EPIDEMIOLOGICAL SHIFTS AND RISK BEHAVIOURS FOR ORAL AND OROPHARYNGEAL CANCERS IN MULTICULTURAL POPULATION OF BRITISH COLUMBIA, CANADA

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE STUDIES

(Craniofacial Science)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

March 2012

ABSTRACT

Research problem

Although smoking prevalence in British Columbia (BC) is decreasing, numbers of oral cancers are increasing. This change may reflect new emerging risk factors, including an increase in human papillomavirus (HPV) infections and greater immigration from high-risk countries. Currently, in BC there is no data on the trends in oral cancer incidence and survival by ethnicity or by etiologically clustered oral cancer subsites (oral cavity cancers, OCC, which are predominantly tobacco related; and oropharyngeal cancers, OPC, which are predominantly HPV-related).

Methods

Oral cancers were retrieved from BC Cancer Registry (BCCR) from 1980 to 2006 and the following information collected: names, demographic, tumor, treatment and outcome information. When specific information was not complete, chart review was done. South Asian (SA) or Chinese ethnicities were determined by using previously generated ethnic surname list. Age-adjusted incidence rates (AAIR), age-specific incidence rates (ASIR) and 5-year survival rates for these three populations were calculated by sex, grouping the cancers into etiologically clustered subsites. Calculations were done for each year from 1980 to 2006. An ethnographic study was then conducted to describe the patterns of access, use and perceptions of SA men towards chewing tobacco-containing betel quid (BQ). Extensive field work included participant observations and semi-structured interviews.

Findings

We have for the first time shown that the incidence of HPV-related OPC has surpassed that of tobacco-related OCC in men. For female, the incidence rates of OPC increased and OCC unchanged. AAIR for OCC was highest in SA males and females while rates of OPC were highest in general population males and Chinese males. Survival rates for OCC were unchanged and for OPC improved in males. SA had poorest survival rates for OCC. Ethnographic findings revealed that among SA males chewing tobacco-containing BQ was viewed as a culturally accepted practice. Availability of BQ, perceived benefits of chewing, ability to conceal the habit, and a lack of awareness of health risks also supported chewing practices.

Conclusion

These findings provide a strong foundation for continued work in this field aimed at identifying effective prevention and treatment strategies for oral cancer.

PREFACE

This preface is prepared according to the guidelines of Faculty of Graduate Studies of University of British Columbia (UBC).

Dr. Ajit Auluck originally conceived the idea for this research project, obtained ethics approval certificates, collected data, performed data analysis, and was primarily responsible for writing the dissertation document and publications arising from this work. While Dr. Auluck was the primary contributor, all committee members provided valuable guidance and support throughout the research project and in preparation of this dissertation. Conceptualization of the research idea was first published as a letter to editor "Auluck A, Rosin MP, Hislop G. Oral cancer awareness among immigrant Indo-Canadian community of Vancouver, BC. Rural Remote Health. 2008;8(2):1004". Subsequently, it was further developed into a commentary which was also published in the same journal "Auluck A, Hislop G, Poh C, Zhang L, Rosin MP. Areca nut and betel quid chewing among South Asian immigrants to Western countries and its implications for oral cancer screening. Rural Remote Health. 2009;9(2): 1118". The effects of chewing on biological processes and clinical features associated with oral premalignant lesions were published in a literature review, "Auluck A, Rosin MP, Zhang L, Sumanth KN. Oral submucous fibrosis, a clinically benign but potentially malignant disease: report of 3 cases and review of the literature. J Can Dent Assoc. 2008;74(8): 735-40", which was reproduced in the dissertation.

Drs. Lewei Zhang and Miriam Rosin were the dissertation supervisors while Drs. Joan Bottorff and Greg Hislop were dissertation committee members. Drs. Zhang, Hislop and Rosin took a lead role in conceptualization of this dissertation research and provided

ongoing guidance and input throughout the process of conceptualizing and conducting the quantitative component of this research. Dr. Bottorff provided valuable suggestions and feedback in the initial research design of this dissertation research and took the lead role in the qualitative component of this work. Dr. Chris Bajdik, a senior scientist and epidemiologist at the BC Cancer Agency, provided input and guidance regarding data analysis in Chapters 4 (incidence trends) and 5 (survival analysis). More specifically, Dr. Bajdik checked all statistical calculations, formulas and tables used in calculating incidence and survival rates. Although primary drafts of each chapter and resulting publications were prepared by Dr. Auluck, the final versions required significant constructive feedback and discussions from all committee members.

Drs. Zhang, Hislop and Rosin contributed significantly in Chapters 4, 5 and 6, and, therefore, are recognized as co-authors on the submitted manuscripts. The results from Chapter 4 (incidence trends) led to a publication, "Auluck A, Hislop G, Bajdik C, Poh C, Zhang L, Rosin M. Trends in oropharyngeal and oral cavity cancer incidence of human papillomavirus (HPV)-related and HPV-unrelated sites in a multicultural population: the British Columbia experience. Cancer. 2010; 116(11):2635-44". . The results from Chapter 5 (survival analysis) resulted in a submitted manuscript, titled "Gender and ethnicity specific shifts in survival of oropharyngeal and oral cavity cancers in British Columbia, Canada". This manuscript is currently under review for consideration of publication. Ethics approval for the above was obtained from the BC Cancer Agency Research Ethics Board, number H08-00839.

Dr. Bottorff provided guidance for the qualitative component of this dissertation research as well as being actively involved in overall design of this research project. She played an instrumental role in qualitative research design and was actively involved in meetings to develop strategies for data collection and recruitment of participants in the ethnographic study. Her vast experience and expertise provided guidance in developing a framework for data coding and data analysis. Her valuable feedbacks in regular monthly meetings strengthened the analysis and interpretation of qualitative data, which is presented in Chapter 6. Dr. Hislop also provided feedback on the research design, committee meetings, participant recruitment strategies and editing of this qualitative chapter. Drs. Bottorff and all other committee members are recognized as co-authors for a manuscript which is planned for submission. Ethics approval for this part of dissertation research was obtained from the BC Cancer Agency Research Ethics Board, number H08-01930.

Dr. John Hay, a radiation oncologist at the BC Cancer Agency, provided feedback on data analysis and writing for Chapter 5 and is also recognized as a co-author for the submitted manuscript on survival. Dr. Catherine Poh was consulted during the initial development of the research design and is recognized as a co-author in a commentary and the published manuscript on incidence in Chapter 4**.**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LISTS OF ABBREVIATIONS

"% " - Percentage

AAIR – Age-adjusted incidence rates

APC – Annual percent change

ASIR – Age-specific incidence rates

AVL – Available

BC – British Columbia

BCCR- British Columbia cancer registry

BQ - Betel quid

CI – Confidence interval

Cum_survival - Cumulative survival rates

Globocan – Global cancer trends

HIV – Human immunodeficiency virus

HPV – Human papilloma viral infections

IARC – International agency for research on cancer

ICDO - International classifications of diseases in oncology

MeSH – Medical subject heading

NA – Not available

NRT – Nicotine replacement therapy

OCC – Oral cavity cancers

OPC – Oropharyngeal cancers

OPL – Oral premalignant lesion

OR – Odds ratio

OSF – Oral submucosal fibrosis

SA – South Asian

SCC – Squamous cell carcinoma

SEER – Surveillance epidemiology and end results

SPSS – Statistical package for the social sciences

TNM – Tumour-node-metastasis classification staging system

UK – United Kingdom

US – United States

WHO – World health organization

ACKNOWLEDGEMENTS

I would like to acknowledge the support of all the individuals who helped in the completion of this dissertation. This has been a journey that would not be possible to walk alone. I greatly value and appreciate the continuous inspiration, social and emotional support from my family, friends and mentors. Each played a pivotal role to make this research happen. Support was also received from other scientists, clinicians and colleagues along the way.

I want to express my gratitude for the support and mentorship provided by my committee members who each touched my life in different ways: Dr. Miriam Rosin, Dr. Lewei Zhang, Dr. Greg Hislop and Dr. Joan Bottorff. Working with each of them was a privilege and a blessing. Other key individuals were Dr. Chris Bajdik, Dr. John Hay, Dr. Michele Williams, Dr. Catherine Poh, Dr. Morteza Bashah, Dr. Huijin Jiang, Lorna Lee, Asif Javan, Paul Whigton and Helen Chiu who provided encouragement and support throughout my graduate studies.

I would like to thank the South Asian community members (Charan Gill, Suki Grewal, Jas Cheema) for their guidance and advice for this research. A special thanks to the South Asian men who participated in this study. They believed in this research project and their willingness to participate was essential for the completion of this research work. A big thank you to each of them.

I would like to thank my parents (Professor Vinay Auluck and Dr. Sunita Auluck) and my lovely wife (Dr. Suman Auluck) who provided a rock solid support that enabled me to take time off from family responsibilities to complete this dissertation research.

This dissertation would not be completed but for the support of my mentor Dr. John O'Keefe and his wife Lucie Beland-O'Keefe who helped me immensely in making a cultural transition to Canada, providing valuable guidance and support throughout my graduate studies.

Lastly, I would like to thank my funders who provided me with the financial support to complete my doctoral education. I would like to thank Dr. Carmen Loiselle and PORT (Psychosocial Oncology Research Training) for providing the financial support through the Canadian Institute of Health Research (CIHR) to undertake this transdisciplinary research project. During my doctoral research, I also received funding, travel bursary and awards from the following organizations: Institute of Cancer Research (ICR) and Institute of Health Services and Policy Research (IHSPR) through PORT, Canadian Public Health Agency (CPHA), Canadian Association of Public Health Dentistry (CAPHD), British Columbia Cancer Agency (BCCA), Canadian Association of Psychosocial Oncology (CAPO) and the Jospen Tonzetich Fellowship from Faculty of Dentistry, University of British Columbia. I am grateful to each one for providing financial support to complete my doctoral studies.

Finally, I would like to thank the BC Oral Cancer Prevention Program and its members, students, administrative staff and consultants with whom I had an opportunity to work and interact during my dissertation research studies.

DEDICATION

This thesis is dedicated to my parents (Professor Vinay Auluck and Dr. Sunita Auluck), to my wife Dr. Suman Auluck, my sister Anjali Kakkar and my mentors Dr. John O'Keefe and Lucie Béland-O'Keefe, all of whom provided me with immense support and encouragement to complete this doctoral research.

CHAPTER 1: INTRODUCTION

Oral cancer is a substantial but under-recognized issue globally, with more than 320,000 new cases reported annually[1] which are characterized by poor survival outcomes. There is a 20-fold geographical variation in the incidence of oral cancer, with two-thirds of these cases seen in developing countries. The countries with the highest rates of oral cancers are in South and Southeast Asia (e.g., Sri Lanka, India, Pakistan and Taiwan)[2]. In 2002, there were 127,459 deaths caused by oral cancer across the world, of which 96,720 occurred in less-developed countries[3].

A growing body of evidence suggests that the etiology of oral cancers is heterogeneous and that it is changing globally. Traditionally, tobacco and alcohol have been recognized as major risk factors; however, human papillomavirus (HPV) is now seen as having an increasingly important role in development of oral cancers, especially at some subsites. A strong association of HPV is seen with the tonsils, base of tongue and other oropharynx sites (hereafter termed oropharygeal cancers, OPC) while HPV is less strongly associated with other oral sites, such as the ventrolateral tongue, gingiva, cheek, palate and floor of mouth (hereafter termed oral cavity cancers, OCC) where tobacco and alcohol play a major role[4-6]. There is a worldwide recognition of the need to study the temporal trends in incidence and survival of oral cancers at various subsites. These studies are important to assess the impact of HPV, tobacco and alcohol upon the epidemiology of oral cancers and provide essential data for guiding treatment and prevention initiatives[6-15].

According to Canadian cancer statistics, the numbers of oral cancer cases are steadily increasing in Canada; from 2002 to 2010 the number of new oral cancer cases increased from

2100 to 3400[16]. The relative survival rate is poor as compared to many other cancers such as cervix, breast and prostate[16]. The increase in cancer incidence is partly due to the aging population in Canada; however, increased immigration from high-risk countries like India[17] may also play a role. According to the 2006 census, South Asians (SAs) and Chinese are now the two largest visible minority groups in Canada[18]. China shows high rates of smoking among adult males, although the reported oral cancer rates are low for that country[3]. This discrepancy between the etiological factors and disease prevalence may be due to the poor cancer registration and reporting systems in China.

The majority of SA immigrants to Canada come from India, Pakistan, Bangladesh and Sri Lanka[2]. SAs are the fastest growing ethnic minority group in Canada; between 2001 and 2006, the growth rate in the SA population was 37.7% while that in the general population was only 3.9%[19]. The notion that an increase in SA immigrants is accompanied by an increase in oral cancer is supported by studies from a number of countries. For example, a recent study from the United Kingdom (UK) showed that oral cancer incidence rates are higher among SAs as compared to non-SAs, with relative risks for SA men being 1.36 times higher than non-SAs[20].

It is important to note that the etiology of oral cancers in SAs is different than in the general population. In addition to well-known risk factors like smoking and alcohol, the higher incidence of oral cancers in SA countries is attributed to the common habit of using oral chewing products[21,22]. Furthermore, these habits have been reported to continue among SAs in the UK after migration and hence play a role in their higher oral cancer rates[23-30].

We have previously reported that oral chewing products were widely available in British Columbia (BC), suggesting the possible continuation of their usage after immigration and the

potential for an increase in oral cancer rates among SA immigrants[31]. Among oral chewing products, betel quid (BQ) is a very popular habit in SA countries, where it has strong socio-cultural significance and social acceptance[32]. Therefore, a better understanding of socio-cultural influences regarding its use is required to make culturally sensitive health promotion programs.

The long-term goal of this dissertation research was to provide information to help guide in the development of a comprehensive oral cancer control plan for the diverse multicultural populations in BC. This research was comprised of three research projects: the first two projects used quantitative research methods (epidemiology) and the third project used qualitative research (ethnography). As a starting point, epidemiological studies were done to calculate the incidence and survival rates for oral cancer, looking at rates in the general population and among SAs and Chinese. The ethnic groups examined in this research were limited to SAs and Chinese because they are the two largest minority groups in BC and there is a high prevalence of risk behaviours for oral cancer in their home countries. Differences in both incidence and survival rates were investigated by sex because of reported gender differences in risk behaviours related to oral cancer.

SA men living in BC were found to have the highest incidence and poorest survival rates for OCC. This finding resulted in a decision to conduct a qualitative study to better understand the socio-cultural context of tobacco-containing betel quid usage among immigrant SA men in BC. The researcher's interest in this line of investigation was enhanced by his experience in oral medicine in India (where clinicians struggle to get patients to stop betel quid chewing), and his language competency (Punjabi and Hindi), familiarity with SA culture, and established connections with the SA community in Vancouver, BC. Wide varieties of oral chewing products

are associated with oral cancer. For the purpose of this qualitative study, the use of tobacco-containing betel quid (BQ) products became a focus because it was sold openly in BC and BQ chewing was considered to be a socially acceptable habit. Preliminary observations in the local SA community in Vancouver suggested that tobacco-containing BQ was the most common oral chewing product used by SA men. Although advertised as being sold without smokeless tobacco, observation showed that SA men usually added smokeless tobacco.

This dissertation research had three objectives: 1) to describe the incidence trends of OPC and OCC by sex and ethnicity, 2) to describe the survival trends of OPC and OCC by sex and ethnicity and 3) to describe the socio-cultural context of chewing tobacco-containing BQ among SA men.

The following thesis is organized as follows: first, a chapter will be presented on background literature relevant to the thesis. This will be followed by a synoptic overview of the mixed methodology used in the dissertation. Following this, each of the three projects will be presented in separate chapters. The final chapter integrates the findings, describes the implications of this research and suggests future research directions.

CHAPTER 2: BACKGROUND LITERATURE

There is an increasing recognition that global changes are occurring in both incidence and survival for oral cancer. This change has been primarily associated with alterations in a population's exposure to risk factors, such as smoking cessation or HPV infection, although improvements in disease detection rates and treatment regimes also play a role. It is also becoming increasingly evident that these changes in temporal trends are most apparent when specific oral cancer subsites are examined.

A better understanding is needed about who is at greatest risk, what subsites are associated with the greatest shifts in incidence and survival rates, and what strategies should be undertaken to promote oral cancer prevention among high-risk groups. An exploration of these features at a population level is an important first step towards identifying effective detection, prevention and treatment strategies for oral cancer.

The thesis focuses on the exploration of the temporal trends in oral cancer in BC by examining incidence and survival rates in the province. Incidence and survival rates are examined by sex and subsite to identify at-risk groups, looking at the general population and at SA and Chinese populations. The latter populations are the largest immigrant groups in BC. Finally, in order to better understand socio-cultural context of one risk behaviour associated with oral cancer in a high-risk group, an ethnographic study was done of tobacco-containing BQ chewing among SA men.

In this chapter, the background literature on which this study was based is presented. A summary of this literature is provided in the following sections. The first section presents literature describing the epidemiology of oral cancer with particular attention to its global

incidence and survival patterns with respect to age, ethnicity and subsites, where possible, and oral cancer rates among SA immigrants. The second section describes known risk factors associated with oral cancer. In the third section clinical presentation of cancers at different oral subsites is described. In the fourth section factors affecting survival of oral cancers is summarized. Finally, a review of the literature on the socio-cultural context of risk behaviours among SAs is presented.

Global epidemiology of oral cancers

Epidemiological studies focusing on oral cancer have been undertaken in a number of countries and have made important contributions to the understanding of this disease. Global variations in the incidence of oral cancers have been linked to differences in risk behaviours among different populations, with highest incidence rates found among South and Southeast Asian countries (Sri Lanka, India, Pakistan and Taiwan), Western Europe (France), Eastern Europe (Hungary, Slovakia and Slovenia), and in the Pacific regions (Papua New Guinea)[2]. A recent study compared age-adjusted incidence rates of oral cancer (standardized to the world population) and found the highest incidence in SA countries (Pakistan and India) for both sexes. Incidence rates among men in Pakistan and India were 18.9/100.000 (95% CI, 17.2 - 20.6) and 8.1/100,000 (95% CI, 7.9 - 8.3), and among women were 18.0/100,000 (95% CI, 16.0 - 20.0) and 5.0/100,000 (95% CI, 4.8 - 5.2), respectively. Comparatively, the incidence of oral cancer in Canada was much less, at 2.7/100,000 (95% CI, 2.6 - 2.8) among men and 1.4/100,000 (95% CI, 1.3 - 1.5) among women[3]. Although China has a high prevalence of smoking (particularly among men) reports suggest surprisingly low incidence rates for oral cancer in both men [2.1/100,000 (95% CI, 1.1 - 1.3)] and women [1.2/100,000 (95% CI, 1.1 - 1.3)][3]. This

discrepancy has been largely attributed to underreporting of cancer registration in China; hence, the reported incidence rates of oral cancer in China are not reliable.

Not only do oral cancer incidence rates vary among different populations and regions, but evidence from epidemiological studies indicates that survival rates also differ. A recent study of 25 population-based cancer registries from 12 countries showed that the 5-year age-standardized relative survival rate for oral cancers was lowest in India at 37% (95% CI, 26 - 45) and highest in China at 67% (95% CI, 44 - 71)[33]. However, this study did not report survival rates separately for OPC and OCC among men and women. Data from the Canadian Cancer Statistics showed that 5-year survival rates for oral cancer in Canada was between the rates in India and China, at 63%[16], and this data was not available separately for OPC and OCC.

There is an increasing global recognition of HPV as an important etiological factor in development of OPC, while OCC remains largely associated with tobacco and alcohol. Hence, there is an increasing interest in subsites and oral cancer trends have recently been reported separately for OPC and OCC and its subsites, with reports from the United States (US)[34-36], Norway[7], Sweden[6], Netherlands[8], Finland[9], Denmark[10], Australia[11], France[12], Germany[13], England[14] and Spain[15]. There are discrepancies in the methodologies and completeness of information provided in these articles; however, these researchers suggest that among men the incidence rates of OPC and its subsites (tonsils and base of tongue) are increasing in all countries except France, where the incidence among men is decreasing[12]. Among women, the incidence rates of OPC and its subsites are also increasing except in the US, where the incidence among women is decreasing[35,36]. Only a few of these studies reported the incidence rates of OCC and its subsites. Among men, OCC incidence rates are decreasing in the US[35,36] and increasing in the

Netherlands[8], Denmark[10], Germany[13], England[14] and Spain[15]. Among women, OCC rates are decreasing in the US[35,36] and increasing in the Netherlands[8], Denmark[10] and France[12], remaining unchanged in Australia[11] and Germany[13]. Therefore, the epidemiology of oral cancers varies widely among different countries and it may vary among different ethnic groups within a country based on different exposures to risk factors.

Reports of trends in survival rates for OCC and OPC from population-based cancer registries are limited to 5 published studies, 2 from the US[35,36], 1 from Canada[37], 1 from Germany[13] and 1 from Sweden[38]. The data in these publications suggest that OCC and OPC survival rates have improved in the US, Canada and Sweden among both men and women and remained stable in Germany. However, there were limitations to these comparisons because one study only reported temporal trends in overall 2-year survival rates with and without radiation treatment[36], while the other four studies reported 5-year survival rates but did not include data separately for all OPC and OCC subsites[13,35,37,38]. These studies are summarized below in Table 1.

Globally, there were also reported sex differences in the incidence of oral cancers. Male to female ratios have been reported for OPC in the US of 2.6:1[36], Sweden of 3.4:1[6], Netherlands of 2.3:1[8], Finland of 3.4:1[9], Denmark of 2.8:1[10], Australia of 3.1:1[11], and Germany of 6:1[13]. Male to female ratios have been reported for OCC in US of 1.6:1[35,36], Australia of 3.3:1[11] and Germany of 3:1[13]. Therefore, both OPC and OCC are primarily affecting men.

International comparisons of OPC and OCC rates are directly influenced by the extent of coverage and completeness of cancer registration systems, and these are not very well developed in countries like India and China. For example, the estimated age-standardized incidence rates

were calculated from data which covered 3.4% of the Indian population, 1.2% of the Pakistani population and 1.4% of the Chinese population, compared to 76.1% of the Canadian population[3]. Another limitation is the difference in the population structures among and within different countries. For fair comparisons, a consistent criterion should be used to estimate current and projected oral cancer burden. The International Agency for Research on Cancer (IARC) initiated the GLOBOCAN (global cancer trends) project to calculate the global cancer burden for different countries[39], reporting current and projected numbers of new oral cancer cases and deaths for selected countries using the most recent data available at IARC.

Population-based studies of incidence and survival for oral cancers: a critical review

Search strategy

In preparing the following section, research literature was reviewed to understand the changing trends in incidence and survival rates of oral and oropharyngeal cancers in different countries. A systematic literature search was conducted using PUBMED (US National Library of Medicine, Bethesda, MD, USA). MeSH (medical subject headings) terms for 'oral cancer' were identified (see paragraph below). The search was conducted using these MeSH terms for 'oral cancers' AND 'humanpapilloma viral infections' OR 'HPV' OR 'papillomavirus' AND 'incidence trends' OR 'survival trends'. Secondary search criteria included a study limitation to humans and to English literature; however, no date restrictions were imposed for publications. Using this search strategy 32 articles were identified. In addition, general search terms were used to identify articles in the following fashion: a) the search term 'incidence trends of oral cancers and oropharyngeal cancers' led to 54 articles, b) the search term 'survival trends of oral and oropharyngeal cancers' led to 22 articles, c) the search term 'oral cancer epidemiology' lead

to 11,473 articles and d) the search term ‘oropharyngeal cancer epidemiology’ lead to 1350 articles.

Example of search strategy

MeSH terms for ‘oral cancer’ (‘mouth neoplasm’ OR ‘neoplasm, mouth’ OR ‘neoplasms, oral’, OR ‘oral neoplasms’ OR ‘neoplasms, mouth’ OR ‘cancer of mouth’ OR ‘mouth cancers’ OR ‘mouth cancer’ OR ‘cancer, mouth’ OR ‘cancers, mouth’ OR ‘oral cancer’ OR ‘cancer, oral’ OR ‘cancers, oral’ OR ‘oral cancers’ OR ‘cancer of the mouth’) AND ‘human papillomavirus infection’ OR ‘HPV’ OR ‘papillomavirus’ AND ‘incidence’ OR ‘survival trends’.

Study eligibility

Articles were included for review if they had following criteria: 1) original articles which used a population-based database or cancer registry, 2) reported either incidence rates or survival rates, or both, and 3) reported on subsite groupings which allowed for comparison of epidemiological trends of oropharyngeal and oral cavity cancers separately. If there were multiple articles from the same country incorporating much of the same data, we chose the article that had the most comprehensive data and that followed the above inclusion criteria. Articles were excluded if they were 1) a clinical trial, 2) evaluated effect of interventions or treatment modalities, or 3) focussed on trends by histology or recurrence rates only. Thirteen articles were found that met the above criteria.

In addition to the above strategy, other theses and dissertations on this topic were searched using the proquest dissertation and thesis database at the UBC library and similar

search criteria; however, no master's or doctoral dissertations with matching results were found. Reference lists for all selected articles were also hand searched to identify additional articles of relevance. All the articles were read, critically analyzed and presented in Table 1.

In the critical analysis of key population-based studies identified in this search, a wide variation was found in the way data analyses were conducted. Researchers often did not describe epidemiological trends for all OPC and OCC subsites and ethnicity was not considered except in a couple of studies from the US[35,36]. Data assessing the impact of HPV on oral cancer incidence emerged in studies conducted in a number of countries, but few studies assessed its impact on survival. There was no data assessing the impact of HPV from population-based cancer registries from either SA countries or China, or among immigrants from these high-risk countries to western countries. There was only one Canadian study, from Ontario[37], which reported on the trends for oral cancer at different oral subsites but not for all OPC and OCC subsites or by ethnicity. Therefore, this dissertation research examined incidence and survival trends by sex and ethnicity for all OPC and OCC subsites. These findings will provide important data to assess the impact of HPV on the epidemiology of oral cancers in BC and also inform about the developing ethnic disparities in oral cancer epidemiology.

Oral cancer among South Asian immigrants in western countries

Since oral cancer has been reported to be an important health problem among SA immigrants, key articles were identified which focused upon oral cancer risk and the importance of addressing oral cancer control among SA immigrants in western countries[20,23-30,40-56]. Taken together, these studies suggest that numerous oral chewing products of SA origin are readily available in the UK and US, both commercially and self made[52,56]. Furthermore, studies in the

UK have reported an increased risk for oral cancer among SA compared with non-SAs which may be attributed to the continuation of oral chewing behaviours[20].

There is a need for a multi-disciplinary and inter-sectoral approach for developing oral cancer prevention programs for SA immigrants which will range from reducing risk behaviours to including health education programs and oral cancer screening. Several approaches have come from the very detailed work of investigators in the UK. The Open Mouth Cancer campaign in that country is targeted towards the Bangladeshi community and to increasing knowledge about tobacco products (both smoking and smokeless tobacco products) and early signs of oral cancer[48]. Nunn[47] et al reported on the outcomes of oral cancer screening among SAs in the same location in the UK. A total of 1320 persons received oral cancer screening, 75 of whom were referred for further investigation. Of these, 9 patients were diagnosed with dysplastic lesions and 8 showed potentially dysplastic lesions without dysplasia. Other suggested approaches have included provision of tobacco cessation interventions to SA communities (including nicotine replacement therapy)[29,42], increasing the inclusion of SAs in current tobacco control initiatives (in response to confusion about nicotine replacement therapy in that community)[45], promotion of increased compliance with legal controls and enforcements (given the wide accessibility to chewing tobacco products)[56], and the provision of health care professions such as dental students with a holistic integrated approach to oral cancer prevention that is tailored to the SA community[57].

It is important to remember that SAs are not a homogeneous group and the use of tobacco-containing BQ with areca nut (an important risk factor for oral cancer) has religious and cultural meaning in some SA communities. Much of the work done to date has been with

Bangladeshis and Gujaratis. There was a paucity of literature on Punjabi Sikhs, who represent the majority of the BC immigrant population. Hence, this dissertation addresses this important gap in the literature.

The following section will review literature on the risk factors associated with oral cancer from a global standpoint, examining key factors in both developed and developing countries.

Risk factors

The literature describing the etiological factors for oral cancer which also affect the epidemiology of oral cancers has focused on: a) age and sex, b) tobacco, c) alcohol, d) betel quid chewing, e) HPV infections and f) different combinations of these risk factors. Each of these will be discussed in more detail in the following section.

Age and sex

As age increases, the risk for oral cancer also increases. Among US men aged 40-59 years, the risk for developing oral cancer is 11 times that of men under the age of 40 years. For men above 60 years, this risk increases to 21 times. Women have lower risk for developing oral cancer as compared to men. For women aged above 40 years and 60 years, the risks are 5 and 12 times higher, respectively, compared to women under the age of 40 years[58].

It is believed that the majority of oral cancers are diagnosed at an older age because of accumulated lifelong exposure to carcinogens, which leads to permanent DNA damage. Hence, changes in population demographics can cause important shifts in cancer risk among populations in different parts of the world. For decades, the proportion of very young have outnumbered the

elderly globally, but in the next few years people aged 65 years and above will outnumber children aged ≤ 5 years[59]. It is expected that by 2030, one in every eight people in the world will be above 65 years of age. The age group of above 85 years is one of the fastest growing world populations. This rapid increase in the number of elderly is occurring in both the developed and developing countries[59].

Canada has a high proportion of older persons and its population is aging rapidly. With this demographic shift it is expected that oral cancer rates will also increase. There has been a 20-fold increase in the percentage of those 85 years of age and older from 1921 to 2001, with 430,000 Canadians currently in this age group. This is mainly due to two factors. Firstly, Canada has one of the best health care systems in the world and life expectancy is among the highest in the world and is expected to further increase. In 1997, life expectancies were 75.8 years and 81.4 years for men and women, respectively; these are estimated to increase by 2041 to 81 years and 86 years, respectively[60]. Secondly, Canada has a larger, aging so-called "baby-boomer" cohort when compared to other industrialized countries. In 2001, one in every eight Canadians was aged 65 years or over (13%, 3.92 million persons). It is projected that by 2026 this ratio will be one in every five Canadians (20%). The most dramatic shift in these population demographics is caused by "baby boomers" (those born between 1946 and 1965), which will cause an increase in the elderly population (65 years of age and older) from 6.7 million in 2021 to 9.2 million in 2041 (25%). It is projected that this age group will continue to grow and by 2041 will reach 1.6 million people (4% of overall population)[60].

Oral cancer does not occur frequently in people who are less than 40 years of age. However, among such individuals, there appear to be two types of oral cancers. One type is

similar to that seen in older oral cancer patients, with similar risk habits and rates of disease progression[61]. The second type has no known risk factors and the cancer progresses more quickly than most oral cancers[62]. This latter type often includes young females who present at a more advanced stage, possibly due to diagnostic delays attributed to the lack of known risk factors[63]. They may be at an increased risk due to inherited susceptibility to the disease. Several possibilities have been suggested, including defects in the ability to metabolize carcinogens or repair DNA damage induced by such agents or an altered immunity[64,65]. Recent reports suggest that this early age at onset may also be occurring in young men under 40 years[66]. Of interest, an increasing number of young patients are seen to have HPV-associated oral cancers, suggesting that an etiological change may also be involved[67].

In summary, it is important to study the age and sex specific incidence and survival trends for oral cancers since these can provide valuable information about cancer patterns and changes in etiologic agents.

Tobacco

Tobacco, derived from leaves of a plant that belongs to genus *Nicotiana,* is a well-established risk factor for oral cancer whether it is consumed by smoking or used in smokeless forms. When tobacco is smoked, nicotine is absorbed through the lungs, but when it is chewed, nicotine is absorbed through the oral mucosa. Nicotine quickly diffuses into the blood and within seconds it reaches the brain. It binds to nicotinic acetylcholine receptors which cause vasoconstriction, increasing heart rate and mental alertness. However, after 30 minutes nicotine levels in the brain fall rapidly and this creates craving. Thus, the nicotine in tobacco in both smoked and smokeless forms creates dependency among its users and is addictive[68].

Traditional uses of tobacco in rituals and ceremonies are related to its presumptive medical and therapeutic applications as a purgative[69] and stimulant; for toothaches, headaches, colds and fevers; and for its calming and relaxing effect to suppress hunger and thirst. For example, aboriginals in South America and Australia consumed tobacco to reduce hunger, travel long distances without fatigue, and excite warriors prior to fighting[70]. Tobacco was consumed initially to quench thirst because it produced extra salivation, and tobacco juice was used to disinfect cuts and relieve effects of snake and insect bites[71].

Over the last century, tobacco consumption has moved from traditional uses that may be largely ceremonial to become one of the most common of lifestyle habits globally. Tobacco companies produce about five and a half trillion cigarettes per year[72]. The largest numbers of consumers of cigarettes are in Asia, Australia and the Far East (2715 billion cigarettes), followed by the Americas (745 billion), Eastern Europe and former Soviet economies (631 billion) and Western Europe (606 billion)[73,74]. There are currently about a billion men in the world who smoke (includes both daily and occasional smokers), with a prevalence of 35% among men in developed countries and 50% in developing countries[72]. Globally, about 250 million women smoke, with a prevalence of 22% in developed countries and 9% in developing countries[73].

It is estimated that in the 20th century about one hundred million people died because of tobacco use[73]. If the current rates of tobacco consumption continue, it is projected that about a billion people will die from this habit in the 21st century. The majority of these deaths will occur in low- or middle-income countries. In 2010, it is estimated that about 6 million people died because of tobacco use, of which 72 percent were in lower- or middle-income countries. These rates will increase to 83 percent by 2030. The majority of these deaths can be prevented

by reducing tobacco consumption through public health education and health promotion programs[73].

Continued efforts through public health programs have reduced smoking in many parts of the world. In the US, prevalence of smoking decreased from 41.9 to 18.0% between 1965 and 2007; this change has been associated with a parallel decrease in the incidence rates of tobacco-related oral cancers[36,75-78]. In Canada, the prevalence rates for smoking in 1965 among men and women were 61% and 38%, respectively; in 2007, these rates had dropped to 20% and 18%, respectively[79]. In contrast, in France, smoking rates are decreasing in men but increasing in women. From 1953 to 2010, smoking prevalence in France among men decreased from 72% to 31.8% but among women increased from 17% to 25.7%, which resulted in differences in oral cancer rates[12]. In Australia, smoking rates are also decreasing among men but not among women[11]. Despite the decreasing prevalence in rates of smoking in many developed countries, the absolute numbers of smokers are expected to increase because the world population is increasing. In order to make global comparisons in tobacco consumption rates, the World Health Organization has provided the tobacco atlas[72]. This atlas shows that smoking rates vary according to gender in many countries.

While the smoking prevalence is decreasing in both Canada and the US, its prevalence in China and India continues to be high. In 2010, there were 301 million adults who were current smokers in China, with prevalence rates of 52.9% and 2.4% among men and women, respectively[80]. Among individuals aged 20-34 years and ever daily smokers, a majority (52.7%) started smoking before the age of 20 years. About 6 in 10 adults reported workplace smoking. In a typical week, about 7 in 10 non-smoking adults were exposed to second-hand smoke. The

frequency of exposure to second-hand smoke at the workplace and in the home was 63.3% and 67.3%, respectively[80].

In India, the prevalence of tobacco use (both smoked and smokeless tobacco) in 2009-2010 was 47.9% in men and 20.3% in women. Prevalence of smoking rates was 24.3% and 2.9% in men and women, respectively, while prevalence of smokeless tobacco rates was 32.9% and 18.4%, respectively. The age at initiation for tobacco consumption among men and women was 18.1 years and 14.7 years, respectively, and 60.1% of daily users consumed tobacco within thirty minutes of waking up. Exposure to second-hand smoke in the home and at the workplace was 52.3% and 29.0%, respectively[81]. High prevalence of smokeless tobacco use in India is because of the emergence of a large number of new products whose increasing use has been reported not only among men, but also among children, teenagers, and women. Tobacco is used in many different varieties and forms which can be used either orally or nasally. However, most popular forms of tobacco products are used in chewing forms. A specific feature of tobacco products used in SA countries is their wide range of both commercially prepared products and custom preparations that cater to individual preferences. A majority of these oral chewing products are placed in the mouth either below the cheek or lip and are either sucked or chewed upon.

The focus on oral cancer in this research led to an interest in common oral chewing products. There is a wide variety of oral chewing products. Those that are commonly used in BC are briefly reviewed in Table 2. Nicotine and pH levels in these smokeless tobacco products vary, with pH levels ranging up to 10.1 and nicotine levels up to 10.2mg/g[71]. Detailed descriptions of historical perspectives of chewing behaviour, chemical composition or products,

manufacturing, regulations, and studies on humans and animals can be found in two International Agency of Research on Cancer (IARC) monographs[71,82].

It is not known how immigration to BC of persons from India and China, both countries with high prevalence of tobacco use, will impact the incidence of and survival from oral cancer in BC. Currently there is no data on ethnic differences for oral cancer in BC. It is known that there is high prevalence of smokeless tobacco use among SA immigrants in several countries. When this thesis work began it was not known whether the use of oral chewing products containing smokeless tobacco was a common practice in BC after immigration and if so what the most commonly used forms were. These questions were addressed in this thesis.

Alcohol

Alcohol is another well-established risk factor for oral cancers and many other cancers. It is the product of fermentation of carbohydrates by yeast. Ethanol is metabolised to acetaldehyde, which interferes with DNA methylation, synthesis and repair and binds to protein and DNA, causing damage leading to abnormal cell proliferation[83-85]. It also acts indirectly to affect clearance of carcinogens in heavy users where the liver is damaged by frequent alcohol consumption. Absorption of alcohol occurs through the stomach and small intestine, and it reaches the central nervous system where it reduces activity of the inhibitory neurotransmitters and increases the activity of dopamine, providing reward and satisfactory sensations.

The risk of oral cancer associated with alcohol consumption is dose-dependent. For people consuming about 4-5 drinks daily, there is 2 to 3 times higher chance of developing oral

cancer as compared to never drinkers[17,86]. The risk of developing oral cancer among former drinkers is also higher as compared to never drinkers[87].

The alcohol content in different beverages varies from 5 to 40%. In beer and wine, there is incomplete fermentation of carbohydrates and alcohol content varies from 3 to 18%. Spirits are distilled products and contain 30% or more alcohol[88]. As the alcohol content in the beverages varies, the volume with equivalent alcohol amount also differs. An 8-ounce glass of beer, 4-ounce glass of wine and 1 ounce of spirits have been calculated to contain the same amount of alcohol and are used for evaluating the amount of alcohol consumed[17].

Alcohol is widely consumed for social purposes, enjoyment, facilitating relaxation and as a fatigue reliever. Recent WHO statistics suggest that worldwide about two billion people consume alcohol and these rates are expected to increase in the future. Among the different types of beverages consumed worldwide, beer accounts for 37% , spirits for 33% and wines for 30%[74].

Betel quid chewing

In addition to well-known risk factors of tobacco and alcohol consumption, the higher incidence of oral cancers in SA countries is attributed to the common habit of using oral chewing products, including betel quid (BQ)[21,22]. Chewing betel quid is a very common practice that has existed for about 2000 years in South Asian countries. In recent years there has been an addition of smokeless tobacco leaves to BQ, and this has now become a common component[71]. This risk behaviour is associated with a high, dose-dependent carcinogenic potential. Interestingly, tobacco, alcohol and BQ chewing act synergistically and have common characteristics: (1)

globally, they each have a very high prevalence of use: one billion men and 250 million women smoke cigarettes, more than 600 million chew BQ, and two billion consume alcohol; (2) low-dose consumption may not be recognized as harmful by the user; and (3) these risk behaviours can lead to addiction. BQ with or without smokeless tobacco is an independent risk factor for oral cancer[89,90].

