial detection of the HRL (SIG or PSG), the timeline from initial lesion detection \( T_0 \) to diagnosis, the type of HP involved in the journey from detection to diagnosis, and the diagnostic outcome of an HRL. Time is illustrated in days (Figure 2.2) or in months (Figures 2.3 – 2.6). The experiences of all 150 cases, with patient study identifications (IDs) indicated, are presented.

**2.3.5.1 Time Lag from Initial Detection to Diagnosis of < 30 Days**

Figure 2.2 shows an event calendar chart with time in number of days, that represents the referral pathway for patients who experienced a detection to diagnosis period of less than 30 days \( (N = 26) \). Nine (35%) of the HRLs were from the Self-Identified Group (SIG) and 17 (65%) of the HRLs were from the Professionally Screened Group (PSG). All in the SIG are SCC or CIS. All patients in this group experienced no time delay and saw an HP at least once per year. Eighteen (69%) of the patients had regular dental follow-up of at least once per year.
Figure 2.2  Time Lag from Initial DTD for SIG vs. PSG (T < 30 Days)

Upper panel is for cases with a diagnosis of SCC or CIS and lower panel is for cases with a diagnosis of DD2 or DD3. SIG  or PSG  used to indicate individual involved with the initial detection of the HRL; Dentist , Registered Dental Hygienist , Dental Specialist , Medical Doctor , or Medical Specialist used to indicate the HP involved in the journey from detection to diagnosis; CIS  or SCC above the X-axis and DD2  or DD3  below the X-axis used to indicate the diagnostic outcome of HRL; and CIS  or SCC above the X-axis and Moderate Dysplasia/DD2  or Severe Dysplasia/DD3 below the X-axis used to trace the journey. Time interval used was by days, with T₀ indicating time of first HP visit.
2.3.5.2 Time Lag from Initial DTD of ≥1 Month and < 3 Months

Figure 2.3 shows an event calendar chart, with time in number of months, that represents the referral pathway for patients who experienced a detection to diagnosis (DTD) period greater than or equal to 1 month and less than 3 months (N = 50). Twenty-nine (58%) of the HRLs were from the SIG and 21 (42%) of the HRLs were from the PSG. SIG lesions included diagnostic results of 90% (N = 26) squamous cell carcinomas (SCCs), while 43% (N = 9) of the PSG lesions resulted in SCCs. Seventeen (81%) of the HRLs in PSG (Patient IDs 9, 25, 36, 43, 44, 45, 67, 79, 82, 91, 96, 109, 112, 115, 120, 135, and 160) were identified by a dental professional (Registered Dental Hygienist (RDH), Dentist (DDS) or Dental (DDS) Specialist). All patients in this group experienced no time delay, and 45 (90%) in this group saw an HP at least once per year. Thirty-four (68%) of the patients had regular dental follow-up of at least once per year.
Figure 2.3  Time Lag from Initial DTD for SIG vs. PSG (1 ≤ T < 3 Months)

Upper panel is for cases with a diagnosis of SCC or CIS and lower panel is for cases with a diagnosis of DD2 or DD3. SIG □ or PSG ○ used to indicate individual involved with the initial detection of the HRL; Dentist ◊, Registered Dental Hygienist ♦, Dental Specialist ★, Medical Doctor ◇, or Medical Specialist ▣ used to indicate the HP involved in the journey from detection to diagnosis; CIS △ or SCC ▲ above the X-axis and DD2 ▲ or DD3 ▲ below the X-axis used to indicate the diagnostic outcome of HRL; and CIS — — or SCC — — above the X-axis and Moderate Dysplasia/DD2 — — or Severe Dysplasia/DD3 — — below the X-axis used to trace the journey. Time interval used was by months, with T₀ indicating time of first HP visit.
2.3.5.3 Time Delay from Initial DTD of ≥ 3 Months and < 6 Months

Figure 2.4 shows an event calendar chart, with time in number of months, that represents the referral pathway for patients who experienced a detection to diagnosis (DTD) period greater than or equal to 3 months and less than 6 months (N = 28). Twenty-two (79%) of the HRLs were from the SIG and 6 (21%) were from the PSG. In the PSG, all were due to professional delay, e.g., waiting for referral for biopsy. In the SIG, 13 (59%) patients showed patient delay (Patient IDs 5, 38, 71, 90, 93, 124, 127, 134, 141, 143, 149, 157, and 158), with some citing lack of awareness for the delay (N = 5 (38%), Patient IDs 5, 71, 90, 127, and 149). There were 6 (27%) patients in the SIG that showed time delay from the first HP seen to the diagnosis. The reasons included waiting for a specialist’s appointment for at least 3 months (N = 6 (100%); Patient IDs 99, 108, 129, 138, 156 and 162), treating for other diseases or conditions (N = 2 (33%); Patient IDs 129 and 162), and/or patient delay due to lack of awareness (N = 2 (33%), Patient IDs 99 and 138). 3 (11%) of the SIG patients did not have delay on the part of the patient or professional alone. However, these patients (Patient IDs 7, 49 and 159) had a combined time delay to diagnosis of 3 months or more.

In summary for this group, 43% (6 PSG and 6 SIG) patients experienced professional delay, i.e., waiting for the referral, and 46% (13 SIG) were mainly due to patient delay. Additionally, 11% (3 SIG) had a combined total time delay to diagnosis of 3 months or more when considering both the time from initial self-identification to first HP visit and from first HP visit to diagnosis. All (28, 100%)
patients saw an HP at least once a year, and 21 (75%) of the patients had regular
dental follow-up of at least once per year.
Upper panel is for cases with a diagnosis of SCC or CIS and lower panel is for cases with a diagnosis of DD2 or DD3. SIG ■ or PSG ○ used to indicate individual involved with the initial detection of the HRL; Dentist ◊, Registered Dental Hygienist ◊, Dental Specialist ★, Medical Doctor ◊, or Medical Specialist ◊ used to indicate the HP involved in the journey from detection to diagnosis; CIS ▲ or SCC ▲ above the X-axis and DD2 △ or DD3 △ below the X-axis used to indicate the diagnostic outcome of HRL; and CIS — — or SCC — — above the X-axis and Moderate Dysplasia/DD2 — — or Severe Dysplasia/DD3 — — below the X-axis used to trace the journey. Time interval used was by months, with T_0 indicating time of first HP visit, and time of 3 months indicated by vertical - - -.
2.3.5.4  Time Delay from Initial DTD of ≥ 6 Months and < 30 Months

Figure 2.5 shows an event calendar chart, with time in number of months, that represents the referral pathway for patients who experienced a detection to diagnosis (DTD) period greater than or equal to 6 months and less than 30 months (N = 30). Twenty-one (70%) of the HRLs were from the SIG and 9 (30%) were from the PSG. In the PSG, 7 (78%) were due to professional delay, e.g., waiting for referral for biopsy, and 2 (22%) were due to patient delay, e.g., not following through with specialist referral. In the SIG, 15 (71%) patients showed patient delay (Patient IDs 2, 10, 61, 68, 73, 74, 87, 94, 97, 126, 133, 146, 155, 163, and 166), with 33% (N = 5, Patient IDs 2, 74, 94, 97, and 133) citing lack of awareness for the delay.

There were 12 (57%) patients in the SIG that showed time delay from the first HP seen to the diagnosis. The reasons include waiting for a specialist’s appointment for at least 3 months (N = 8 (67%); Patient IDs 68, 74, 78, 117, 146, 155, 163, and 169), delay in referral to a specialist (N = 3 (25%); Patient IDs 4, 10, and 77), delay in performing the biopsy (N = 2 (17%); Patient IDs 10 and 14), treating for other diseases or conditions (N = 2 (17%); Patient IDs 4 and 10), and/or patient delay due to lack of awareness (N = 5 (42%); Patient IDs 4, 74, 77, 78, and 117).