BQ is a combination of betel leaf (Piper betel), areca nut (Areca catechu), slaked lime (Ca(OH)2) and catechu (Acacia catechu) along with spices; it can be prepared with and without smokeless tobacco[22]. Smokeless tobacco contains nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, among other carcinogenic components; areca nut contains arecoline and 3-(methylnitrosamino) propionitrile. Lime provides reactive oxygen radicals[91]. Chewing BQ leads to production of potentially carcinogenic nitrosamines, including 3 methyl nitrosopropionitrile, and generates reactive oxygen species due to auto-oxidation of polyphenols (enhanced by the alkaline pH of slaked lime) which promotes carcinogenesis[92]. In addition, BQ chewing is also associated with increased risk for esophageal cancers, hypopharyngeal cancers, lung cancers, pancreatic cancers[93] and breast cancer[94].

Globally, about 10 to 20 percent (600-1200 million people) of the world's population use BQ, which makes it among the top psychoactive substances after nicotine, alcohol and caffeine[95]. The highest prevalence of BQ use (25-50%) is reported in the South-East Asian countries[95]. An inter-country Asian betel-quid consortium study found that the prevalence of chewing rates among SA men was 10.7 to 43.6 percent[96]. In a national survey from India, the rates of consumption of oral chewing products among men in urban and rural India were 20.7% (19.1 million) and 31.1% (71.4 million), respectively, while among women these rates were 8.6% (7.6

million) and 13.3% (30.4 million), respectively[97]. Studies among SA children and teenagers showed that 60-70% tried BQ and many of them then became regular users[98]. SA persons also continue to chew after migration to other countries, including the US and UK[23-26,49,54,99,100]. Early in the development of this dissertation the use of oral chewing products was found to be prevalent among immigrants from SA countries to BC[31].

Reasons for the continuation of oral chewing products are diverse. Chewing BQ helps in extracting alkaloids like arecoline, which is a cholinergic agonist that acts on the muscuranic receptors and affects the nervous system via acetyl choline. Other psychoactive alkaloids present in areca nut are arecaidine, guvacoline, and guvacine. Physiological actions caused by these alkaloids increase the muscle tone, slow heart rate, constrict the pupils and heighten mental alertness. BQ ingredients cause numerous metabolic and neurological changes[101] which can occur even with a single use[102] and thereby encourages addiction behaviour. Betel nut was found to have a high score of 7.3 out of 10 on a severity dependence scale[103].

Researchers have examined the reasons that people give for chewing BQ to understand patterns of usage. Many poor people have been reported to chew areca nut to avoid boredom and suppress hunger[104-106]. A cross-sectional quantitative study of 204 Bangladeshi adolescents from the UK reported that 42% of those who used BQ chewed it because of its refreshing feeling, 35% chewed it because of its good taste, 29% used it as a snack, and others used it because it helped them to relieve stress or they believed it would strengthen teeth and gums[27]. Another study from the UK among 11 Gujarati Indian chronic chewers reported positive psychosocial effects including relaxation, improved concentration, mood lifting, enhanced sense of satisfaction after betel nut chewing, reduced appetite and weight loss[41]. A US cross-sectional study of 130 Indian-

Gujarati and Bangladeshi immigrants cited the following beneficial effects of chewing BQ by the study chewers: relieving constipation, improving stamina, fighting cold, relieving tension and improving mood[54]. These studies indicate that reasons for chewing vary considerably in different contexts and reflect users' beliefs about the benefits of this practice.

Although the prevalence of chewing BQ with and without smokeless tobacco is very high in India, there are few pharmacological interventions to assess the usefulness of different therapies for its cessation. However, health promotion and education programs have been shown to reduce the use of BQ and smokeless tobacco[107-110]. With an increasing use of oral chewing products in India and a high prevalence of its use among the school children and socio-economically disadvantaged populations, there are a number of international collaborative projects currently functioning in India to make appropriate programs for discouraging the use of tobacco. Some of the currently active projects are: Project MYTRI[111-114] (Mobilising Youth for Tobacco-Related Initiatives in India) targeting the school children in Delhi and Chennai, India; Project ACTIVITY[115], a community-based tobacco prevention approach targeting youth in low-income communities in India; and Project Quit Tobacco International[116,117] focusing on culturally appropriate approaches for tobacco cessation in India and Indonesia.

Given the significant immigration from South Asian countries like India (where chewing is a common habit) to BC, a better understanding of the reasons and perceptions of the most commonly used oral chewing products among SA immigrants in BC is needed to guide the development of strategies to reduce the burden of oral cancer. This is one of the objectives of this dissertation.

Human papillomavirus infection

Recent evidence from molecular and epidemiological studies suggests that the aetiology of oral cancers is changing and that HPV may be playing an increasingly significant role in cancer development, especially at some OPC subsites[4]. This observation is supported by early reports in the US that showed that the overall incidence of head and neck cancers (all subsites combined) was decreasing[36,77], a decrease largely attributed to the decline in rates of OCC and associated reduction in smoking rates[36]. In contrast, a dramatic increase in the incidence of OPC has been observed in the US and globally[8,34,36,118,119].

Evidence for the association of HPV infection with the increase in OPC incidence comes in large part from studies showing the association of HPV-DNA with OPCs[120]. These studies have shown that the HPV-DNA is localized to the cell nuclei in OPC tissue samples, that it is integrated into the host DNA and that viral genes are being actively transcribed[121,122], as has also been demonstrated for cervical cancers[123]. HPV is now thought to be a major cause of OPC in developed countries, with estimates ranging from 45 to 90% of cases[5,124,125]. This variation may reflect population differences in the involvement of HPV in OPC. However, since the methodology used to determine HPV prevalence varies among studies the precise range in HPV involvement across countries is still unclear.

Further evidence for the association of HPV and OPC comes from temporal studies on its association with OPC. A study from Sweden has tested archived oropharyngeal tumour samples for HPV status in samples obtained over decades. This study reported a dramatic increase in the proportion of tonsillar cancers associated with HPV from 23% in the 1970's to 93% in 2006-

07[125] . A further recent study from the US has shown a similar trend with HPV DNA present in 16% of OPC in 1984-1989 and 73% during 2000-2004[126].

Although HPV is an important cause of OPC, it is still unclear how much it contributes to oral cancers at other sites. It is generally accepted that a proportion of these cancers may be HPV-associated, although this involvement is likely to be notably smaller than for OPC. A recent study from Toronto, Canada, has reported that prevalence of HPV-DNA in OPC and OCC was 73% and 4%, suggesting the HPV involvement is predominantly at OPC sites[127].

Epidemiologic evidence for the association of HPV with OPC comes from case-control studies that have consistently shown an association of HPV-positive OPC cases with a higher number of sexual partners[128,129]. These studies support the involvement of sexual transmission of the infection in the development of these cancers[5,130]. The reports suggest that a change in sexual practices (i.e., greater numbers of oral sex partners and oral sex at an earlier age in comparison to past generations) may be responsible for the increase in the incidence of OPC[128,131]. Other modes of transmission may also occur, such as by saliva transfer and deep kissing which have both been associated with increased risk[130]. However, the absence of a high number of sexual partners does not exclude the diagnosis of HPV-positive patients[129,131]. There are also reports of oral HPV infection among children, suggesting that HPV infection may be gradually acquired during childhood[132].

The risk for tonsillar cancers is elevated among men whose wives had cervical cancer and concordant infections are seen among both husbands and wives, further supporting the hypothesis of sexual transmission[133]. To date, only one population-based study has showed that patients who were HPV-seropositive subsequently developed OPC[134], providing evidence for a

temporal association between the infection and later disease development. It is likely that oral HPV infection alone is not sufficient to cause OPC because HPV is highly prevalent in most populations, with a majority of individuals being infected at some point in their lives. A current hypothesis is that it is the inability to clear infections that renders some individuals more susceptible to the disease. This is supported by studies that show that oral HPV infection is more frequent among people with immunosuppression such as human immunodeficiency virus (HIV)-positive patients[135].

Although the association between HPV and OPC is becoming increasingly accepted in both clinical and scientific arenas, there are still many unresolved issues that require further research[136,137]. These include a need for more studies to better understand the natural history of oral HPV infection, the factors associated with its clearance and persistence, and its association with OPC. It is also important to investigate and understand why the disease arises predominantly in men and whether the natural history of oral HPV infection differs in men and women. This information is essential for the development of more targeted approaches to both primary and secondary prevention for individuals with tumours with HPV involvement.

Clinical interest in the identification of HPV in OPC has been driven in recent years by observations of improved survival rates for HPV-associated OPC and by case-control studies that demonstrate an association of the presence of HPV in tumours with better survival rates[138-141] This improvement in survival for HPV-associated tumours has been attributed to several possible factors: the younger age of patients with such tumours as compared to those without an HPV association (hence less comorbidity), the frequent absence of tobacco and alcohol use (the latter

being associated with a wider spread of the tumour and a greater difficulty in managing the disease) and possibly a better response to treatment[120,140,142-144].

In summary, there is a need to examine incidence and survival patterns for oral cancer, considering OPC and OCC separately as well as their subsites. Sex differences in these epidemiological shifts should be studied to identify differences, if any. This thesis explores for the first time these patterns in BC as a first step towards showing a potential impact of HPV on oral cancers.

Diet

Diet has also been shown to have an effect on oral cancer occurrence, either directly via the carcinogens present in food and food additives or indirectly by consumption of components in the diet that alter metabolic carcinogen detoxification. Together, these mechanisms may have an effect on the amount of DNA damage to the tissue and hence on oral cancer risk. In addition, although less understood, bioactive food components can interact with specific genes, altering expression and thus changing the quantity of key proteins involved in phenotypes which influence the host and affect cancer outcomes[145]. Unbalanced diets which lack essential nutrients can lead to oxidative stress which can damage the DNA. Therefore, it is important to maintain free radical defences by maintaining healthy dietary habits.

Fruits and vegetables provide an important source of fibre and antioxidants which are believed to play a role in preventing oral cancer[146] and counterbalancing the detrimental effects of carcinogens like tobacco, alcohol and BQ[147]. Studies have shown an association between the consumption of such foods and a reduced risk of oral and head and neck cancers[148]. Other

micronutrients and trace elements like vitamin C, E, lycopene, folate and zinc may also influence oral cancer risk. Individuals who consume higher levels of tobacco, alcohol or BQ may not consume enough fruits and vegetables which might cause DNA damage and simultaneously reduce an individual's ability to repair that damage[149]. In addition, low fruit and vegetable consumption and deficiency in micronutrients such as folate may contribute to the development of oral cancers[150,151].

Researchers have also reported correlations between dietary fat and carcinogenesis[152]. Fats can alter the integrity of cell membranes, thereby affecting the receptor and enzymes functions, nutrient metabolism and increasing lipid peroxidises.

Although the important role of diet in the etiology of oral cancers was recognized, this role was not included in the inspection of cancer trends reported in this research.

Combination of risk factors

There is no single known cause of oral cancer. While some risk factors like tobacco act as initiators of disease, current evidence suggests that factors like alcohol act as promoters, facilitating disease progression. In fact, some risk factors appear to act synergistically. For example, alcohol dehydrates the oral mucosa and increases the permeability to tobacco carcinogens which increases the risk for developing oral cancer.

The synergistic effects of BQ chewing and alcohol with smoking are multiplicative on oral cancer risk. Combination of moderate drinking (8–25 drinks weekly) and smoking (20– 45 cigarette packs yearly) dramatically increases the risk for developing oral cancer. A study from India showed that the odds ratios (OR) for developing oral cancer were 3.19 in individuals who

chewed BQ (with smokeless tobacco) , 4.63 with smoking, and 1.65 with alcohol consumption. However, for individuals who combined BQ chewing, smoking and alcohol, the OR was 11[22]. In North America, a synergistic effect of 30 times increase in risk has been reported for combinations of tobacco smoking and alcohol consumption[17].

A case-control study has shown an interaction of tobacco smoking and HPV upon survival for OPC. The mechanism is unknown[141] . One hypothesis is that smoking affects clearance of HPV infection, with chronic infection being associated with the development of OPC. This association has been mainly discussed with respect to cervical cancer[138,139]. Further research is required to better define the association and to determine the impact of combined exposures on clearance of oral HPV infection and occurrence of OPC[153,154]. However, since oral HPV infection is more common in smokers as compared to non-smokers, this may support the possibility that smoking delays clearance of HPV virus[155].

Finally, there are also emerging reports supporting an interaction between BQ chewing and HPV infections on oral cancer incidence[156]. A preliminary study from India showed a higher prevalence of HPV in oral premalignant lesions (e.g., oral submucous fibrosis); further epidemiologic and pathologic studies with larger sample sizes are required to establish a causal association[157].

The above discussion suggests that the etiology of oral cancer is very complex and changing. The disease results from an interplay among a number of risk factors which may operate differently for OPC and OCC and for their subsites.

Clinical presentation at different subsites

The largest proportion of cancers seen in the head and neck region are squamous cell carcinomas[158]. These carcinomas include the lip, tongue, tonsil, cheeks, gums, floor of mouth, palates and pharynx (including oropharynx, nasopharynx and hypopharynx) and salivary glands. For this thesis, the primary interests were histologically confirmed squamous cell carcinoma in the oral cavity and oropharynx. Oral squamous cell carcinomas all occur within the mucosa lining epithelium; however, the histological structure of the mucosa linings varies at different locations. This may affect susceptibility to various carcinogens; hence, risk factors may vary at different oral subsites. For example, in western countries SCC from the oropharynx such as palatine tonsils and lingual tonsils are increasingly found to be associated with HPV infection[5,9,159] while the remainder of oral squamous cell carcinomas are mostly related to smoking and alcohol consumption, tongue and floor of mouth cancers being most common[160]. In other parts of the world, including SA countries, the most common oral cancer sites are gum and check where the chewing products are placed[21]. Therefore, epidemiological studies of oral cancer at different oral subsites and in different populations can yield important information about risk behaviours and habits.

Oral cancers can occur in all intraoral sites; however, in the oral cavity the majority of cancers are concentrated in the lower part of the mouth, particularly in the ventrolateral tongue and floor of the mouth. It is not totally clear why these sites have much higher oral cancer incidence rates, but a number of hypotheses exist. One theory is based on the thickness of the epithelium: these sites have either no or a thin keratinized layer and thinner epithelium provides less of a barrier to carcinogens to reach basal cells, the target of carcinogens, as compared to

thicker epithelium in the low-risk oral sites[161,162]. Another popular theory is the reservoir theory: the floor of the mouth and the ventrolateral tongue are located in the lower half of the oral cavity where carcinogens in the saliva may pool, increasing the exposure to carcinogens[163]. In contrast, the hard palate and dorsum of the tongue are very rarely affected, not only because they are not usually immersed in saliva but also because they have keratinized epithelium that is less permeable to carcinogens.

There are important differences in etiology, clinical presentation and progression of oral cancer at the various subsites including the external lip, oral cavity (inner lip, tongue, floor of the mouth, gum, cheeks and palates), and oropharynx (base of tongue and tonsils). Each will be discussed below.

Sunlight exposure can cause cancers of the external lips. A common early presentation of external lip cancers is an area of thickening, induration, crusting or shallow ulceration of the lip, less than a centimetre in diameter. Spread of cancer mainly occurs by submental lymph nodes which are the first group of nodes to become involved. Subsequent spread to other lymph nodes is slow.

Oral cancers from the rest of the oral cavity usually present as a white or red patch, lump, exophytic growth, an ulcer, or as an ulcero-proliferative growth, with rolled out edges. [21,160]. Oral cancers caused by chewing products are more likely to have a verrucous appearance than smoking induced oral cancer. In addition, they are more likely to be associated with oral submucous fibrosis. As cancer progresses it infiltrates and becomes fixed to the surrounding tissues. The affected lymph nodes are enlarged and hard, the surface becomes irregular and the lymph nodes become fixed to the deeper tissues and skin.

Located posterior to the oral cavity and pharynx is Waldeyer's ring: pharyngeal tonsil, tubal tonsil, palatine tonsil and lingual tonsil, from superior to inferior of the ring. Of these, two tonsils, palatine and lingual tonsils, are located at the oropharynx. Palatine tonsils, frequently referred to as the "tonsils", are bilateral structures situated in the tonsillar beds and consist of lymphoid tissues with 10-30 crypts lined by the surface epithelium[9]. Lingual tonsils are rounded masses of lymphatic tissue located at the base of the tongue and there is only one crypt for each lingual tonsil. The surface of both the palatine and the lingual tonsils is covered by stratified squamous epithelium and a similar type of epithelium lines the crypts. It is speculated that HPV-associated tonsillar squamous cell carcinomas originate from the epithelium of the crypts; whereas HPV-unrelated tonsillar squamous cell carcinomas emerge from the tonsillar surface epithelium[9]. These tumours usually spread through the jugulo-digastric nodes and deep cervical group of lymph nodes.

Based on these observations, the various oral subsites were grouped for the dissertation into OPC and OCC and this grouping is described in Chapters 4 (incidence) and 5 (survival).

Factors affecting survival

Oral cancers have a poor prognosis as compared to malignant neoplasms at other body sites[16] The quality of life in the terminal stages of cancer is also poor[164]. The length of survival after treatment depends upon many factors. Well-established prognostic factors for oral cancer include: a) disease stage at diagnosis, b) delay in treatment, c) etiology, d) presence of second primary or recurrences, e) histology, f) location in mouth and g) age.

Oral cancer progresses from a precancerous to cancerous lesion, finally leading to the invasion of the cancer cells into underlying connective tissues. At first, the cancer is small and confined to the mucosal site (early-stage malignancy). With time it becomes larger, invading surrounding tissues and spreading to distant sites through lymphatics to lymph nodes or blood vessels to other sites or organs of the body (late stage)[165].

Tumour stage at the start of treatment depends both on the growth rate of the tumour and the delay in diagnosis. Because the stage of disease is critical to survival, it is used to guide the choice of the treatment plan. According to the TNM classification (Table 3), each carcinoma is given a score for tumour size (T), lymph node metastasis (N) and distant metastasis (M). These features are combined together to give an overall score of stage I, II, III or IV. Larger tumour size, spread to lymph node (number, size of lymph node, site of lymph node) and distant organ or tissues indicate late stage.

Unfortunately, most patients with oral carcinoma present at late stages, that is in stage III or IV[166] Larger tumours are more difficult to manage and, hence, have poorer prognosis and survival. The greater the extent of lymph nodal involvement, the poorer the prognosis and survival chance. Survival rates are better if oral cancer is detected at an early stage. For example, if tongue lesions are detected at an early stage, the 5-year survival rate is 71%; if detected at a late stage, the survival rate is only 37%[17].

The earlier the diagnosis and earlier the treatment, the better the outcome. Treatment delay permits further spread of the tumour, resulting in a poorer chance of long-term survival.

Management of oral cancer is complex and depends upon the age and medical condition of the patient as well as its exact site, degree of spread (stage) and histological type. An appropriate treatment protocol must be selected for each individual case, taking these features into account. Treatment may be either by surgery or radiotherapy, or both, for curative or palliative purposes. Chemotherapy is most often associated with metastatic spread.

Early-stage intra-oral carcinomas are generally treated by surgery alone or in combination with radiotherapy. Surgery alone is preferred for small carcinomas which may be easily excised. Radiotherapy is sometimes carried out by implantation of radioactive material into and around the neoplasm (brachytherapy) although this has become less frequent recently, or by exposure to beams of x-rays or gamma-rays from x-ray generators or radioactive isotopes such as cobalt (teletherapy). Ionizing radiation damages both normal and neoplastic tissues, so treatment planning is essential. The lesion is accurately localized by means of imaging techniques and a dose, usually around 60 GY (gray), is delivered to the oral lesion. Damage to surrounding tissues is limited by fractionating the dose over many visits and by applying external beams from many angles, avoiding radiosensitive tissues such as the eye and bone. For teletherapy, a mask is made to fit the patient's head to allow reproducible beam angulation between visits. In general, surgery is the mainstay treatment for the cancers affecting the cheeks, gums, tongue and floor of mouth; radiation is the main treatment modality for cancers affecting the tonsils and oropharynx.

Surgery is indicated when cancer has invaded bone or when there has been a poor response to or recurrence after irradiation. The aim is to excise the carcinoma with as wide a margin as possible, ideally 1 cm or more. Small margin excision may not guarantee removal of

the carcinoma, resulting in recurrence of tumour at its original site; however, wider excision may make reconstruction difficult. Chemotherapy has serious complications and side effects and hence its use is less common in oral cancer patients. Chemotherapy is used when there are widespread metastases or in recurrent cases which are in close proximity to vital anatomical structures. The use of drugs as radiosensitisers along with radiotherapy is becoming a more frequent practice especially for OPC.

Personalized medicine focuses upon the clinical decision by systematically using genetic, molecular or other information about an individual patient for selecting their therapeutic or preventive care[167]. Therefore, personalized medicine accounts for genetic or individual differences of patients in addition to taking into account their family history, socio-economic circumstances and risk behaviours for tailoring individual care to patients. A very active area of discussion currently is whether or not the presence of HPV-DNA in oral cancers should be used to guide treatment choices. This discussion is driven by the observations of a better response of cancers with HPV-DNA in them to treatment and the frequent observation that oral cancer patients with such change are often younger that those without HPV involvement and the long-term consequences of treatment could be severe. Whether treatments can be tailored to such patients to minimize morbidity is not known.

Socio-cultural context of oral cancer risk behaviours

Oral cancer is influenced by behaviours that place individuals at risk for the disease. Engagement in these health risk behaviours is directly influenced by the social-cultural context in which people live their everyday lives. In this dissertation, SA men in BC were identified as a high-risk group for oral cancer. This prompted us to review the literature related to the socio-

cultural influences that may affect the risk behaviours among South Asians. This review of current knowledge is summarized below and provided direction for conducting the qualitative component of this research.

The importance of socio-cultural factors in influencing risk factors (e.g., smoking, alcohol use and BQ chewing) is demonstrated in both qualitative and quantitative (described above in etiological risk factor section) studies. Qualitative studies on smoking behaviours among SAs reveal that age, sex, tradition and religion influence smoking attitudes and behaviours in complex ways. For example, among SA men living in Bangladeshi and Pakistani communities in Newcastle, UK, smoking was considered a part of socializing, sharing and male identity; whereas among women, smoking was associated with shame and stigma and was hidden from family members[168]. Religious beliefs and practices have also been observed to be a factor contributing to variations in risk behaviours among SA groups[168]. A cross-sectional survey of SA men in the UK found that Muslims chewed more tobacco and BQ, while Punjabi Sikhs consumed more alcohol, and Hindus chewed, smoked and consumed alcohol[49]. Together these studies suggest that socio-cultural beliefs are important influencing factors in relation to behaviours that place individuals at risk for oral cancer.

The practice of chewing BQ with tobacco is particularly prevalent among SAs and socio-cultural factors appear to support its use. In SA countries, BQ chewing starts at an early age and adults do not object to young children indulging in this behaviour because it is considered a part of normal life[22,169,170]. Areca nut has a longstanding history, tradition and socio-cultural significance. Among Hindus, areca nut is considered auspicious and used in religious ceremonies where it is considered a vital ingredient of food for the God. When religious idols

and sacred images are absent, areca nut (whole nut without its husk) is used to offer prayers. Religious beliefs suggest that God blesses this fruit, which is then distributed among its followers. These traditional beliefs encourage its use at social gatherings and weddings[105,170]. Of interest, although BQ and areca nut are not considered auspicious among Muslims, it is consumed by them in SA countries as well as after immigration to western countries[23-26,46,54,171,172]. Areca nut is also regarded to be good for health and considered to be part of traditional "ayurvedic" medicine. Areca nut may be used as an astringent, mouth freshener, taste enhancer, purgative, intoxicant, and aid for indigestion, impotency and gynaecological problems, treatment of parasitic intestinal infection and prevention of pregnancy-related morning sickness[106].

Over time, there has been an increasing use of smokeless tobacco along with areca nut (a psychoactive alkaloid) in BQ, which has led to increasing dependency and addiction in users. These preparations are made according to an individual's need for nicotine by using higher grades of tobacco leaves and making the quid into different sizes to satisfy their requirement.

Several qualitative studies were identified in the literature that specifically focused upon oral chewing products and tobacco use among SAs[45,55,173,174]. Two of these studies were conducted in India, one focusing on the use of tobacco products (both smoking and smokeless) among college students[173] and the other study on the use of areca nut among rural residents in a remote Indian village[174]. Perceptions about tobacco consumption among the Indian college students were that smoking cigarettes enhanced man`s masculinity, relieved boredom and enhanced social status while *gutka* (mixture of areca nut and tobacco) gave more of a kick, was good to relieve boredom and was used for quitting smoking[173]. In the second study, a high

prevalence of areca nut use was found in the remote Indian village, beginning at as early an age as 15 years. This practice was reported due to intense peer pressure, lack of knowledge on the harmful effects of areca nut products and indifference by the elder parents and friends about the use of areca nut by the young[174].

Only a few studies have been conducted among SA immigrants to western countries. One study reported that SA men in the UK had poor access to tobacco cessation programs and hence tobacco-containing BQ was used as a smoking cessation aid instead of nicotine replacement therapy[45]. A separate study in the US suggested that there was lack of knowledge about the health effects of using smokeless tobacco products and that the use of these products in the US was continued to maintain a sense of cultural identity among SA immigrants[55]. There remains a lack of understanding of the socio-cultural influences on tobacco-containing BQ use among SAs in western countries, and as far as can be determined there have been no previous studies examining these influences on oral chewing behaviours in Canada. Despite the high prevalence of tobacco-containing BQ use among SA men, gender influences have also not been well described. It is important to address these knowledge gaps to guide the development of effective oral cancer prevention programs.

In summary, BQ may be chewed for a variety of reasons ranging from health beliefs to social norms to addictions; hence, in this dissertation an ethnographic study was conducted to better understand the socio-cultural context in which SA men continue to engage in chewing tobacco-containing BQ. The rich description and understanding that an ethnographic study can provide is valuable in developing culturally sensitive and gender-appropriate health promotion and education programs for SA men.

Summary of literature review

This literature review shows that there is a small but growing number of papers focusing upon the epidemiological shifts in oral cancer examining trends in OPC and OCC and a need to better explore such change by subsite, sex and by ethnicity globally. In addition to epidemiological research, there is growing need for conducting qualitative research to better understand the epidemiologic data and to provide a framework for future interventions. The mixed method research approach used in this dissertation to address these issues will be discussed in the next synoptic methods chapter.

Table 1: Summary of the findings from key articles from literature review.

Author and year	Population	Years of follow-up	Source of data	Sex	Ethnicity	OPC and OCC subsites	Incidence rates	Survival rates
Incidence studies								
Bloomberg[10] et al, 2011	Denmark included analysis of 26,474 cases	1978-2007	Cancer Registry	+	-	-	OPC and OCC increasing for both men and women. (Greatest increase was for OPC)	Not applicable
Braakhuis[8] et al, 2009	Netherlands included analysis of 2,753 cases	1989-2006	Cancer Registry	+	-	+	OPC increasing significantly for both men and women. OCC increasing for both men and women but at a lesser rate	Not applicable
De Souza[15] et al, 2011	Spain from regions of Granada, Murcia, Navarre, Tarragona and Zaragoza included analysis of 12,134 cases	1988-2017 (projected)	The database is available on the webpage of the International Agency for Research on Cancer (IARC),and has been published in editions VII, VIII and IX of Cancer Incidence in Five Continents	+	-	-	OPC increasing for both men and women. OCC decreasing for men and increasing for women	Not applicable
Hammerstedt[118] et al, 2006	Sweden included analysis of 515 cases	1970-2002	Cancer Registry	+	-	+	Tonsillar cancers increased for both men and women	Not applicable

Author and year	Population	Years of follow-up	Source of data	Sex	Ethnicity	OPC and OCC subsites	Incidence rates	Survival rates
Hocking[11] et al, 2011	Australia included analysis of 37, 223 cases	1982-2005	National Cancer Statistics Clearing House database	+	-	- OCC + OPC	OPC increasing for both men and women. OCC decreasing for men and unchanged for women	Not applicable
Ligier[12] et al, 2011	France included analysis of 82,985 cases	1980-2005	11 registries in French National mortality database,	+	-	-	OPC and OCC decreasing for men and increasing for women	Not applicable
Mork[7] et al, 2010	Norway included 2,315 cases	1981-2005	Cancer Registry	+	-	-	OPC rapidly increasing for both men and women. (Rates 2-3 times higher for men as compared to women)	Not applicable
Reddy[14] et al, 2010	England included 40,138 cases	1985-2006	National Cancer Information Service (Cancer Registries)	+	-	- OCC + OPC	OPC and OCC increasing for both men and women	Not applicable
Survival Studies								
Hammerstedt[38] et al, 2011	Sweden included analysis of 7,180 cases	1960-2004	Cancer Registry	+	-	+	Not applicable	Tonsils and base of tongue cancers improving in both men and women. Tongue cancer with very modest improvement

Author and year	Population	Years of follow-up	Source of data	Sex	Ethnicity	OPC and OCC subsites	Incidence rates	Survival rates
Incidence and Survival studies								
Brown[35] et al, 2011	United States included analysis of 58,204 cases	1977-2007	Surveillance, Epidemiology, and End Results (SEER) program	+	+	-	OPC increasing in White men, decreasing in Black men. OPC and OCC decreasing in both White and Black women	OPC improving in both White and Black men. OCC improving in both White and Black men, in White women, and unchanged in Black women
Chaturvedi[36] et al, 2008	United States included 45,769 cases	1973-2004	Surveillance, Epidemiology, and End Results (SEER) program	+Incidence - Survival	+	-	OPC increasing for White men and decreasing for Black men, and White and Black women. OCC decreasing for White and Black men and women	OPC and OCC improving (data not presented by gender)
Gupta S[37] et al, 2009	Ontario, Canada included 19,573 cases	1984-2001	Cancer Registry	+Incidence - Survival	-	-	OPC increased for men and decreased for women. OCC decreased incidence decreased in both sexes.	OPC and OCC improving in both men and women
Lichius[13] et al, 2010	Germany included 3,821 cases	1996-2005	Thuringian Cancer Registry	+	-	-	OPC increasing for both men and women. OCC increasing for men, unchanged for women	No changes in OPC and OCC for both men and women

Symbols in the sex, ethnicity and OPC and OCC subsite fields represent the following: "+" indicates that the indicated variable was considered in the paper; "-" indicates that the variable was not considered; when variables were considered for one parameter but not for the other this is indicated separately in the field, e.g., "+" incidence but "–" survival in a column indicates that data was presented for incidence trends by sex but not for survival trends. Similarly, "+" OPC and "-" OCC in column indicates data was presented for OPC subsites but not OCC subsites**.**

Table 2: List of some South Asian oral chewing products which were found to be used in British Columbia while conducting dissertation research.

Name	**Contents**
Betel quid (paan)	Betel quid with tobacco, commonly known as *paan* or *pan*, consists of four main ingredients: (i) betel leaf (*Piper betle*), (ii) areca nut (*Areca catechu*), (iii) slaked lime and (iv) tobacco. Smokeless tobacco is an important ingredient for these products and these quids can be prepared either at a vendor or at home.
Paan masala	A powdered mixture of areca nut and slaked lime with spices and flavoring agents.
Zarda	*Zarda* consists of tobacco, lime, spices and vegetable dyes. Tobacco leaves are broken up and boiled with lime and spices until dry. The mixture is dried and coloured with vegetable dyes. *Zarda* is generally chewed mixed with finely chopped areca nuts and spices. It is often used as an ingredient in betel quid.
Gutka	*Gutka* is manufactured commercially and consists of sun-dried, roasted, finely chopped tobacco, areca nut, slaked lime and catechu mixed together with several other ingredients such as flavourings and sweeteners. These are available in small packets which are held in mouth, sucked and chewed upon.
Khiwam	*Khiwam* consists of tobacco extract, spices and additives which are used along with betel quid.
Khaini	*Khaini* is made from sun-dried or fermented coarsely cut tobacco leaves
Mawa	*Mawa* is a mixture of small pieces of sun-cured areca nut with crushed tobacco leaves and slaked lime.
Mishri	*Mishri* is made from tobacco that is baked on a hot metal plate until toasted or partially burnt, and then powdered. It is applied to the teeth and gums as a dentifrice.

Name	Contents
Red tooth powder	It is a fine tobacco powder that is red in color and contains additional herbs and flavoring agents and is used as a dentifrice in South Asian countries.

Products were chosen for this table because they were later shown in dissertation work to be available in British Columbia. Descriptors are adapted from the IARC Monograph on the Evaluation of carcinogenic risks to humans, Volume 89, Smokeless tobacco and some tobacco-specific N-nitrosamines, 2007, with contents confirmed to be applicable to the BC population).

Table 3: TNM classification of oral cancer[175]

Primary tumour	Description
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumour more than 4 cm in greatest dimension
T4a (lip)	Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)
T4a (oral cavity)	Tumour invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b (lip and oral cavity)	Tumour invades masticator space, pterygoid plates, or skull base; or encases internal carotid artery
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis as specified in N2a, 2b, 2c below
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

CHAPTER 3: SYNOPTIC METHODS

This dissertation research utilized a mixed methods approach which comprised three research projects, as shown in Figure 1. The first two projects used quantitative epidemiologic research methods in order to determine trends in incidence and survival of oral cancers in BC using the provincial population-based cancer registry. As HPV infection has been identified as a new emerging risk factor for oral cancer, this analysis was done separately for OPC and OCC, and trends were then examined by sex and ethnicity in order to identify high-risk groups, focusing on the two largest immigrant populations in BC: SA and Chinese. The third project used a qualitative ethnographic research approach to develop a better understanding of the socio-cultural context of oral chewing practices among immigrant SA men in BC with a focus on chewing tobacco-containing BQ. BQ chewing is a common practice in SA men, both in SA countries and among SA immigrants in western countries.

The mixed method approach used in this dissertation drew upon the strengths of both quantitative and qualitative methods[176,177]. Quantitative epidemiological methods are appropriate for determining a population-based profile of trends in oral cancer incidence and survival. Epidemiology involves the study of disease in human populations and attempts to determine what factors are associated with disease. It uses the scientific method in the generation and testing of hypotheses. Descriptive epidemiology, as was used in this dissertation research to describe the incidence and survival patterns for oral cancer in BC, allows for the study of the distribution of frequencies and patterns of disease within groups in human populations. It deals with groups of people rather than individual persons[178]. The qualitative study in this dissertation research involved the use of ethnographic methods. Ethnographic research methods[179-182] are

appropriate for enriching the understanding of socio-cultural factors underlying health risk behaviours and were used in this dissertation project to examine beliefs and practices related to tobacco-containing BQ chewing among immigrant SA men in BC. Ethnographic research is a kind of social research that examines taken-for-granted everyday practices from the perspective of participants. This qualitative research method is characterized by the use of field work involving multiple methods of data collection (e.g., participant observation, interviews, photographs) and an inductive approach that allows categories and meaning to emerge from the analysis rather than imposing these from existing models or testing pre-determined hypotheses.

Mixed research methods are increasingly employed to investigate complex phenomena. The sequential use of quantitative and qualitative methods in this dissertation research were used to extend knowledge of oral cancer and underlying health risk behaviours and provide a basis for the development of appropriate interventions at population level.

Research objectives and aims

The objective of the first research project was to describe the incidence trends of OPC and OCC in BC. It had 3 specific aims:

1. To compare the age-adjusted incidence rates (AAIR) and age-specific incidence rates (ASIR) of OPC and OCC and its subsites by sex and ethnicity.
2. To study temporal trends in AAIR of OPC and OCC and subsites by sex in the BC general population.
3. To compare temporal trends in AAIR of OPC and OCC with temporal changes in smoking rates by sex in the BC general population.

The objective of the second project was to describe the survival trends of OPC and OCC in BC. It had 5 specific aims:

1. To compare the stage at diagnosis of OPC and OCC by sex and ethnicity.
2. To compare temporal trends in stage at diagnosis of OPC and OCC by sex in the general population.
3. To compare temporal trends in 5-year disease-specific survival rates of OPC and OCC and its subsites by sex using Kaplan Meier curves and log rank tests.
4. To compare 5-year disease-specific survival rates of OPC and OCC by stage at diagnosis, nodal status and tumour size using Kaplan Meier curves and log rank tests.
5. To compare 5-year disease-specific survival rates of OPC and OCC by sex and ethnicity using Kaplan Meier curves and log rank tests.

Finally, the objective of the third project was to describe the socio-cultural context of chewing tobacco-containing BQ among SA men living in British Columbia. The questions which guided this qualitative research were:

1. What are the socio-cultural beliefs and social norms associated with use of tobacco-containing BQ among different SA subcultural groups (i.e., Hindus, Muslims and Sikhs)? What is the impact of religious beliefs upon BQ chewing behaviours?
2. What may be the reasons for tobacco-containing BQ chewing to be considered a socially acceptable habit? What were the perceived benefits?
3. What factors influenced selection and use of different tobacco products (e.g., tobacco-containing BQ and cigarettes)?

4. What were the influences of western society, peers and family on these chewing behaviours?
5. What factors account for the popularity and non-popularity of tobacco-containing BQ? What motivates SA men to chew these products? What do they dislike about these products?

Study setting

The study was conducted in BC, Canada, where cancer is a reportable disease. The first two projects used secondary data from the British Columbia Cancer Registry (BCCR), which is a population-based cancer registry. The BCCR data are used to generate cancer statistics on the BC population for the purpose of monitoring the burden of cancer in the province. It contains personal and demographic information as well as diagnosis and death information on all cases of cancer diagnosed in BC residents. The sources of registration include haematology and pathology reports, death certificates, hospital reports and cancer treatment centers. The BCCR is estimated to cover at least 95% of all cancer cases in the province.

Data from population-based cancer registries play an important role in providing information about the incidence and survival of cancers in a defined population. This information is also important for assessing and controlling cancer at a population level and creating a surveillance system to monitor trends. Analysis of data from population-based cancer registries can also help in identifying high-risk target groups in relation to socio-demographic factors (e.g., age, sex) so that prevention approaches can be directed to specific population subgroups. Framing appropriate public health policies using trends in the cancer registry can

have economic benefits for governments by timely allocation of appropriate resources which will reduce the economic burden of health care.

For this dissertation all histologically confirmed cases of oral cancer diagnosed in BC between 1980 and 2006 were identified and regrouped into etiological clustered groups, namely OPC (predominantly associated with HPV) and OCC (predominantly associated with tobacco). Trends in incidence and survival were studied in the general population and in the two largest immigrant populations in the province, namely SA and Chinese.

The third project was conducted in an urban neighbourhood of Vancouver where residents are predominantly SA immigrants and shops, restaurants and Gurdwaras have sprung up to meet their needs. The community, sometimes referred to as "little India," includes a Punjabi market that stretches five blocks along a main street. The large majority of Indo-Canadians within Vancouver are of Sikh origin.