In summary for this group, 63% (7 PSG and 12 SIG) experienced professional delay, and 57% (2 PSG, 15 SIG) were due to patient delay. 20% (6 SIG) experienced both patient and professional delay. Among this group, 26 (87%) of the patients saw an HP at least once a year and 22 (73%) of the patients had regular dental follow-up of at least once per year.
Figure 2.5  Time Delay from Initial DTD for SIG vs. PSG (6 ≤ T < 30 Months)

Upper panel is for cases with a diagnosis of SCC or CIS and lower panel is for cases with a diagnosis of DD2 or DD3. SIG ■ or PSG ○ used to indicate individual involved with the initial detection of the HRL; Dentist ◊, Registered Dental Hygienist ◈, Dental Specialist ★, Medical Doctor ◆, or Medical Specialist ▲ used to indicate the HP involved in the journey from detection to diagnosis; CIS △ or SCC ▲ above the X-axis and DD2 △ or DD3 ▲ below the X-axis used to indicate the diagnostic outcome of HRL; and CIS — — or SCC —— above the X-axis and Moderate Dysplasia/DD2 — — or Severe Dysplasia/DD3 ——— below the X-axis used to trace the journey. Time interval used was by months, with $T_0$ indicating time of first HP visit, and time of 3 months indicated by vertical - - -.
2.3.5.5  *Time Delay from Initial DTD of ≥ 30 Months*

Figure 2.6 shows an event calendar chart, with time in number of months, that represents the referral pathway for patients who experienced a detection to diagnosis (DTD) period greater than or equal to 30 months (N = 16). Ten (62.5%) of the HRLs were from the SIG and 6 (37.5%) of the HRLs were from the PSG. In the PSG, all were due to professional delay, e.g., treatment for other conditions, waiting for referral for biopsy or delay in referral for biopsy. In the SIG, 5 (50%) patients showed patient delay (Patient IDs 23, 24, 56, 86, and 164), with 80% (N = 4, Patient IDs 23, 24, 56 and 86) citing lack of awareness for the delay. There were 7 (70%) patients in the SIG that showed time delay from the first HP seen to the diagnosis (Patient IDs 24, 35, 37, 40, 52, 53, and 164). The reasons include waiting for specialist’s appointment for at least 3 months (N = 4 (57%); Patient IDs 24, 40, 52, and 164), delay in referral to a specialist (N = 4 (57%); Patient IDs 24, 35, 37, 40), delay in performing a biopsy (N = 2 (29%); Patient IDs 53, 164), patient delay in following through with referral (N = 1 (14%); Patient ID 52), and/or patient delay due to lack of awareness (N = 5 (71%); Patient IDs 24, 37, 40, 52, and 53).

In summary for this group, 81% (6 PSG and 7 SIG) experienced professional delay, and 38% (6 SIG) were due to patient delay. 19% (3 SIG) experienced both patient and professional delay. All 16 of the patients saw an HP at least once a year and 15 (94%) of the patients had regular dental follow-up of at least once per year.
**Figure 2.6  Time Delay from Initial DTD for SiG vs. PSG (T ≥ 30 Months)**

SIG □ or PSG ⊘ used to indicate individual involved with the initial detection of the HRL; Dentist ◊, Registered Dental Hygienist ◈, Dental Specialist ☆, Medical Doctor ⊖, or Medical Specialist ⬠ used to indicate the HP involved in the journey from detection to diagnosis; CIS △ or SCC ▲ used to indicate the diagnostic outcome of HRL; and CIS — ⊖ or SCC — ▲ used to trace the journey. Time interval used was by months, with $T_0$ indicating time of first HP visit, and time of 3 months indicated by vertical - - -.
2.3.6 Symptoms Associated with HRL

Thirty percent (N = 45; 7% from SIG and 93% from PSG) patients were asymptomatic; while others made multiple responses with respect to the symptoms that they experienced as a result of their HRLs. The most common symptoms reported were pain (53%), non-healing ulcers (45%), lumps (14%), tissue colour changes (11%), and difficulties with chewing (5%; see Table 2.5). Figure 2.7 illustrates the distribution of symptoms for pre-invasive HRL, early-stage and late-stage cancer as a percentage of total response for each symptom, where invasive SCCs were mostly associated with symptoms, while pre-invasive HRLs were mostly asymptomatic (15% vs. 57%; see Table 2.5). Of note, 15% of cancers (13% early-stage cancers; 20% late-stage cancers) were asymptomatic (Table 2.5 and Figure 2.7).

2.3.7 Initial Reaction to HRL Symptoms

The patients made multiple responses with respect to the feelings that they experienced as a result of discovering the symptoms of their HRLs. Over half of the patient (53%) had no reaction to the HRL symptoms they experienced and 60 (40%) were concerned, 54 (36%) were fearful, 3 (2%) were uncertain, and 5 (3%) did not respond (Table 2.5).
Table 2.5  Symptoms and Reactions with Respect to Diagnostic Delay

<table>
<thead>
<tr>
<th>Reported Symptoms*</th>
<th>Total (N = 150)</th>
<th>Non-Invasive Lesions (Dysplasia, CIS) (N = 53)</th>
<th>Early Stage SCC (N = 67)</th>
<th>Late Stage SCC (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>45 (30)</td>
<td>30 (57)</td>
<td>9 (13)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Pain</td>
<td>80 (53)</td>
<td>19 (36)</td>
<td>46 (69)</td>
<td>15 (50)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>67 (45)</td>
<td>15 (28)</td>
<td>35 (52)</td>
<td>17 (57)</td>
</tr>
<tr>
<td>Lump</td>
<td>21 (14)</td>
<td>5 (9)</td>
<td>7 (10)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Colour Change</td>
<td>17 (11)</td>
<td>5 (9)</td>
<td>10 (15)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Difficulty Chewing</td>
<td>8 (5)</td>
<td>0 (0)</td>
<td>5 (7)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (11)</td>
<td>4 (8)</td>
<td>8 (12)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Initial Reaction to Symptoms*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>5 (3)</td>
<td>4 (8)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Nothing</td>
<td>79 (53)</td>
<td>24 (45)</td>
<td>38 (57)</td>
<td>17 (57)</td>
</tr>
<tr>
<td>Concern</td>
<td>60 (40)</td>
<td>22 (42)</td>
<td>29 (43)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Fear</td>
<td>54 (36)</td>
<td>19 (36)</td>
<td>24 (36)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>3 (2)</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Time Delay to 1st Health Professional Consultation</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 Months</td>
<td>117 (78)</td>
<td>43 (81)</td>
<td>48 (72)</td>
<td>26 (87)</td>
</tr>
<tr>
<td>≥ 3 Months</td>
<td>33 (22)</td>
<td>10 (19)</td>
<td>19 (28)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Time from 1st HP to Biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 Months</td>
<td>103 (69)</td>
<td>37 (70)</td>
<td>46 (69)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>≥ 3 Months</td>
<td>47 (31)</td>
<td>16 (30)</td>
<td>21 (31)</td>
<td>10 (33)</td>
</tr>
</tbody>
</table>

*Multiple responses possible

Figure 2.7  Most Common Symptoms Associated with HRLs with Respect to Staging (Precancer/Early-Stage/Late-Stage)

![Symptoms Graph]

- Precancer (N = 53)
- Early SCC (N = 67)
- Late SCC (N = 30)

Total N = 150
2.4 Discussion

This is a feasibility study to explore patients’ experience from detection to diagnosis of an HRL. The sample population, which includes patients from the Oral Oncology (OO) Clinic and the Head and Neck New Patient (HNNP) Clinic at the BC Cancer Agency, captured 75% of the potentially surgical oral cancer patients in British Columbia.

With 52 (88%) of the HRLs in the PSG detected by a registered dental hygienist (RDH), dentist (DDS), or dental specialist, dental professionals play an essential role in screening and early detection of HRLs. Dental Professionals were first seen for more premalignant lesions (68%), while Medical Professionals were seen for more late-stage SCCs (77%, \( P = 0.0005 \)). Ever smokers were more likely to have their HRLs professionally screened than never smokers (\( P = 0.05 \); see Table 2.3). This suggests that oral cancer screening and detection by health professionals may be risk factor driven, and further investigation is needed to explore this finding. The data indicates the importance of dental professionals in regular screening activities for early detection of HRLs.

According to our data, 65% of the HRLs were cancers and there were delays in time to diagnosis (49%). The delay can be due to the part of patients and/or health professionals. Cut-off points of \( \geq 3 \) months in patient delay and \( \geq 6 \) months in professional delay have been found in the literature to demonstrate a significant adverse impact on HRL prognosis (Teppo and Alho, 2008). Almost half
(49%) of the patients experienced a time delay from HRL detection to diagnosis of 3 months or longer (see Table 2.1). Strikingly, almost half (47%) of the patients were unaware of oral cancer. The mean time (± SD) from detection to first health professional seen was significantly longer in those not aware of oral cancer compared to those who were aware (9.1 ± 21.6 months vs. 3.5 ± 5.0 months, \( P = 0.004 \)). The patient’s awareness of oral cancer may hamper the early detection of this disease.

More patients (58%) in the SIG were found to be associated with time delay compared with those in the PSG (36%) (\( P = 0.007 \), see Table 2.2). This was mainly due to patient delay as a result of denial or ignorance before they were motivated to be assessed by health professionals. Methods of raising the awareness of oral cancer and the concept of early detection for better outcomes remain challenges.

There were 46 patients experiencing time delay from first HP seen to diagnosis. The reasons for the delays need further investigation, but the observations suggest that there are delays in being seen by a Specialist for biopsy after referral from a general practitioner with a few instances of patients with multiple visits to HPs (3 or more HPs seen; see Table 2.4) before biopsy, or for treatment of various reactive conditions. However, the patient delay due to denial or lack of awareness cannot be completely ruled out.
Almost half of patients (74, 49%) experienced time delay from detection to diagnosis. The reasons for time delay are complicated, and are mainly (44, 59%; 19 PSG, 25 SIG) due to professional delay (waiting for referral, delay in referral being made, delay in performing a biopsy or treatment for other conditions), and 49% (N = 36; 2 PSG, 34 SIG) are due to patient delay (lack of awareness or not following through with recommendations to see a specialist), while 12% (N = 9; all SIG) are a combination of both professional and patient delay. 4% (3 SIG) did not experience either patient delay or professional delay, however resulted in a total time delay to diagnosis of 3 months or more. Among these patients, 95% (N = 70) saw a healthcare professional at least once per year with 83% (N = 58) of the patients having regular dental follow-up of at least once per year.

Dental Professionals were first seen for more premalignant lesions (70%), while Medical Professionals were seen for more late-stage invasive squamous cell carcinomas (77%, \( P = 0.0002 \); see Table 2.1). There is a strong correlation between frequency of dental visits and identification of HRLs by healthcare professionals (\( P = 0.004 \); see Table 2.3). Patients who saw a dental professional at least once per year were more likely to have premalignant lesions identified (\( P = 0.001 \); see Table 2.1). This supports the notion of promoting regular dental visits at least once a year, regular opportunistic oral cancer screenings, and also increasing access to dental professionals in the early detection of HRLs. However, the frequency of medical visits does not appear to affect whether an HRL is self-identified or identified through screening by a health professional (\( P = 0.22 \); see Table 2.3). Additionally, staging of
the HRL does not appear to be correlated with whether or not a patient visits a doctor at least once a year ($P = 0.60$; see Table 2.1).

Premalignant lesions are more apt to be asymptomatic and detected through screening versus symptom driven appointments. Pain, non-healing ulcers and chewing difficulties are associated with both early-stage and late-stage SCCs, but lumps are more frequently associated with late-stage SCCs. (see Table 2.5). SIG lesions are also more likely to have symptoms of pain, non-healing ulcers, and/or lumps and chewing difficulties ($P = 0.0001$), which prompted patients to seek health care. Comparatively, precancerous lesions and those in PSG are not associated with symptoms. This information can be used in promoting awareness of the symptoms of HRLs to watch for in order to encourage people to seek healthcare sooner or for HPs to refer their patients for further investigation sooner.

The representativeness of the entire BC population may be arguable. This research is to prepare for the next step in the province-wide roll out for a true population based data collection with inclusion of geographic factors, for example, the accessibility of specialists and dental clinics etc. However, patients recruited were invited to participate opportunistically as they presented to the Vancouver Centre of the BC Cancer Agency (BCCA). Rapport with patients was established as a result of the face to face setting of the clinic. Consequently, rate of recruitment was 86%. This high recruitment might not have been possible if questionnaires were mailed to potential study participants instead. Additionally, self-reporting and memory bias may also occur as a result of the retrospective nature of some of the
questions in the study questionnaire. However, an eligibility criterion of excluding patients diagnosed with an HRL more than 12 months from the time of questionnaire minimizes the self-reporting and memory bias.

Updates to the ETD questionnaire are recommended prior to utilization in a larger scale study. Such updates include adding instructions at the top of the questionnaire to fill in the entire box to indicate an answer. Socio-demographic questions to be added include ethnicity, postal code, annual family income, and education levels, to make the data collection more comprehensive and to reduce the workload. The question regarding which health professionals are seen regularly, should be quantified in order to clarify its meaning, i.e., *The term “regularly” refers to health professional visits of at least once per year.* Other questions to be considered for inclusion in the questionnaire include those that address gaps in the literature and study. Such questions pertain to risk factors (i.e., HPV exposure and oral sexual behaviour, alcohol use). Other questions regarding reasons for delay in diagnosis after initial examination by a health professional should be added, i.e., *If a referral to a specialist was recommended, did you see the specialist within 3 months?* Use check boxes for “Yes” and “No”. *If no was selected, what is the reason?* Use check boxes with a number to indicate the sequence and to collect additional professional delay factors, i.e., “*I was on the wait list to see a Specialist for ____ month(s), I have been treated using an oral topical agent or oral rinse for ____ month(s)*”, or the number of different health professionals seen prior to the
biopsy of HRL. To explore the type of HPs involved in early detection, a question regarding their health utilization should be included.
3. Study II: Tobacco Usage and Diagnosis (TUD)

3.1 Objectives

The objectives of Study II are: 1) To identify patients who ever smoke within 5 years of a diagnosis of a high-risk oral lesion (HRL), 2) To collect data regarding demographics, tobacco usage, and any tobacco-related behavioural changes prior to and after the diagnosis of an HRL, and 3) To identify possible facilitators and barriers in tobacco cessation.

3.2 Method

3.2.1 Study Population

This is an extension of Study I. Individuals who were 19 years and older, read, speak and understand English, received a biopsy of first HRL within 12 months, and had a history of smoking at least 100 cigarettes in their lifetime within 5 years of the questionnaire were eligible for the study. To reduce the recall bias, we limited our patients to a smoking history within 5 years. This study has been approved by the UBC/BCCA Ethics Review Board (H10-01406). Written informed consent was obtained before proceeding with the survey (see APPENDIX A.3). Study II: Tobacco Usage and Diagnosis, or TUD, includes individuals from a pilot study of 25 patients recruited from patients in the OO clinic to help test and develop the final form of the survey. Figure 2.1 illustrates the research method for
this study. Study II: Tobacco Usage and Diagnosis follows the path of the orange arrows in the flowchart.

### 3.2.2 Questionnaire

A survey-style questionnaire was designed with questions relating to smoking behaviour modification prior to or after the diagnosis of a High-Risk Oral Lesion (HRL), nicotine addiction and barriers to tobacco cessation. The questionnaire (see APPENDIX A.4) included 34 questions with a selection of categorical check boxes and fill-in-the-blanks to collect quantitative and qualitative data that could easily be completed by an individual without assistance. Socio-demographic data collected included information on gender, date of birth, ethnicity, language fluency, education level, living situation, employment status, and annual family income. Questions on tobacco usage included: *At what age did you start smoking? On average, how many cigarettes a day did/do you smoke? What is the total number of years that you have smoked? Before your diagnosis of the high-risk oral lesion, how many cigarettes did you smoke? After your diagnosis of the high-risk oral lesion, how many cigarettes did you smoke? (Participants were then given boxes to enter their numerical answers. Number of cigarettes refer to the number smoked per day.) Do you smoke now? (Participants were instructed to check off “Yes” or “No”, and if “Yes”, to continue to another designated question.)* Questions only applicable to participants who stopped smoking included: *How long ago did you stop smoking? If you quit, what is the reason for why you quit? What is this quit time in relation to your diagnosis?* (Participants were instructed to check off the
appropriate category or categories.) Other questions relating to tobacco usage included: Have you tried to quit smoking before the diagnosis of the high-risk oral lesion? Have you tried to quit smoking after the diagnosis of the high-risk oral lesion? (Participants were instructed to check off the appropriate category or categories.) Questions on participant perceptions of tobacco cessation included: What do you see as the good things or advantages that would happen if people quit smoking? What do you see as the bad things or disadvantages that would happen if people quit smoking? In your experience or from others, what would make it difficult to quit smoking? In your experience or from others, what would make it easier to quit smoking? If a person quit smoking today, do you think he/she would live longer? Who do you think would object if you quit smoking? Who do you think would support you if you quit smoking? Which individuals are most important to you in your decision to quit smoking or not? (Participants were instructed to check off the appropriate category or categories.) Questions relating to tobacco cessation intention and tobacco usage experience that are only applicable to participants who continue to smoke included: Do you intend to quit smoking now? (Participants were instructed to check off “Yes” or “No”, and if “No”, to continue to another designated question.) What is the reason you intend to quit? If you do not intend to quit, what is the reason? In your past experience, have you ever felt a need to cut down or control your smoking but had difficulty doing so? In your past experience, have you ever been annoyed or angry with people who criticize your smoking or say that you should quit smoking? In your past experience, have you ever felt guilty about your smoking or about something you did while smoking? In your past experience, have
you ever smoked within half an hour of waking? In your past experience, have you ever had the following symptoms when you went without a cigarette for any length of time? In your past experience, did the symptoms go away after you smoked a cigarette? (Participants were instructed to check off the appropriate category or categories.) Additional data relating to the date of biopsy, pathological diagnosis, and anatomical site of the lesion was obtained through data collection via the BC Cancer Agency database. The data was analyzed using unpaired Student’s t – test or ANOVA for means analysis of continuous parametric data, and contingency tables with Fisher’s Exact or Chi-squared test for non-parametric or categorical data.