Data collection and analysis for the quantitative epidemiological study

All head and neck cancer with a coding of COO-CO14 (according to ICDO-3) were requested and retrieved from BCCR for the time period 1980 to 2006. All histology codes were then studied in detail and cases of SCC and its variants were only included in the analysis. In order to identify and remove duplicate cases, surnames, first and second names as well as agency ID and date of birth were compared. When all these variables matched a case was considered a true duplicate and was excluded from the final analysis. Since this analysis was concerned with incident cases, all recurrences and second primaries were also removed from the dataset. Then, the completeness was checked and the following information was collected on these cases: age,

gender, date of diagnosis, date of death, oral subsite, histology, method of diagnosis, cause of death and stage at diagnosis. This process of data cleanup took approximately 3-4 months to complete.

Calculation of AAIR involved reorganization of the registry data into age groups (by decade) by sex for OPC and OCC, and each subsites for each study year (1980, 1981, 1982 … 2006). This involved the construction of more than 600 tables [26 (number of years) x 2 (both sexes) x 2 (OPC and OCC) x 6 (OPC and OCC subsites)] for incidence analyses and additional tables were made for survival analyses. BC population demographics were also obtained for each study year, data was requested for ethnic groups from BC statistics and used as denominators and population weight factors for calculating AAIR.

ICDO site and histology coding

As both the incidence and survival projects involved analysis over time, changes in ICDO coding over the study period were considered. BCCR staff ensured that, for all sites, coding was consistently updated and finally based upon ICDO-3 coding. This ensured that different oral subsites were not analyzed for different time periods. The following anatomical subsites were classified as OCC: mucosa on inner lips (COO.3-COO.5, COO.8), ventrolateral tongue (CO2.0-CO2.3, CO2.8, CO2.9), gums (CO3.0-CO3.9, CO6.2), floor of mouth (CO4.0-CO4.9), palate (CO5.0- CO5.9), and cheek (CO6.0, CO6.1). OPC included base of tongue and lingual tonsil (CO1.9, CO2.4), tonsils (CO.90, CO9.1, CO9.9), wall and overlapping lesions of oropharynx (C10.2, C10.3, C10.8, C10.9), and Waldeyer's ring (C14.2). To ensure that only invasive squamous cell carcinoma cases were included in the analysis, all the histology codes were

individually checked and only cases with squamous cell carcinoma confirmed by pathology reports were included.

Tumour-node-metastasis (TNM) staging information

TNM staging classification had also undergone changes over the study period. However, the most recent and accepted classification was adopted in 2002. All cases were restaged according to this TNM classification of 2002, using the information available in the BCCR. Early stage was defined as Stage I (T1N0M0) and Stage II (T2N0M0) while late stage was defined as Stage III (T3N0M0 and T1 or T2 or T3N1M0) and Stage IV (T4N0 or N1M0, Any T, N2, or N3M0, Any T, any N, M1).

Identification of ethnic groups

Ethnicity was not recorded in the BCCR. Hence, this necessitated identification of SA and Chinese oral cancer cases by using previously generated ethnically sensitive surname lists. These lists had been previously generated using several resources (telephone directories, the Screening Mammography Program of BC, ethnic surname lists generated by other researchers in the UK and US, Naam Pehchaan software) and had been used in earlier BCCR population-based studies of other cancer sites[183,184]. Cases with oral cancer identified using these surname lists were then manually cross-checked and confirmed by experienced SA and Chinese researchers who were well versed in conducting research among ethnic groups. This process ensured that ethnic cases included in final analysis indeed represented the SA and Chinese ethnic populations.

Data analysis

Using this data, incidence and survival trends were determined by ethnicity and gender for OPC and OCC and its subsites, comparing the two time periods: 1980-1993 and 1994-2006 (for incidence) and 1994-2005 (for survival). Further details are described in both the incidence Chapter 4 and survival Chapter 5.

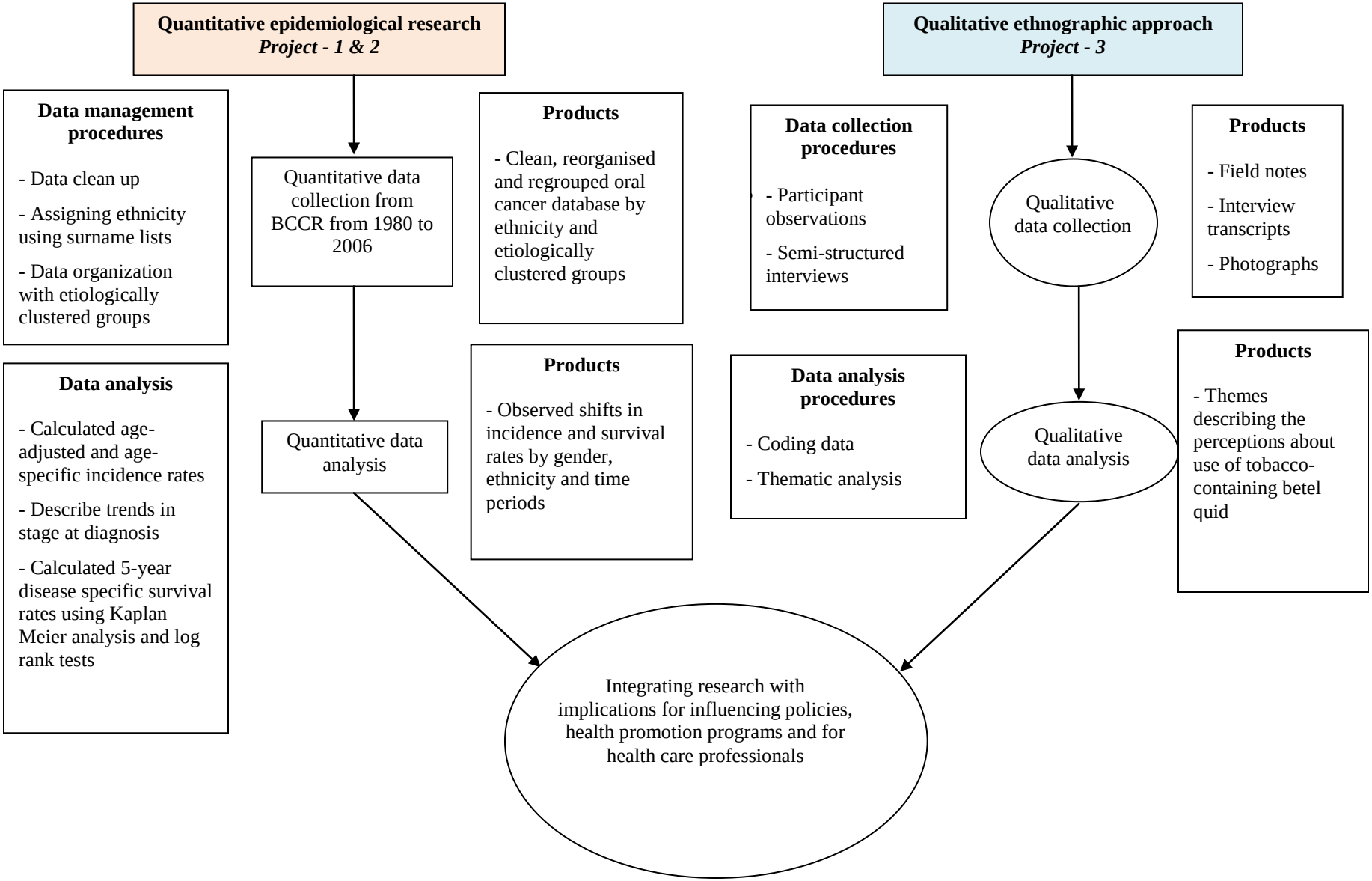
Data collection and analysis for the qualitative ethnographic study

Ethnographic research is particularly eclectic in its employment of multiple methods of data collection in natural settings[185,186]. This range of data collection methods allows for the researcher to triangulate, or cross check, the accuracy of collected data and analytical insights. Therefore, in the ethnographic study that comprised the last phase of this dissertation research, extensive field work was used in an SA community that included participant observations (documented with field notes and photographs) as well as semi-structured interviews. Data on the purchase of tobacco-containing BQ, its preparation and its marketing by the shopkeeper was collected by participant observations in one shop selling BQ. In addition, data on SA men's chewing habits, socio-cultural beliefs associated with chewing, factors influencing their choice of smoking or chewing, and what they liked or disliked about their chewing habits were collected by individual semi-structured interviews. Participants recruited for interviews met the following eligibility criteria: (1) self identification as SAs (whether immigrants or Canadian citizens); (2) voluntary agreement to participate in the study and to provide an informed consent form; (3) ability to converse in Punjabi, Hindi, or English, and (4) self-reported user of tobacco-containing BQ. Data collection and analysis occurred concurrently.

Data analysis

Ethnographic analysis of the field observations and semi-structured interviews involved a non-linear inductive process of coding, sorting, theorizing and reflecting upon the data and analytic process. N-Vivo computer software, designed specifically for qualitative research, was used to facilitate data management and analysis. The analytic process was also guided by gender-based analysis. In this approach, a gender lens was used to examine the data for the influence of gender roles and gender identities (e.g., related to masculinity) on health-related practices. Further details are described in Chapter 6.

Figure 1: Overall project research design



CHAPTER 4: TRENDS IN INCIDENCE OF OROPHARYNGEAL AND ORAL CAVITY CANCERS IN MULTICULTURAL POPULATION: THE BRITISH COLUMBIA EXPERIENCE

Introduction

There is growing recognition that the HPV status of head and neck tumours impacts biology, clinical features and outcome and that knowledge of such status could lead to new strategies for prevention and management[36,118,187-189]. In contrast to the clearly defined role of HPV in virtually all cases of cervical cancer, current evidence suggests that etiology of head and neck cancers is more heterogeneous, with HPV playing an essential role in some tumours and less of a role in others. For example, HPV-related cancers arise mainly from the tonsil, base of tongue and other oropharynx (hereafter termed OPC). HPV is less strongly associated with other oral sites, such as the ventrolateral tongue, gingiva, cheek, palate and floor of mouth (hereafter termed OCC) where tobacco and alcohol are major etiological factors[21,190].

Knowledge generated by examining trends in incidence rates for OCC and OPC may shed light on the burden of these cancers and differences in etiology in different ethnic populations. However, the breakdown of incidence rates for OCC and OPC is often lacking. Similarly, there is little such data reported for ethnic groups. Etiological factors are known to vary between and within countries. For example, the highest rates of OCC are in SA countries, which has been associated with BQ usage, a practice that preferentially targets the gingiva and cheek[21,160]. Studies of migrants have shown that cancer incidence often reflects that of their home country as they bring past exposures and lifestyle habits to their adopted country[20,40] and may contribute to variations within a country.

BC is ideally situated to investigate ethnic differences in OCC and OPC incidence because it is comprised of a largely multicultural population that is growing primarily through immigration, mainly from SA and China[184]. In this chapter data from the population-based BCCR was used to report on the temporal trends and incidence patterns for OCC and OPC between 1980 and 2006. This time period was selected because immigration became more common from India to BC after 1980. Our ultimate goal is to use this information as baseline data upon which a comprehensive oral cancer control plan can be created that includes tailored strategies for diverse population groups.

Materials and methods

Study population

Case selection

This study was approved by the research ethics board at the BC Cancer Agency. Cases were identified from the population-based BCCR for the period from 1980 to 2006, selecting for cases with a histological diagnosis of invasive SCC in the oral cavity or oropharynx, as defined by histology and site codes from the International Classifications of Diseases in Oncology, 3rd edition (ICDO-3). Histology codes included: 8050 to 8076, 8078, 80713, 80723, 80733, 80743, and 80833; site codes are listed in Table 4. (A description of the histology codes in provided in appendix C.)

Site codes C14.0 (pharynx not otherwise specified) and C14.8 (overlapping lesions of lip, oral cavity, and pharynx), totalling 179 and 4 cases, respectively, in the general population were excluded because these cancers may include naso- or hypopharynx. When

a patient had multiple cancers, only the primary cancer was considered. A total of 4,895 cases met the criteria and were included in the analysis. Registry data were collected on the cancer characteristics (site, histology, date of diagnosis) and patient's demographics (age, sex, given name, surname).

Identification of SA and Chinese ethnicity

Since ethnicity and place of birth are not recorded in the BCCR, SA and Chinese cases were identified from the 4,895 selected cases using previously generated ethnic surname lists[183,184]. When surnames of cases were found to match the ethnic surname list, these names were then manually verified by SA and Chinese researchers.

Data collection and statistical analysis

Age-adjusted incidence ratios (AAIR) and age-specific incidence rates (ASIR), with 95% confidence intervals (CI), were calculated separately for OCC and OPC. The AAIR were standardized to the 1991 BC general population and ASIR for ethnic groups were calculated using ethnic population data for 1991. In order to examine for temporal trends in incidence, AAIR were then calculated by year in the general population for the total time period 1980 to 2006 and the annual percent change (APC) in incidence rates was calculated for the entire time period from 1980 to 2006, and for the earlier and later time periods (from 1980 to 1993, and 1994 to 2006, respectively). These two time periods were selected to avoid any potential bias due to coding misclassification (ICDO coding changed in the early 1990s and the registry adopted the change after 1992) and to compare for temporal trends. APC was calculated by fitting a least squares regression line to the natural logarithm of the rates, using the calendar year as the regression variable and rejecting the hypothesis that

APC equalled 0 if the P-value was <0.05. The numbers of cases were too small to examine for temporal trends in the two ethnic groups.

Results

Of the 4,895 cancer cases identified in this study, 85 were from SAs and 133 from Chinese. A total of 1,801 (36.8%) were OPC and 3,094 (63.2%) were OCC in the general population, compared with 14 (16.5%) and 71 (83.5%) cases in SAs, respectively, and 37 (27.8%) and 96 (72.2%) cases in Chinese, respectively (Table 4).

Temporal trends in AAIR for OPC and OCC by sex in the general population

The temporal trends in AAIR for OPC and OCC in the general population are shown by sex in Figure 2. For men (Figure 2A), OPC showed a significant increase in AAIR from 1980 to 2006 (APC, 0.84; P < 0.001). The changes in AAIR were then compared in earlier (1980 to 1993) and later (1994 to 2006) time periods and significant increases were found in both periods, (APC, 0.61; *P* < 0.02 and APC, 0.87; *P* < 0.001 respectively), with a greater increase in the later period. In contrast, OCC showed a significant decrease in AAIR from 1980 to 2006 (APC, -0.63; *P* < 0.001). Initially, AAIR marginally increased in the earlier time period (APC, 0.25; *P* = 0.38) but then decreased in the later time period (APC, -0.42; *P* = 0.14). For most of the period from 1980 to 2006, AAIRs for OPC were lower than those for OCC; however, differences steadily narrowed and equalized in 2004. Notably in 2006, the AAIR for OPC surpassed OCC, at 4.08/100,000 and 3.00/100,000, respectively.

For women (Figure 2B), OPC showed a significant increase in AAIR from 1980 to 2006 (APC, 0.58; P = 0.001). The increase was not significant in the earlier time period

(APC, 0.46; P = 0.10); however, the increase was significant in the later time period (APC, 0.68; *P* = 0.01). OCC showed a non-significant increase in AAIR from 1980 to 2006 (APC, 0.04; *P* = 0.09). The increase was seen only in the earlier time period, (APC, 0.37; *P* = 0.19), which was then followed by a decrease in the later time period (APC, -0.05; *P* = 0.87). Men showed higher AAIRs than women for both OPC and OCC for all time periods examined (Figure 3A & B).

Temporal trends in AAIR for OPC and OCC by subsite and sex in the general population

The temporal trends in AAIR for OPC and OCC by subsites (Table 4) in the general population are shown by sex in Figure 4. In both sexes, the AAIRs for OPC were highest for tonsils, followed by base of tongue, and finally other oropharynx, while AAIRs for OCC were highest for ventrolateral tongue, floor of mouth, and finally cheek and gums.

For OPC in men (Figure 4A), the AAIR for all three sites increased significantly from 1980 to 2006: for tonsil (APC, 0.87; $P < 0.001$), for base of tongue (APC, 0.67; $P < 0.001$), and for other oropharynx (APC, 0.56; $P = 0.002$). Both earlier and later periods showed increases for all three sites; however, the increases were significant only in the later period for the tonsil (APC, 0.74; $P = 0.002$), and base of tongue (APC, 0.85; $P < 0.001$) but not for other oropharynx (APC, 0.18; $P = 0.55$). The increases in the earlier period were not significant for any of the sites (all $P > 0.05$). For OCC in men (Figure 5A), AAIRs increased significantly from 1980 to 2006 for ventrolateral tongue (APC, 0.47; $P = 0.01$) but decreased significantly for floor of mouth (APC, -0.56; $P = 0.002$) and cheek and gums (APC, -0.38; $P = 0.05$). The rates increased in both earlier (APC, 0.57; $P = 0.03$) and later

periods (APC, 0.37; *P* = 0.19) for ventrolateral tongue and decreased in both earlier (APC, -0.23; *P* = 0.44) and later (APC, -0.61; *P* = 0.02) periods for cheek and gum, while it increased in earlier (APC, 0.29; *P* = 0.31) but decreased in later (APC, -0.43; *P* = 0.12) periods for floor of mouth.

For OPC in women (Figure 4B), AAIRs increased for tonsil (APC, 0.36; *P* = 0.06) and base of tongue (APC, 0.24; *P* = 0.23), although not significant from 1980 to 2006, whereas the rate was stable for other oropharynx (APC, 0.02; *P* = 0.91). In the earlier period, there was a non-significant increase for tonsils (APC, 0.42; *P* = 0.12), and decreases for both base of tongue (APC, -0.34; *P* = 0.21) and other oropharynx (APC, -0.07; *P* = 0.78). In the later period, the AAIR showed non-significant increases for all three sites: ventrolateral tongue (APC, 0.38; *P* = 0.19), base of tongue (APC, 0.11; *P* = 0.78), and other oropharynx (APC, 0.55; *P* = 0.06). For OCC in women (Figure 5B), AAIRs increased non-significantly from 1980 to 2006 for ventrolateral tongue (APC, 0.30; *P* = 0.12) and cheek and gums (APC, 0.09; *P* = 0.62) but decreased significantly for floor of mouth (APC, -0.41; *P* = 0.03). The earlier time period showed non-significant increase for 3 sites: ventrolateral tongue (APC, 0.45; *P* = 0.11), floor of mouth (APC, 0.06; *P* = 0.82) and cheek and gum (APC, 0.22; *P* = 0.43). The later time period showed non-significant decrease for ventrolateral tongue (APC, -0.15; *P* = 0.61) and for floor of mouth (APC, -0.13; *P* = 0.65) but marginal non-significant increase for cheek and gums (APC, 0.08; *P* = 0.78).

AAIR for OPC and OCC by subsite, sex and ethnicity

For OPC, the AAIR in men was highest in Chinese, followed by the general population, and lowest in SA (Table 5). The highest AAIRs were found in the tonsil for

both Chinese and general populations. AAIRs in women were highest in the general population. For OCC, the AAIR in men were highest in SA, followed by Chinese, and lowest in the general population. On examining specific OCC subsites in men, the highest AAIRs were found in the ventrolateral tongue for both general and Chinese populations. Of note, the highest AAIR in SA men was found in the cheek and gums. The highest AAIR in women was found in Chinese, followed by SA, and last the general population. On examining specific OCC subsites in women, the highest AAIRs were found for the ventrolateral tongue in all 3 population groups. Of interest, the AAIR for cheek and gums was higher in SA women than in Chinese women and in the general female population.

ASIR for OPC and OCC by subsite and sex in the general population

Figure 6 and Figure 7 shows ASIR for OPC and OCC by topographic site and sex. For OPC, the ASIRs were very low for young people 35 to 44 years of age and younger, and rose with age, reaching the highest ASIRs between the ages of 55-64 years for both men (11.1/100,000; 95% CI, 10.0 - 12.1) and women (3.9/100,000; 95% CI, 3.3 - 4.6). On examining specific OPC subsites in men (Figure 6A), peak ASIRs were found for the age group 65-74 years for the base of tongue (4.9/100,000; 95% CI, 4.1 - 5.7) and other oropharynx (1.6/100,000; 95% CI, 1.2 - 2.1), whereas they occurred one decade earlier, at 55-64 years, for the tonsil (6.0/100,000; 95% CI, 5.2 - 6.8). Similar findings were noted in women (Figure 6B): peak ASIRs were found for the age group of 65-74 years for the base of tongue (1.6/100,000; 95% CI, 1.2 - 2.0) and other oropharynx (0.6/100.000; 95% CI, 0.3 - 0.8), and one decade earlier, at 55-64 years, for the tonsil (2.1/100.000; 95% CI, 1.6 - 2.5).

For OCC, ASIRs in men steadily increased with age, reaching the highest ASIR between the ages of 65-74 years and then plateauing (Figure 7A). On examining specific OCC subsites in men, the highest incidence was in the age group of 65-74 years for tongue (5.5/100,000; 95% CI, 4.7-6.4) and floor of mouth (4.6/100,000; 95% CI, 3.8-5.3), while for cheek and gums it was at 75 years and above (5.4/100,000; 95% CI, 4.4-6.5). The ASIRs in women continued with a sharp increase with increasing age (Figure 7B). The highest incidence in women by subsite was in age group 75 years and above for tongue (4.6/100,000; 95% CI, 3.8-5.5) and for cheek and gums (5.7/100,000; 95% CI, 4.8 - 6.6), while it was in 65-74 years for floor of mouth (2.0/100,000; 95% CI, 1.6 - 2.5).

For mean age, those with OCC were significantly older than those with OPC in both men (62.2 ±12.8 years vs. 60.5±10.8 years, respectively) and women (67.3 ±14.3 years vs. 63.3±11.95 years, respectively), both $P < 0.001$.

ASIR for OCC by ethnicity

Figure 8 shows the ASIR for OCC in SA, Chinese and the general population. In both sexes, ASIRs were similar in all three populations up to the age group of 45-54 years. For men, ASIRs continued to increase, peaking at the age group of 65-74 years in all three population groups, with the greatest rise in ASIR in SA (37.7/100,000; 95% CI, 19.1 - 57.1). After age 74, ASIRs slightly decreased in the Chinese and general population but sharply fell in SA. For women, ASIRs showed a steady increase with increasing age in Chinese and the general population; however, ASIRs rose sharply to reach peak at the age group of 65-74 years (25.4; 95% CI, 11.0 – 39.0) in SA, followed by a sharp fall. The numbers of cases were too low to examine ethnicity in OPC or specific subsites of OCC.

Discussion

Recent epidemiological, pathological and molecular studies have led to a growing acceptance of the involvement of HPV in the etiology of head and neck tumours and the need to consider such exposures along with conventional risk factors. There is growing evidence of decreasing incidence for OCC and increasing incidence for OPC that may reflect changes to behaviours: the former associated with changes in tobacco consumption, the latter associated with HPV infection. A recent Surveillance Epidemiology and End Results (SEER) study in the US showed an increase in incidence for OPC, with equalization in incidence rates for OCC from 1973 to 2004[36]. Results of this research not only support these findings but also, for the first time, show that the incidence of OPC has now surpassed OCC in men. A similar less dramatic but increasing trend was also found in women.

The finding of a decrease in the incidence of OCC reflects a decreased tobacco consumption several decades earlier, for the effects of tobacco on cancer incidence can only be observed after a latency period of about 25 years[191]. In fact, smoking rates in Canada from 1965 to 1991 (Figure 9) have shown a sharper decline in men (-52.4%) than women (-21.3%), supporting the observation of a more significant fall in incidence for OCC in men than in women in recent years. Since there has been a further continued decline in smoking rates in BC, a continued decline in incidence of OCC in the coming years could be expected. Of interest, rates are stable or declining for all OCC subsites, except ventrolateral tongue, in both sexes.

In contrast, an increase was found in incidence of OPC. These cancers are primarily caused by HPV infection that may be transmitted through oro-sexual practices[192].

Increasing social acceptance of premarital sex, multiple sex partners and oral sex over the last several decades[193-195] have likely contributed to increased oral HPV infection. In support of this possibility, a recent US study has reported an association between oral sex and open-mouthed kissing with the development of oral HPV infection[130]. The increase in incidence for OPC may continue for some time, although the advent of HPV vaccination in women may result in a decline in incidence for OPC in several decades, at least in women.

The findings support the importance of including sex in studies of these cancers. While some studies do not report incidence rates separately for sex[36], the studies that do report rates separately for sex show that incidence rates for males are increasing[6,189] but for females rates are either increasing at a slower pace[6] or stable[189]. In addition, it is important to consider both age and subsite when examining incidence patterns. The results showed that OPC was diagnosed at younger ages than OCC in both sexes. This observation has been reported elsewhere[36,189].

Since there is wide variation in incidence of OPC and OCC by subsite in different geographical regions around the world[196,197], and since countries like Canada are growing mainly through immigration, it is important to examine for ethnic differences in OCC and OPC rates to help the development of cancer control programs. BC is ideally situated to investigate such change since it is comprised of a largely multicultural population that is growing mainly through immigration from SA and China. In fact, the population growth rates in Canada for SA and Chinese were 37.7% and 18.2%, respectively, between 2001 and 2006[19]. By using ethnic surname listings, incidence rates could be examined for OPC and OCC in SA and Chinese. Again, ethnic differences in cancer incidence were found by sex:

men were at much higher risk than women for both OPC and OCC in both ethnic groups, which is consistent with findings reported from most other countries around the world[6,36,118,125,187,189,197]. Increased incidence in men has been largely attributed to heavier indulgence in risk behaviours like smoking, alcohol and oro-sexual practices[189,197]. However, sex differences in the ethnic groups must be interpreted with caution because this area has received little investigation and the numbers of cases were small in this study, especially for SA.

There is a shortage of high-quality data on oral cancer incidence in Asia Pacific regions, including China[196]. This may partially explain the reports of very high smoking rates and yet very low incidence rates of OCC in China[196,198,199]. The observed decline in AAIR for OCC in the BC general population may not hold true for SA and Chinese because in their countries of origin tobacco consumption rates are not declining but increasing, especially among young adults who may continue their risk behaviour even after immigration to Canada. In fact, higher AAIR was found for OCC in both SA and Chinese than the general population in both sexes. The sharp rise in tobacco usage in India and China in recent years may result in a further increase in AAIR for OCC in the immigrant populations from these countries into Canada in the coming years, in contrast to the declining AAIR trend in the BC general population.

Another interesting observation in this study was that not only did SA men have the highest AAIR for OCC, but these cancers were most frequently seen in the cheek and gums (rather than the ventrolateral tongue and floor of mouth as seen in the Chinese and general populations). A predilection for the cheek and gum in OCC was also found for SA females.

This observation would support the hypothesis that there is a high prevalence of BQ and smokeless tobacco usage in the SA population in BC. Studies from the UK[20,40,200] have also reported higher incidence of these cancers among SA immigrants, and a report from the US suggests that SA immigrants continue chewing BQ after immigration[54].

Highest AAIR for OPC were found in Chinese men, despite some pathological and molecular studies that have shown the absence of HPV in tonsillar cancers of Chinese patients[201]. The lowest AAIR for OPC was found in SA in both sexes, which may be explained in part by less social acceptance for premarital sex among SA, resulting in lower HPV infection[202].

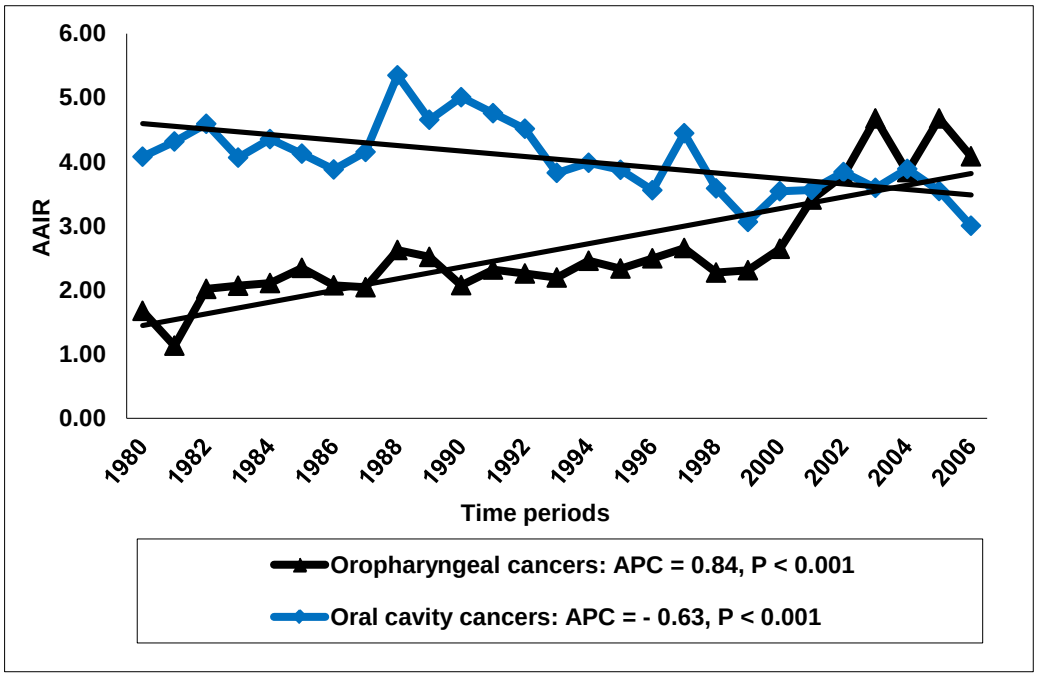
This study had several strengths: an established long-term population-based cancer registry, a multicultural province with large SA and Chinese populations, and a recently established provincial oral cancer screening program. A limitation reported previously[189] was the possible effect of changes in registry coding classification from ICDO-01 to ICDO-02 in the early 1990s, but interestingly rates for OPC increased in the later time period when there was no coding difference. However, cancer registry staff assured us that the older classification systems were transferred appropriately to the new coding system. Another limitation was the use of surname listings to identify SA and Chinese instead of ethnicity data. The numbers of identified cancer cases might be underestimated due to omission of surnames that are shared between Anglo-Asians and other ethnic groups (e.g., British), the omission of Muslims names, interracial marriages, and misspellings of surnames in cancer registry database. However, this methodology has been previously used by us[183,184,203] and is widely accepted[20,200,204,205]. A third limitation is the high likelihood that not all cancer

cases within the SA and possibly Chinese immigrant populations were reported in the provincial cancer registry. Dentists play a major role in detection of oral cancer in BC; however, many elderly Chinese immigrants do not access dental services in Canada[206] and field observations and interviews among the SA population by one researcher (AA) suggest that dental care is often sought for fiscal reasons back in India; therefore these cancers would not be registered in BC, resulting in an underestimation of cancer cases in these populations. A fourth limitation is an inability to comment upon any differences in cancer rates in first or subsequent generations. Country of birth or immigration status is not recorded in the cancer registry. A final limitation is the lack of determination of HPV status at the anatomical site where the cancer developed. A recent study on tonsillar carcinomas from Sweden reported an increasing incidence in OPC cancers from 1970-2007[6,125], with molecular analysis showing a majority of these cancers were associated with HPV infection[125,207].

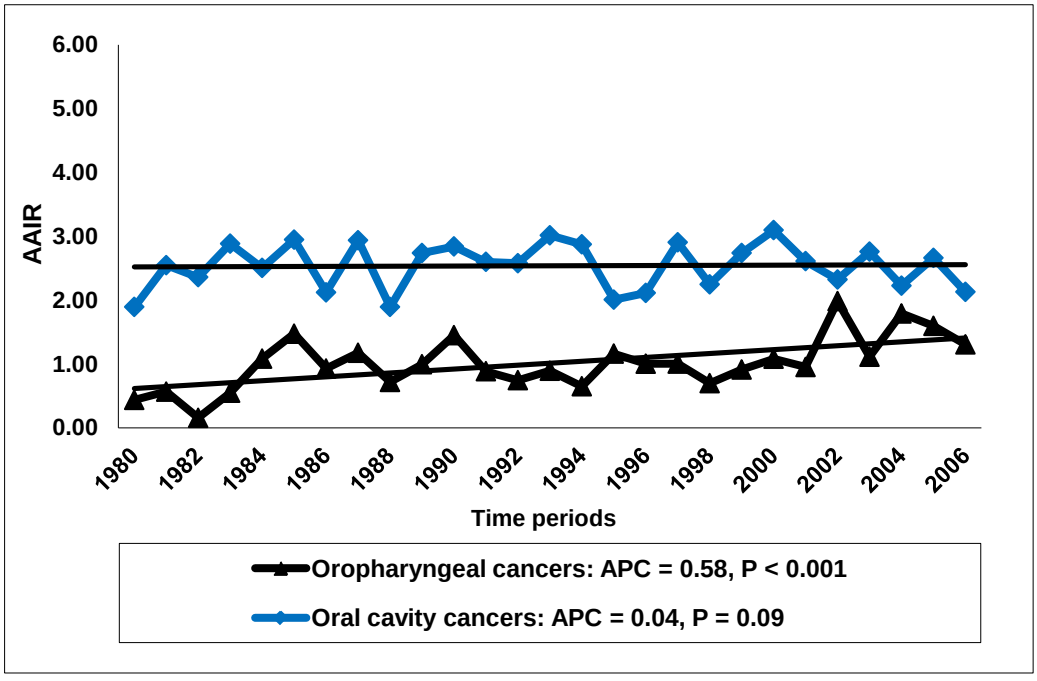
In conclusion, these study results have for the first time shown that the incidence of OPC has now surpassed OCC in the BC male population. Ethnic minorities in BC are at higher risk for both OPC and OCC among men and OCC among women. There is a need for more targeted culturally appropriate oral cancer prevention programs.

Figure 2: Age-adjusted incidence rates (AAIR) for oropharyngeal and oral cavity cancers from 1980 to 2006: (A) for men and (B) for women in the total study population.

(A)



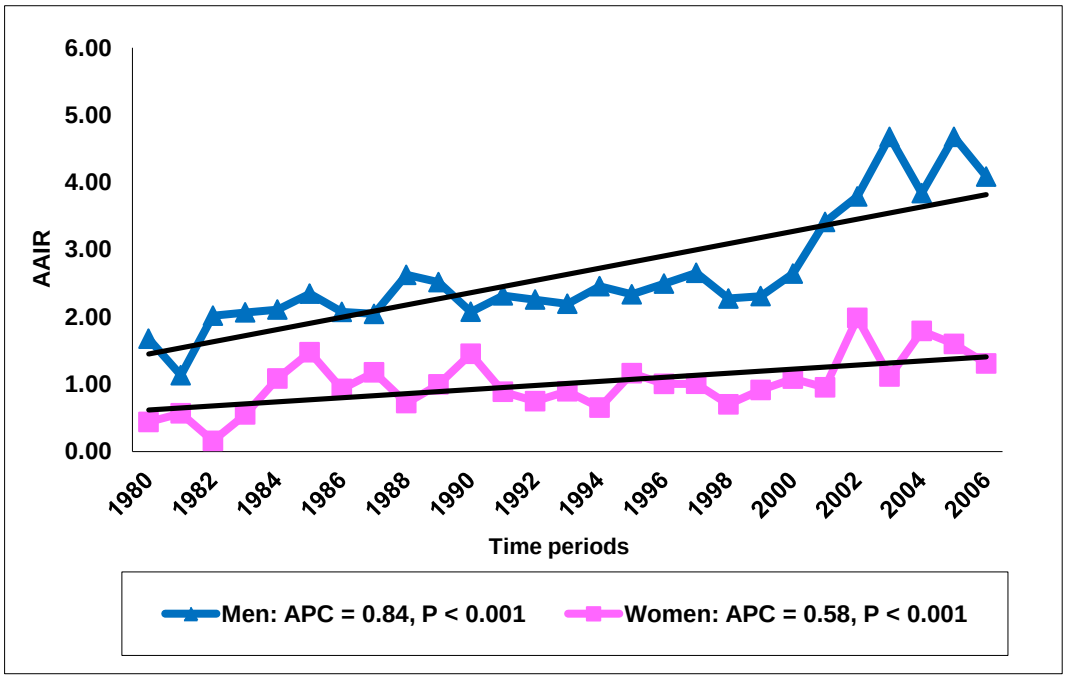
(B)



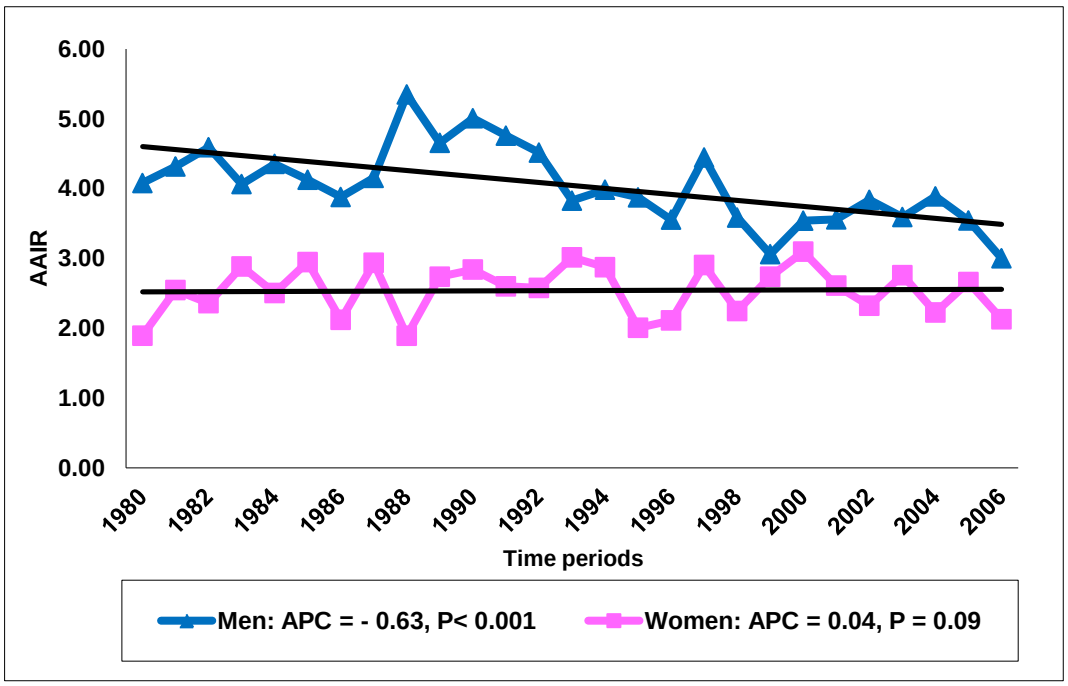
* Rates are per 100,000 populations and are age adjusted to the 1991 BC general population. APC (annual percentage change); APC is significantly different from 0 ($P < 0.5$).

Figure 3: Age-adjusted incidence rates (AAIR) in men and women from 1980 to 2006: (A) oropharyngeal cancers and (B) oral cavity cancers in the total study population.

(A)



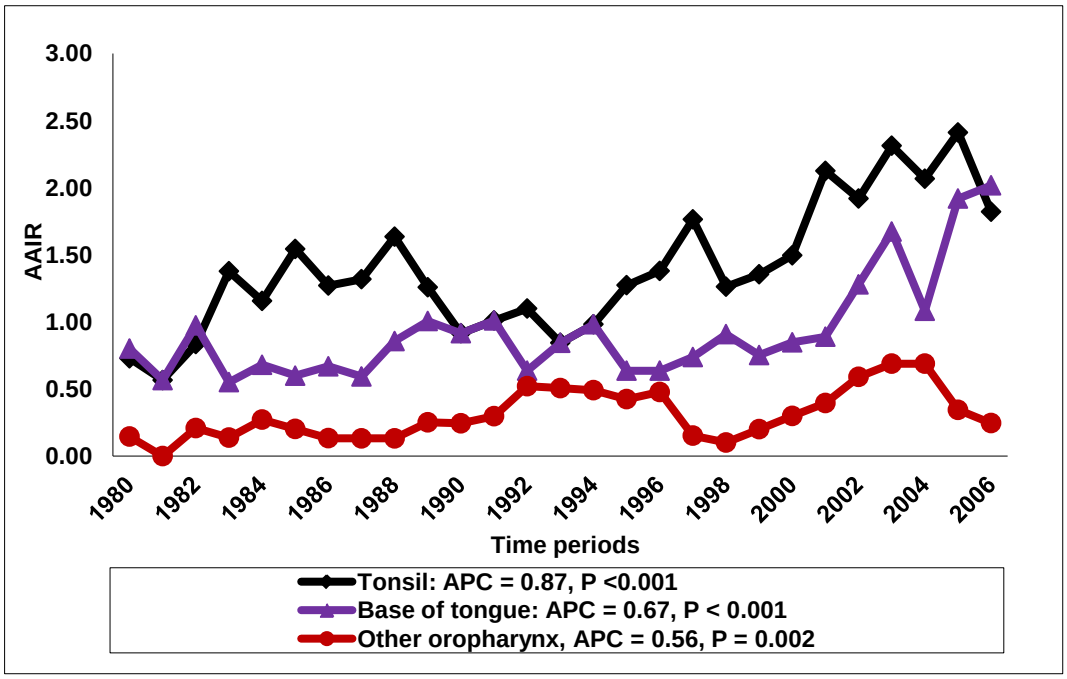
(B)



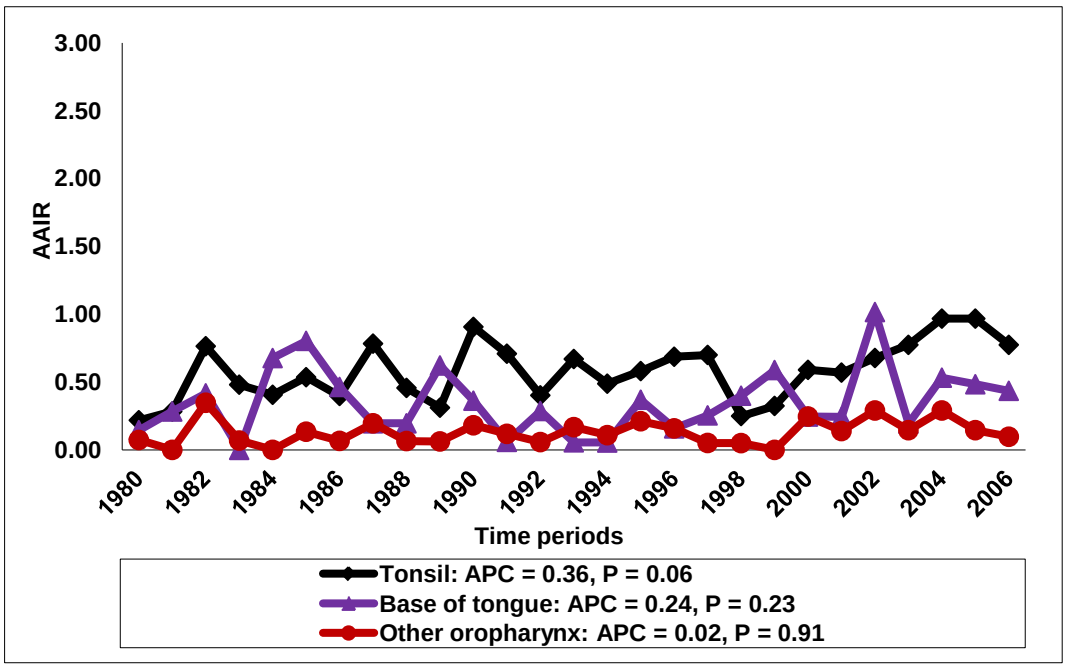
* Rates are per 100,000 populations and are age adjusted to the 1991 BC general population. APC (annual percentage change); APC is significantly different from 0 (P < 0.5).

Figure 4: Age-adjusted incidence rates (AAIR) for oropharyngeal cancer subsites from 1980 to 2006: (A) for men and (B) for women in the total study population.

(A)



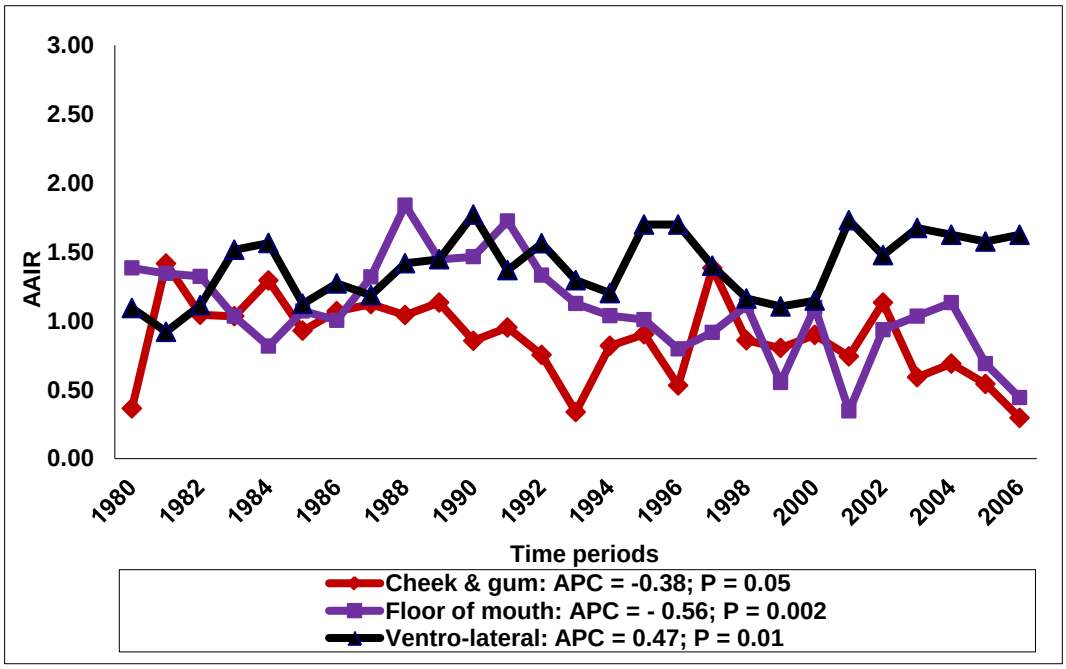
(B)



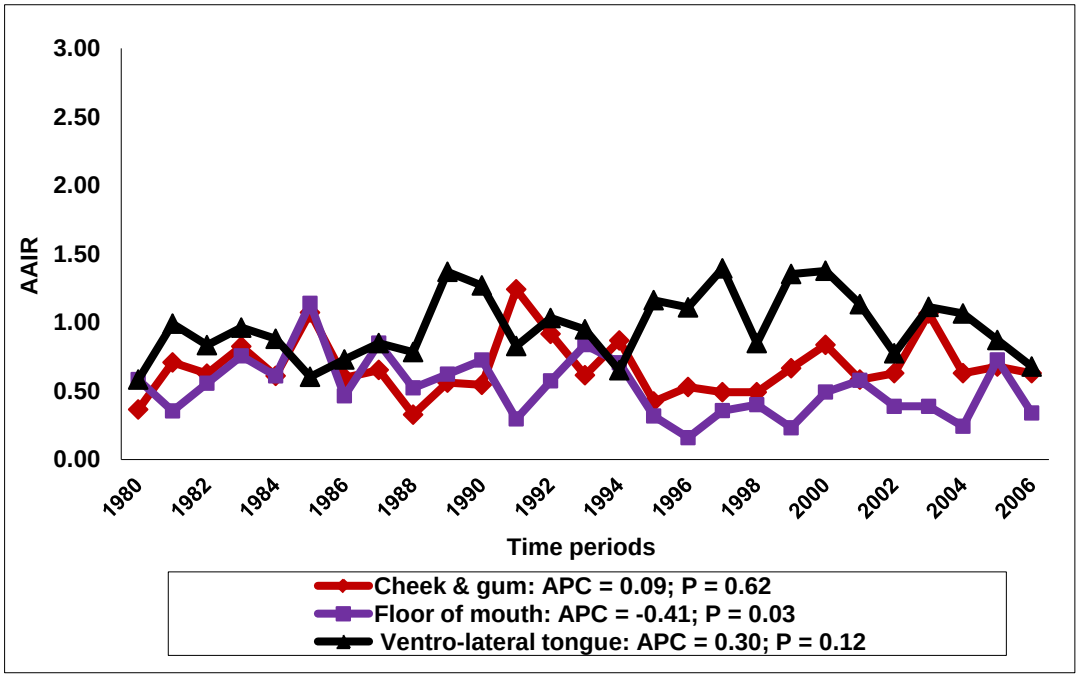
* Rates are per 100,000 populations and are age adjusted to the 1991 BC general population. APC (annual percentage change); APC is significantly different from 0 ($P < 0.5$).

Figure 5: Age-adjusted incidence rates (AAIR) for oral cavity cancer subsites from 1980 to 2006: (A) for men and (B) for women in the total study population.

(A)



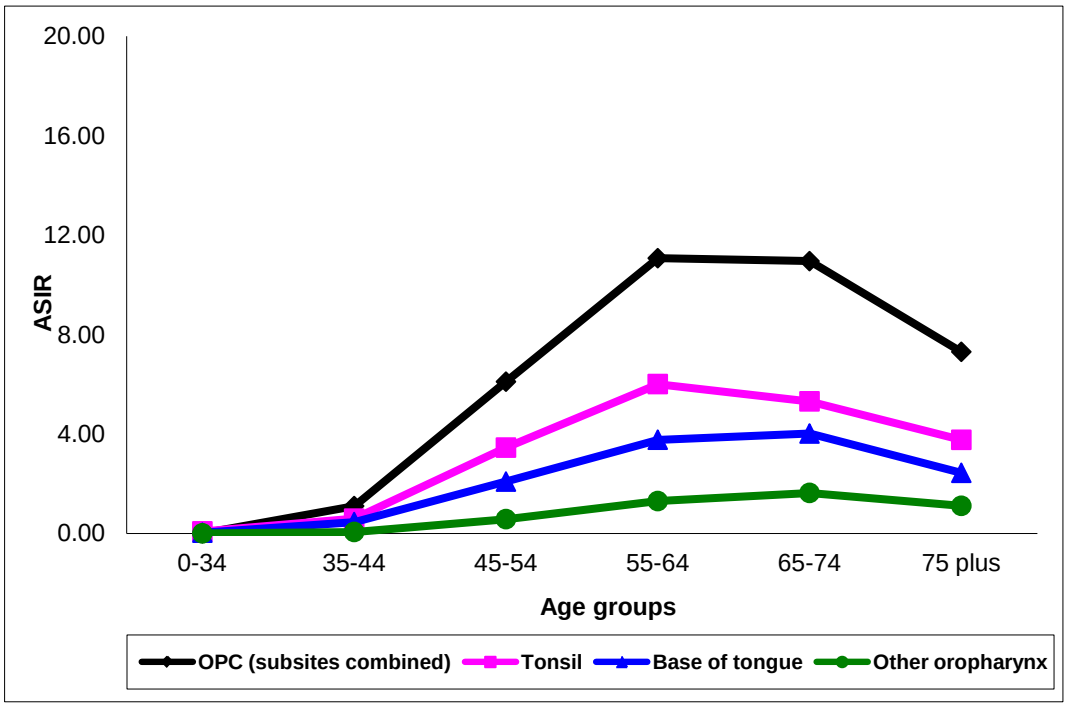
(B)



* Rates are per 100,000 populations and are age adjusted to the 1991 BC general population. APC (annual percentage change); APC is significantly different from 0 ($P < 0.5$).

Figure 6: Age-specific incidence rates (ASIR) for oropharyngeal cancers and its subsites from 1980 to 2006: (A) for men and (B) for women in the total study population.

(A)



(B)

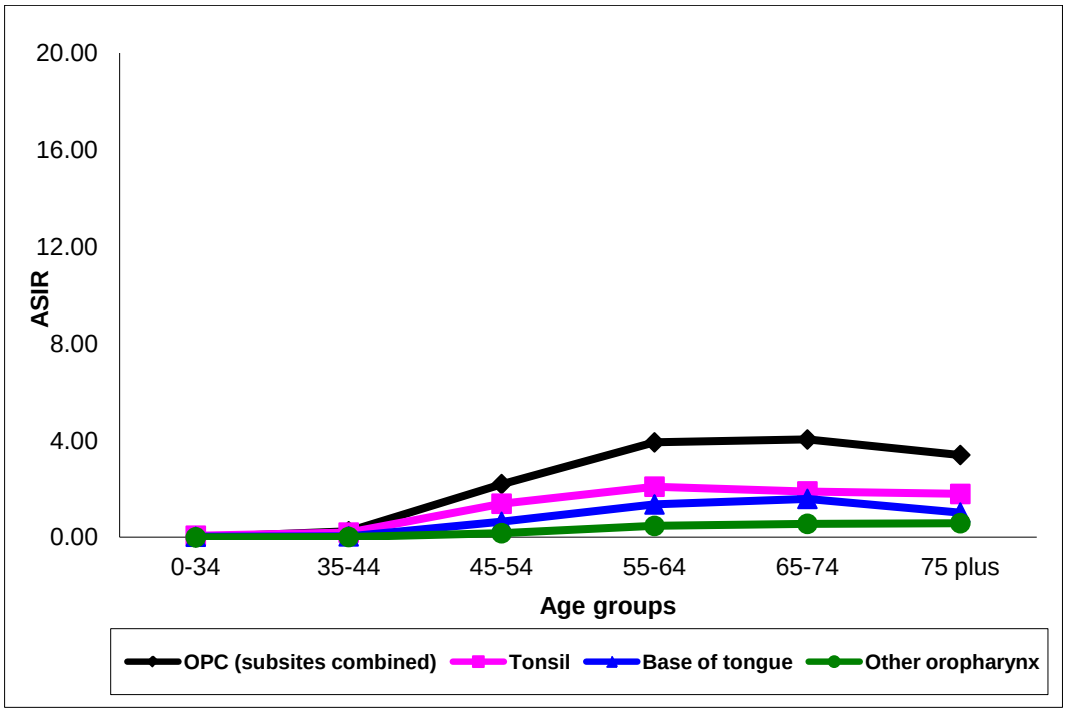
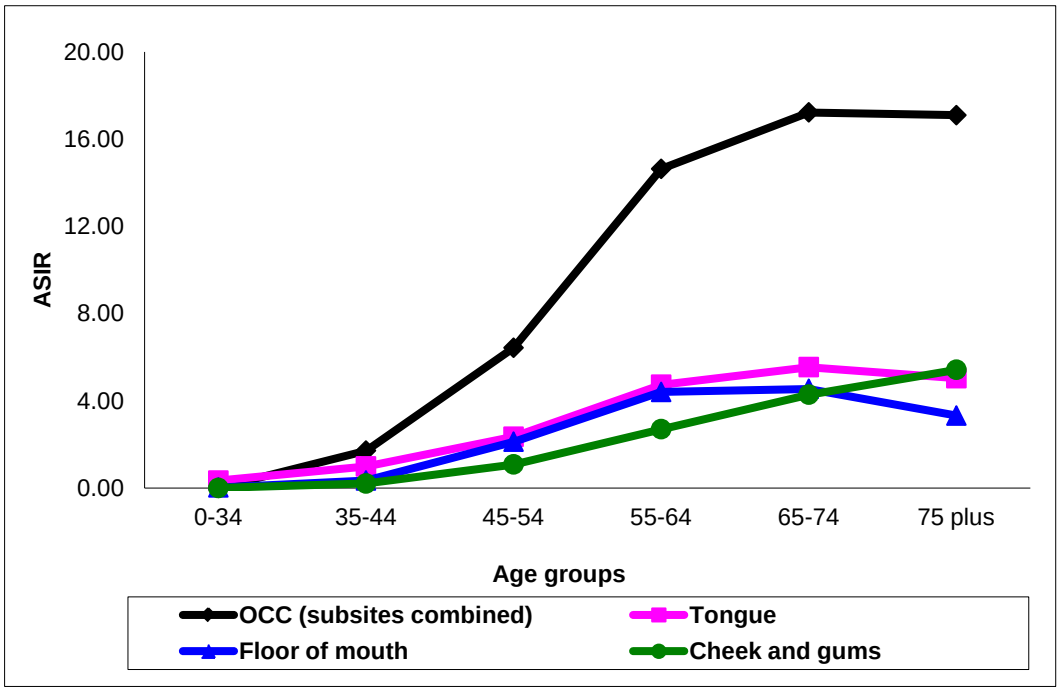


Figure 7: Age-specific incidence rates (ASIR) for oral cavity cancers and its subsites from 1980 to 2006: (A) for men and (B) for women in the total study population.

(A)



(B)

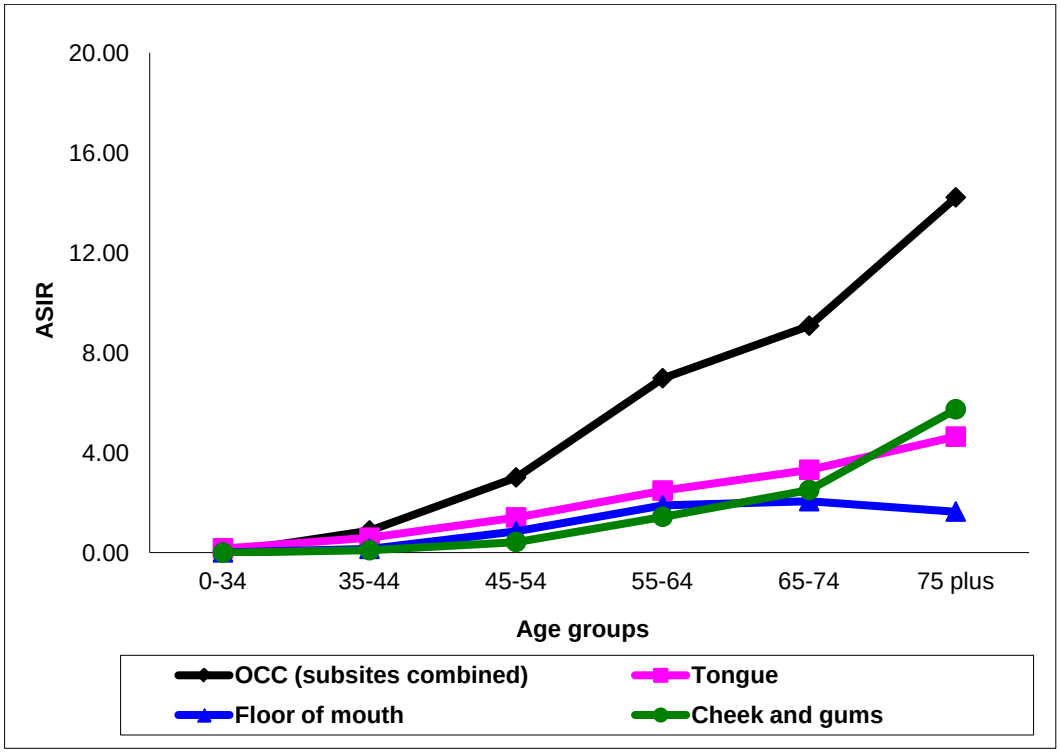
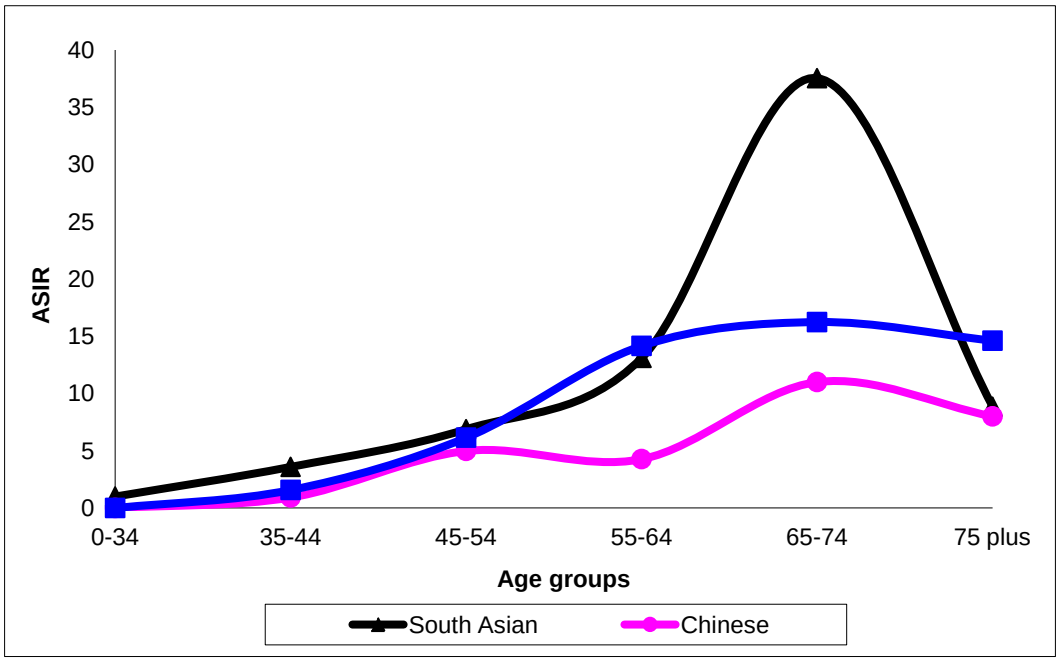


Figure 8: Age-specific incidence rates (ASIR) for oral cavity cancers by ethnicity from 1980 to 2006: (A) for men and (B) for women in the total study population.

(A)



(B)

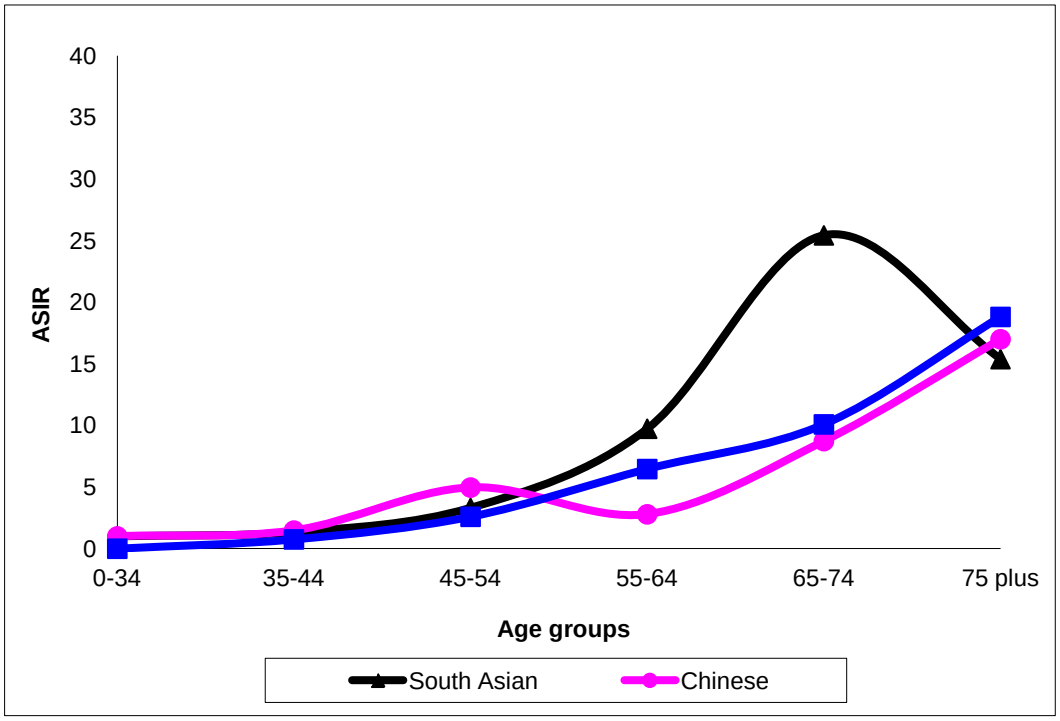
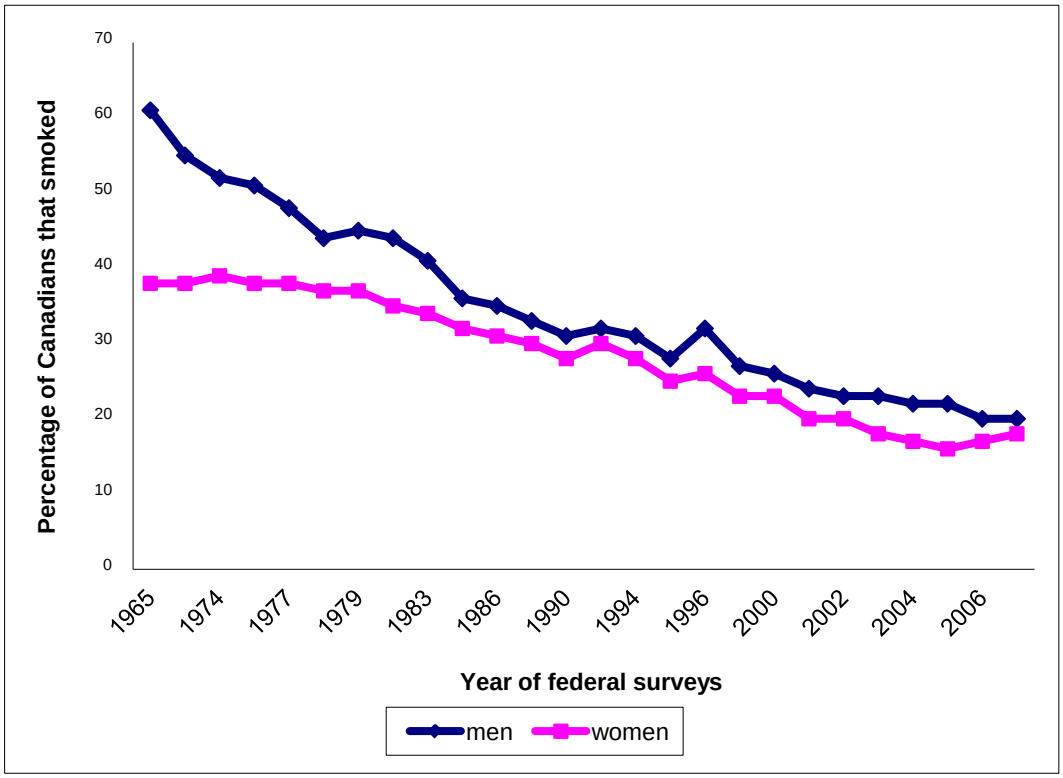


Figure 9: Prevalence of smoking rates in Canada from 1965 to 2007 (Data accessed from http://www.smoke-free.ca/factsheets/pdf/prevalence.pdf).



(**Prevalence rates are people aged 15 years and above who were either a daily or occasional smokers.)

Table 4: Numbers of cases at different subsites for oropharyngeal and oral cavity cancers in the general population, South Asian (SA) and Chinese from 1980 to 2006 in the total study population.

ICDO-3 Code	Site descriptions	No. of cases in general population	No. of cases in SA	No. of cases in Chinese
Total number of cases		4895	85	133
Oropharyngeal cancers				
C09.0, C09.1, C09.8, C09.9	Tonsil	963	6	17
C01.9, C02.4	Base of tongue	623	7	16
C10.2, C10.3, C10.8, C10.9	Other oropharynx	215	1	4
Total		1801	14	37
Oral cavity cancers				
C02.0-02.3, C02.8, C02.9	Ventrolateral tongue	1134	31	59
C03.0-03.1, C03.9, C06.0-06.2	Gum and cheek	734	30	17
C04.0-04.1, C04.8-04.9	Floor of mouth	746	3	13
C00.3-00.5, C05.0, C06.8-06.9, C05.1-05.2, C05.8-05.9	Other mouth (mucosa of lip, soft and hard palates and others)	395	7	7
Total		3094	71	96

Table 5: Age-adjusted incidence rates (AAIR) for oropharyngeal and oral cavity cancers by subsite, sex and ethnicity from 1980 to 2006 in the total study population.

	General population			**South Asians**			**Chinese**		
	N	**AAIR**	**95%CI**	**N**	**AAIR**	**95%CI**	**N**	**AAIR**	**95%CI**
Oropharyngeal cancers (sites combined)									
Men	1285	2.9	1.2-4.7	8	0.9	0-2.3	31	3.6	1.3-5.7
Women	516	1.2	0.1-2.3	6	0.7	0-1.7	6	0.5	0-1.8
Specific sites									
Tonsils									
Men	682	1.6	1.3-1.8	4	NA	NA	15	1.7	0-3.4
Women	281	0.6	0.4-0.8	2	NA	NA	2	NA	NA
Base of tongue									
Men	450	1.0	0.8-1.2	3	NA	NA	12	1.1	0-2.3
Women	172	0.4	0.2-0.5	4	NA	NA	4	NA	NA
Other oropharynx									
men	152	0.3	0.2-0.4	1	NA	NA	4	NA	NA
Women	63	0.1	0.0-0.2	0	NA	NA	0	NA	NA
Oral cavity cancers (sites combined)									
Men	1886	4.3	3.8-4.7	42	5.6	2.1-9.8	47	5.1	1.6-8.5
Women	1208	2.7	2.3-3.0	29	4.4	1.8-7.8	49	5.3	2.0-8.6
Total	3094			71			96		
Specific sites									
Ventrolateral tongue									
Men	668	1.5	0.9-1.2	18	2.3	0.2-4.7	30	2.5	0.3-4.7
Women	466	1.1	0.4-0.8	13	1.9	0.1-4.0	29	2.9	0.5-5.3
Total	1134			31			59		
Floor of mouth									
Men	501	1.2	0.8-1.4	1	NA	NA	9	1.1	0-2.6
Women	245	0.6	0-0.7	2	NA	NA	4	NA	NA
Total	746			3			13		
Cheek and gums									
Men	404	0.9	0.7-1.1	20	2.8	0.5-5.5	7	0.7	0-1.6
Women	329	0.7	0.3-0.9	10	1.6	0.01-3.6	10	1.2	0-2.6
Total	733			30			17		
*NA- Not Available as the numbers of cases were less than 5.									

CHAPTER 5: GENDER AND ETHNICITY SPECIFIC SURVIVAL TRENDS OF OROPHARYNGEAL AND ORAL CAVITY CANCERS IN BRITISH COLUMBIA

Introduction

The etiology of oral cancer has changed in developed countries as tobacco usage has declined. Increasing attention is now being placed on the role of human papillomavirus (HPV) infection. In a recent hallmark study, Chaturvedi[36] et al examined changes in the incidence and survival of oral cancer in the US from 1973 to 2004. They used reported differences in HPV association at specific anatomic sites to classify cancers into two categories: oropharyngeal cancers (OPC: tonsils, base of the tongue and other oropharyngeal subsites), which are more strongly associated with HPV infection, and oral cavity cancers (OCC: ventrolateral tongue, gum, cheeks, floor of the mouth, palate and lips), which are less strongly associated with HPV. They reported a significant increase in the relative proportion of OPC to OCC cancers and a striking improvement in survival rates for OPC[36]. Subsequently, a molecular epidemiological study by this group has provided strong evidence that recent changes in incidence and survival of OPC in the US are caused by HPV infection[126]. This was attributed to coincidental changes in smoking and sexual behaviours[126].

This has become a very active area of research. Since the Chaturvedi et al publication there have been reports of change in incidence for OPC or its subsites from many countries[6-15,35].

Interest in these shifts in incidence is driven by results from case-control and observational studies that suggest that the presence of HPV in tumours can have a profound effect on survival, although smoking history still contributes to outcome even among HPV-related cancers[138-141]. There are 5 major reports in the literature of trends in survival rates for OCC and OPC from population-based cancer registries, two from the US[35,36], and one each from Canada[37], Germany[13] and Sweden[38]. The data in these publications suggest that OCC and OPC survival rates have improved in the US, Canada and Sweden among both men and women and remained stable in Germany. However, there were limitations to these comparisons. For example, one study only reported temporal trends in overall 2-year survival rates with and without radiation treatment[36], while the other studies reported 5-year survival rates but did not include data separately for all OPC and OCC subsites[13,37,38]. Importance of further breakdown by gender and ethnicity was shown by one recent study from the US, in which differences were found in incidence and survival rate among Blacks and Whites by gender[35].

In Chapter 4, a parallel study was performed in BC to that done by Chaturvedi[36] et al using the BCCR to explore changes in incidence and survival of OPC and OCC in BC with respect to HPV involvement, gender and ethnicity[208]. The BC population of approximately 4.1 million persons is well placed for a study of ethnicity. Currently nearly a quarter of individuals belong to a visible minority[18], the two largest groups being SA and Chinese, and this proportion is expected to increase dramatically in the coming years[18,209]. Oral cancer cases were clustered into OPC and OCC. The incidence of OPC was seen to increase in both genders; however, this increase was more dramatic in men, where it surpassed OCC. Also noted was a higher incidence of OCC amongst SA men and women and a higher incidence of OPC amongst

Chinese men[208]. In this chapter, the same population-based data on oral cancer from the BCCR was used to examine survival rates for OPC and OCC by gender, ethnicity and stage of disease, also determining rates for subsites within these two groupings. The data show that both gender and ethnicity are important when examining temporal shifts in incidence and survival and that gender differences become more apparent with subsite analysis.

Materials and methods

Study population

The BCCR records more than 95% of all the cancer cases in the province and captures death data from provincial vital statistics. Using data from this registry, all incident cases of oral cancer diagnosed between 1980 and 2005 were identified and followed to December 31, 2005. A total of 4,649 primary cases were identified with a confirmed histological diagnosis of invasive squamous cell carcinoma, using International Classifications of Diseases in Oncology, 3rd edition (ICDO-3) histology codes: 8050 to 8076, 8078, 80713, 80723, 80733, 80743, and 80833. These cases were then placed into two etiologically clustered groupings, OPC and OCC, based upon the association with HPV infection[36,208], resulting in 1,705 cases of OPC and 2,944 cases of OCC. The histological codings for OPC included base of tongue (C01.9, C02.4), tonsils (C0.90, C09.1, C09.9), and other oropharynx (C10.2, C10.3, C10.8, C10.9); and for OCC included ventrolateral tongue (C02.0-C02.3, C02.8, C02.9), gingiva (C03.0-C03.9, C06.2), cheek (C06.0, C06.1), palate (C05.0- C05.9), and floor of mouth (C04.0-C04.9). These groupings of anatomic sites are described more fully in Chapter 4.

Data collection and statistical analysis

Registry data were collected on cancer characteristics (anatomic site, histology, date of diagnosis, tumour stage), patient demographics (name, age, gender) and vital statistics (date of death, cause of death) for the primary oral cancer. The registry records the clinical parameters of T, N and M (tumour size, nodal status, and metastasis, respectively); these were used to determine stage at diagnosis according to the American Joint Committee of Cancer classification of 2002[210]. Early stage (localized disease) was defined as Stage I (T1, N0, M0) or Stage II (T2, N0, M0), and late stage (distant and metastatic disease) was defined as Stage III (T3, N0, M0 or T1-3, N1, M0) and Stage IV (T4, N0, M0 or T1-4, N2- 3, M0 or T1-4, N1-3, M1). The data were checked for completeness; duplicate records and recurrences were removed; and discrepancies were corrected with the assistance of registry staff.

As with most cancer registries, ethnicity was not recorded in the BCCR database. Previously constructed SA and Chinese surname lists were used to assign ethnicity to the OPC and OCC cases, which were manually verified by SA and Chinese researchers. This method has been successfully used to identify ethnic groups in other registry-based studies[183,184,205,211]. The research ethics board at the BC Cancer Agency approved this study.

Disease-specific survival rates were determined separately for OPC and OCC from the date of diagnosis to the date of death from oral cancer, or to the date of censorship (31st December, 2005). Cases were censored at the last date that they were known to be alive or at their date of death from other causes. These rates were analyzed by gender, ethnicity (SA, Chinese, and the general population, with the latter excluding SA and Chinese),

subsites, stage at diagnosis (early- and late-stage) and nodal status using Kaplan-Meier curves with log-rank tests. In addition, actuarial life tables were stratified by gender and calendar period of diagnosis and were used to calculate 5-year survival rates with 95% confidence intervals (CI) for OPC and OCC cases by gender, subsites, stage at diagnosis and nodal status. Temporal trends in these 5-year disease specific survival rates were examined by gender by comparing the two time periods: 1980-1993 and 1994-2005. 1993 was the mid-point of the study and was used in a previously published incidence paper[208]. Frequency distributions in the stage at diagnosis (early-, late-stage) were then determined separately for OPC and OCC by ethnicity from 1980-2005 and tested for significance using the Chi-square test. Temporal trends in staging distributions were examined by gender and subsites for the total study group, as the numbers were too small to look at trends by ethnicity.

All analyses were done using Statistical Package for Social Sciences (SPSS) version 18; all statistical tests were two-sided, and a P value of 0.05 or less was considered statistically significant.

Results

Temporal trends in survival rates

Survival rates of OPC and OCC were compared in the overall time period from 1980 to 2005 and then a temporal analysis was done by examining rates in two time periods (1980-1993 and1994-2005). The overall analysis showed that there was significantly better survival for OCC than OPC, and that this was apparent in both men (P = 0.002, Figure 10A) and women (P = 0.02, Figure 10B). However, survival in males and females did not differ

significantly for either OPC or OCC (Figure 10C and D, Table 6). Gender difference became apparent for both cancer groupings when the two time periods were examined (Figure 11A-D, Table 7). The survival rates for OPC improved in the second time period (1994-2005), although this improvement was statistically significant only in men ($P< 0.001$, Figure 11A). In contrast, the survival rates for OCC showed a non-significant decrease among men in the second time period (1994-2005, Figure 11C). For women survival rates in the two time periods were stable (with only 0.6% increase observed in the 5-year survival rate in the second time period, Figure 11D, Table 7).

Temporal trends in survival rates by subsites

Survival rates were further compared for OPC and OCC subsites by gender. From 1980 to 2005, there were significant differences in survival among the OPC subsites, apparent for both genders ($P < 0.001$, Figure 12A and 11B). For OCC subsites, significant differences were observed only among women ($P = 0.03$, Figure 12D). Temporal trends in survival rates for subsites were then examined by gender (Figure 13, 14, Table 7). Among the OPC subsites, survival rates in men significantly improved for tonsils ($P = 0.04$, Figure 13A) and base of tongue ($P < 0.001$, Figure 13B) in the second time period but not for the other oropharynx (Figure 13C). For women, survival rates showed marginal improvement for base of tongue ($P = 0.06$, Figure 13E) but not for tonsils (Figure 13D) and other oropharynx (Figure 13F). Among the OCC subsites, survival rates in men remained stable for ventrolateral tongue ($P = 0.55$, Figure 14A) and gum and cheek ($P = 0.75$, Figure 14B) but decreased for floor of mouth, although not significantly ($P = 0.18$, Figure 14C). Survival rates in women marginally

improved for ventrolateral tongue (P = 0.07, Figure 14D), decreased for floor of mouth (P = 0.04, Figure 14F) and remained stable for gum and cheek (P = 0.68, Figure 14E).