3.2.3 Definitions of Terminologies Used in the Study

Ever Smoker in the context of this study means an individual with a history of smoking at least 100 cigarettes in his or her lifetime. Smoker in the context of this study means an individual with a history of smoking at least 100 cigarettes in his or her lifetime who 1) is currently smoking, or 2) has stopped smoking less than 1 year. Former Smoker in the context of this study means an individual with a history of smoking at least 100 cigarettes in his or her lifetime, but has stopped smoking for one year or more. Never Smoker means an individual who 1) has never smoked a cigarette, or 2) has smoked less than 100 cigarettes in his or her lifetime. For other definitions, please refer to Section 2.2.3.
3.3 Results

3.3.1 Demographics and Lesion Characteristics

Between September 2008 and August 2011, among 135 screened patients, 58 (43%) patients were found to be eligible for the study and completed questionnaires. Table 3.1 shows the demographic and lesion characteristics of all participants. These patients were mainly male (N = 41, 71%), Caucasian (N = 53, 91%) and mid-aged with a mean age (± SD) of 58.2 ± 9.2 years [range: 39-82 years]. Among these patients, 4 (7%) quit prior to diagnosis of an HRL, 21 (36%) quit smoking after diagnosis of an HRL and 33 (57%) continued to smoke, with 79% (N = 26) decreasing their tobacco usage. They were categorized into Quit Before Diagnosis (QBD; N = 4, 7%), Quit After Diagnosis (QAD; N = 21, 36%), and Continues to Smoke (CTS; N = 33, 57%) for comparison (Table 3.1). Although there were more females in the QBD group, there was generally no difference among the groups in terms of gender, mean age, ethnicity, disease staging, and anatomical sites. Among those QAD, 95% cited the diagnosis of the HRL as the strongest reason to quit.
Table 3.1  Demographic Characteristics of Participants

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total</th>
<th>Quit Before Dx (QBD)</th>
<th>Quit After Dx (QAD)</th>
<th>Continues to Smoke (CTS)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>N = 58 (100%)</td>
<td>N = 4 (7%)</td>
<td>N = 21 (36%)</td>
<td>N = 33 (57%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 (71)</td>
<td>1 (25)</td>
<td>17 (81)</td>
<td>23 (70)</td>
<td>0.08</td>
</tr>
<tr>
<td>Female</td>
<td>17 (29)</td>
<td>3 (75)</td>
<td>4 (19)</td>
<td>10 (30)</td>
<td></td>
</tr>
<tr>
<td>Age Mean Age ± SD</td>
<td>58.2 ± 9.2</td>
<td>58.2 ± 10.7</td>
<td>60.6 ± 10.1</td>
<td>56.6 ± 8.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>53 (91)</td>
<td>4 (100)</td>
<td>17 (81)</td>
<td>32 (97)</td>
<td>0.10</td>
</tr>
<tr>
<td>Other</td>
<td>5 (9)</td>
<td>0 (0)</td>
<td>4 (19)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever-Smoker</td>
<td>58 (100)</td>
<td>4 (100)</td>
<td>21 (100)</td>
<td>33 (100)</td>
<td></td>
</tr>
<tr>
<td>No Change in Smoking</td>
<td>7 (12)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7 (21)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>26 (45)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>26 (79)</td>
<td>NA</td>
</tr>
<tr>
<td>Stop &lt; 1 Year</td>
<td>12 (21)</td>
<td>0 (0)</td>
<td>12 (57)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Former Smoker ≥ 1 yr</td>
<td>13 (22)</td>
<td>4 (100)</td>
<td>9 (43)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precancer</td>
<td>33 (57)</td>
<td>3 (75)</td>
<td>12 (57)</td>
<td>18 (55)</td>
<td>0.70</td>
</tr>
<tr>
<td>Early Stage</td>
<td>15 (26)</td>
<td>1 (25)</td>
<td>4 (19)</td>
<td>10 (30)</td>
<td></td>
</tr>
<tr>
<td>Late Stage</td>
<td>10 (17)</td>
<td>0 (0)</td>
<td>5 (24)</td>
<td>5 (15)</td>
<td></td>
</tr>
<tr>
<td>Anatomical Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>20 (35)</td>
<td>2 (50)</td>
<td>8 (38)</td>
<td>10 (31)</td>
<td>0.47</td>
</tr>
<tr>
<td>Floor of Mouth</td>
<td>17 (29)</td>
<td>1 (25)</td>
<td>5 (24)</td>
<td>11 (33)</td>
<td></td>
</tr>
<tr>
<td>Soft Palate</td>
<td>3 (5)</td>
<td>1 (25)</td>
<td>1 (5)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>18 (31)</td>
<td>0 (0)</td>
<td>7 (33)</td>
<td>11 (33)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Smoker vs. Decrease vs. Stop vs. Former Smoker

*P-Value compares QBD vs. QAD vs. CTS for variables listed within each grouping
3.3.2 Tobacco Consumption Before and After HRL Diagnosis

To identify the tobacco usage behavioural changes before and after HRL diagnosis, the TUD patients were organized into three categories according to their daily cigarette consumption in relation to 20 cigarettes (1 pack) prior to HRL diagnosis. The three categories were: 1) Initial tobacco usage of less than 20 cigarettes per day (N = 25; Figure 3.1), 2) Initial tobacco usage of 20 cigarettes per day (N = 19; Figure 3.2), and 3) Initial tobacco usage of greater than 20 cigarettes per day (N = 14; Figure 3.3). There was a significant difference in the number of patients who quit among the 3 groups ($P = 0.009$) and between those who smoked less than 20 and greater than or equal to 20 cigarettes per day ($P = 0.005$). Patients who smoked less than 20 cigarettes per day were more likely to quit smoking, when compared to those who smoked 20 cigarettes or more per day (64% vs. 27%). Similarly, patients who smoked 20 cigarettes or more per day were more likely to continue their smoking behaviours when compared with patients who smoked less than 20 cigarettes per day (73% vs. 36%).
Figure 3.1 Number of Cigarettes Smoked Before HRL Diagnosis vs. After HRL Diagnosis (Initial Tobacco Usage of < 20 Cigarettes/Day)

This figure shows how smoking less than 20 cigarettes a day may influence patient ability to quit tobacco use. 16 (64%) patients who smoked less than 20 cigarettes per day quit smoking, with 3 (12%) quitting prior to HRL diagnosis and 13 (52%) quitting after HRL diagnosis. 9 (36%) of patients in this group continued to smoke, with 3 (33%) of those who continue to smoke remaining at the same number of cigarettes, and 6 (67%) of the patients who continue to smoke, decreasing their tobacco usage. With the majority of patients in this group quitting or decreasing their tobacco usage, it appears that patients are more likely to quit when they smoke fewer than 20 cigarettes per day, when compared to patients who smoke 20 cigarettes or more per day.
Figure 3.2  Number of Cigarettes Smoked Before HRL Diagnosis vs. After HRL Diagnosis (Initial Tobacco Usage of 20 Cigarettes/Day)

This figure shows how smoking 20 cigarettes (1 pack) a day may influence patient ability to quit tobacco use. 7 (37%) patients who smoked 20 cigarettes per day quit smoking after HRL diagnosis. 12 (63%) of patients in this group continued to smoke, with 1 (8%) continuing to smoke the same number of cigarettes, and 11 (92%) of the patients decreasing their tobacco usage. With the majority of patients in this group continuing their tobacco usage, but attempting to decrease the number of cigarettes, it appears that perhaps smoking 20 cigarettes a day may influence a patient’s likelihood or ability to quit, when compared to patients who smoke less than 20 cigarettes per day.
This figure shows how smoking more than 20 cigarettes (1 pack) a day may influence patient ability to quit tobacco use. 2 (14%) of patients who smoked more than 20 cigarettes per day quit smoking, with 1 (7%) quitting prior to HRL diagnosis. 12 (86%) of patients in this group continued to smoke, with 2 (17%) continuing to smoke the same number of cigarettes, and 10 (83%) of the patients decreasing their tobacco usage. With the majority of patients in this group continuing their tobacco usage, but attempting to decrease the number of cigarettes, it appears that perhaps smoking more than 20 cigarettes a day may influence a patient’s likelihood or ability to quit, when compared to patients who smoke less than 20 cigarettes per day.
### 3.3.3 Tobacco Cessation Intent

Twenty-one (36%) of the current smokers stated an intent to quit their tobacco habits, 6 of them were undetermined and 6 showed no intent to quit. Comparing those with intent to quit and those with no intent to quit, there was no difference in gender, ethnicity, or disease staging (see Table 3.2), with the exception of mean age. Patients who showed no intent to quit seemed to be older than those who had an intent to quit ($P = 0.008$, see Table 3.2).