Temporal trends in survival rates by stage at diagnosis, tumour size and nodal status

Survival rates were compared for OPC and OCC by gender and stage at diagnosis for the overall time period from 1980 to 2005 (Figure 15, Table 8, Table 9). As expected, survival for early-stage disease was significantly better than late-stage disease for OPC in men (P = 0.004, Figure 15A) and women (P = 0.001, Figure 15B), and for OCC in men (Figure 15C) and women (Figure 15D, both at P < 0.001) (Table 8). However, when a temporal analysis was done of the two time periods, the association of early-stage disease with improved survival in OPC was apparent for both time periods only in females (Figure 16B and Figure 17B, Table 8). There was a shift in patterns for OPC in males from the expected association in the earlier time period to no significant difference between survival rates for early- and late-stage disease in men in the later time period (Figure 16A, Figure 17A, Table 8). In contrast, temporal analysis of OCC trends showed better survival with early-stage disease for both time periods in each gender (P < 0.001) (Figures Figure 16C, Figure 16D, Figure 17C and Figure 17D, Table 9).

To better understand this data, associations of survival with T (size of tumour), N (nodal status) and M (metastasis) components for OPC and OCC were looked at in the two time periods (Table 8 and Table 9). For OPC there was a strong association of T with survival for overall and both time periods for males and females (P < 0.001, Figure 25A, Figure 25B, Figure 26A, Figure 26B and Figure 27A, Figure 27B). Although females showed the expected

association of N (nodal status) with survival for overall (Figure 28B) and both time periods (Figure 29B and Figure 30B), this was found only for the first time period for males (Figure 28 A) but not found for overall (Figure 29A) and second time period (Figure 30A). Whether M contributed significantly to staging could not be ascertained as there were not enough cases with M data. For OCC Survival trends were as expected for both overall and two time periods. With increasing T (Figure 25C, Figure 25D, Figure 26C, Figure 26D, Figure 27C and Figure 27D) and N stage (Figure 28C, Figure 28D, Figure 29C, Figure 29D, Figure 30C and Figure 30D) there was poorer survival.

Temporal trends in stage at diagnosis

In order to determine if there has been a temporal shift in the staging distribution for OPC and OCC (Figure 24), the proportions with late-stage disease for all subsites combined and for specific subsites by gender were examined. For OPC overall, the proportions with late-stage disease increased in the second period from 78.8% to 83.3% (P = 0.08) in men and from 72.1% to 75.2% (P = 0.48) in women. In men, this increase is mainly seen in tonsils (from 70.0% to 82.5%, P = 0.001), whereas in women it is seen both in tonsils (from 68.4% to 73.6%, P = 0.40) and other oropharynx (from 60.0% to 82.8%, P = 0.07), although neither site is significant. The base of tongue showed a slight decrease in both genders (in men from 89.7% to 84.8%, P = 0.21 and in women from 92.5% to 75.0%, P = 0.30). For OCC overall, women showed a decrease in proportion with late-stage disease in the second time period, from 43.4% to 37.4% (P = 0.09); this decrease was less apparent in men (from 47.7% to 45.2%, P = 0.39). The decrease in late-stage disease in women was apparent across all OCC subsites, most

notably in the gum and cheek (from 61.5% to 46.7%, P = 0.02). In men, the decrease in late-stage disease was also mainly seen in the gum and cheek (from 61.9% to 50.4%, P = 0.04).

Survival rates and stage at diagnosis by ethnicity

Survival rates were then determined by gender and ethnicity, considering 3 population groups (SA, Chinese, and the general population, with the latter excluding SA and Chinese) (Figure 25, Table 10). This analysis was viewed as exploratory as current numbers are too small for temporal analysis. Better survival rates were seen for OPC and OCC in Chinese, and this was apparent for both genders. The lowest survival for OCC was noted in SA, and for OPC in the general population, once more apparent for both genders.

The distributions of stage at diagnosis were determined by ethnicity (Table 11). Higher proportions of late-stage disease were seen for OPC in Chinese and for OCC in the general population. This was seen in both genders.

Discussion

Survival for both OPC and OCC is changing in BC. This chapter examined temporal trends in oral cancer survival using population-based data specifically focusing on gender and exploring associations among SA and Chinese as well as the general population. Gender and ethnicity were found to be critical determinants of survival. Overall, the data showed an improvement in survival for OPC between 1980-1993 and 1994-2005, although this trend was significant only for men. Survival trends for OCC were non-significant in either gender. When the data were examined by subsites, gender differences became apparent. For OPC,

there was significant improvement for both tonsils and base of tongue cancers in men but only marginal improvement for base of tongue cancers in women. For OCC, there was a marginal improvement for cancers at the ventrolateral tongue in women but a significant decrease in the floor of mouth cancers. Only the latter was observed in males but the change was not significant. These differences in survival by subsite and gender need to be explored in other populations and with larger numbers.

Conventionally, survival rates are influenced by detection of the disease at an earlier stage which impacts treatment choice. The data showed a shift to a detection of a greater proportion of cases with late-stage disease for OPC in recent years, especially in men, suggesting that the improvement in survival for OPC is not associated with detection of early-stage disease. Of note, however, is that in men the association of stage and survival disappeared in the second time period of the study with similar survival curves for early- and late-stage disease. A study by Aziz[212]et al from Sweden has also reported the lack of difference in survival rates for early- and late-stage disease, with tumour size associated with outcome but not nodal status. Aziz did not report on T and N stage differences and survival by gender. It is interesting that this change in association of survival with nodal status was apparent only among males in this study and this observation needs to be examined in other populations to determine its generalizability and to look for underlying causes.

The majority of OPC cases in this study received radiation therapy. Some improvements in treatment protocols have occurred over the study period in BC, such as refinement of fractionation for radiotherapy and the more recent integration of concurrent chemotherapy, which may partly be responsible for the improvement of survival rates of OPC

among men, as found in this study. Since the shift in the proportion of late-stage disease for OPC occurred primarily in men (non-significant change in women), it is feasible that there may be treatment difference by gender although such a possibilitiy is unlikely to produce the gender differences in survival that were observed. Since treatment data are not appropriately recorded in BCCR, this could not be examined further.

At least a portion of the observed improvement of survival rates for OPC in BC might be attributed to the increasing proportion of HPV-positive cancers and the reductions over time in tobacco exposure. The way in which tobacco and HPV interact to impact on OPC development is as yet poorly understood. The earliest population-based data comes from Sweden, where shifts in both HPV-DNA positivity in OPC and smoking prevalence have been reported along with alteration to OPC incidence and survival. Incidence of OPC in Sweden increased 2.6-fold in men between 1970 and 2002 (from 1.3 to 3.6 per 100,000) and 3.8-fold in women (from 0.23 to 0.82 per 100,000)[6]. A subsequent molecular study showed a parallel increase in the number of HPV-positive OPC cases, from 23% in 1970s to 79% in 2000-07[125] ($P < 0.001$). Of interest, from 2003 to 2007, a higher prevalence of HPV was observed among women (95.4%) than in men (81.6%)[125]. From 1960 to 2004, 5-year survival rates for tonsils in Sweden improved by 29.1% and 17.9% for men and women, respectively; for base of tongue rates improved by 29% and 26.2%, respectively[38]. During the same time period, quite different patterns of smoking were observed for men and women. Smoking rates were much higher in men than women in 1946-50; however, by 1991-95, these rates had decreased among men but increased among women[213]. In contrast to reports from Sweden, the incidence of OPC in the US has increased predominately in men[36]. A recent

molecular analysis in the US did not examine gender differences[2]. However, it did show that the prevalence of HPV increased from 16.3% (1984 to 1989) to 71.7% (2000 to 2004). In addition survival was significantly longer for HPV-positive than for HPV-negative patients[126].

Data on HPV-DNA presence in OPC are as yet not available in BC; however, parallel changes to those seen in Sweden have occurred in the BC population, with incidence and survival rates increasing in both genders (although improvements in survival are significant only for men). However, unlike Sweden, smoking rates in BC from 1965 to 2007 have shown a decline for both genders, sharper in men (from 51% to 17.9%) than women (from 38% to 11.1%)[214]. A comparison of future shifts in OPC incidence and survival in BC and Sweden will be of interest.

The development of more refined studies on impact of interactions of HPV and smoking on the natural history of OPC are critical. It has been suggested that changes to sexual behaviour (increase in number of sexual partners, more frequent oral sex) may be responsible for alterations in OPC incidence. However, smoking is recognized as an important co-factor that helps in clearance or persistence of HPV infection which can lead to development of cervical cancer[153,154]; hence the interplay of these two factors could have significant impact on OPC incidence and survival. Case-control[140] and population-based[126] studies have suggested that HPV-positive oral cancers have better survival rates than HPV-negative cancers; however, smoking status affects survival of HPV-positive tumours[141,144]. The percentage of former or current smokers among HPV-positive tumours in these studies was very high (65%[141] and 70%[144]). It will be important in the future to capture more data

prospectively on both HPV and smoking status in order to better understand how these factors affect different genders and subpopulations.

Overall, there was no significant change in survival for OCC for either sex. However, a trend towards change became apparent when subsites were examined. There was a decrease in survival for floor of mouth cancers in both sexes, although significant in women only. For women, there was a marginal improvement in survival for the ventrolateral tongue. The underlying cause of these changes is not known. Floor of mouth cancers are more difficult to treat and this might have an impact on survival; however, treatment protocols at this site have not changed significantly over the study period. Further investigation is needed to determine whether similar changes in incidence and survival of OCC subsites are apparent in other countries and to determine the underlying factors influencing these changes.

Non-significant differences in survival were apparent for OCC among ethnic groups in this study, with poorer survival in SAs and better survival in Chinese, as compared to the general population. This pattern was similar in both men and women for OCC, showing a marginal trend in men. The numbers were too low to examine survival trends for OPC by ethnicity and gender. Given the small numbers of cancer cases in the two ethnic groups, the analysis was considered to be only exploratory in nature; however, the findings are promising as an important indicator of future survival trends in BC, as immigrants from Asia and SA are becoming a sizeable proportion of the BC population[18]. No literature could be found on trends in incidence and survival for OPC and OCC by gender in Asia and SA countries, which are the most common countries of origin for

immigrants to BC. This is particularly relevant as oral cancer is a leading contributor to the cancer burden in these countries. Lifestyle habits often continue after immigration, especially in first generation immigrants, and this would apply to oral chewing products like tobacco-containing betel quid (areca nut, lime and tobacco) which increases the risk of oral cancers and second or multiple primary tumours, with the associated poor survival rates[215]. As previously reported, oral chewing products are used among SA immigrants in BC[31] and there is a need to further understand the socio-cultural context of these chewing behaviours. This is done in Chapter 6.

This study also suggests that there are ethnic differences in the staging distribution at diagnosis, at least in the BC population. Late-stage disease was more common in the general population for OCC and in the Chinese for OPC, regardless of gender. These differences in staging distribution may perhaps reflect differences in screening practices and other behaviours leading to a diagnosis of oral cancer. This observation is currently under consideration by the BC Oral Cancer Prevention Program (http://www.bccancer.bc.ca/PPI/Screening/oral/about.htm), which is establishing a population-based surveillance system and making programs for prevention of OPC and OCC. This work will guide public health policy for all residents in BC.

In conclusion, survival is the ultimate indicator that may reflect changes in disease processes and response to interventions and treatment. This study's findings show that it is imperative to consider both gender and topographic subsites of OPC and OCC when conducting survival analysis. This may result in small numbers for specific subsites but the findings will provide valuable insight into what is occurring at these subsites. Analyses

further emphasize the need for collaborative studies and pooling of data in order to explore for similar trends elsewhere. Finally, given the global impact of immigration and the changing profiles of etiological factors, it is critical that ethnicity also be considered in survival analysis of OPC and OCC.

Figure 10: Disease-specific survival rates from 1980-2005 for OPC and OCC: (A) in men, (B) in women; by gender (C) in oropharyngeal cancers, (D) in oral cavity cancers.

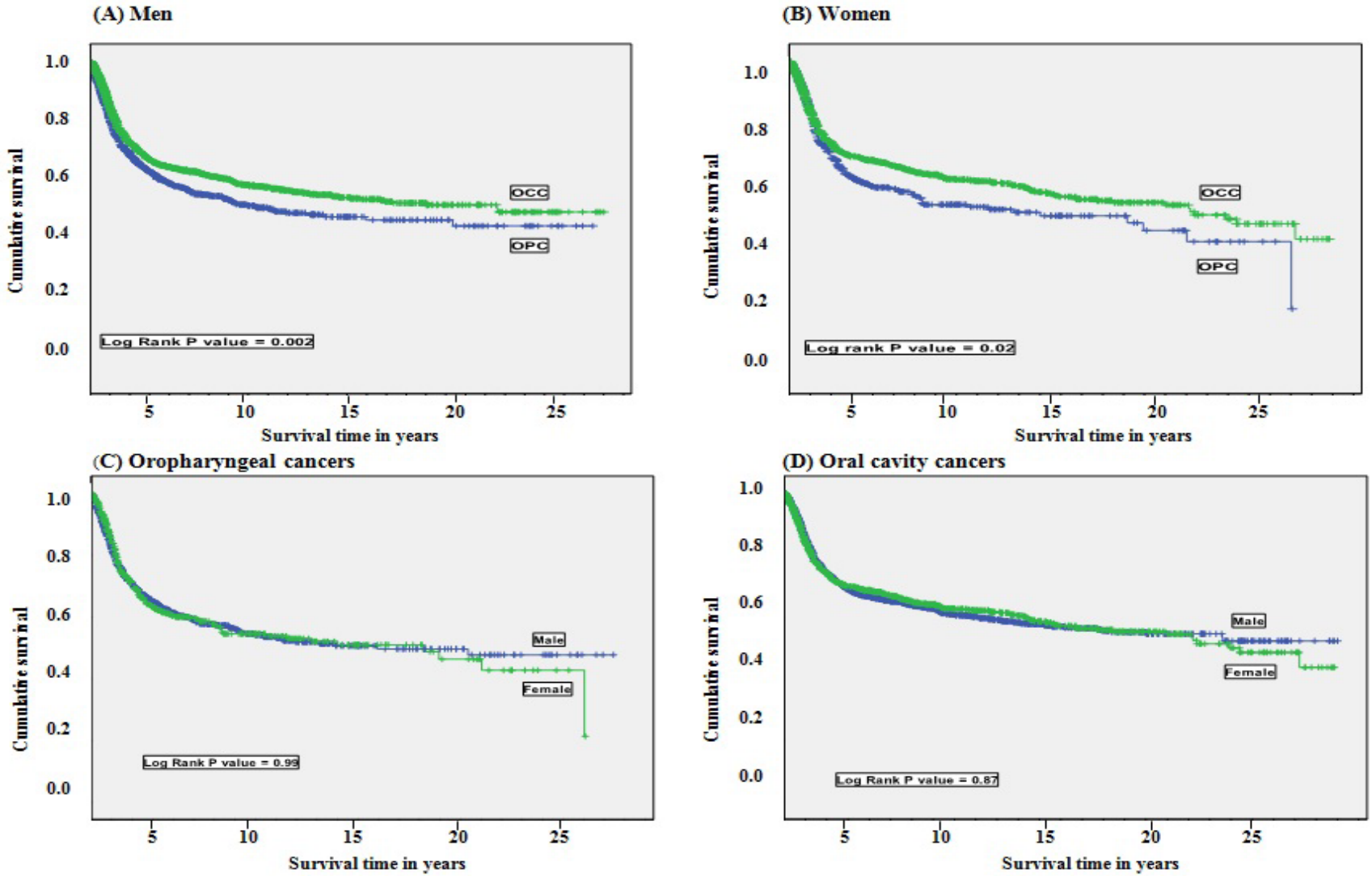


Figure 11: Temporal trends in disease-specific survival rates of OPC and OCC by gender and time periods: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

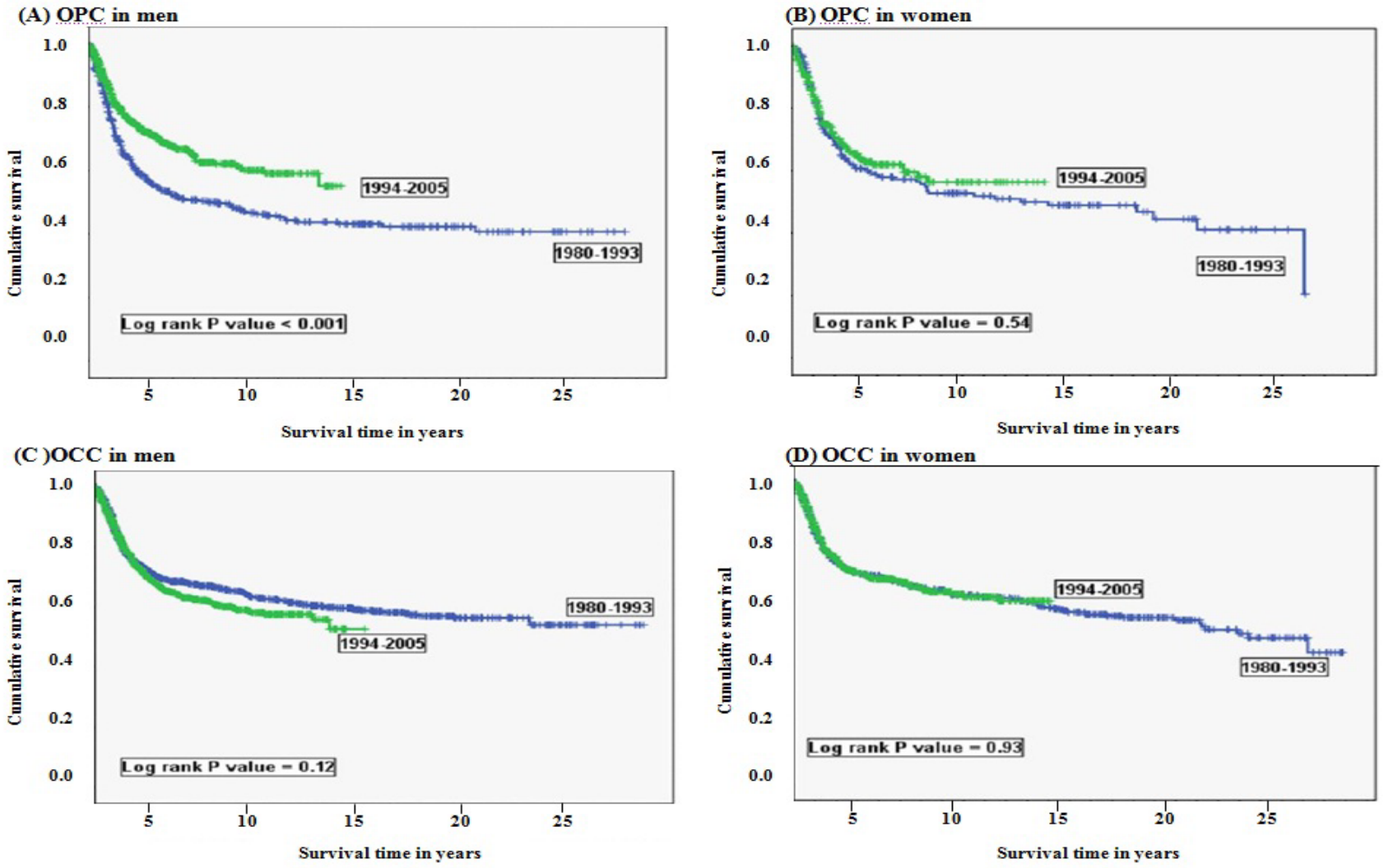


Figure 12: Disease-specific survival rates for OPC and OCC subsites by gender from 1980 to 2005 in the total study population: (A) for OPC subsites in men, (B) OPC subsites in women, (C) OCC subsites in men and (D) OCC subsites in women.

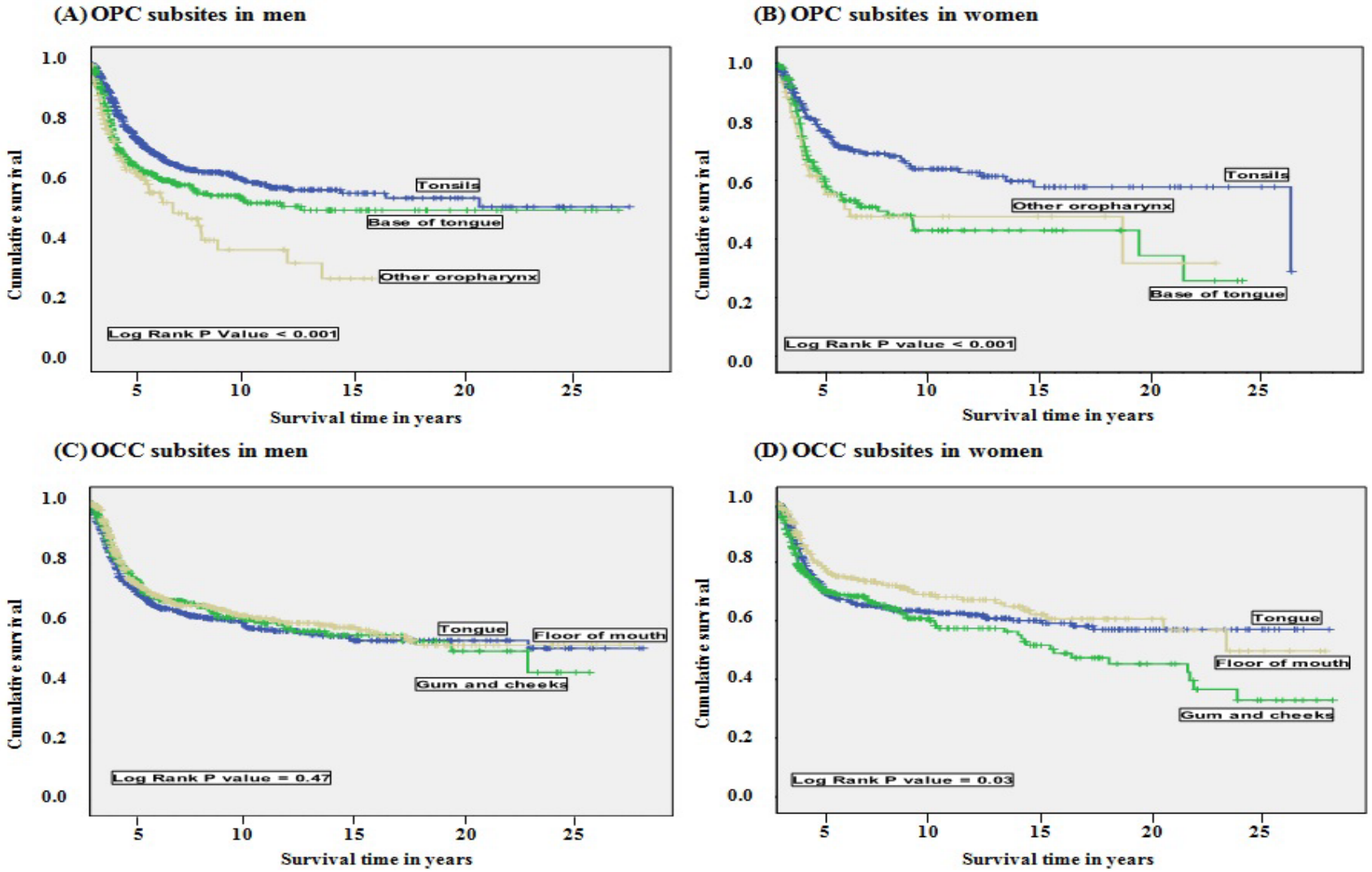


Figure 13: Temporal trends in disease-specific survival rates for OPC subsites by gender in the total study population: tonsils (A) in men, (D) in women; base of tongue (B) in men, (E) in women; other oropharnynx (C) in men and (F) in women.

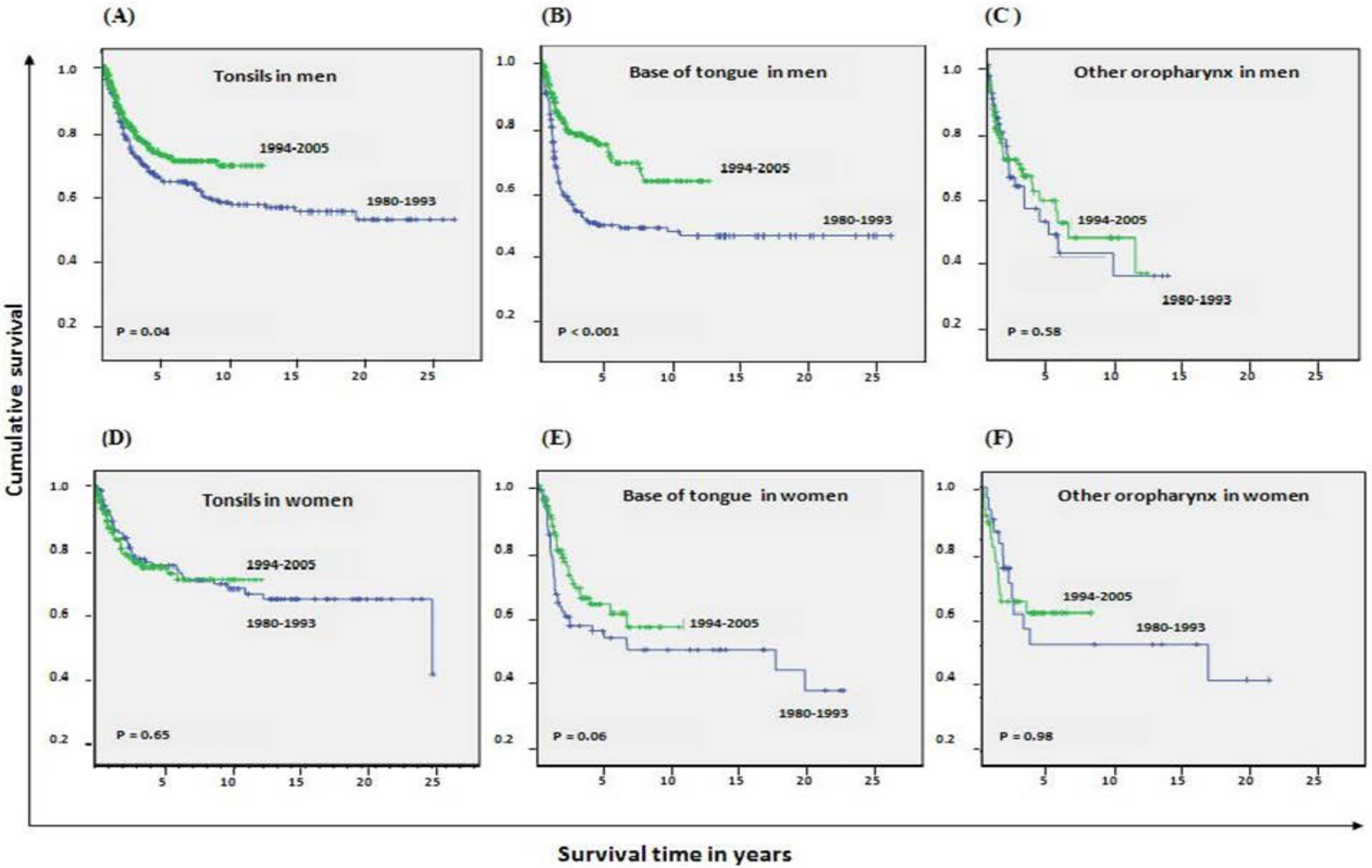


Figure 14: Temporal trends in disease-specific survival rates for OCC subsites by gender in total study population: ventrolateral tongue (A) in men, (D) in women; gum and cheeks (B) in men, (E) in women; floor of mouth (C) in men and (F) in women.

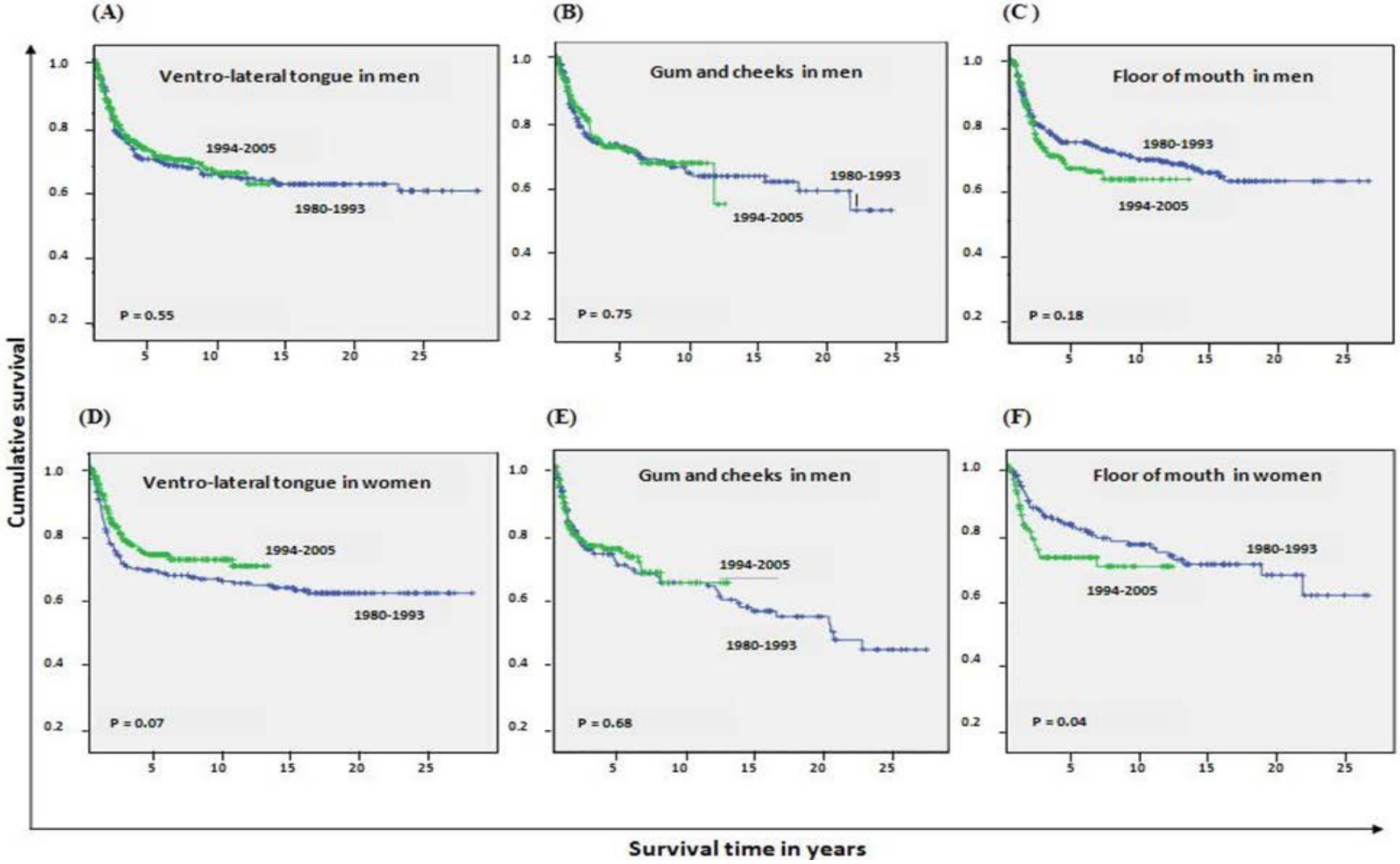


Figure 15: Disease-specific survival rates for OPC and OCC by gender and stage at diagnosis from 1980 to 2005 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

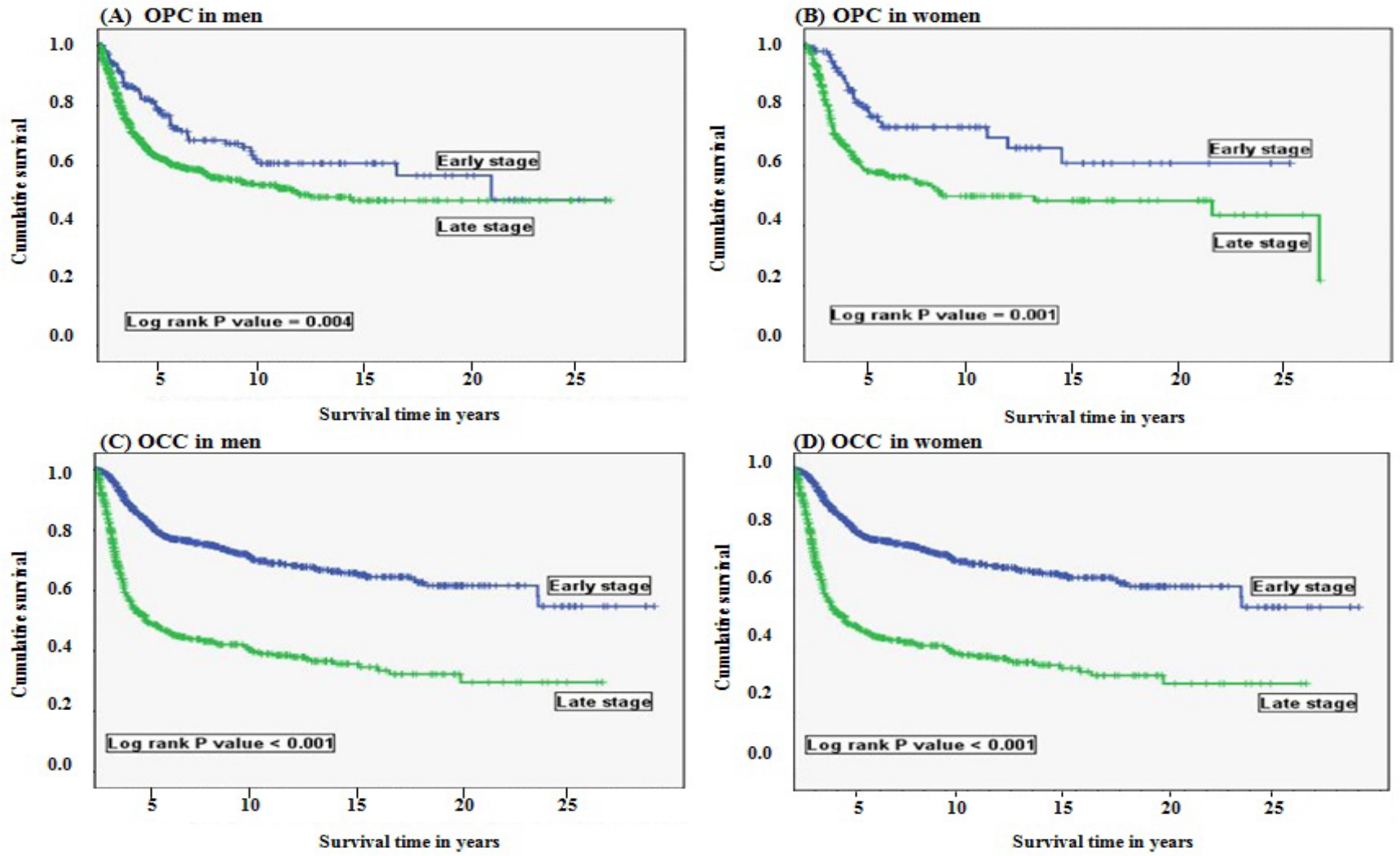


Figure 16: Disease-specific survival rates for OPC and OCC by gender and stage at diagnosis from 1980 to 1993 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

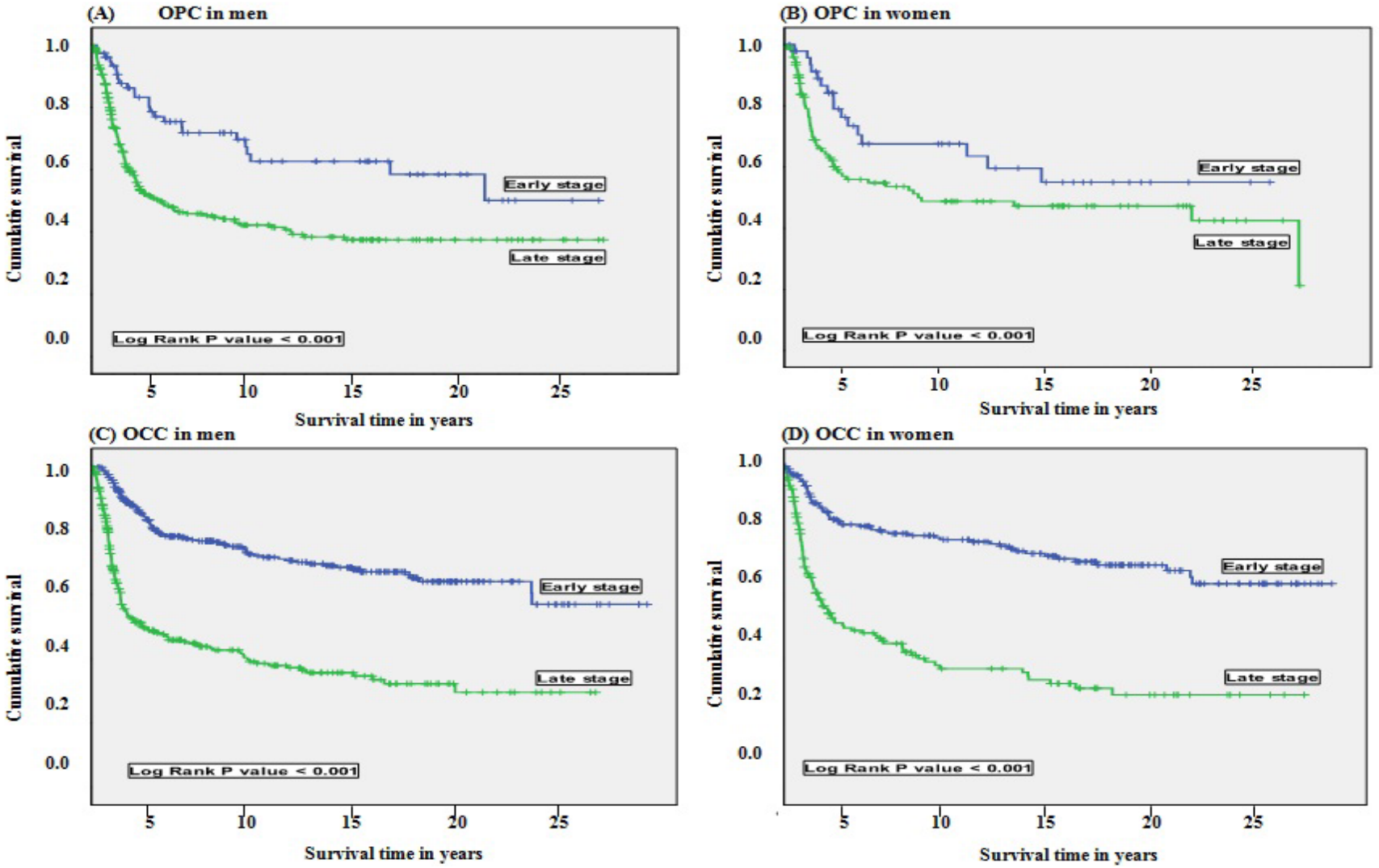


Figure 17: Disease-specific survival rates for OPC and OCC by gender and stage at diagnosis from 1994 to 2005 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men, and (D) OCC in women.

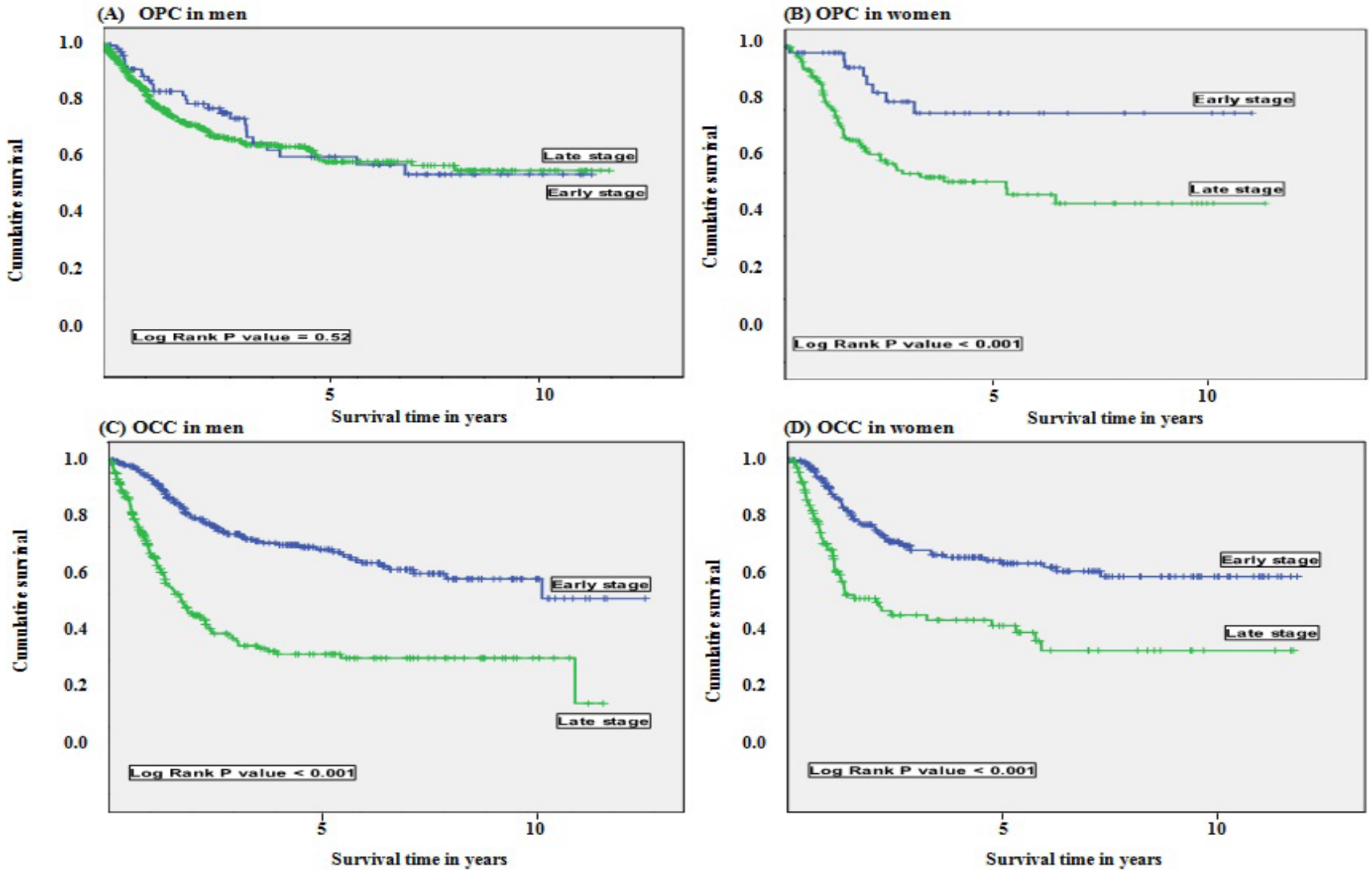
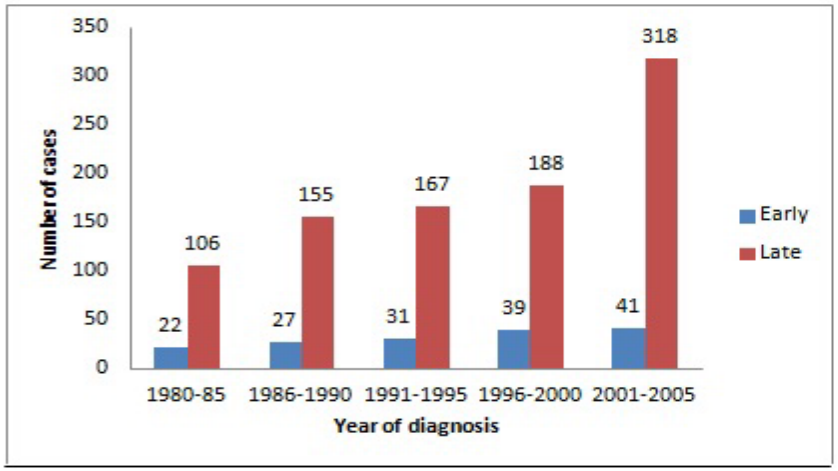
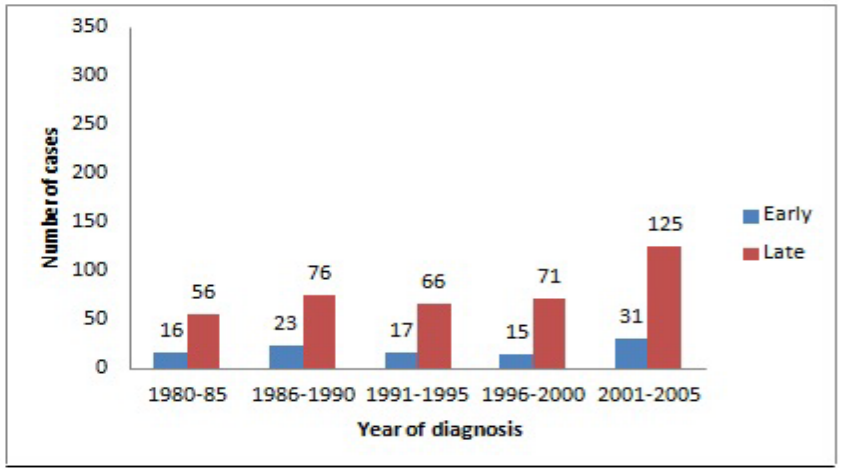


Figure 18: Temporal trends in staging distributions for OPC and OCC by gender from 1980 to 2005 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

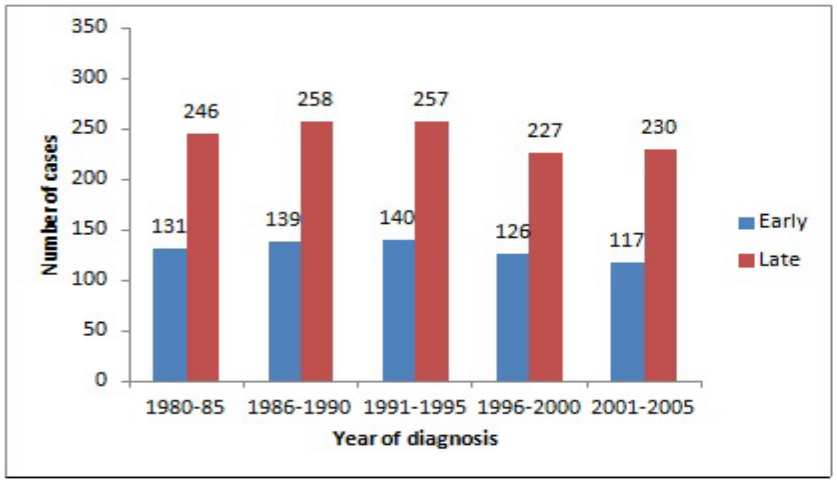
(A) OPC in men



(B) OPC in women



(C) OCC in men



(D) OCC in women

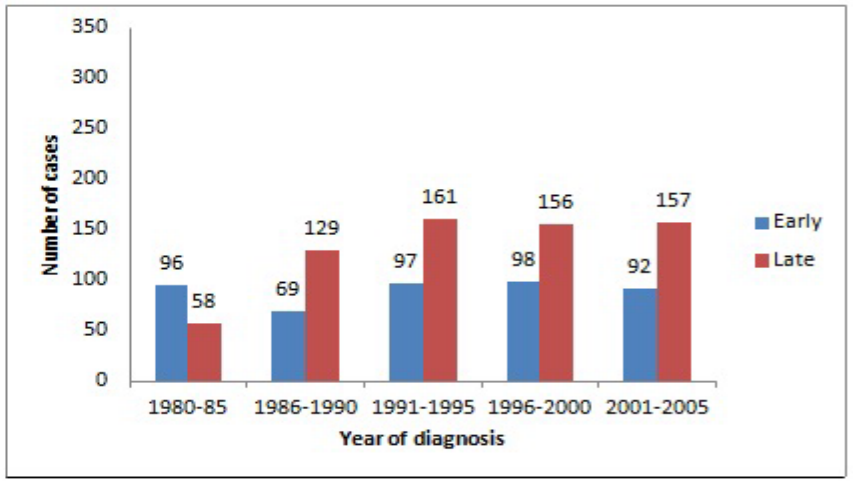


Figure 19: Survival rates of OPC and OCC by ethnicity from 1980 to 2005 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

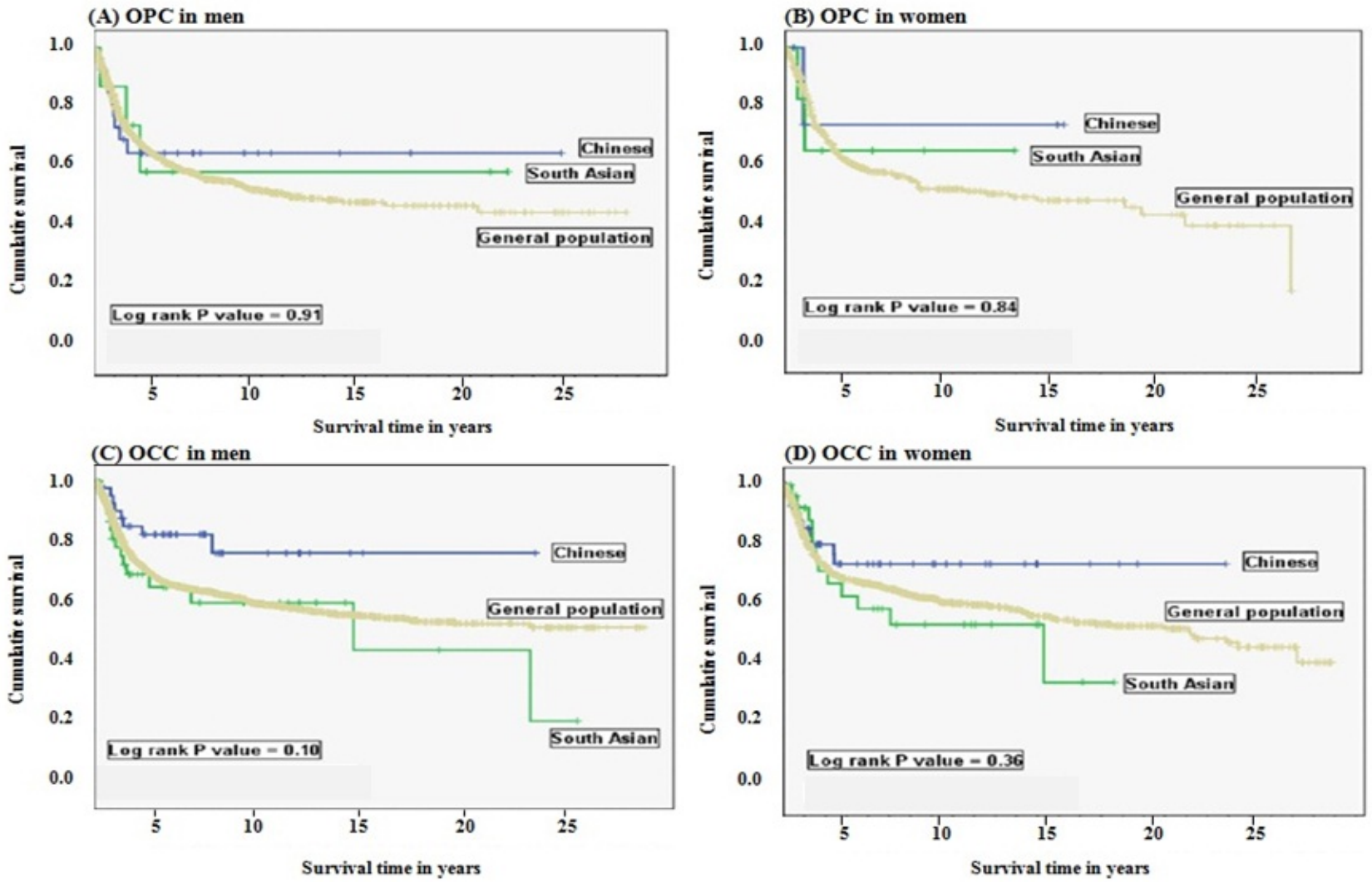


Table 6: 5-year disease specific survival rates for oropharyngeal cancers (OPC) and oral cavity cancers (OCC) by gender from 1980 to 2005 in the total study population.

	Men			**Women**		
	No. of cases	**Survival Rate**	**95% CI**	**No. of cases**	**Survival Rate**	**95% CI**
OPC *(includes tonsils, base of tongue, other oropharynx)*	1214	59	56.0 - 62.3	491	59.3	54.2 - 64.3
OCC *(includes ventrolateral tongue, gum and cheeks, floor of mouth, other mouth that includes lips, soft and hard palate and other other mouth parts)*	1786	64.7	62.2 - 67.2	1158	66.8	63.7 - 69.3

Table 7: Temporal trends in 5-year disease-specific survival rates for OPC and OCC by gender in the total study population.

	Men						Women					
	1980-1993			1994-2005			1980-1993			1994-2005		
	No. of cases	Survival Rate	95% CI	No. of cases	Survival Rate	95% CI	No. of cases	Survival Rate	95% CI	No. of Cases	Survival Rate	95% CI
OPC (*subsites combined)*	455	50.7	45.7 - 55.7	759	64.8	60.5 - 69.1	208	57.2	50.2 – 64.8	283	61.9	55.1 – 68.7
OPC subsites												
Tonsils	240	58.2	51.4 - 65.0	441	67.1	61.7 - 72.5	114	69.8	60.0 - 79.2	151	69.3	61.3 - 78.1
Base of tongue	164	42.5	34.5 - 50.5	251	65.6	57.8 - 73.4	70	42	31.1 - 53.7	95	55.3	43.2 - 67.4
Other oropharyn	51	39.1	21.0 - 57.1	97	51.5	38.5 - 64.8	24	40.4	18.1 - 62.7	37	52.3	34.9 - 69.7
OCC *(subsites combined)*	920	67.1	63.8 - 70.4	866	62.3	58.6 – 66.0	551	66.6	62.5 – 70.7	607	67.2	62.9 – 71.5
OCC subsites												
Tongue	284	60.5	55.5 - 66.3	345	63.2	57.4 - 69.08	194	60.7	53.7 - 67.9	253	67.7	61.3 - 74.1
Gum and cheeks	192	65	57.6 - 72.4	191	65.7	57.9 - 73.5	151	63.4	55.0 - 71.8	165	67.9	59.9 - 75.9
Floor of mouth	272	69.4	63.6 - 75.2	203	59.6	51.6 - 67.6	136	76.5	69.1 - 83.9	102	66.2	56.1 - 76.3

Table 8: 5-year disease specific survival rates by stage at diagnosis, nodal status and tumour size for OPC by gender and time periods.

Oropharyngeal cancers									
		1980-2005			1980-1993			1994-2005	
	No. of cases	Survival rate	95% CI	No. of cases	Survival rate	95% CI	No. of cases	Survival rate	95% CI
Men									
Early stage	174	68.5	60.5-76.5	76	71.8	60.9 - 82.7	98	64.5	52.5 - 76.4
Late stage	771	57.7	53.6-61.8	282	45.9	39.5 - 52.3	489	65.8	60.6 - 71.0
Nodal status									
NO	321	61.5	55.3 - 67.7	148	64.2	55.8 - 72.6	173	58.2	49.2 - 67.6
N1	247	68	65.0 - 69.6	102	52	41.5 - 62.5	145	71.5	62.5 - 80.5
N2	384	63.9	58.1 - 69.7	69	48.3	35.2 - 61.4	315	67.5	60.9 - 74.1
N3	136	38.5	28.2 - 48.8	69	30.7	18.6 - 42.8	67	47.9	29.9 - 65.9
Tumor size									
T1	221	81.9	76.1 - 87.7	57	76.8	65.0 - 88.3	164	84	77.4 - 90.6
T2	397	62.3	56.7 - 67.9	131	57.8	48.6 - 67.0	266	64.9	57.7 - 72.1
T3	306	47.8	41.0 - 54.6	135	49.1	39.5 - 58.7	171	46	35.1 - 56.9
T4	151	34.6	25.2 - 44.0	65	23.1	11.8 - 34.4	86	44.5	30.4 - 58.6
Women									
Early stage	104	72.8	62.8-82.9	48	67.6	52.9 - 82.3	56	79	65.7 - 92.3
Late stage	294	55.5	48.9-62.1	124	53.7	44.1 - 63.3	170	57.3	48.3 - 66.3
Nodal status									
NO	179	69.6	62.6 - 77.4	81	66.3	55.0 - 77.6	98	73.3	63.0 - 83.6
N1	113	66.9	57.1 - 76.7	51	66	52.5 - 79.5	62	67.2	52.9 - 81.5
N2	115	53.7	43.2 - 64.2	28	53.3	33.7 - 72.9	87	53.2	40.5 - 65.9
N3	48	17.3	3.4 - 31.2	28	15.4	0 - 31.2	20	17.4	0 - 44.2
Tumor size									
T1	98	79.4	74.9 - 83.9	32	71.3	54.3 - 88.3	66	87.7	78.3 - 97.1
T2	167	61	56.5 - 65.5	67	63	50.3 - 75.7	100	62.1	50.6 - 73.6
T3	133	43.9	36.1 - 51.7	71	55.8	43.5 - 68.1	62	43.5	28.5 - 58.5
T4	47	39	32.2 - 45.8	19	7.3	4.5 - 21.4	28	46.8	25.3 - 68.3

Table 9: 5-year disease specific survival rates by stage at diagnosis, nodal status and tumour size for OCC by gender and time periods.

Oral cavity cancers									
	No. of cases	**Survival rate**	**95% CI**	**No. of cases**	**Survival rate**	**95% CI**	**No. of cases**	**Survival rate**	**95% CI**
Men									
Early stage	655	75.3	71.8-78.8	350	76.7	72.0 - 81.4	305	73.3	67.7 - 78.9
Late stage	571	43.3	38.6-48.0	319	43.8	40.7 - 49.8	252	42	34.6 - 49.4
Nodal status									
NO	908	70.1	66.8 - 73.4	587	72.5	68.2 - 76.8	321	67	61.8 - 72.2
N1	238	50.3	43.3 - 57.3	174	52	43.4 - 60.6	64	46.6	34.3 - 58.9
N2	149	27.3	18.5 - 36.1	130	23	8.0 -38.0	19	29.3	18.8 - 39.8
N3	61	7.6	0 - 15.6	45	8	0 - 16.6	16	22.2	0 - 48.6
Tumor size									
T1	368	81	72.0 - 90.0	183	84.1	78.5 - 89.7	185	74.2	67.0 - 81.4
T2	548	62.2	53.6 - 70.8	285	63.5	57.7 - 69.3	263	57.7	50.7 - 64.7
T3	198	50.5	41.1 - 59.9	103	46.7	36.0 - 57.4	95	40.3	28.6 - 52.0
T4	251	30.4	14.8 - 46.8	145	37.6	29.0 - 46.2	106	40.1	28.8 - 51.4
Women									
Early stage	457	74.7	70.4-79.0	219	79	73.4 - 84.6	238	70	63.4 - 76.6
Late stage	310	46.8	40.4-53.2	168	44.8	36.6 - 53.0	142	50.4	41.4 - 60.3
Nodal status									
NO	653	68.9	65.0 - 72.8	321	69.7	64.5 - 74.9	332	68.1	62.5 - 73.7
N1	111	54.2	43.9 - 64.5	64	57.6	44.7 - 70.5	47	48.6	31.4 - 65.8
N2	79	30.4	17.7 - 43.1	19	NA	NA	60	39.7	31.9 - 47.5
N3	20	11.3	0 - 26.0	16	13.5	0 - 30.7	4	NA	NA
Tumor size									
T1	260	76.3	70.7 - 81.9	108	83.1	75.7 - 90.5	152	70.7	62.5 - 78.9
T2	338	67.8	62.0 - 73.2	160	70.1	62.7 - 77.5	178	65.5	57.7 - 73.3
T3	116	40.5	30.4 - 50.6	72	40.7	28.2 - 53.2	44	40.3	23.1 - 57.5
T4	158	39.2	30.2 - 48.2	78	37.6	25.7 - 49.5	80	44.7	31.8 - 57.6
NA - Not applicable as there were not enough cases									

Table 10: 5-year disease-specific survival rates for OPC and OCC by gender and ethnicity from 1980 to 2005.

	South Asian		Chinese		General population	
	Survival rate	**95%CI**	**Survival rate**	**95%CI**	**Survival rate**	**95%CI**
OPC						
Men	60	24.4 - 95.6	66.1	47.9 - 84.4	59	56.0 - 62.3
Women	66.7	47.5 - 104.3	75	32.5 - 1.17	59.3	54.2 - 64.3
OCC						
Men	60.9	43.3 - 78.5	82.8	71.8 - 93.5	64.7	62.2 - 67.2
Women	60.5	41.3 - 79.7	74.8	61.1 - 88.5	66.8	63.7 - 69.3

Table 11: Distribution of stage at diagnosis for OPC and OCC by gender and ethnicity from 1980 to 2005.

	South Asian						Chinese						General population					
Oropharyngeal cancers (OPC)																		
	M	**Number**	**%**	**F**	**Number**	**%**	**M**	**Number**	**%**	**F**	**Number**	**%**	**M**	**Number**	**%**	**F**	**Number**	**%**
	8	8	100%	6	6	100%	29	24	82.76%	6	5	83%	1177	887	75.36%	479	414	86.43%
Early		2	25%		1	16.67%		3	12.50%		0	NA		184	20.74%		109	26.33%
Late		6	75%		5	83.33%		21	87.50%		5	100%		703	79.26%		305	73.67%
Oral cavity cancers (OCC)																		
	M	**Number**	**%**	**F**	**Number**	**%**	**M**	**Number**	**%**	**F**	**Number**	**%**	**M**	**Number**	**%**	**F**	**Number**	**%**
	40	29	72.50%	29	22	75.86%	47	26	55.32%	47	29	61.70%	1701	1279	75.19%	1080	798	73.89%
Early		17	58.62%		17	77.27%		17	65.38%		18	62.07%		684	53.48%		477	59.77%
Late		12	41.38%		5	22.73%		9	34.62%		11	37.93%		595	46.52%		321	40.23%
With staging information: Oropharyngeal: South Asian=14/14 (100%), Chinese= 29/35 (82%), General population=1301/1656 (78%); Oral cavity cancers: South Asian=51/69 (74%), Chinese= 55/94 (59%), General population=2077/2781(74%)																		

CHAPTER 6: HIDDEN BEHIND THE CULTURAL CURTAINS: USE OF TOBACCO-CONTAINING BETEL QUID AMONG SOUTH ASIAN IMMIGRANT MEN IN BRITISH COLUMBIA

Introduction

Globally, oral cancer incidence rates are highest in South Asian (SA) countries where there is a higher prevalence of oral chewing products, in addition to alcohol consumption and smoking[22,197]. There is a wide range of oral chewing products, which are described in detail in Table 2 (background literature), and all of these forms are carcinogenic[89,91]. According to the National Tobacco Survey of India, oral chewing habits are very prevalent among men in India, with prevalence rates of chewing in urban and rural settings being 20.7% (19.1 million persons) and 31.1% (71.4 million persons), respectively[97]. Chewing habits start at an early age (13-15 years) and are considered to be an integral part of culture and everyday life[174].

Betel quid (BQ) is one of the most common oral chewing products used by immigrant SA. The combined carcinogenic effects of the constituents of this chewing product (i.e., arcea nut, tobacco, lime) are evident among immigrant SAs residing in western countries such as Canada, the US and the UK[24,49,54]. In the UK, SA men had a relative risk of 1.36 for oral cancers as compared to non-SA men[20] and this higher risk was attributed to the continuation of chewing habits after immigration. Similar trends were observed in BC, with SA men having 1.33 times the risk of oral cancer as compared to men in the general population[216]. Little in-depth knowledge exists about the patterns and reasons for continuation of chewing habits among SA men following immigration. A UK study among 204 Bangladeshi adolescents (51.5% boys) reported numerous reasons for plain BQ chewing, including its refreshing qualities (42%), taste (35%), as a snack (29%), to strengthen teeth (12.3%) and to relieve stress (11.6%)[27]. A US

study of 130 Bangladeshi (n=96, 58% men) and Indian-Gujarati (n=42, 54% men) participants reported that SAs chewed BQ for health benefits, such as relieving constipation, improving stamina, fighting cold, relieving tension and improving mood[54]. However, none of these surveys reported the results separately for men and women.

It is timely and important to explore SA men's perceptions regarding commonly used oral chewing products like tobacco-containing BQ in BC because 1) SAs are among the largest and fastest growing immigrant groups, 2) there are reports of high-risk oral lesions among SA immigrants associated with chewing[217,218], and 3) SA men have higher risk of oral cancer as compared to the general population[216] with an increased frequency of cancers seen at oral subsites (e.g., gum and cheeks) that are associated with oral chewing products[21,160,208]. A better understanding about the use of oral chewing products like tobacco-containing BQ and practices related to its use among SA men is needed in order to develop culturally sensitive and targeted health promotion and harm reduction programs for this high-risk group.

Background literature

Oral chewing products and oral cancer

Oral cancer among SAs has been associated the use of oral chewing products as well as smoking and alcohol consumption. Oral chewing products most often contain areca nut, lime smokeless tobacco, each of which has carcinogens. Smokeless tobacco contains nitrosonornicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; areca nut contains arecoline and 3-(methylnitrosamino) propionitrile. Lime provides reactive oxygen radicals[91]. Each of these carcinogens has individual and combined roles in oral carcinogenesis. The natural

history of oral cancer progression suggests that areca nut and tobacco act as initiators of oral carcinogenesis and their use is associated with high-risk oral premalignant lesions, including leukoplakia and OSF. Both areca nut (due to psychoactive alkaloids) and smokeless tobacco (due to nicotine) are addictive; hence their combination increases the potential for dependency among its users[219]. Preparations of oral chewing products are made to cater to individual tastes and create dependence on these products. For example, different varieties and amounts of tobacco leaves are used in preparations to satisfy needs for nicotine. Studies have shown that level of toxins and nicotine content in these tobacco leaves are extremely high[44].

Social and cultural context of oral chewing products

BQ leaves and areca nut have a longstanding tradition and socio-cultural significance among SAs. They are auspicious ingredients in Hinduism, used both in religious ceremonies and for honouring individuals. Among the followers of the Hindu religion, areca nut (*Supari*) is considered to be a vital ingredient of food for the God (*Bhagwan*). In the absence of idols and other sacred images, the fruit (whole nut without its husk) is used by Hindus while offering prayers[105,106], which is blessed by God and then distributed to the followers. Little is known about the influence of these religious beliefs upon the use of these products among SA men. Traditionally, areca nut was chewed because it was thought to be an astringent, mouth freshener after meals, taste enhancer, purgative, and an effective treatment for parasitic intestinal infections[105,106]. The religious and health beliefs associated with these products are so prevalent in many SA cultures that these products are very commonly offered at important social gatherings and weddings as a mark of respect to honour guests[105,220]. However, the use of plain BQ is also very popular among other religious groups, including Muslims and Sikhs, and reasons

for this popularity are unknown[27,49]. In Sikhism, the use of addictive substances such as alcohol and tobacco are prohibited by religious beliefs[221] ; hence, tobacco containing preparations of oral chewing products are unacceptable among Sikhs. Interestingly, recent reports from India suggest that oral chewing products containing smokeless tobacco are becoming popular among the Sikhs[222].

Regulation of oral chewing products

In India, a few states have banned the production, sale and storage of oral chewing products (e.g., Maharashtra, Tamil Nadu, Goa and Andra Pradesh). However, it is extremely difficult to reinforce these regulations because production and sale of these products occur through a large, highly decentralized and informal sector in India which operates outside government control[104,132]. Within North America, the US Food and Drugs administration maintains a high alert for the importation of areca nut products and in Canada the sale of smokeless tobacco is regulated. However, there are currently no specific laws and regulations in the Canadian Tobacco Control Act for sales, marketing and use of oral chewing products like tobacco-containing BQ. In the UK, labels to display ingredients were often lacking on the packets used to dispense oral chewing products and instructions related to their use were missing[104]. When the product labels displayed constituents, in subsequent analysis some ingredients were found to be missing from the labels. In some cases, oral chewing products were found to contain nonpermitted food additives in excessive amounts. Samples of raw ingredients, such as betel quid (*paan)* leaves, were also examined and found to be contaminated with salmonella[44,104]. Despite these findings, oral chewing products remain unregulated in Canada and are readily available in SA markets.

Epidemiology of oral chewing products

Oral cancer incidence rates are projected to increase in epidemic proportions in some populations[223], largely attributed to chewing habits. Betel (areca) nut is the fourth most common psychoactive substance in the world (after caffeine, alcohol and nicotine) and there are currently 700 million chewers around the world[95]. Areca nut is the main psychoactive substance in BQ. It is increasingly common to chew in South Asian countries and this practice is rapidly gaining in popularity[224]. For example, an epidemiological study of 99,598 residents in Mumbai, India showed that the prevalence of chewing areca nut among men was 37.8% while the prevalence of smokeless tobacco use was 45.7%[225]. Another epidemiological study in India also reported the prevalence of smokeless tobacco among school-aged boys to be from 4.5% to 20% in different parts of the country. [226]. The practice of oral chewing products often continues among SAs after immigration to western counteries[7,46,49]. India is a leading source of immigration to BC, and oral cancer incidence rates among SA men are higher than the general population; hence it is important to understand the perspectives about most commonly used oral chewing products like tobacco-containing BQ among SA immigrants in BC.

Method

An interpretative ethnographic approach was used for this study. This is an effective method to investigate complex health issues and build a socio-cultural contextual understanding of health risk behaviours[179,182]. The usefulness of ethnographic methods in enriching our understanding of health behaviours of immigrants is well recognized[180-182]. This ethnographic study was a part of mixed-method research project which was conducted in the BC Oral Cancer Prevention Program (http://www.bccancer.bc.ca/PPI/Screening/oral/default.htm). Ethical

approval for the research project was obtained from the University of British Columbia Research Ethics Board.

Study setting

The study was conducted in Vancouver, BC, which has the second largest SA population in Canada. According to the 2006 census, there were 208,535 people who identified themselves as SA, the majority originating from India. The study community was situated in the well-defined urban core with a variety of SA shops.

The province of BC has been a leader in implementing tobacco control policies, regulating the sale of tobacco and providing for smoke-free environments. However, the sale of oral chewing products like tobacco-containing BQ remains unregulated. These oral chewing products are imported into Canada, primarily from India and East Africa. Many of these oral chewing products are exclusively sold in SA shops and grocery stores where they are freshly prepared according to an individual's preference. The average cost of a freshly prepared tobacco-containing BQ at the time of the study ranged from $1.25 to $1.75 per quid; pre-packaged smokeless tobacco and areca nut pouches ranged from $2 to $4 per pouch. Large containers of areca nut were valued at $10, while that with smokeless tobacco leaves ranged from $25 to $75 (depending upon the quality of tobacco leaves). Slaked lime, used for mixing along with BQ, was available in small plastic tubes at a cost of $0.50 to $1.00. These raw ingredients were individually available for people to make tobacco-containing BQ at home.

Data collection

Data collection consisted of participant observations and individual semi-structured interviews (Appendix B) in the SA community. In the initial phase of the study, advice was sought from several community leaders on ways to enter the field and enlist the support of BQ shop owners to facilitate observations and recruit participants for this study. This led to the identification of one BQ shop owner who agreed to support this research project. Although participant observations were conducted at various venues around the market, restaurants and adjacent community centre in the study community, the majority of the observations and recruitment of participants for interview occurred at this BQ shop, located in the centre of a SA market. The BQ shop sold many types of oral chewing products, Indian snacks, cold drinks, chocolates, candies, ice creams, phone cards, SA magazines, newspapers etc. Smokeless tobacco leaves were sold mixed with BQ and wrapped in paper or plastic pouch, according to the customer's preferences. The BQ shop had two rooms: an outer main room area with racks of food items on display and a small table stall containing BQ leaves and ingredients (kept ready for quick and easy preparation), and another small room for storage of stock and only accessible by the shop owner. The shop owner sat behind the stall in the main room area. During participant observations at the shop, one research team member (AA) stood beside the shop owner to observe, interact and communicate with the customers purchasing BQ.

Data collection occurred over a period of nine months and resulted in 300 hours of field work, which included 47 participant observations and 15 semi-structured interviews. Data were collected by a researcher (AA) who was well versed in SA culture and is multilingual (English, Hindi and Punjabi). Detailed field notes were taken during the participant observations

(Appendix B) in the community and in the BQ shop. In the shop observations focused on practices associated with the purchase of tobacco containing BQ and how it was prepared and marketed by the shopkeeper. Individuals purchasing tobacco-containing BQ were engaged in brief conversations to assist with interpretation of observations. Photographs were also taken of the products and around the BQ store. Some participants were reluctant to talk about their chewing habits inside the shop because many tried to keep their chewing habits to themselves and were concerned that if they stood inside the shop for a long time they would be noticed by their friends or relatives. Interviews were, therefore, conducted at nearby restaurants or while walking in an adjacent community park.

Eligibility criteria of participants for interviews were: (1) self identification as SAs (whether immigrants or Canadian citizens); (2) voluntary agreement to participate in the study and to provide informed consent form; (3) ability to converse in Punjabi, Hindi or English; and 4) self-reported user of tobacco-containing BQ. Participant observations were conducted at this BQ shop. Participants for the semi-structured interviews were also recruited from the same BQ shop through an open sampling strategy, known as snow ball sampling, which is a non-probability sampling technique to include participants who were willing to provide their experiences and insights about tobacco-containing BQ. The shopkeeper helped the researcher (AA) recruit participants for interviews. Referrals from the initial participants were then sought to encourage other SA men who chewed tobacco-containing BQ to participate in the interviews. These sampling strategies allowed the investigators to deliberately select the participants who chewed tobacco-containing BQ in order to maximize opportunities to obtain an in-depth understanding about chewing behaviours. Interviews were conducted until theoretical saturation was reached. Of the 62 men who were invited to be interviewed, 15 agreed and provided

informed consent. Common reasons for declining participation were reluctance to talk about chewing habits which were hidden from mainstream society, not willing to sign a consent form, and fear of disclosure of information from the interviews to their family in spite of assurance of confidentiality.

The mean age of the 15 men who participated in interviews was 36.8 years (ranging from 25 to 60 years). The study sample included men from three religious groups (Muslims = 6, Sikhs = 4 and Hindu = 5). The mean duration of the participants' stay in Canada was 16.5 years (ranging from 2 to 38 years). At the time of the study, all of the men self-reported as regular chewers; the average age they initiated chewing was 19.9 years (ranging from 8 to 42 years). The majority (n=12) of the face-to-face semi-structured interviews were conducted at a nearby restaurant in the language of the participant's choice over a cup of coffee and snacks. The interview questions were informed by the fieldwork observations and focused on participants' chewing habit, socio-cultural beliefs associated with chewing, the factors influencing their choices for smoking and chewing, and what they liked or disliked about their chewing habits. The semi-structured interview guide was pilot tested and the questions were found to produce rich data. Conducting field observations and interviews concurrently enabled clarification and verification of the data collected. All interviews were audio-taped and transcribed verbatim by the researcher (AA). Each interview lasted about 45 to 60 minutes. Data collection and analysis occurred concurrently in an iterative fashion. As a result, as the study proceeded, field observations became more focused, and additional questions were added to interviews to answer questions raised during analysis of the data and to verify and refine emerging themes.

Data analysis

Ethnographic analysis involves a non-linear inductive process which includes coding, sorting, theorizing and reflecting upon the analytic process[227]. In this study, the dataset included field notes of participant observations, transcribed semi-structured interviews and photographs. All participant observations were recorded by hand in English while interviews were conducted in Punjabi, Hindi or English (as requested by the participant) and were transcribed into English by a research team member (AA). N-Vivo, a computer software program, was used to facilitate coding, data retrieval, data organization and analysis. A careful reading was done of all transcribed interviews and field notes as the first step in data analysis. All data were reviewed line-by-line, highlighting important ideas and paying attention to segments of data that contained cultural knowledge or experiences reflecting common practices, patterns and inconsistencies. Free nodes and tree nodes were created and discussed with the investigative team members until agreement was reached. All data was then coded using this framework. Codes were expanded and collapsed in response to recurring and converging patterns until key concepts were identified and agreed upon by the investigative team. Cultural themes were developed to describe patterns from both within and across coded data following an iterative process. Monthly research team meetings were held to discuss coding, and develop the analysis. The investigative team discussed the emerging conceptualizations of themes and descriptive notes were made for all the themes detailed in the findings. One of the investigative team members (AA) conducted the bulk of data analysis. That member was aware of the cultural and contextual insights provided by the participants. Reflexive accounts and analytic decisions were documented.

The validity of the findings in this study is supported through methodological coherence (reflected in the fit between the research question and the methods used), appropriate and adequate sampling, the use of multiple data collection strategies, and incorporating verification strategies into the qualitative research process[228,229]. A number of verification strategies were used. For example, follow-up questions were included in interviews to verify our understandings of men's experiences based on field observations and earlier interviews. Questions were also added to interviews to verify and refine emerging themes as the analysis progressed. Prolonged engagement in the field provided the opportunity to check and compare observations over time. The researcher's (AA) in-depth knowledge of the SA culture and responsiveness and sensitivity to nuances in the data were also instrumental in directing an incremental and systematic process of checking and confirming during each step of this research. Together these strategies shaped and directed the research during its development and contributed to the validity of the findings.

Results

Although many participants had resided in Canada for many years, chewing BQ remained an important and accepted practice among SA men. Chewing practices were reinforced because of easy availability, lack of restrictions on sales and cultural norms. While the prevalence of chewing practices among SA men was perceived to be high, participants constructed their chewing practices as "hidden" from mainstream society. They believed it was possible to hide this habit because BQ was kept inside the mouth and thus remained unnoticed by others. In addition, because BQ was a culturally accepted chewing product, men were able to hide the fact that they were chewing tobacco-containing BQ from family and friends. There were three dominant themes that emerged during the analysis of data from participant

observations and semi-structured interviews: the socio-cultural and societal influences on the patterns of use and consumption of BQ, the constructions of benefits associated with its use, and the risks associated with chewing BQ. To provide a context for understanding SA men's perspectives related to the use of tobacco-containing BQ, it is necessary to first describe its patterns of access and purchase.