**Table 3.2 Tobacco Cessation Intent in Relation to Demographics**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Total (N = 58)</th>
<th>Already Quit (N = 25)</th>
<th>Intends to Quit (N = 21)</th>
<th>No Intent to Quit (N = 6)</th>
<th>Undeclared (N = 6)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 (71)</td>
<td>18 (72)</td>
<td>15 (71)</td>
<td>4 (67)</td>
<td>4 (67)</td>
<td>0.99</td>
</tr>
<tr>
<td>Female</td>
<td>17 (29)</td>
<td>7 (28)</td>
<td>6 (29)</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>Mean Age ± SD</td>
<td>58.2 ± 9.2</td>
<td>60.2 ± 10.0</td>
<td>55.3 ± 6.9</td>
<td>66.2 ± 6.7</td>
<td>51.3 ± 8.1</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Caucasian</td>
<td>53 (91)</td>
<td>21 (84)</td>
<td>21 (100)</td>
<td>5 (83)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (9)</td>
<td>4 (16)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Ever-Smoker</td>
<td>58 (100)</td>
<td>25 (100)</td>
<td>21 (100)</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>No Change in Smoking</td>
<td>7 (12)</td>
<td>0 (0)</td>
<td>6 (29)</td>
<td>1 (17)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Decrease</td>
<td>26 (45)</td>
<td>0 (0)</td>
<td>15 (71)</td>
<td>5 (83)</td>
<td>6 (100)</td>
<td></td>
</tr>
<tr>
<td>Stop &lt; 1 Year</td>
<td>12 (21)</td>
<td>12 (48)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Former Smoker ≥ 1 yr</td>
<td>13 (22)</td>
<td>13 (52)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.42</td>
</tr>
<tr>
<td>Precancer</td>
<td>33 (57)</td>
<td>15 (60)</td>
<td>10 (48)</td>
<td>3 (50)</td>
<td>5 (83)</td>
<td></td>
</tr>
<tr>
<td>Early Stage</td>
<td>15 (26)</td>
<td>5 (20)</td>
<td>7 (33)</td>
<td>3 (50)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Late Stage</td>
<td>10 (17)</td>
<td>5 (20)</td>
<td>4 (19)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td></td>
</tr>
</tbody>
</table>

*P-Value compares Already Quit vs. Intends to Quit vs. No Intent to Quit vs. Undeclared for variables listed within each grouping.
3.3.4 Patient Perceptions Regarding Barriers and Facilitators to Tobacco Cessation

In general, these patients reported an understanding of the advantages of tobacco cessation. The advantages cited include monetary savings (51, 88%), decreased cancer or cardiovascular disease risk (49, 84%), better health (46, 79%), being able to breathe more easily (45, 78%), decreased tobacco smoke body odour (44, 76%), and decreased coughing (40, 69%; see Table 3.3). Some of the perceived disadvantages for tobacco cessation included smoking habit recurrence (57%), stress (50%), and weight gain (41%; see Table 3.3). Main barriers for tobacco smoking cessation included stress (67%), smoking enjoyment (64%), not being ready to quit (60%), and having friends who smoke (31%; see Table 3.3). Facilitators for tobacco cessation included a knowledge of decreased health risks (71%), availability and use of tobacco cessation aids (43%), friends and family who do not smoke (38%), support of family and friends (33%), and availability of tobacco cessation programs (24%; see Table 3.3).
Table 3.3  Patient Perceptions Regarding Tobacco Cessation

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 58 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Save Money</td>
<td>51</td>
<td>(88)</td>
</tr>
<tr>
<td>Decrease in Cancer/CVD Risk</td>
<td>49</td>
<td>(84)</td>
</tr>
<tr>
<td>Healthier</td>
<td>46</td>
<td>(79)</td>
</tr>
<tr>
<td>Breathe Easier</td>
<td>45</td>
<td>(78)</td>
</tr>
<tr>
<td>No Body Odor</td>
<td>44</td>
<td>(76)</td>
</tr>
<tr>
<td>Cough Less</td>
<td>40</td>
<td>(69)</td>
</tr>
<tr>
<td>Better Sense of Taste and Smell</td>
<td>37</td>
<td>(64)</td>
</tr>
<tr>
<td>Better Control Over Life</td>
<td>36</td>
<td>(62)</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>(14)</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td>N/A</td>
<td>1</td>
<td>(2)</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 58 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quit in Past but Smoking Recurs</td>
<td>33</td>
<td>(57)</td>
</tr>
<tr>
<td>Stress</td>
<td>29</td>
<td>(50)</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>24</td>
<td>(41)</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>(16)</td>
</tr>
<tr>
<td>None</td>
<td>9</td>
<td>(16)</td>
</tr>
<tr>
<td>N/A</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td><strong>Barriers</strong></td>
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<tr>
<td>N = 58 (100%)</td>
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</tr>
<tr>
<td>Stress - Smoking is Relaxing</td>
<td>39</td>
<td>(67)</td>
</tr>
<tr>
<td>Like to Smoke</td>
<td>37</td>
<td>(64)</td>
</tr>
<tr>
<td>Not Ready</td>
<td>35</td>
<td>(60)</td>
</tr>
<tr>
<td>Friends Smoke</td>
<td>18</td>
<td>(31)</td>
</tr>
<tr>
<td>No Cessation Program Access</td>
<td>8</td>
<td>(14)</td>
</tr>
<tr>
<td>Cessation Aids Expensive</td>
<td>5</td>
<td>(9)</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>(29)</td>
</tr>
<tr>
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<td>(3)</td>
</tr>
<tr>
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<td>(0)</td>
</tr>
<tr>
<td><strong>Facilitators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 58 (100%)</td>
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<td></td>
</tr>
<tr>
<td>Decrease in Health Risks</td>
<td>41</td>
<td>(71)</td>
</tr>
<tr>
<td>Cessation Aids</td>
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<td>(43)</td>
</tr>
<tr>
<td>Friends/Family Who Do Not Smoke</td>
<td>22</td>
<td>(38)</td>
</tr>
<tr>
<td>Friends/Family Support</td>
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<td>(33)</td>
</tr>
<tr>
<td>Cessation Program</td>
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<td>(24)</td>
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<td>(29)</td>
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<td>6</td>
<td>(10)</td>
</tr>
<tr>
<td>N/A</td>
<td>0</td>
<td>(0)</td>
</tr>
</tbody>
</table>

*Multiple Responses
3.3.5 Recurrence of High-Risk Oral Lesions

There were a total of 5 (9%) recurrent HRL cases after treatment during the study period, with an average follow-up time (± SD) of 45.5 ± 37 months. Four (80%) of these 5 patients continued to smoke after the first lesion was diagnosed ($P = 0.39$). Figure 3.4 shows a Kaplan Meier survival curve of recurrence of HRL in relation to follow-up time. Continuing to smoke after an HRL diagnosis appears to be associated with recurrence of HRLs. Since the follow-up time is limited, the data is still immature.
Figure 3.4  Probability of development of recurrence from time of diagnosis to outcome between patients who continue to smoke and quit after the diagnosis of an HRL
3.4 Discussion

This is a pilot study to assess the impact of the diagnosis of an HRL to a patient’s decision on smoking habit, which is one of the main risk factors for oral cancer and its recurrence. The diagnosis of an HRL is indeed a pivotal factor for these patients to stop or reduce the number of cigarettes, with 36% who quit successfully and 45% who reduced the number of cigarettes (see Table 3.1). For those who continue to smoke, smoking recurrence (57%) and stress (50%) were cited as deterrents for quitting, while main barriers for tobacco cessation included stress (67%), smoking enjoyment (64%), and not being ready to quit (60%; see Table 3.3). Interestingly, they agreed that knowledge of decreased health risks (71%) was the main facilitator for successful cessation, in addition to the availability and use of tobacco cessation aids (43%). These findings support the need for tobacco cessation initiatives that 1) target patients who continue to smoke after diagnosis of an HRL, 2) educate the public regarding oral cancer risk factors, 3) provide support for all phases of tobacco cessation in terms of stress management and facilitating a decision to quit, and 4) provide tobacco cessation aids for facilitating successful quitting.

Number of cigarettes consumed prior to diagnosis of an HRL appeared to be a contributing factor in tobacco cessation. Thirteen (52%) of 25 patients who smoked less than 20 cigarettes a day prior to diagnosis of an HRL quit their tobacco usage after diagnosis (see Figure 3.1), while 7 (37%) of 19 patients who smoked 20 cigarettes a day (see Figure 3.2) and 1 (7%) of 14 patients who smoked more
than 20 cigarettes a day prior to HRL diagnosis (see Figure 3.3) quit after being diagnosed. The data suggests that despite attempts to decrease tobacco consumption, increased initial nicotine intake and dependence may be associated with increased difficulties with tobacco cessation. A combined therapy of support programs and nicotine replacement therapy (NRT) in varying dosages in relation to nicotine dependence has been shown to be effective for tobacco cessation (Tang, Law et al., 1994; Silagy, Mant et al., 2000). Therefore, tobacco cessation initiatives which incorporate NRT, tailored according to nicotine dependence, alongside tobacco cessation support programs, are a possible strategy in addressing the differences in tobacco cessation based on number of cigarettes consumed. Further investigation into the role of tobacco cessation aids and/or support services to address nicotine dependence in transitioning to decreased tobacco consumption is needed.