Patterns of access and purchase of tobacco containing betel quid

The majority people who visited the BQ shop were SA men. Such shops provided an environment for social networking and a place where SA men could openly talk about the challenges they faced in their new country of settlement. In the shop, SA newspapers were kept for people to read and the walls displayed advertisements for major Indian festivals. Some men who were chronic chewers and who resided at some distance from the market lingered in the shop, taking time to read the newspapers and talk with others as their tobacco-containing BQ was prepared by the shop owner. Importantly, these preparation practices catered to the customer's individual preferences, taste, and desire to have a fresh product, as well as provided a relatively low-cost form of tobacco. Those who could not afford to pay were offered products on credit. Although a range of oral chewing products were available in the shop the most commonly used among SA men, based on the participant observations and interview data, was tobacco-containing BQ. While these products were sold exclusively in BQ shops, some regular chewers preferred to buy individual components for their quids (i.e., areca nut, lime, betel leaves, smokeless tobacco, Figure 26) and prepare fresh quids for themselves at home. The individual quid components, such as smokeless tobacco and betel nuts, were openly displayed and sold in SA grocery stores along with other food items (Figure 27). Homemade quids were cheaper than

store bought tobacco-containing BQ preparations and western forms of smokeless tobacco. Plain BQ were also sold and consumed in some SA restaurants (Figure 28).

The paper or plastic pouches used to dispense tobacco-containing BQ sold in the shop did not display any health warnings, instructions about the contents contained within them or instructions about the use of these products. The cost of tobacco-containing BQ varied according to the quality of smokeless tobacco leaves which were added to them, as indicated by the number on the container: numbers 300 or 600 were considered as premium tobacco leaves varieties whereas numbers 120 or 180 were considered as regular tobacco leaves varieties. In addition, there were no warning signs in the shop or near the cash counter restricting the sales of tobacco-containing BQ to minors. In contrast, sales of western forms of smokeless tobacco were regulated and taxed, making these forms of tobacco more expensive than the Indian forms. Although the sales and marketing of plain or tobacco-containing BQ usually occurred by word of mouth, there were many display boards in the market advertising plain BQ as Indian mouth fresheners (Figure 29). There were also pamphlets available in the markets which were used for advertising these products (Figure 30) and these were available for circulation to the chewers.

Socio-cultural and societal influences on use of betel quid

Various social and cultural influences figured prominently in the chewing practices of SA men. Plain BQ chewing was positioned as a centuries old habit that was part of everyday life in SA countries, as detailed by a 60-year-old participant who chewed tobacco-containing BQ daily and resided in Canada for 28 years: “It is like western people will drink coffee, smoke cigarettes or drink wine for fun, our community [South Asians] people will chew BQ for fun and its flavours”. In addition, chewing represented a way for SAs to stay connected with their cultural

roots and homeland, as explained by a 29-year-old participant who had resided in Canada for the last 11 years:

> Whenever I come to this [SA] market I will chew BQ. In Delhi, BQ chewing is very common and when I chew it then I feel connected to Delhi. If by spending one dollar I can have an experience of being in India then it saves 1400 dollars in my travel.

As a deeply embedded cultural practice, BQ chewing was not viewed as a problem by SA men and rarely did they challenge or question its benefits or health risks. A 65-year-old man who has lived in Canada for the last 30 years explained:

> When someone tells you this is a centuries old building, you accept it and do not question how it was made or who made it, same thing is with chewing BQ … it's [BQ] a centuries old habit, you just chew it.

One of the important roles of BQ in SA culture is its use to demonstrate respect[105] and honour; this is reflected in the common practice of offering BQ to guests. Field observations confirmed that BQ was offered to both young and old at SA social functions and gatherings. These observations were supported by interview participants, who recounted that it was introduction to BQ at social gatherings that led to them becoming regular chewers, as explained by this 30-year-old man (16 years in Canada): "They asked me to try it in a wedding party and that's how I started chewing it". Many other SA men were encouraged by friends to try BQ as a social gesture of friendship, which later became a habit, as suggested by this 60-year-old man (35 years in Canada): "My friend said come on man you chew it, I am paying for you and then I started chewing it".

While chewing plain BQ was viewed as an integral part of everyday life for SA men, the practice also held religious significance. The ceremonial use of betel nut and leaf in Hinduism was often acknowledged and supported in the interviews. One 53-year-old man (32 years in Canada) stated: "When you are doing prayers then you offer betel nut to the God along with the leaf, clove and *eliachi* [cardamom], you put all of them together". A 39-year-old man (17 years in Canada) explained: "In Hinduism they offer betel nut and betel leaves in temples to the God but the religion does not say anything for chewing it". In fieldwork in the community, some people were observed buying bulk quantities of betel leaves and whole nuts for religious ceremonies.

Interestingly, among Muslims the popularity of chewing tobacco-containing BQ was not found to be associated with religious beliefs. Rather, tobacco-containing BQ chewing was viewed as acceptable because, unlike alcohol, there were no restrictions on its use. One older 65-year-old man (30 years in Canada) stated: "Islam says that alcohol is bad because after drinking you will lose your head [senses and control over yourself] but by chewing tobacco or smoking you do not lose your senses, it is okay". This view was shared by younger SA men as well:

> I am a Muslim so I never tasted alcohol. Alcohol is prohibited in Quran (holy book of Muslims), that's why I don't drink. Muslims are not suppose to drink. If you are drinking in Muslim countries and you are caught for the first time, you get 80 lashes, this is the punishment, second or third time again 80 lashes but fourth time you will be beheaded….. Tobacco is not forbidden for us [among Muslims] and its use is acceptable among Muslims. They [Muslims] are one of the heaviest tobacco consumers in the world. However, during Ramadan Muslims prefer not to take tobacco. (39-year-old man, 17 years in Canada)

Among Sikhs, however, tobacco use is prohibited on the basis of religious beliefs. This restriction influenced the purchasing practices among Sikh men who used tobacco-containing BQ. Interviews and field observations showed that Sikhs preferred to buy BQ and smokeless tobacco at grocery stores because they were looked upon with suspicion by members of their communities if seen near BQ shops. Religious restrictions on tobacco use encouraged Sikh men to secretly chew these products, as detailed by a 45-year-old man (22 years in Canada):

> Tobacco is prohibited in Sikh religion that is why our people (Sikhs) chew it [tobacco-containing BQ] hidden from the society. If you are a Sikh and someone sees that you are chewing these things then he will see you differently because he dislikes that you are a Sikh but you are chewing it [tobacco-containing BQ].

Participants reported that chewing habits were popular among the Sikhs in BC because there are no strict religious prohibitions on lifestyle choices and behaviours in western countries. A 60-year-old-man (35 years in Canada) explained: "In [SA dominated community] people who have turban will even chew tobacco because there is too much freedom in this country; you cannot say anything to these people". Occasionally the Sikh chewers would consume these products in company of other SA men at public places:

> I was traveling in a bus and there was a Sikh sitting beside me. I wanted to chew my tobacco-containing betel quid but I was thinking that there is a Sikh with me and I should not chew it because Sikhs do not chew tobacco. But when I could not control myself, I twisted on one side and tried to take out and put quid in my mouth. This Sikh asked me whether I can give him a quid too. Sikhs here are only for name to keep their turbans and beard but they chew tobacco (44-year-old man, 12 years in Canada).

Living in western society also influenced the chewing practices of SA men. While spitting juices immediately after chewing in public places is a very common habit in India, SA men had to modify these practices in BC because spitting in western society is discouraged and viewed as an untidy habit, as one 53-year-old chewer (32 years in Canada) explained: "A guy who used to work in our mill ... after chewing the quid he used to spit it out, it used to look very bad to see people spitting here [Canada], so after some time he stopped spitting". Spitting the coloured juices produced by chewing would leave a permanent stain on floors and walls which was viewed negatively in western society. Rather than spitting, BQ chewers developed techniques to deal with the juices, such as keeping the juices in their throats until they found an acceptable place to spit, or simply swallowing the juices. One 32-year-old man (11 years in Canada) explained:

> To be a professional chewer you need to master a lot of other things like how to chew and hold juices properly in your throat. They say when you need to do something you invent something new …. Necessity is mother of invention. In this search you learn how to deal with the juices. When you start tasting the juices coming out of quid, you try to hold them in your throat and when you see a proper place like a bush or mud then you spit out, not on the walls or streets. Sometimes if you do not find right place you take the juices inside your body.

In addition to modifying their chewing practices to hide it from western society, some SA men were also challenged to hide these behaviours from their families and friends. Many men preferred to chew in isolation and in the privacy of their homes in order to avoid being seen. They often kept the chewing products out of the sight of their family members. One young 25-year-old man (3 years in Canada) explained: "My wife wants me to leave this habit but she does not understand that I need it, so when I get up and go to bathroom, I just keep it [tobacco-

containing BQ] in my mouth". This was confirmed during observation when one man quipped that in order to "earn the respect" of his wife and family he had to chew when he was alone. Another reason for SA men to chew in private was the excessive salivary secretion produced by chewing which impaired their ability to speak, as one man explained:

> When you have it [tobacco-containing BQ] in your mouth there is so much salivation, you cannot speak properly. I know when some people try to speak then *thook doosre par girta hai* [spit falls on the other person]… This is very embarrassing so you need to chew it [tobacco-containing BQ] when you are alone. (39-year-old man, 12 years in Canada)

A few SA men were very addicted to chewing and hence were not worried about the esthetic and social appearance of chewing in western society, as explained by a 54-year-old man (23 years in Canada) who had chewed regularly for 30 years: "While chewing even if one side of my mouth is half an inch bigger I damn care about it. I chew my quid when I want and when it's in the mouth, I do not care about anything".

The literature suggests that in SA countries it is considered disrespectful for youngsters to smoke in front of their family and elders[168]. However, chewing is considered a socially acceptable habit. Therefore, the young SA men under the guise of chewing plain BQ [without smokeless tobacco], chewed tobacco-containing BQ to satisfy their urge for nicotine as well as maintain the social norms and respect for their family members:

> Young people will hide the fact that they add smokeless tobacco to their quid. They will tell elders that they are having just the plain BQ because no one is going to go inside their mouth and check what's in it. I cannot smoke at home … so I had to think of an alternative way to get nicotine, and I started chewing. I

> used to keep it [tobacco-containing BQ] in my pocket and whenever I had an urge to have it during my studies or exams then I will take it out of my pocket and keep it in my mouth. (25-year-old man, 2 years in Canada)

Overall, cultural identity and social connectivity are important components of SA culture and BQ is often shared as a demonstration of closeness and affection. These value systems play an important role in initiation and continuation of chewing BQ, and hidden behind this cultural habit men use tobacco-containing BQ. Religious prohibitions and the weakening of these beliefs after migration to western countries also play a role in influencing chewing practices. In summary, strong intersections were found between cultural, religious, social, and societal values and chewing behaviours among SA men in BC.

Constructions of benefits associated with chewing tobacco-containing betel quid

SA men focused on the benefits associated with chewing tobacco-containing BQ. Based upon the participant observations and interview data, three main benefits were identified: as an appropriate accompaniment to Indian meals, as a way to improve work performance, and as a habit preferable to smoking. Each perceived benefit will be discussed in the following section.

An appropriate accompaniment to Indian meals

SA restaurants in the study community commonly offered BQ (without tobacco) to customers following meals. Participants perceived that the properties of BQ made it an ideal accompaniment to Indian meals because it acted as an effective mouth freshener, counteracting the taste and smell of onions, garlic and spices in Indian food. As a "natural" mouth freshener, one man viewed BQ as better than other artificial mouth fresheners which have "additives" (30-

year-old man, 16 years in Canada). Another participant compared BQ chewing to chewing gum as a way to keep one's mouth clean:

> It is the motion associated with BQ chewing which I find most enjoyable which is similar to the motion associated with chewing gums. It keeps your mouth moving and wet that is why people in western countries enjoy chewing gum. Some people smoke because they enjoy inhaling smoke. Similarly, we [SAs] like chewing because we enjoy both the flavours and motion which keeps mouth clean. (40-year-old man, 5 years in Canada)

Some mentioned that BQ provided a satisfying way to end a meal. For example, several men thought of plain BQ as a "kind of dessert with less sweet." Others touted plain BQ as a digestive aid, based on the belief that the BQ leaf had "digestive enzymes." Still others considered that the acceptability and enjoyment of tobacco-containing BQ chewing provided them with a way to meet their need for tobacco. Accordingly, these men thought that BQ provided a useful alternative to counteract the desire to smoke tobacco after meals, both at work or at home. One young man stated:

> You eat so much food that you feel sleepy and want to smoke. But we need to work, and every time we cannot smoke after meals especially at home, so you feel like chewing [tobacco-containing BQ]. This is an added advantage because chewing smokeless tobacco leaves alone is bitter and can cause vomiting. But chewing tobacco leaves along with BQ makes it more enjoyable and tastier. (39-year-old man, 17 years in Canada)

A way to improve work performance

The men also associated tobacco-containing BQ chewing with their ability to work by improving both mental and physical performance. A young man who recently immigrated to Canada stated:

> At that time [in school] it was extremely difficult to learn and memorize complex chemistry tables. But when we had these [BQ] in our mouth we could recall those complex tables. If we chewed while writing exams, not only our writing speed increased but we could recall answers as well. (25-year-old man, 2 years in Canada)

For some men, BQ chewing improved their ability to do hard physical work, as stated by a 60-year-old man (35 years in Canada): "After chewing I see people become more energetic and they work like horses". However, for others, BQ use was linked with combined improvements in mental and physical ability: "Once I chew I am totally into my work, my mind does not deviate here or there, but I only do my work and enjoy doing it" (58-year-old man, 23 years in Canada). Another 45-year-old man (22 years in Canada) stated, "chewing opens your eyes, keeps you awake and you can keep driving all night". This was consistent with the view expressed by another young man who explained that in western countries people drink coffee or tea to get aroused, but he preferred to chew:

> Chewing is like brain food, just like you need food for your body, you also need food for your brain. You need to do pretty heavy work the whole day and you require something to wake you up in morning and help you go to work. When I work in the restaurant suddenly a big bus of customers will come. There are so many orders, how to do so much work in so less time. So you require this brain food, you take it and you will work faster. (58-year-old man, 23 years in Canada)

A better habit than smoking

Many participants considered one of the main benefits of chewing tobacco-containing BQ products was a distinct advantage over smoking. This perception was based upon their knowledge about the harmful effects of cigarettes and smoking. For example, one man

explained: “In cigarettes there are 300 chemicals including cyanide but quid is a natural form of tobacco; it’s a leaf without chemicals, it’s organic” (39-year-old man, 17 years in Canada). Perceptions about the safety of chewing products also extended to other comparisons with smoking:

> Smoking damages your lungs, it is bad for you but chewing does not damage your lungs. When I used to smoke a lot of cigarettes like 20-30 a day, I used to become breathless, have dry mouth, burning in my chest. Sometimes, I even had vomiting but I do not have these problems with this [tobacco-containing BQ]. (55-year-old man, 6 years in Canada)

Perceptions about the safety of tobacco-containing BQ chewing products were reinforced by a belief that they contained less nicotine, as one man stated: “It [tobacco-containing BQ] has less nicotine, that’s why we [SAs] need to continuously keep chewing on it” (39-year-old man, 17 years in Canada). Also, chewing was thought to be safer for family and friends because, unlike second-hand smoke from cigarettes, chewing did not harm other people. BQ chewing was preferred over smoking among those who were concerned about the smell associated with smoking: “After smoking a cigarette there is bad smell from your mouth and clothes, people come to know you smoke but after chewing your mouth smells good”. (60-year-old man, 35 years in Canada). These views were similar to observations made in a brief conversation with a young SA man who stated that his smoking is seen as repulsive by his girlfriend but the fragrance of BQ is acceptable to her.

Tobacco-containing BQ chewing was also perceived to have distinct advantages over smoking when in public places: “I feel that I am a lucky guy to be able to have smokeless

tobacco on a plane but smokers can't have their cigarettes" (55-year-old man, 6 years in Canada), and at home:

> When I used to smoke then I had to wake up in middle of the night and go out and smoke cigarettes but now that I am chewing, I need not go out of house in the middle of night to take it, I just keep it in my mouth. When I wake up, I gargle and throw it [tobacco-containing BQ] out of the mouth. (45-year-old man, 22 years in Canada)

A few men preferred to chew tobacco-containing BQ rather than smoke tobacco because of cost, as explained by a 39-year-old man (17 years in Canada): "For the cost of one packet of cigarettes which lasts only for a day I can buy supply of tobacco-containing BQ or smokeless tobacco for a week". For one man, cost savings also resulted from the need to use less alcohol when chewing: "You get higher kick when you chew along with drinking alcohol, you drink less and it saves money". (58 year-old man, 23 years in Canada)

Some men who also smoked pointed to the advantages of using both tobacco-containing BQ and cigarettes. One man stated: "The mouth freshening property of BQ helped them get rid of the smell associated with smoking" (25-year-old man, 2 years in Canada). This was consistent with views of other SA men captured during participant observations who believed that the natural ingredients of BQ would cool the throat and chest after smoking and reduce its harmful effects.

Tobacco-containing BQ chewing was perceived to reduce the tobacco intake from smoking. One man explained, "A good thing about BQ chewing is that you cannot chew a lot because if you chew for a long time then your mouth will start paining and lime will burn your

tissues" (45-year-old man, 22 years in Canada). Although lime can damage oral mucosa, it was considered to be an essential constituent of quid, as explained by a 25-year-old man (2 years in Canada):

> Lime in our quid is like salt in the food, without it there is no taste. The more the lime in the quid, the more is its strength. So if you want to have more kick from nicotine you do not add more tobacco to it, just add some extra lime. This is how you control your tobacco intake.

Among men who had a history of smoking cigarettes, chewing tobacco-containing BQ was perceived to have the additional benefit of being a "natural" smoking cessation aid, as detailed by a 30-year-old man (16 years in Canada):

> [Tobacco-containing] BQ is like an Indian version of a nicotine gum or patch and just like in the western countries they have introduced NRT to aid people to leave smoking, we [SAs] chew [tobacco-containing] BQ which is a natural way to stop smoking.

In summary, these findings demonstrate SA men's positive perceptions about chewing tobacco-containing BQ, and support for their chewing habits.

Constructions of risks associated with chewing tobacco-containing betel quid

The majority of participants thought that tobacco-containing BQ was less harmful than smoking cigarettes and were unaware that BQ and smokeless tobacco were risk factors for oral cancer. Some men doubted the need for cancer prevention programs for SA persons, as demonstrated by an older man:

> I find it difficult to understand how these people [Canadians] can get cancer when they walk in sunlight. I used to work in Indian villages under intense sunlight for years but never developed skin cancer. In Canada, people develop lung cancer with second-hand smoke but I know so many chronic smokers in India who have not developed any cancer. In Indian villages there were traditional stoves which produced a lot of smoke but never anyone got cancer. Here [Canada] people exaggerate things and these are not applicable to us [SAs], our genes are strong and we [SAs] are genuinely healthy. I am chewing these things for so many years and I know it is totally harmless. (55-year-old man, 6 years in Canada)

A few men were concerned about the effects of BQ chewing on the mouth, as detailed by a 60-year-old man (35 years in Canada): "Betel nuts will hurt and prick, it will prick all over the mouth. Your teeth will become brown and the gums will be destroyed …. you can see the roots of the teeth right up to the bone". Other men attributed the lime in BQ as a harmful ingredient, as explained by a 30-year-old man (16 years in Canada):

> The lime in the quid is very strong and it can burn the gums and oral tissues. You can deal with pain but burning is very bad, it damages your gums…. A time comes when all your gums are gone and all your teeth have no support, people start to lose teeth and it can lead to gum cancer too.

Overall, SA men were not aware of the risk for oral cancer associated with BQ chewing and perceptions of harm were limited to oral effects such as gum damage.

Discussion

This study provides important insights about SA men's constructions of their chewing habit and perceptions about the benefits and risks associated with chewing tobacco-containing BQ. These empirical findings suggested that SA men continued chewing in order to participate

in SA cultural practices and social activities, to preserve long-standing traditions from their homelands, and to satisfy their need for tobacco. Some SA men perceived that living in a western country with no strict religious prohibitions on lifestyle choices and behaviours presented the opportunity to use tobacco concealed in accepted cultural practice without the negative social and health consequences associated with smoking cigarettes. This study details the complex socio-cultural connections underlying SA men's chewing habits as well as men's dependency on tobacco-containing BQ.

Although plain BQ chewing was viewed as an accepted and normalized practice among SA men, it was constructed as an unacceptable practice in mainstream western society. SA men, however, found ways to continue chewing outside the view of mainstream society (and sometimes their families). They positioned tobacco-containing BQ chewing as similar to smoking by Western men, but with a number of advantages over smoking. The ways that men use smoking to act out their identities and masculinities have been described elsewhere[230]. Evidence also showed that chewing tobacco-containing BQ is associated with masculinity. For example, benefits of chewing related to improved mental and physical performance and enhanced control over tobacco use correspond with reported SA men's masculinities[182,231]. The desire for individually prepared tobacco-containing BQ, often to get a "kick," and their professed ability to conceal chewing from others and from mainstream society may also reflect autonomy and risk taking, additional aspects of masculinity. Furthermore, by considering a gender relations approach, it is possible to examine men's and women's interactions with each other and the circumstances which contribute to health opportunities and constraints[232]. This research suggests that men found ways to circumvent women's efforts to discourage chewing tobacco-containing BQ, such as restricting chewing to times which were culturally acceptable (e.g.,

following meals or at social gatherings) or when absent from their families. Chewing tobacco-containing BQ also provided an inexpensive way to consume tobacco, positioning men as responsible and savvy consumers. These findings add to a growing body of literature which indicates that gender, as a determinant of health, can be effective in providing new understanding to men's health-related practices. As such, gender and socio-cultural influences should be considered when developing approaches to prevent and reduce tobacco-containing BQ chewing among SA men.

Canada has been a world leader in implementing health warnings on tobacco products, including picture-based warning messages; however, warnings for smokeless tobacco products are less stringent. Currently, tobacco-containing BQ plastic or paper wraps contain either no warning labels or labels with false information such as "mouth fresheners", sweets or candies. Public awareness about the health risks associated with BQ and its constituent products including smokeless tobacco could be increased with appropriate product labelling. Policies supporting the addition of health warnings on all packaging of tobacco-containing BQ and the posting of health warnings in retail outlets selling these products are important first steps. Findings of this research suggest that health advocates need to work closely with SA communities to enhance awareness about the health effects of tobacco-containing BQ. Efforts to enhance knowledge in SA community about cancer-related topics provide a starting point[180,233,234]. Since BQ has strong connections with Hindu religious practices, collaboration is also needed with religious leaders in order to identify strategies to reduce the harmful health effects of BQ use.

Many SA men who participated in this study were found to be addicted to tobacco-containing BQ. Little is known about how to support those desiring to stop chewing; these

findings provide important insights for developing effective interventions. Recognizing the gender and socio-cultural influences reported in this study, male-centred approaches tailored to support SA men in reducing and stopping chewing are suggested. This study demonstrated that some SA men chewed tobacco-containing BQ to aid in smoking cessation; other approaches are needed to support SA men in quitting smoking. A starting point for health promotion efforts to address chewing habits may be to take advantage of opportunities where SA men commonly meet and socialize. Strength-based approaches have been suggested for addressing a range of men's health issues[182]. Focusing upon men's strengths, rather than their deficiencies, may be important in developing programs for SA men. For example, SA men are often decision makers in family health issues. This could be used as a focal point for health promotion related to BQ chewing. Another approach may be to support autonomous decision making by providing opportunities to explore a range of alternatives to reduce chewing and encourage men to make their own choices. Diversity among SA men also needs to be taken into account. Since some SA men conceal BQ chewing from others and the presence of smokeless tobacco in the BQ products they chew, programs may need to be individualized and offered in such a way that they do not expose men's chewing habits. Free access to nicotine replacement therapy may also be needed for some in order to reduce barriers related to cost and socio-economic status. Based on study findings, smoking cessation aids that hold potential are nicotine replacement therapy in the form of gum in conjunction with healthier alternatives related to reasons for chewing (e.g., digestive aids and mouth fresheners). There may also be a need for assistance in cessation of psychoactive alkaloids (present in acrea nut). Because chewing is practiced by men to reduce stress, stress management may be an important component of programs to support cessation.

The results of this study need to be viewed in the light of its limitations. Data were collected in one urban community in Western Canada, a region known for its strict tobacco control policies and low smoking rates. The influence of these factors on the way men viewed chewing tobacco-containing BQ as a way to circumvent restrictions on smoking and as superior to smoking tobacco may not be evident in regions with less-stringent tobacco control policies and general acceptance of smoking practices. Although the study sample included a reasonably diverse sample of SA men who chewed tobacco-containing BQ, the full range of experiences may not have been captured.

This research's qualitative study provides some significant insights into perceptions of SA men about chewing tobacco-containing BQ and provides directions for health promotion programs and policies. Since the majority of oral cancers caused by these chewing habits are preceded by precancerous lesions, education, health promotion and harm reduction programs will be effective approaches for primary prevention of oral cancers among SA men in BC.

Chewing tobacco-containing BQ increases the risk of oral cancer, and the habit continues to be very popular among SA men in BC. There is a need for policies to regulate the sale and labelling of such oral chewing products. Health promotion programs and harm reduction strategies that are culturally sensitive and male-centered are needed to raise awareness about health risks associated with its use. The findings of this study provide a strong foundation for the development of such initiatives.

Figure 20: Betel quid with sun-dried smokeless tobacco leaves

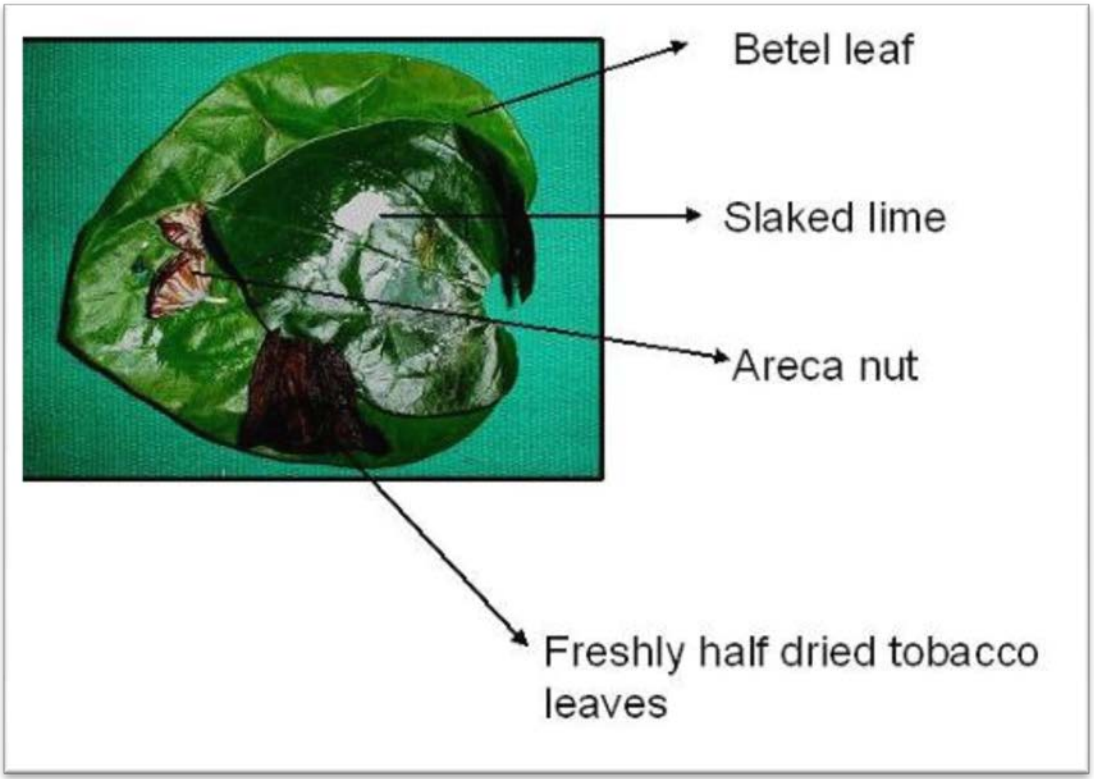


Figure 21: Bulk quantities of areca nut kept on shelves for sales along with grocery items

Figure 22: A menu card from a South Asian restaurant advertising use of betel quid as a form of cultural tradition

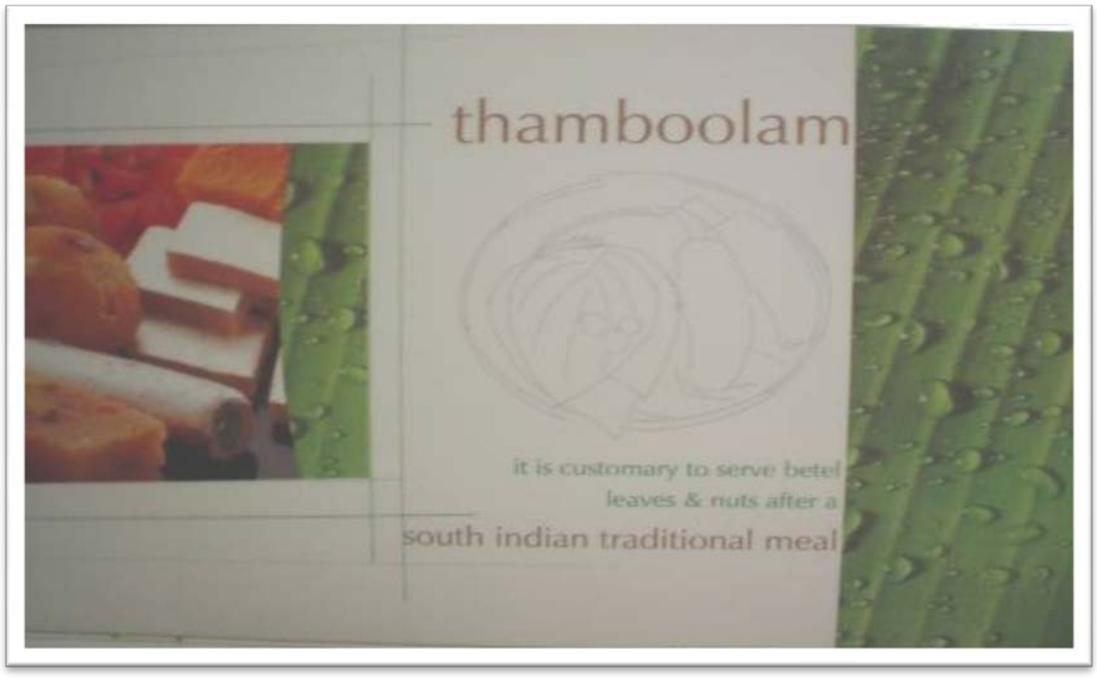
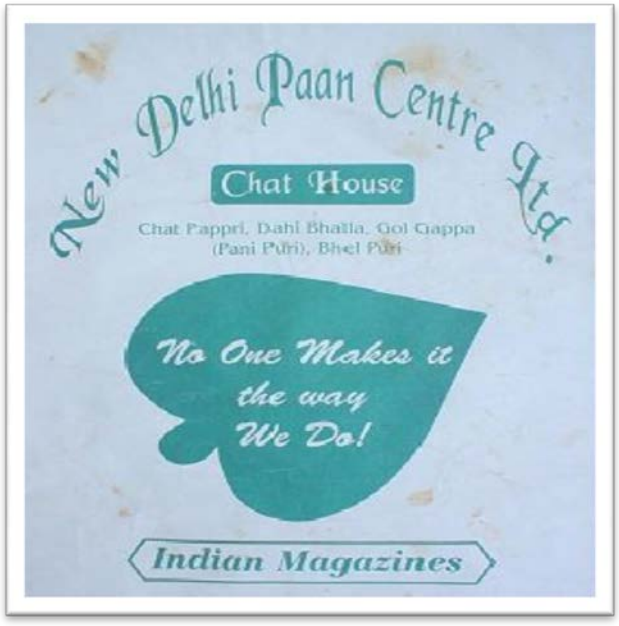


Figure 23: Display boards kept in the market to advertise for betel quid

Figure 24: A pamphlet used for marketing of betel quid



CHAPTER 7: CONCLUSION

The findings of this mixed method dissertation research make a substantive contribution to the understanding of oral cancer. This work is among the first reports in the literature to show epidemiological shifts in incidence and survival rates for OPC and OCC by sex, subsite and ethnicity (South Asians and Chinese). When this dissertation research began, the approach of examining etiological clusters of subsites was very novel. There was a single hypothesis-generating paper, published in 2008, that showed that the incidence of oral cancer at HPV-related sites (OPC) was significantly increasing in men but decreasing in women in the US from 1973 to 2004[36]. This epidemiological study was based upon an earlier report by Gillison et al[120] in 2000 which showed a causal association between HPV infection and OPC. This area of research has subsequently become very active. Since the start of this dissertation others have published on the incidence and survival of OPC and OCC[7,10-15]; however, subsites, sex and ethnicity have not received consistent attention. The quantitative findings of this research demonstrate that these are critical determinants of incidence and survival which also guide in the identification of high-risk groups.

The dissertation showed that some subpopulations shoulder a larger burden of oral cancer than others. SA men were identified as one such subgroup at high risk for OCC. To begin to understand the complex processes that place people at risk, a qualitative ethnographic study was conducted to describe beliefs and practices related to tobacco-containing BQ use among SA men, which is a common practice among them and a well-established risk factor for OCC. This ethnographic research lays the groundwork for developing an understanding of the ways that socio-cultural context shapes and influences health behaviour that places SA men at

risk for oral cancer following immigration. Such understandings provide a basis for identifying approaches to change risky practices and prevent oral cancer in this high-risk community.

The findings from both quantitative epidemiological studies and the qualitative ethnographic study were presented and integrated with the literature in Chapters 4, 5 and 6. In this chapter, key findings from these three studies will be integrated and overall implications for oral cancer control will be discussed. The value of using both quantitative and qualitative studies will also be described. Limitations of this dissertation research will also be presented as well as recommendations for future research.

Key findings and implications for oral cancer control

Effective oral cancer control is dependent on a full understanding of underlying etiology. As such identifying etiological shifts in populations as early as possible is critically important to this endeavour, and this can be difficult. Most often, such findings originate from epidemiological observations which can result in the generation of hypotheses but must be replicated in other populations. This is needed in order to determine how generalizable the findings are to different populations. If these findings are inconsistent, then further hypotheses about what is triggering the observed shifts in different populations at different points in time needs to be explored. For example, in this study differences were observed in survival for some subsites by sex and examined for differences in staging at diagnosis in different time periods (1980-1993 and 1994-2005). Interestingly, the usual observation that early-stage disease is associated with better survival was seen in women for OPC in both time periods. However, in men, survival for OPC was unaffected by stage of disease in the second time period. The

researchers have no explanation for this. It may indicate that etiological shifts in OPC are occurring at a different pace in males or that males and females differ significantly in some other aspect of their natural history. If there are etiological differences in OPC for males and females, detection and treatment strategies might need to be different for the two sexes.

Consistency of findings in different studies and populations is also important to consider when examining for etiological shifts. The results of population-based studies that examined OPC and OCC subgroupings indicate that the incidence of OPC is increasing. This was a consistent observation. In fact, the findings of this dissertation research indicate that in BC the incidence of OPC has surpassed the incidence of OCC in males. There was also agreement across these population-based studies that OPC is predominantly a male disease, although male-to-female ratios vary widely among different countries. Again, no explanation is readily apparent for this.

The investigation of etiological shifts for oral cancer is really at an early stage. All of the population-based studies examining OPC and OCC subgroups have been conducted in developed countries. Also, in most instances researchers examine data only once from each country. There is also a shortage of data on exposures. For example, although the observed trends are consistent with a hypothesis of a shift in etiological factors, with HPV taking a more prominent role for OPC and with tobacco cessation taking a more prominent role for OCC, all studies suffer from the lack of direct exposure data. Few studies have directly linked incidence and survival data to differences in smoking behaviours over time, and there is little data on HPV in general (molecular epidemiology data is only reported from US[126] and Sweden[125]) and

virtually none on changes in behaviour that are thought to be associated with HPV's increasing prominence. This said, the findings of this dissertation research along with the other publications in this area indicate that a change in etiology is occurring which has important clinical ramifications. Together, these observations point to the pressing need to expand research on oral cancer to include cross-country comparisons and to get consensus on the collection and definition of exposure data. For example, universal agreement on how to measure HPV-DNA in tissues or etiologically cluster subsites would greatly facilitate these studies.

For OPC, the literature has begun to focus specifically upon tonsils[235]. The findings in this dissertation research suggest that this is appropriate, because tonsils had the highest incidence rates among the subsites in both males and females; this has also been consistently reported in other studies in the literature (see Chapter 2, Table 1). In addition, subsite analysis is also important for OCC. In both sexes the incidence for the ventrolateral tongue was found to be increasing whereas that for the floor of the mouth is decreasing. This observation is further complicated by differences in survival trends: survival for the ventrolateral tongue is improving, but only in females; for the floor of the mouth it is decreasing in both sexes. This is striking data that needs further exploration and replication.

Although there have been very few survival studies and these have been in different countries, they have generally shown an improvement for OPC. This observation is supported by case-control studies and secondary analyses in clinical trials[140,141,144]. Hence, the etiological transition seen in OPC is also appearing in the survival for these HPV-related subsites. Again,

this needs further investigation and should consider the impact of staging and treatment in different ethnic subpopulations where risk behaviours may differ.

Since risk factors and survival are likely to vary considerably globally, one would expect to see shifts happening at different rates depending on locale. Hence, it is important to get a global perspective on these shifts. From this standpoint, the paucity of data from populations in SA and China is troubling. These are large populations with high exposures to known risk factors for oral cancer (see discussion of smoking and BQ chewing in Chapter 6). The epidemiological literature shows that the incidence is high for oral cancer in SA. The issue of survival is not addressed, although data from a pooled analysis showed that SAs had poor survival[236]. An important limitation of the global data is that cancer registry data is incomplete and generally restricted to small proportions of the total population. Furthermore, these studies do not provide site-specific data that considers etiological subgroupings (i.e., HPV-related, tobacco-related).

To begin to address these issues, SA and Chinese subpopulations in BC, many of whom are recent immigrants, were examined to describe trends in incidence and survival for specific subsites. At times, these numbers are small but they are population-based and reflect real frequencies. This information is helpful to generate hypotheses and future research questions. For example, the incidence of OPC was highest in Chinese males. Given the increase in tobacco consumption in China, especially in males[80,237], and since OPC can be caused by both tobacco and HPV, a key question is whether or not the etiology of OPC in Chinese is more tobacco-related or HPV-related. Adding to this issue is the fact that two small case studies found a very low frequency of HPV-DNA presence in the tonsil cancers[201,238]. Of note, case selection in one of these studies was mainly from males[201].

Additional support for the value of looking at ethnic subpopulations comes from the analysis of both SAs and Chinese in this dissertation research. SA men had the highest incidence for OCC when compared to Chinese and the general BC populations. Furthermore, these cancers occurred at subsites not seen in the general population but which are observed among BQ chewers in India[21]. Together, these data suggest trends that are reflective of the incidence of oral cancer in the home country. Whether the incidence of OPC is also reflective of that found in the home country is unknown.

It is clear from the findings of this mixed method study that ethnocultural influences were evident in both epidemiologic and ethnographic findings. Cultural influences on conceptions of health and illness, health practices and expectations related to health care have been recognized. However, researchers have also pointed to the importance of understanding how people participate in culture, recognizing that this may vary considerably within groups and in different contexts and be influenced by colonial practices and structures in society[239]. The qualitative findings in this dissertation research provide a rich description of cultural influences (e.g., religion, social norms) on SA men's chewing habit and how culturally based practices such as chewing are also shaped by and accommodate social conventions and structures in western society. Also evident in the qualitative findings was evidence that other social factors, such as socio-economic status and gender, also need to be taken into account in understanding risk behaviours. For example, in relation to gender influences, masculine ideals appeared to play an influential role in sanctioning men's use of tobacco-containing BQ. These findings provide further support for considering the role of social as well as biological factors underling epidemiological trends in oral cancer.

In addition to implications discussed above, there are several other implications arising from the dissertation findings. Firstly, these findings point to the importance of developing policies and practices that are tailored specifically for at-risk groups. The unregulated status and ready availability of tobacco-containing BQ were important factors which promoted chewing in the study community. Tobacco-containing BQ poses a significant challenge for Canadian Tobacco Control policies. In 2009, the Canadian Parliament passed Bill C-32, known as the Cracking Down on Tobacco Marketing Aimed at Youth Act, which amended the Tobacco Act by introducing a ban on flavourings and additives in cigarettes, little cigars, and tobacco wrappers ('blunt wraps'). The government opted not to extend the ban to smokeless tobacco, despite recommendations from health agencies and youth groups to do so. Rather, Health Canada requested additional study on the use of smokeless tobacco before making any further recommendations[240]. This findings in this dissertation suggest that the sale of smokeless tobacco in BQ needs urgent attention as the lack of health warnings is contributing to perceptions that these products are safe alternatives to cigarette smoking. Policies are also needed to regulate the content of lime in tobacco-containing BQ. Reduction in lime as a harm reduction strategy would make less nicotine and alkaloids available during chewing and reduce the damage caused by lime in generating free radicals and promoting carcinogenesis. The qualitative methods used in this study provide a useful approach for developing the kind of in-depth understanding of risk behaviours in at-risk groups that is needed to guide the development and implementation of culturally appropriate and gender-sensitive initiatives.

Secondly, there is need to address the limitations in cancer registry data. Current data fields limit the ability to study risk behaviours, and monitor the success of prevention and

treatment initiatives. There is a need to augment registry databases to collect exposure data or, at least, provide the means for data linkage with other exposure databases. For example, ethnicity and complete treatment data are rarely collected. There is also need for consistency in databases across registries to facilitate comparisons across regions and countries.

Thirdly, there is need to develop global networks and supporting infrastructure to support oral cancer control efforts on an international level. International collaborations could accelerate research to understand the roles of different risk factors and shifts in these factors across different populations. This would also help address the problem of small numbers in some subgroups. International networks would also support advances in knowledge related to social influences on oral cancer and the development of prevention and cessation initiatives through collaborative research and knowledge exchange. Public health interventions to help SA immigrants stop chewing smokeless tobacco products have recently been launched by the National Institute for Health and Clinical Excellence in the UK; these initiatives may guide the adoption of similar startegies for SA immigrants in BC[241].

Fourthly, there is a pressing need to raise awareness among dental practitioners about the trends in incidence and survival in oral cancer and at-risk groups. Programs to support oral cancer screening in high-risk communities are currently underway in Canada[242] and other western countries[47]. However, in addition to oral cancer screening, dental practitioners need to be encouraged and supported to provide information about oral cancer and risk behaviours to at-risk patients in culturally appropriate and gender-sensitive ways. The development of health promotion resources for use by dental practitioners is, therefore, a priority. These research

findings also have implications for the education of dental professionals. Dental students need to be made aware of the etiology of oral cancers, including tobacco-containing BQ among SAs, and its implications and the need to consider such knowledge while doing oral assessments and diagnoses and during clinical decision-making. In addition, dental curriculae should include instruction on the presentation of oral cancer and risk profiles for different ethnic groups.

Finally, the findings of this dissertation have implication for policy. The implementation of comprehensive tobacco control policies in Canada has led to significant reductions in smoking rates across the country[243]. The findings of this dissertation research indicate that there are significant challenges and gaps in the application of tobacco control policy when tobacco is distributed in the form of tobacco-containing BQ. However, there is an urgent need to extend these tobacco control policies to include tobacco-containing BQ. This will be challenging because Canadian tobacco policy makers and law enforcement bodies are largely unaware of these products. Additional legislations may be required for controlling amount of areca nut and lime in tobacco-containing BQ. The research findings will help inform efforts to include tobacco-containing BQ under Canadian Tobacco Control Policies.

Study limitations

The findings of this dissertation need to be considered in the light of its methodological limitations. Although the BCCR provided a comprehensive provincial population-based, long-term data set for the epidemiological analysis of incidence and survival, there were some limitations in using these data. The inclusion criteria for case selection required histopathological confirmation of squamous cell carcinoma. However, not all cases of OPC

undergo biopsy, instead simply undergoing fine needle aspiration. Hence, these cases were missed. Since fine needle aspiration has become a more-common practice in recent years, the increase in incidence for OPC reported in this dissertation reflects an underestimate of the true increase. The BCCR used in this study also lacks information on ethnicity in its database. This necessitated the use of ethnic surname listings to identify the SA and Chinese cancer cases, which was only possible because of the availability of previously developed and validated surname lists for these two ethnic populations[183,184]. These surname lists, developed locally for the BC population, would result in an underestimate of the true number of cancer cases in these two ethnic groups. Another limitation of the BCCR was the lack of complete treatment data in its database. The BCCR does not record radiation dose and chemotherapy regimens. An attempt was made to obtain this data from other sources for the survival analysis, as treatment is an important prognostic indicator. However, this information was not readily available. Given the growing awareness of the importance of HPV status in the etiology of OPC, the absence of HPV status in the tumour tissue was also an important limitation. This necessitated the defining of HPV-related and HPV-unrelated subsites based on reports in the literature. However, such grouping will not inform us about the cancer trends in patients with no risk factors.

Although a rich description about the use of tobacco-containing BQ was generated using ethnographic methods, this ethnographic research only focused upon tobacco-containing BQ chewing among SA males who have immigrated to BC and may not be generalizable to SA men living in other contexts. BC is well known for having strong tobacco control policies. Not included were SA females because more SA males than females accessed tobacco-containing BQ and the researcher (AA) who conducted the study was male. The researcher had in-depth

knowledge of the SA culture and was well aware that it is not culturally appropriate for a male to conduct prolonged interviews with female participants in the SA community.

Finally, there is a wide range of oral chewing products used among SA which contain similar ingredients (areca nut, smokeless tobacco and lime). The study findings cannot be applied to other oral chewing products. In this study, all participants chewed tobacco-containing BQ; however, they were not excluded if they were concurrently chewing some other oral chewing products.

Implications for future research

In Chapters 4, 5, and 6, a number of issues for future research were identified that related to the specific findings reported in each of these chapters. There are additional implications for research based on the study findings as a whole.

Further research is needed to understand the natural history of oral cancer and further the understanding of the etiological role of HPV in OPC. Many unanswered questions remain, such as 1) how are oral HPV infections transmitted, 2) how does the natural history of HPV differ for cancers occurring in the mouth and the cervix, 3) what role does tobacco use and other co-factors play in the persistence or clearance of oral HPV infection, 4) what subgroups with persistent oral HPV infection subsequently develop OPC, and 5) whether or not OPC is proceeded by oral premalignant lesions. To understand the natural history of oral HPV infection there should be standardization of methodologies for HPV-DNA analyses in specimens.

There is also a need for prospective clinical trials to guide oral cancer treatment recommendations which should consider targeting specific subsites.

Since immigration is projected to increase in Canada, there is need to consider ethnicity in these epidemiological analyses of oral cancers. There is also the need to focus on the dissemination strategies for health promotion and education materials to high-risk populations for which social networks provide a useful starting point[244]. The literature suggests that lack of knowledge about the western health care system, language barriers, experiences of discrimination and racism have been reported to contribute to SA immigrants' poor participation rates in cancer screening programs and underutilization of health care services[245,246]. Therefore, studies should focus on accessing the barriers and facilitators of oral cancer screening among SA. Although beyond the scope of this dissertation, additional qualitative studies are clearly needed in Chinese in order to describe their at-risk behaviours and to better understand their beliefs and practices related to oral cancer. Information from these qualitative studies could be used to develop culturally relevant health promotion and education materials and oral cancer prevention programs for each of these ethnic groups.

Further study of the availability and access to tobacco-containing BQ in SA communities in other regions in Canada would also provide needed evidence to identify strategies to support the development and implementation of regulatory policies (e.g., to control contraband imports; to ensure accurate labelling of products as containing tobacco). For example, a province-wide survey is warranted to describe the prevalence of use of tobacco-containing BQ and concurrent tobacco products among SAs and other population subgroups.

Conclusion

The etiology of oral cancer is very complex and changing. This dissertation research showed that trends in incidence and survival differ for OPC and OCC, possibly due to changes in

the underlying etiological factors associated with these different sites which might target different subpopulations, such as SA men. These changes in trends will have implications for treatment and management of oral cancers. The findings also support an emerging role for HPV in the etiology of OPC which may have serious implications for patient management; further, biological, behavioural and clinical research is clearly required. The findings also point to the need for bringing tobacco-containing BQ under the Canadian Tobacco Control Policies and for developing and implementing a culturally appropriate and gender-sensitive health promotion program for SAs in order to increase their awareness about the ill-effects of tobacco-containing BQ. There is clearly a need for more research in the area of oral cancer on the global scale. The findings of this dissertation research provide a strong foundation for continued work in this field and aimed at identifying effective detection, prevention and treatment strategies for oral cancer.

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APPENDIX A: RESEARCH PROJECT CONSENT FORM

Consent form for participation in qualitative interviews

Social and cultural context of betel quid chewing behaviours among South Asian community members in BC

Subject Information and Consent Form

BCCA REB # H08-01930

BCCA Principal Investigator:	**Dr. Miriam Rosin**
Cancer Control Research	
Project Co-Investigators:	
Dr. Joan Bottorff	Health and Social Development/UBC, Okanagan
Dr. Catherine Poh	Faculty of Dentistry/UBC
Dr. Lewei Zhang	Faculty of Dentistry/UBC
Dr. Ajit Auluck	Faculty of Dentistry/UBC
Sponsors:	BC Cancer Foundation
	Royal Bank of Canada

Background

Thank you for responding to our request for volunteers to participate in this study and for allowing us to interview you and learn more about the social and cultural context of betel quid chewing behaviours in your community. With a better understanding of this experience, we hope to better understand how to make culturally appropriate health promotion programs for the South Asian community in British Columbia.

Your participation is voluntary and your health care will not be affected whether or not you agree to participate in this study. However, participation may make you more aware of your dental health and behaviours, which might cause you to do more about it. This study is being conducted as part of Dr. Ajit Auluck's doctoral thesis.

Purpose

The purpose of this study is to collect information about your risk behaviours that may affect your oral health. Your experiences will help us develop better information and educational resources for promoting healthy lifestyles and health for South Asians.

Who Can Participate In This Study?

You may participate in this study if:

- You are of South Asian ethnicity, whether an immigrant or a Canadian citizen.
- You are over age 18.
- You can clearly speak and understand English, Punjabi or Hindi.
- You fully understand the study and give your informed consent to participate as demonstrated by signing this consent form.

Study Procedures

Your participation will involve an interview in which you will be asked questions regarding your behaviours that may affect your health. The interview will last approximately 1 hour. With your consent, this interview will be audio recorded. In addition, you will complete a short general questionnaire about yourself.

If any information is missed during the interview, you may be contacted by telephone. You might also be invited to participate in a focus group, a small group that includes others like you led by a researcher, where you will be asked to provide feedback on the study findings.

Benefits & Risks

There are no risks associated with your participation in this study. If you feel uncomfortable with any question you can choose not to answer that particular question. Although there is no direct benefit to you from this study, we hope that the information learned from you may improve the health care provided to your community in the future. For taking time out to participate in this study you will be reimbursed $20.

Confidentiality

Your confidentiality will be respected to the extent permitted by applicable laws and regulations, and your 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. All information and materials associated with this study will be kept behind locked doors or in secure computer files.

Your rights to privacy are legally protected and guaranteed 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.

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. Miriam Rosin, or co-investigator, Dr. Ajit Auluck, at ###-####-####.

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 ###-####-####.

Subject Consent

I understand that participation in this study is entirely voluntary. I may choose not to participate or I may withdraw from the study at any time. 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	Printed name	Study Role	Date

Person Obtaining Consent

If this consent process has been done in a language other than that on this written form, with the assistance of a 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.

☐ The person signing below acted as a translator for the subject, during the consent process.

Signature of Person Assisting in the Consent Discussion	Printed Name	Date

APPENDIX B: RESEARCH PROJECT DATA COLLECTION TOOLS

Guide for the qualitative interviews

Q1) We are interested in learning about the use of betel quid (paan) among South Asians after they come to Canada. In what situations would I find these products being chewed here in Vancouver?

Probes: Who is most likely to be chewing paan in Vancouver? When? Where? How does this compare with India [your home country] (probe – what do you think are the most important differences? What is the same?)

Q2) What are the places in Vancouver where betel quid can be bought? How do people come to know about the places where these products are available?

Probes: Any problems in buying these products? Any restrictions for anyone buying them? Do people buy directly or ask someone to buy for them, ie, women asking husbands to buy them?

Q3) How do you think peoples' habits related to chewing in Canada have changed? [Probes – is it different for men and women? Older and younger people? How its different compared to India?]

Q4) When do people start to chew betel quid (paan) in Canada? How does this usually happen? When do people stop using it? [Probe: any difficulties with this?]

Q5) What are your own personal chewing habits? [Probes: When do you chew? With whom? When is chewing most enjoyable? What do you like most about it? Is there anything that you dislike about it?]

Q6) We are interested in knowing more about the reasons that people chew betel quid (*paan with smokeless tobacco, areca nut etc).* What do you think are some of the reasons people chew?

Q7) Can you tell us of any traditional, religious or cultural beliefs associated with use of betel quid?

Q8) In your opinion, what are the most important health effects of chewing betel quid?

Probes: Why do you think people chew them after meals?

Q9) What, if any, harmful effects do you think there might be with regular chewing?

Probes: Do you think chewing of betel quid has any effect on color of teeth or skin of the mouth?

Q10) How do you think most people like to chew betel quid? Do they keep it at some particular place in the mouth or do they chew it like any other normal food?

Probes: Do you think some people keep it between their gum and cheek?

Q11) After chewing betel quid do you think the contents are usually swallowed or do you think most people spit the contents and juices out?

Probes: How does this compare with the way people chew in India? [Is it normal for people to swallow juices or the contents after chewing?]

Q12) Who are the people who are most likely to chew these betel quid regularly? [Probe if necessary: Is it only men who chew betel quid or do you think that women and children also chew betel quid?] How many betel quids do you think most people may chew on an average in a day? A week? Who chews the most? The least?

Q13) What kinds of functions is betel quid often served at (e.g., parties or social functions)? Can you please share some of your experiences with us?

Q14) Is there anything else you will like to tell me which I haven't asked?

Thank you for your time.

Demographic survey

Participant Code: _____ Age: _____ Gender: _____ Religion: _____

1. What is your most fluent language:

   □ English □ Punjabi □ Hindi □ Other, please specify _____

2. What is the highest grade (or year) of high school or elementary school that you have completed?

   Grade ___ Never attended school ____

3. How many years of post-secondary school have you completed (college, university)?

   None ____ Years ____

4. What do you do for work?

   □ Homemaker

   □ Employee, please specify _____

   □ Self-employed, please specify _____

   □ Retired professional, please specify _____

   □ Retired self-employed, please specify_____

   □ Other, please specify_____

5. Who do you live with? Check all that applies to you

   □ Alone;

   □ With spouse;

   □ With other relatives / family members (i.e., children);

   □ With other non-family members (i.e., friends)

   □ Other: _____

6. What is your current marital status? Check one box only:

    □ Married or Living Common Law

    □ Divorced

    □ Separated

    □ Widowed

    □ Never married

7. Ethnicity (by self-identification)

    □ India (East Indian) □ Sri Lankan □ Pakistani; □ Bangladeshi □ Other _____

8. Country of your birth: _____

9. Country of your parent's birth

    Father: _____

    Mother: _____

10. How long you have been in Canada? _____Years

11. When did you come to Canada? _____Years

12. When did you last visit India? _____Years

13. Circumstances for Immigration (e.g., family sponsored; health concerns; retirement):
    _____

14. Family income: □ less than $12,000; □ 12,001 – 50,000; □ >50,000

15. Visited a Dentist in Canada during past 12 months?

    □ Not at all

    □ At least once

    □ At least once a year

□ other, please specify _____

16. Date/place of your last visit to a dentist _____

(Please specify whether Canada or India)

17. Are any of your dental expenses covered by insurance (e.g., dental plan)?

□ Yes □ No □ Do not know

18. Have you smoked 100 or more cigarettes in your life?

□ Yes □ No

If no, which is most important motivator for you

□ Religious/cultural beliefs

□ Family reasons

□ Personal choice

□ Health reasons

□ Other

19. Have you ever consume more than TWO alcoholic beverages per week?

□ Yes □ No

If no, the reason for your non-consumption

□ Religious/cultural beliefs

□ Family reasons

□ Personal choice

□ Health reasons

□ Other

20. Have you had a drink of alcohol (beer, wine or liquor) in the last 30 days?

□ Yes □ No

21. Have you ever used betel quid (paan), paan masala or gutka?

□ Yes □ No

If no, the reason for your non-chewing

□ Religious/cultural beliefs

□ Family reasons

□ Personal choice

□ Health reasons

□ Other

22. Have you chewed betel quid in the last 30 days?

□ Yes □ No

Date of interview: _____ Interviewer:_____

Template for participant observations

Date: **Venue:**

Participant observation #:

a. Occupation _____
_____

b. Recency of stay in Canada _____
_____

c. Social history _____
_____

Make observations about the participants

a. Appearance - clothing, gender and age
_____

_____

b. Verbal behaviour – how interaction was initiated, who initiated it, tone of participant's voice
_____

_____

_____

c. Physical behaviour – what does the participant do and how does he/she act in the setting during the discussion

_____
_____
_____

1. Observe norms/practices related to the purchasing and what type of product people buy from the shop, ie

    a. Betel quid
    b. Betel quid (with areca nut)
    c. Betel quid (with areca nut & tobacco)
    d. Smokeless tobacco (freshly prepared mixture with lime)
    e. Smokeless tobacco (packaged preparation)
    f. Smokeless tobacco with areca nut
    g. Smoking tobacco
    h. Smokeless tobacco and smoking tobacco
    i. Betel quid, smokeless tobacco & smoking tobacco

2. Observe what they do with the product
    a. chew or smoke immediately in the setting
    b. only parcel it for later use
    c. chew few in setting and parcel few for later use

---

3. Observe behaviours that precede or follow up before and after using these products

Precede

After

Template for recording field observations

Date:

Time:

Place:

Venue:

Conducted by:

Context of being present at the site

Setting of selected site (describing what's happening at the site)

Observations

Objective notes	Reflective notes	Interpretations

Future questions

APPENDIX C: DESCRIPTION OF THE HISTOLOGY CODES

Histology codes	Description of histology codes
80503	Papillary carcinoma, Not otherwise specified
80513	Verrucous carcinoma, Not otherwise specified
80520	Squamous cell papilloma, Not otherwise specified
80522	Papillary squamous cell carcinoma
80523	Papillary squamous cell carcinoma
80701	Squamous cell carcinoma, Not otherwise specified
80702	Squamous cell carcinoma in-situ, Not otherwise specified
80703	Squamous cell carcinoma,Not otherwise specified
80713	Squamous cell carcinoma, keratinizing
80723	Squamous cell carcinoma, large cell
80733	Squamous cell carcinoma, small cell
80743	Squamous cell carcinoma, spindle cell
80833	Basaloid squamous cell carcinoma

APPENDIX D: SUPPLEMENTARY FIGURES FROM SURVIVAL ANALYSIS

Figure 25: Disease-specific survival rates for OPC and OCC by gender and tumour size from 1980 to 2005 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

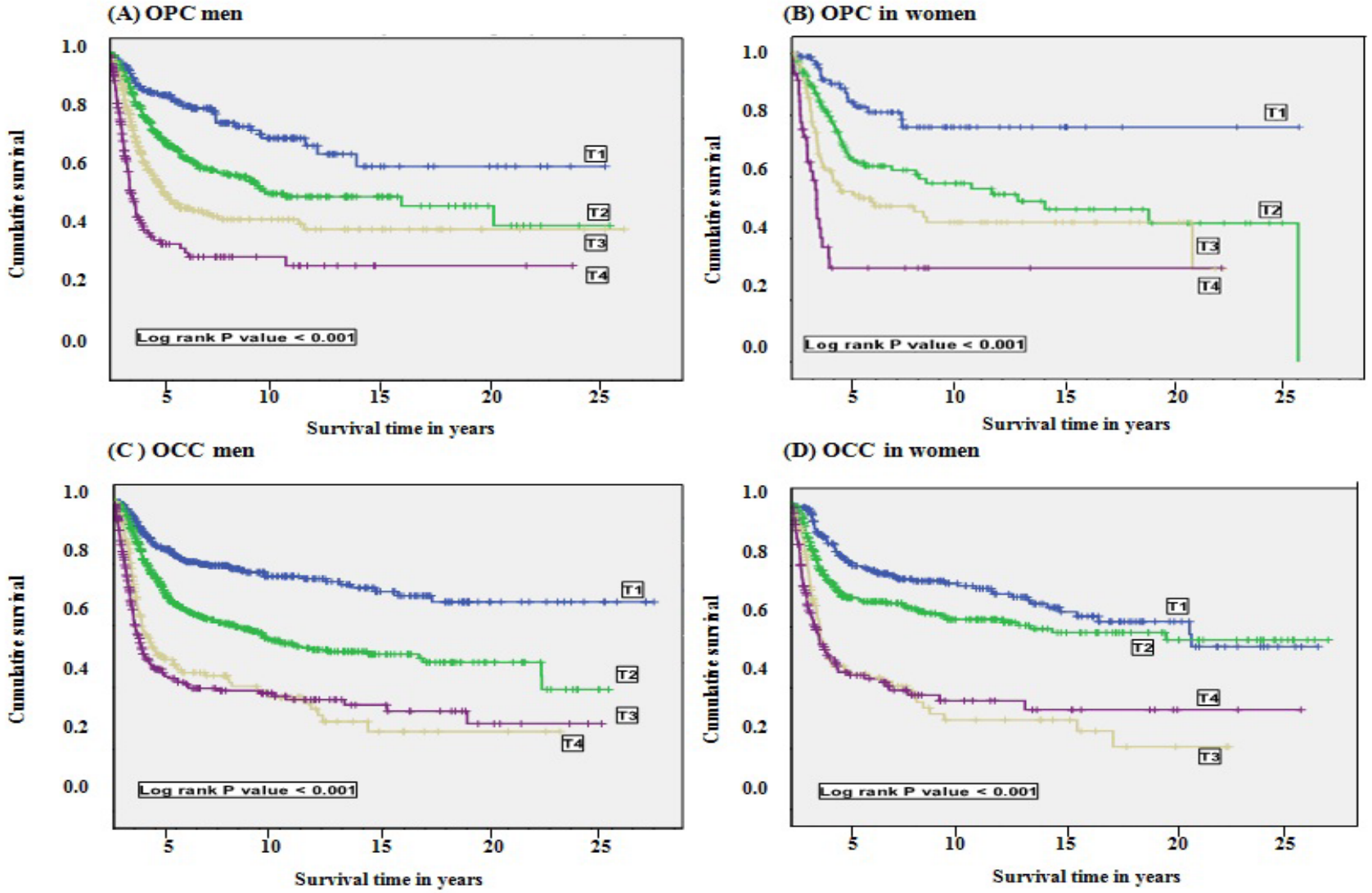

Figure 26: Disease-specific survival rates for OPC and OCC by gender and tumour size from 1980 to 1993 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

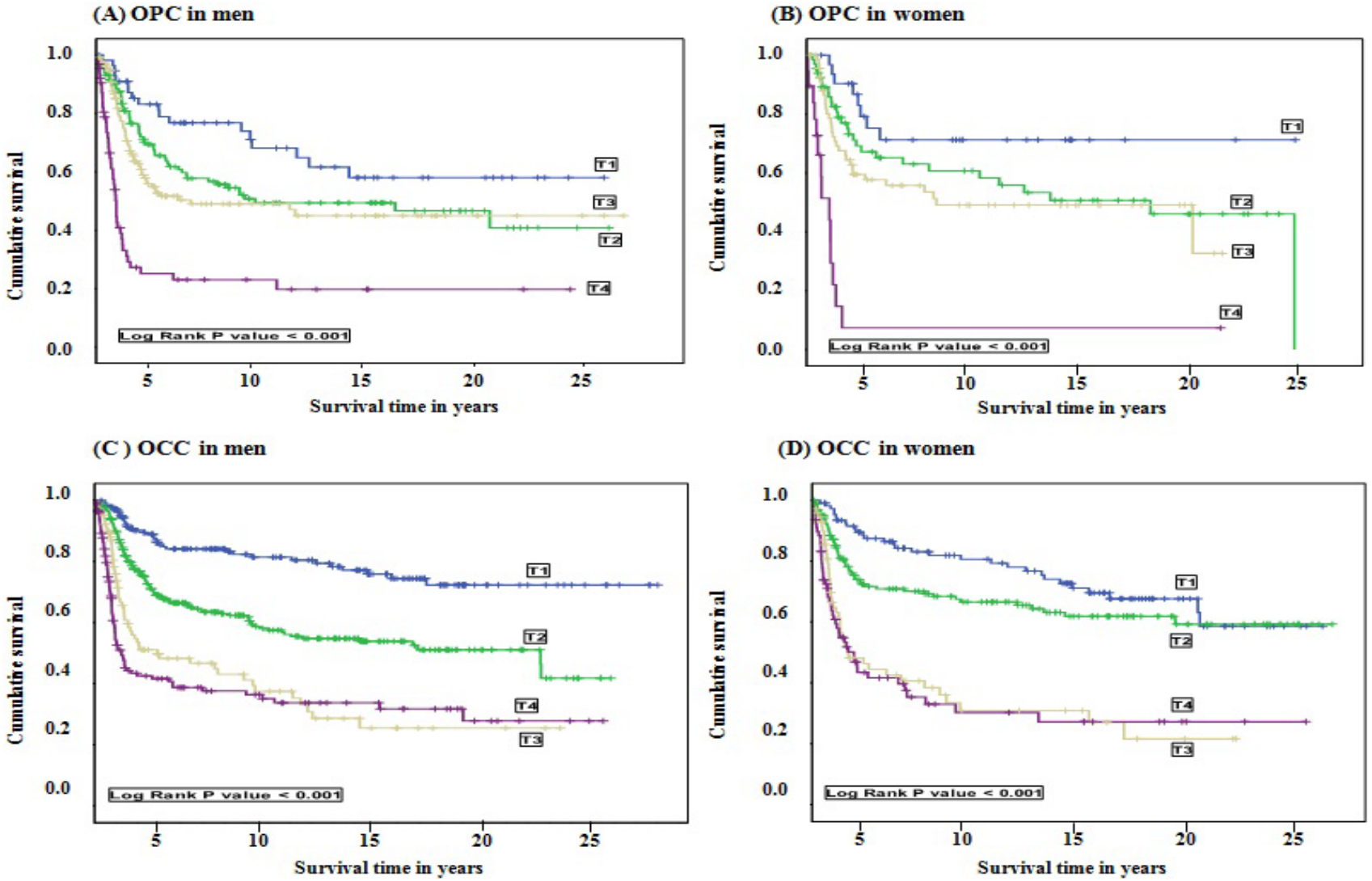

Figure 27: Disease-specific survival rates for OPC and OCC by gender and tumour size from 1994 to 2005 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

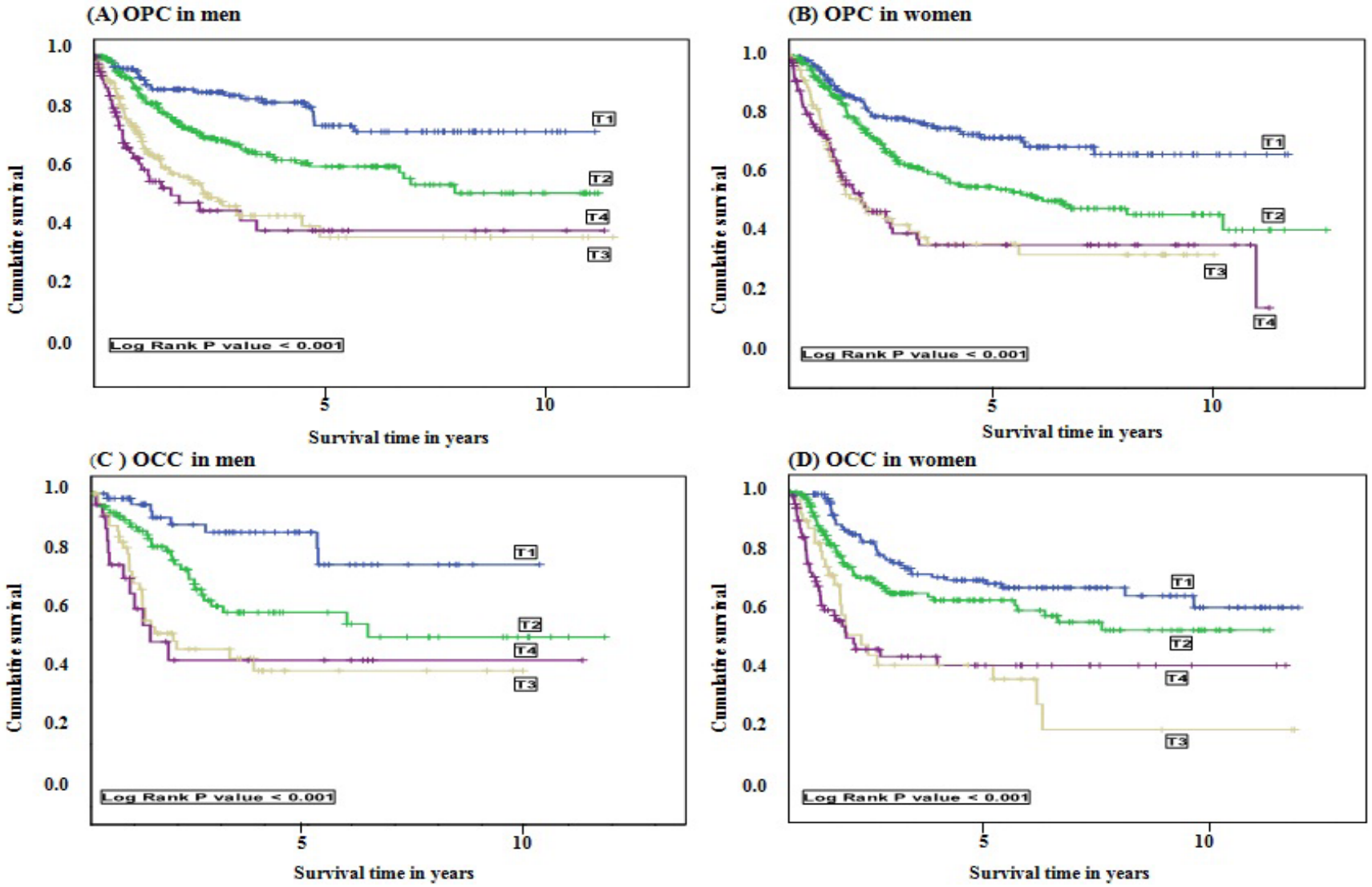

Figure 28: Disease-specific survival rates for OPC and OCC by gender and nodal status from 1980 to 2005 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

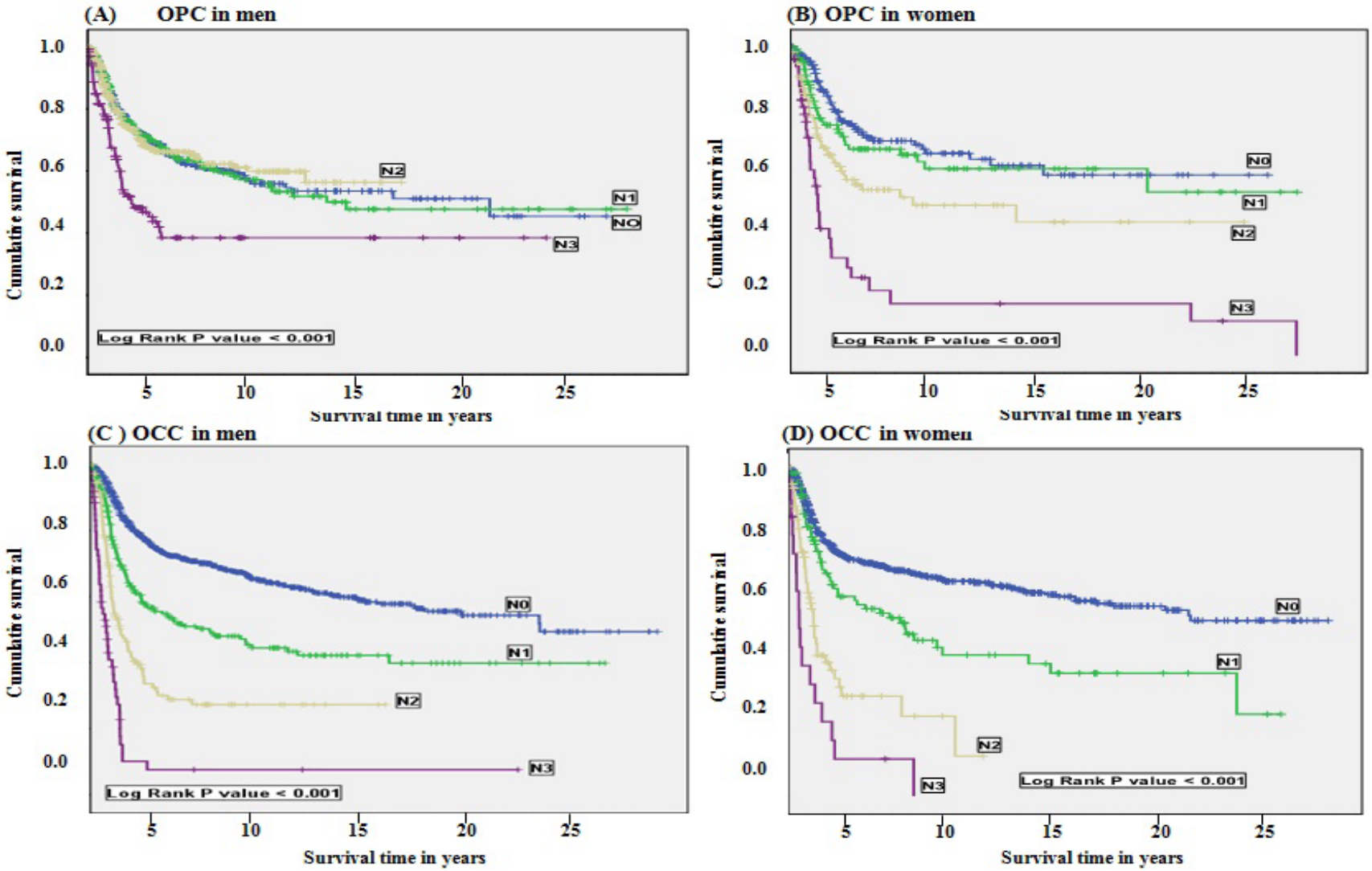

Figure 29: Disease-specific survival rates for OPC and OCC by gender and nodal status from 1980 to 1993 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.

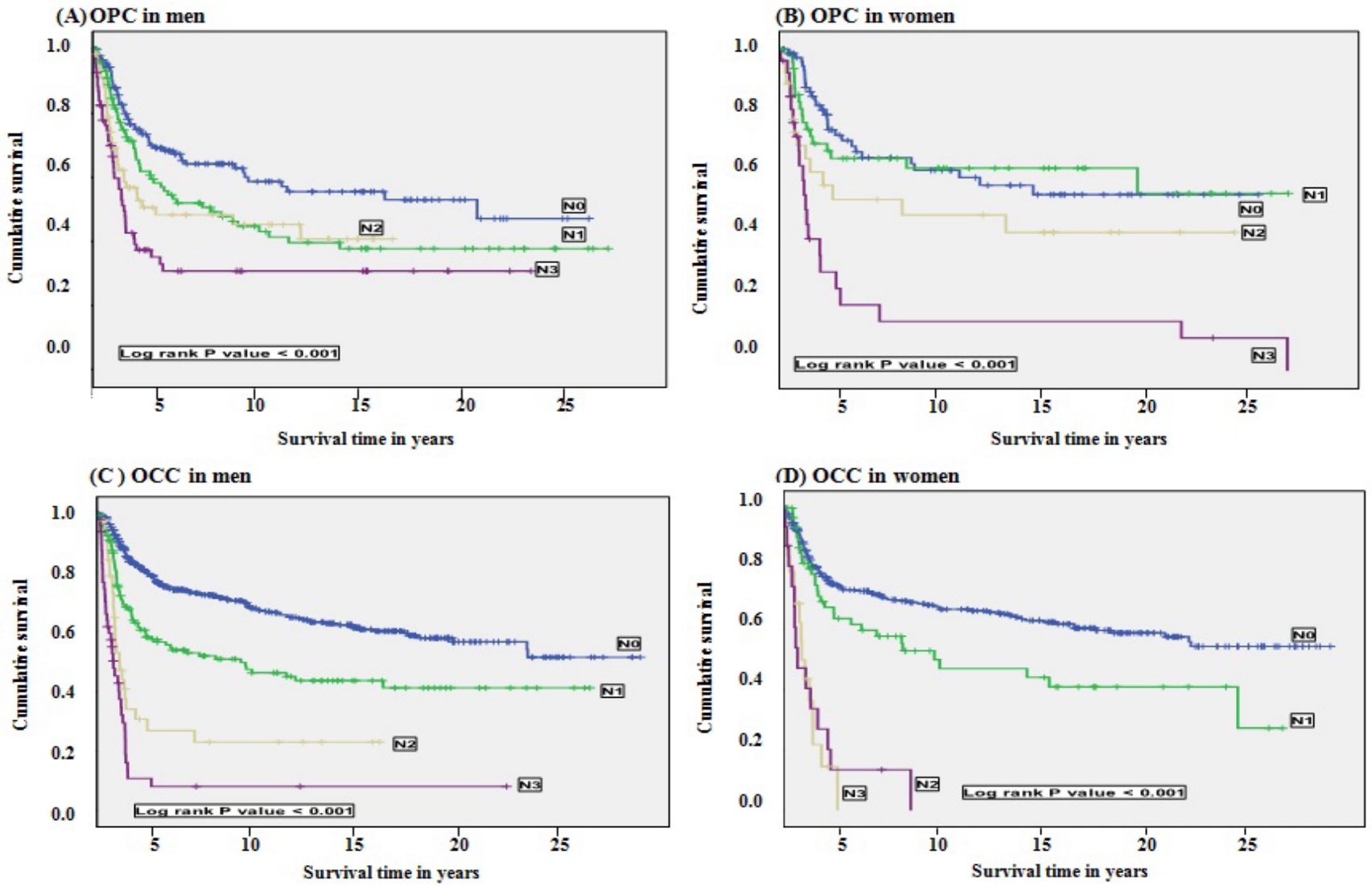

Figure 30: Disease-specific survival rates for OPC and OCC by gender and nodal status from 1994 to 2005 in the total study population: (A) OPC in men, (B) OPC in women, (C) OCC in men and (D) OCC in women.