Twelve (21%) of the TUD patients stated that they had no intention of quitting or were undeclared regarding their tobacco cessation intent at the time of the questionnaire (see Table 3.2). Age at the time of diagnosis of the HRL appears to be an influential factor. Reasons for the age-related tobacco cessation intent need to be investigated further, as increased age appears to be related to a decreased desire to quit.

Five patients experienced recurrent lesions after initial diagnosis and treatment of their HRLs. Studies have shown clearly that continued smoking after diagnosis of an HRL increases risk of recurrent and second primary malignancies by
10-30% and 4-7%, respectively (van Oijen and Slootweg, 2000; Do, Johnson et al., 2003; Kademani, 2007). Due to the small sample size (N = 58) of this study and the short duration of follow-up, the rate of recurrence may not reflect the truth. Further investigation into the relationship of continued smoking after the diagnosis of an HRL is needed to understand its impact on oral health and to support tobacco cessation initiatives targeting ever smoking patients with a diagnosis of an HRL. Additionally, rate of recurrence and follow-up time of at least 5 years after tobacco cessation requires investigation to support findings of a decreased risk of second cancers 5 years after tobacco cessation (Day, Blot et al., 1994)

Due to the small sample, results may not be representative of the tobacco usage behaviours of the general population of ever smokers with a diagnosis of an HRL. However, as a result of the apparently changing tobacco usage trends and adoption of healthier lifestyle choices in British Columbia, there were difficulties in recruiting eligible patients for the study. Expansion of the study into a population-based larger scale study may address the recruitment difficulties in order to gain a better understanding of the changes in tobacco usage behaviours as a result of an HRL diagnosis.

Alcohol has been shown to have a synergistic effect with tobacco to increase carcinogenicity of tobacco nitrosamines on mucosal tissues (van Oijen and Slootweg, 2000; Do, Johnson et al., 2003; Kademani, 2007). The risk of malignant transformation is more than 100 times greater for heavy smokers and drinkers who consume at least 100 g of alcohol per day (Kademani, 2007). Therefore, updates to
the TUD questionnaire to include alcohol consumption as a risk factor are recommended prior to utilization in a larger scale study.

Study results show that despite attempts to decrease tobacco consumption, increased initial nicotine intake and dependence may be associated with increased difficulties with tobacco cessation. To test the impact of nicotine replacement therapy (NRT) and/or tobacco cessation supportive programs on changes in tobacco usage behaviour, questions on type, brand and dosage of NRT (if applicable), as well as type, frequency and duration of supportive program (if applicable) should be considered for inclusion in the TUD questionnaire. To get a more accurate timeline of tobacco cessation, questions regarding the exact date of tobacco cessation, biopsy/diagnosis date, and quit time in relation to the questionnaire should be included (i.e., "When did you quit smoking?", "What was the date of your biopsy?", "How long ago in relation to this questionnaire did you stop smoking?"). Additionally, the role of the healthcare professional in facilitating tobacco cessation is unknown. To explore the role of the Dental Professional (Dentist, Dental Hygienist, Dental Specialist) and the Medical Professional (Medical Doctor, Nurse, Medical Specialist, Alternative Medical Practitioner), inclusion of questions regarding whether recommendations for tobacco cessation and tobacco cessation counselling were provided by any of these individual healthcare professionals is recommended.
4. Conclusion and Future Directions

Oral cancer is a deadly disease and early detection can have better outcome. Screening for oral cancer appears to remain risk factor driven. Recommendations should be made for self-examinations and healthcare professional screenings to take place regardless of known risk factors.

Dental professionals were the main health professionals to identify HRLs, especially in the identification of early HRLs. On the other hand, most of the SIG patients who experienced time delay were due to delays in seeking health care. Therefore, promotion of regular annual dental visits, regular oral cancer screening by dental professionals, and increasing access to dental professionals will facilitate the identification of earlier HRLs at risk of cancer progression, resulting in better prognosis. Additionally, due to knowledge deficits regarding oral cancer awareness, education of patients of the signs and symptoms of HRLs will facilitate the identification of earlier HRLs, earlier healthcare attention, and consequently, better prognosis.

Receiving the diagnosis of an HRL was indeed the main reason for tobacco cessation or reduction. In our study, we have identified main perceived facilitators and barriers for tobacco cessation, and these should be considered for the development of tobacco cessation programs for patients with an HRL. However, the data also suggests that despite attempts to decrease tobacco consumption, increased initial nicotine intake and dependence may be associated with increased
difficulties with tobacco cessation. A customized program might be needed, especially for those long-term and high-dose users.

The results of Study I and Study II will facilitate the development of a refined questionnaire. This questionnaire will be used in a population-based larger scale study to target patients diagnosed with an HRL in British Columbia. The additional data from the larger scale study will assist in identifying the need for oral cancer awareness strategies for both the general public and healthcare professionals.


recurrence in the head and neck retinoid chemoprevention trial." Cancer Epidemiol Biomarkers Prev 10(8): 823-829.


APPENDICES
APPENDIX A.1  Experience to Diagnosis Consent Form
Experiences Leading to Diagnosis

Subject Information and Consent Form

BCCA REB # H07-01942

BCCA Principal Investigator: Dr. Miriam Rosin
Cancer Control Research
Telephone: 604-675-8078

Project Principal Investigator: Dr. Catherine Poh
Faculty of Dentistry/UBC
Telephone: 604-678-8078

Project Co-Investigators:
Heather Biggar (Master student)
Darlene Tam (Master student)

Dr. Greg Hislop
Faculty of Dentistry/UBC
Telephone: 604-675-8057

Dr. Lewei Zhang
Cancer Control Research/BCCA
Telephone: 604-675-8060

Dr. Pamela Gardner
Fraser Valley Cancer Centre/BCCA
Telephone: 604-930-2098 Ext. 4549

Non-Emergency contact numbers are noted at the end of this document under the section heading “Contact”.
Background

You are being invited to participate in this study so that researchers can learn more about your experiences leading to the diagnosis of your recent oral (mouth) condition that was sampled and diagnosed. With a better understanding of this experience, we hope to be able to improve our processes for making this diagnosis.

Your standard of care at BCCA will involve regular monitoring, testing and treatments as deemed necessary to best manage your condition. This study will not affect your management or treatment in any way. Your participation is voluntary and you will continue to receive the best care we can provide whether or not you agree to participate in this study.

Purpose

The purpose of this study is to collect detailed information about your experiences with healthcare personnel from the time that a change in your mouth was first identified until a tissue sample (biopsy) was collected.

Your experiences will provide valuable insight into the process leading to your diagnosis.

Who Can Participate In This Study?

You may participate in this study if:
• You fully understand the study and give your informed consent to participate as demonstrated by signing this consent form.
• You can clearly speak and understand English.
• You have had a tissue sample (biopsy) for an oral condition collected within the past 12 months.

Study Procedures

Your participation will involve an interview in which you will be asked questions regarding your experience during the time period from first suspecting or identifying the condition in your mouth to the time of biopsy. This will include information about the various health professionals you have seen and your overall experience leading up to the biopsy. The interview will last approximately 20 ~ 30 minutes and will take place at one of your scheduled oral medicine exam visits. With your consent, this interview will be audio recorded.
If any information is missed during the interview, you may be contacted by telephone.

Your participation would also include giving permission to access your medical and dental records regarding your oral conditions to supplement information about your diagnostic work-up. You might also be invited to participate in a group discussion (a focus group) where you will be asked to provide feedback on the study findings.

Benefits & Risks

There are no direct benefits to you from participation in this study. However, we hope that the information learned from you may improve the health care provided to your community in the future.

Confidentiality

Your confidentiality will be respected to the extent permitted by applicable laws and regulations and your medical and study records will not be publicly available. No information that discloses your identity will be released or published without your specific consent. Your identity will not be used in any reports about the study. In records that leave this centre you will be identified by a study code only. All information associated with this study will be kept behind locked doors or in secure computer files.

The information gathered from this study, with personal identifiers removed, will be used to better understand and improve the diagnostic process.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor or the UBC BCCA Research Ethics Board.

Compensation

You will not be paid for participating in this study.

You do not waive any of your legal rights for compensation by signing this form.
Contact

We will be glad to answer any questions you may have regarding this research in order to ensure that you fully understand the process.

If you have any questions or desire further information with respect to this study, you may contact the project principal investigator, Dr. Catherine Poh or Darlene Tam or Heather Biggar at 604-675-8057, or Eunice Rousseau with the BC Oral Cancer Prevention Program at (604) 675-8078.

If you have any concerns about your rights as a research subject, you may contact the Research Subject Information Line in the UBC office of Research Services at 604-822-8598.

Subject Consent

I understand that participation in this study is entirely voluntary. I authorize access to my medical record and research data as described in this consent form. I may choose not to participate or I may withdraw from the study at any time and I will continue to be offered the best available medical care. I understand that I may ask questions about this study in the future.

I will receive a signed copy of this consent form including all attachments, for my own records.

I consent to participate in this study.

_________________________________    __________________________   __________
Subject’s Signature                    Printed name                          Date

_________________________________    __________________________   __________
Witness’ Signature                     Printed name                          Date

_________________________________    __________________________   __________
Signature of Person Obtaining Consent  Printed name                          Study Role Date

Experience to Diagnosis Subject Consent Form
Version 2.0: September 13, 2007
APPENDIX A.2  Experience to Diagnosis Questionnaire
EXPERIENCES LEADING TO DIAGNOSIS

Site ID
Patient ID
Initials

Date Filled (YYYY/MM/DD)

Gender
 Male    Female

Date of Birth (YYYY/MM/DD)

1. Which of the following healthcare professionals do you see regularly? (Please mark in all boxes that apply and fill in the number of months. i.e. if it is 2 years, fill in 24 months.)

- Dental Practitioner (Dental/Dental Hygienist/Dental Specialist)
  Once every __________ months

- Medical Practitioner (Family Doctor/Nurse/Alternative Medical Practitioner)
  Once every __________ months

- Other (Please Specify)
  Once every __________ months

2. Have you ever smoked more than 100 cigarettes in your lifetime?

- Yes    No

3. Do you currently smoke?

- Yes    No

4. If you quit, when did you stop smoking? (Approximate date okay, if exact date is not known.)

   __________ / __________ / __________ (YYYY/MM/DD)

5. Who first detected the change (lesion) in your mouth? (Mark one).

- Self
- Nurse
- Dental Hygienist
- Medical Doctor
- Dentist
- Medical Student
- Dental Specialist
- Other (Please Specify)

6. What date was the change (lesion) noticed? (Approximate date okay, if exact date is not known.)

   __________ / __________ / __________ (YYYY/MM/DD)

7. What were the first symptoms you noticed? (Mark all that apply.)

- I did not notice anything until my healthcare professional pointed it out
- Felt a lump
- Sore or uncomfortable lesion/ulcer
- Difficulty chewing
- Change in color
- Other

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8. **What was your initial feeling to discovering your symptoms? (Please mark one only.)**

- [ ] Not concerned
- [ ] Fear and/or concern

9. **What was the first thing that you did after noticing your symptoms? (Please number in order all that apply.)**

- [ ] Discussed with loved ones
- [ ] Used a topical treatment
- [ ] Saw a health practitioner
- [ ] Avoided acidic beverages/foods
- [ ] Watched and waited for the symptoms to go away
- [ ] Did not do anything
- [ ] Changed oral hygiene habits

10. **Which health practitioner first examined the change (lesion) in your mouth? (If your lesion was first identified by a healthcare practitioner, select the next health practitioner that you were referred to.)**

- [ ] Dental Hygienist
- [ ] Dentist
- [ ] Dental Specialist
- [ ] Nurse
- [ ] Medical Doctor
- [ ] Medical Specialist

11. **What was the date of your first visit to this health practitioner? (Approximate date okay, if exact date is unknown.)**

   [ ] [ ] [ ] / [ ] [ ] [ ] (YYYY/MM/DD)

12. **What did the health practitioner recommend you to do?**

- [ ] Watch the change (lesion) and return in 2 weeks if it does not go away
- [ ] Referral to the Medical Doctor
- [ ] Referral to the Dentist
- [ ] Referral to the Medical Specialist
- [ ] Referral to the Dental Specialist
- [ ] Other

13. **Who performed your first biopsy?**

- [ ] Dentist
- [ ] Dental Specialist
- [ ] Medical Doctor
- [ ] Medical Specialist

14. **What was the date of your first biopsy? (Approximate date okay, if exact date is not known.)**

   [ ] [ ] [ ] / [ ] [ ] [ ] (YYYY/MM/DD)

15. **Before noticing your first symptoms, which types of cancer would you say you had heard of?**

   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________

16. **When you received the diagnosis of your oral lesion, how did it make you feel? Did the diagnosis impact your day-to-day activities in any way? (Please continue on the other side of this page if you need more space.)**

   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
   ____________________________________________________________
17. Do you have any further comments regarding your experiences leading to diagnosis of an oral lesion?


18. May we contact you if we need clarification of any of the answers in this questionnaire?

[ ] Yes  [ ] No

This completes the questionnaire. Thank you once again for taking the time to participate in this study. Your contribution is both valuable and greatly appreciated.
APPENDIX A.3  Tobacco Usage and Diagnosis Consent Form
Subject Information and Consent Form

Impact of Diagnosis on Tobacco Usage Behaviour in Patients with High-Risk Oral Lesions

UBC BCCA REB # H10-01406

BCCA Principal Investigator: Dr. Catherine Poh
Cancer Control Research
Telephone: 604-675-8077

Co-Investigators:
Darlene Tam (Graduate student) Faculty of Dentistry/UBC
Telephone: (604) 675-8057

Dr. Jonn Wu H/N Radiation Oncology/BCCA
Telephone: (604) 877-6000 Ext. 2673

Dr. John Hay H/N Radiation Oncology/BCCA
Telephone: (604) 877-6000 Ext. 2660

Dr. Eric Berthelet H/N Radiation Oncology/BCCA
Telephone: (604) 877-6000 Ext. 2673

Sponsor(s): Michael Smith Foundation for Health Research
BC Cancer Agency/BC Cancer Foundation

Non-Emergency contact numbers are noted at the end of this document under the section heading “Contact”. Background

You are being invited to participate in this research study because you have been diagnosed of high-risk oral lesion within the past 12 months, a history of smoking at least 100 cigarettes in your lifetime within 5 years of the interview. In addition, you attend the Oral Oncology Clinic or the Head and Neck New Patient clinic of the BC Cancer Agency at Vancouver site.

This research is funded by Michael Smith Foundation for Health Research and BC Cancer Agency/BC Cancer Foundation.
This consent form will tell you about the study, why the research is being done, how the study will be done and what your role will be if you choose to participate. After reviewing this information, you should know enough to be able to make an informed decision as to whether you want to be in the study. Your participation is voluntary and you may decide not to participate or to withdraw at any time. Your doctors will continue to provide the best available treatment.

Purpose

The purpose of this pilot study is to gain a better understanding of the impact of the diagnosis to the smoking behavioural change, the potential factors that will stop or promote tobacco smoking before or after the diagnosis, and the need for tobacco cessation/reduction strategies targeting subjects. For this, we are conducting interviews and focus group discussions to collect information regarding tobacco usage and any tobacco-related behavioural changes prior to and after the diagnosis of a high risk oral lesion.

Who Can Participate In This Study?

You may participate in this study if:

- You fully understand the study and give your informed consent to participate as demonstrated by signing this consent form.
- You have been diagnosed for the first time with a high-risk oral lesion (including oral squamous cell carcinoma, carcinoma in situ, severe dysplasia and moderate dysplasia) within the past 12 months.
- You have a history of smoking at least 100 cigarettes in your lifetime, within 5 years of this interview.
- You attend the Oral Oncology Clinic or the Head and Neck New Patient clinic of the BC Cancer Agency, are age 19 or over, speak English and are willing to participate in a short fifteen (15) minute interview.
Who Should Not Participate In This Study?

You cannot participate in this if:
• You have quit smoking for more than 5 years before this interview.

Study Procedures

Your participation will involve an interview in which you will be asked questions regarding your habits in past and/or present tobacco usage and your opinions in factors that may promote or stop tobacco smoking.

The interview will take approximately 15 minutes and will take place at one of your scheduled clinical exam visits. If any information is missed during the interview, you may be contacted by telephone.

You might also be invited to participate in a group discussion where you will be asked to provide feedback regarding the quality and length of the study questionnaire, as well as your experience with tobacco cessation.

Risks

There is minimal risk associated with the interview or focus group discussion. You will not incur any personal expenses as a result of your participation in this study.

Benefits

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will help other patients in the future.

Confidentiality

Your confidentiality will be respected to the extent permitted by applicable laws and regulations and your medical and study records will not be publicly available. No information that discloses your identity will be released or published without your specific consent. Your identity will not be used in any reports about the study. In records that leave this centre you will be identified by a study code only, which includes your initials. Your birth date will also be provided if requested by the sponsor or responsible regulatory agency.

All information associated with this study will be kept behind locked doors or in secure computer files.
Research records and medical records identifying you may be inspected by representatives of Health Canada, or the UBC BCCA Research Ethics Board for the purpose of monitoring the research. However, no records that identify you will be allowed to leave the centre. These organizations have policies of strict confidentiality and the individuals inspecting your records must sign a BC Cancer Agency confidentiality form, have the legal right to inspect health records and are bound to confidentiality by specific laws.

Reports concerning your progress and photocopies of certain portions of your medical record, identified by a study code only, may also be sent to:

- Michael Smith Foundation for Health Research and BC Cancer Agency/BC Cancer Foundation.
- UBC BCCA Research Ethics Board, the research ethics committee that oversees the ethical conduct of this study in your centre
- Health Canada

Your family physician will be notified of your participation in the trial so that your study doctor and your family doctor can provide proper medical care.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to insure that your privacy is respected and also give you the right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor or the UBC BCCA Research Ethics Board.

**Compensation**

You will not be paid for participating in this study. However, if you decide to participate in the focus group discussion offered at a later time, you will be provided with $10.00 (Canadian) to compensate and acknowledge your participation.

Because the funding for this study is provided by the Michael Smith Foundation for Health Research and the BC Cancer Foundation, which are organizations based on donated support, no funding has been provided to BCCA for re-imbursement of extra costs.

No funds have been set aside to compensate you for such things as lost wages, disability or discomfort in the event of injury or illness related to the study treatment or procedures.

You do not waive any of your legal rights for compensation by signing this form.
Remuneration

The sponsors of this study may reimburse the BC Cancer Agency for all or part of the costs of conducting this study or they may provide the BC Cancer Agency some or all of the standard or experimental medications being used in this study. However, the investigators conducting this study will not receive any personal payments for conducting this study. In addition, neither the BC Cancer Agency nor any of the investigators or staff conducting this study will receive any direct financial benefit from conducting this study.

Contact

You understand that if you have any questions or desire further information with respect to this study, or if you experience any adverse effects, you can ask your doctor, who is:
Dr. ___________________  Telephone: ___________________

In the event of a research related injury, please speak to your doctor (indicated above) or (after hours) call the centre nearest you and ask for your doctor or, if he or she is not available, the oncologist on call.

Or, you can speak to the doctor who is the principal investigator, Dr. Catherine Poh at (604) 675-8077.

Or, you can speak to the Head of the Oral Oncology or Head and Neck Oncology Program of the BC Cancer Agency. That person can be reached at (604) 877-6000.

If you have any concerns about your treatment or rights as a research subject you may contact the Research Subject Information Line at the UBC Office of Research Services at the University of British Columbia at (604)-822-8598 or toll free at 1-877-822-8598, or by email to: RSIL@ORS.ubc.ca.
Subject Consent

I understand that participation in this study is entirely voluntary. I authorize access to my medical record and research data as described in this consent form. I may choose not to participate or I may withdraw from the study at any time and I will continue to be offered the best available medical care. I understand that I may ask questions about this study in the future.

I will receive a signed copy of this consent form for my own records.

I consent to participate in this study.

Subject’s Signature ___________________________________________ Printed name ___________________________ Date __________

Signature of Person Obtaining Consent

Printed name ___________________________________________ Study Role ___________________________ Date __________

If this consent process has been done in a language other than that on this written form, with the assistance of an interpreter/translator, indicate:

Language: ___________________________

Was the subject assisted during the consent process in one of ways listed below?

☐ Yes  ☐ No

If yes, please check the relevant box and complete the signature space below:

☐ The consent form was read to the subject, and the person signing below attests that the study was accurately explained to, and apparently understood by, the subject (please check if subject is unable to read).

☐ The person signing below acted as an interpreter/translator for the subject, during the consent process (please check if an interpreter/translator assisted during the consent process).

Signature of Person Assisting in the Consent Discussion ___________________________ Printed Name __________ Date __________
APPENDIX A.4  Tobacco Usage and Diagnosis Questionnaire
Tobacco Usage and Diagnosis Questionnaire

Site ID:  
Patient ID:  
Initials:  
Date Filled (YYYY/MM/DD):  

Gender:  
Male  
Female  
Date of Birth (YYYY/MM/DD):  

1. What is your ethnic or cultural heritage (Mark one box only):
   - White (Please Specify)  
   - First Nation  
   - Chinese  
   - Other (Please Specify)  

2. What is the language that you are most fluent in? Mark one box only:
   - English  
   - Chinese (Mandarin/Cantonese)  
   - Other (Please Specify)  

3. What grade of school have you completed?
   - Grade 1-9  
   - Grade 10-12  
   - University/College  

4. Who do you live with? Mark in one box only:
   - Alone  
   - With spouse/partner  
   - With children  
   - Other (Please Specify)  

5. Are you currently working? Mark in one box only:
   - No  
   - Yes  

6. What is your annual family income before taxes? (Family is a group of individuals related by blood or marriage, including common-law or adoption, who currently share a common residence)
   - Less than $12,000  
   - Between $12,000-30,000  
   - More than $30,000  
   - Don't know  
   - Decline to answer  

7. At what age did you start smoking?
   -  
   - years  

8. On average, how many cigarettes a day did/do you smoke?
   -  
   - #/day  

9. What is the total number of years that you have smoked?
   -  
   - years  

10. Do you smoke now?
    - Yes (Go to Question 14)  
    - No  

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11. How long ago did you stop smoking?
- Less than or equal to 1 year ago
- More than 1 year ago

12. If you quit, what is the reason for why you quit? Mark in all that apply:
- Oral lesion
- Spouse/partner
- Children
- Co-workers
- Physician
- Dentist
- Friends
- Not applicable
- Other (Please Specify)

13. What is the quit time in relation to your diagnosis?
- Way before my oral lesion was discovered
- At lesion first detection
- At biopsy
- At oral lesion diagnosis
- At surgery
- Other (Please Specify)

14. Have you tried to quit smoking before the diagnosis of the high-risk oral lesion?
- Yes
- No

15. Before your diagnosis of the high-risk oral lesion, how many cigarettes did you smoke?

16. After your diagnosis of the high-risk oral lesion, how many cigarettes did you smoke?

17. Have you tried to quit smoking after the diagnosis of the high-risk oral lesion?
- Yes
- No

18. What do you see as the good things or advantages that would happen if people quit smoking? Mark all that apply:
- Breathe easier
- Feel healthier
- Cough less
- Save money
- Have better sense of taste and smell
- Not smell of cigarette smoke
- Be at decreased risk of diseases such as cancer and heart diseases
- Have a feeling of control over my life
- Other (Please Specify)
19. What do you see as the bad things or disadvantages that would happen if people quit smoking?

- Gain weight
- Feel too stressed out
- Tried to quit before and I always start smoking again
- Other (Please Specify) ____________

20. In your experience or from others, what would make it difficult to quit smoking? Mark all that apply?

- Smoking makes people feel relaxed
- Personal preference (i.e. like to smoke)
- Cannot afford the nicotine patch or other aids for quitting smoking
- Do not have access to a smoking cessation program
- All of friends smoke
- May not be ready to quit smoking
- Other (Please Specify) ____________

21. In your experience or from others, what would make it easier to quit smoking? Mark all that apply:

- Having access to smoking cessation aids such as the nicotine patch
- Having access to a smoking cessation program
- Friends and/or family do not smoke
- Having the support of my family and friends
- Knowing I would be at decreased risk for health problems
- Other (Please Specify) ____________

22. If a person quit smoking today do you think he/she would live longer?

- Yes
- No

23. Who do you think would object if you quit smoking?

- Nobody
- Others (Please Specify) ____________

24. Who do you think would support you if you quit smoking? Mark all that apply:

- My friends
- My spouse/partner
- My children
- My co-workers
- My physician
- My dentist
- Other (Please Specify) ____________

25. Which individuals are most important to you in your decision to quit smoking or not? Mark all that apply:

- My friends
- My spouse/partner
- My children
- My co-workers
- My physician
- My dentist
- Other (Please Specify) ____________
If you have quit successfully, we congratulate you. If you currently smoke, please answer Questions 26-34.

26. Do you intend to quit smoking now?

- Yes
- No (Go to Question 26)

27. What is the reason you intend to quit? Mark all that apply:

- My oral lesion
- My spouse/partner
- My children
- My co-workers
- My dentist
- My friends
- Myself
- Other (Please Specify)

28. If you do not intend to quit, what is the reason? Mark all that apply:

- Weight gain
- Feel too stressed out
- Have tried to quit before and I always start smoking again
- Like to smoke
- My friends smoke
- Not ready to quit smoking
- Not applicable
- Other (Please Specify)

29. In your past experience, have you ever felt a need to cut down or control your smoking but had difficulty doing so?

- Yes
- No

30. In your past experience, have you ever been annoyed or angry with people who criticize your smoking or say that you should quit smoking?

- Yes
- No

31. In your past experience, have you ever felt guilty about your smoking or about something you did while smoking?

- Yes
- No

32. In your past experience, have you ever smoked within half an hour of waking?

- Yes
- No

33. In your past experience, have you ever had the following symptoms when you went without a cigarette for any length of time? Mark all that apply:

- Feeling agitated
- Difficulty concentrating
- Irritability
- Mood swings
- Other (Please Specify)

34. In your past experience, did the symptoms go away after you smoked a cigarette?

- Yes
- No

Thank you for participating.