ORAL CANCER IN MALAYSIA: AWARENESS, ETIOLOGY, PROGNOSIS, QUALITY OF LIFE AND EARLY DETECTION

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ABSTRACT

It is well established that oral cancer occurs more commonly in developing countries rather than developed countries. Prognosis of patients is poor, mostly attributed to the presentation of disease at advanced stages. The visibility of the tumor, which is located at the head and neck region, further affects the quality of life of these patients. Variations in the risk factors for oral cancer across different geographical regions have also been documented. However, data with regards to oral cancer among the Malaysian population is severely lacking. Realizing the debilitating impact of oral cancer, and in view that it is ranked within the top ten most common cancers among ethnic Indians in Malaysia, the need for information on oral cancer in Malaysia is imperative. In this thesis, a series of original published works on oral cancer in the Malaysian context are presented. These studies encompass a wide spectrum, ranging from i) before the onset of disease; assessing the level of awareness and etiological factors, ii) impact of disease; evaluating the prognosis and quality of life of patients, to iii) secondary prevention of disease; exploring potential tools for the purpose of early detection.

Firstly, the awareness level of the Malaysian public on oral cancer was assessed. Awareness was found to be poor, whereby only about half of the respondents knew of the risk habits and signs and symptoms of oral cancer. Interestingly, gender and ethnic differences were observed in their level of awareness. Mass media was quoted as the main source of information on oral cancer, however our study found that information dissemination through mass media did not confer a significant improvement in the knowledge of the public on signs and symptoms associated with oral cancer.

Following this, we conducted studies on the etiology of oral cancer. The role of tobacco smoking, alcohol drinking and betel quid chewing as risk factors for oral cancer and its synergistic effect were further validated in our study. Findings showed that there

were significant differences in the practice of these risk habits across the different ethnic groups. Further analysis revealed that habit initiation was influenced by gender, ethnicity and combined practice of other risk habits, whereas cessation was associated with practice of another risk habit and the type of cigarette smoked or betel quid chewed. Findings on the etiological role of dietary intake showed that a reported diet pattern loaded with consumption of meat, dairy, fermented food, carbonated beverages and caffeine increased cancer risk, whereas a high intake of fruits and vegetables decreased the risk for oral cancer.

In terms of assessing the disease impact, we determined the prognosis of Malaysian oral cancer patients. The 5-year survival rate was observed to be slightly poorer than the world average statistics. No significant ethnic difference was found in the prognosis of these patients. Larger tumor size, lymph node metastasis and advanced disease stage were elucidated as reliable indicators of prognosis. Apart from clinical factors, the potential of biomarker as an indicator of prognosis was also investigated. Our study on the collagen triple helix repeat containing-1 *(CTHRC1)* gene showed that high expression of *CTHRC1* conferred a poorer patient survival, indicating the utility of this biomarker as a method for prediction of prognosis.

In addition, the impact of oral cancer on patients' health related quality of life (HRQoL) was assessed. At pre-treatment, HRQoL of patients with early stage disease was observed to be better than patients with advanced disease. Significant deterioration in some HRQoL domains were evident until three months post-treatment for advanced stage patients, whereas early stage patients did not show any further significant HRQOL deterioration at three months post-treatment.

In Malaysia, the majority of oral cancers are detected at advanced stages. As it has been established that late stage disease influences patient's prognosis and quality of life, the need for early detection cannot be overemphasized. Thus, we explored the

efficacy of mouth self-examination (MSE) as a possible tool for early detection of oral diseases. Most of the respondents were observed to have difficulties in performing MSE. Although specificity of MSE was high, sensitivity of MSE in detecting lesions was found to be low. Besides MSE, we also evaluated the feasibility of teledentistry as a method for early detection of diseases. Our findings indicated that sensitivity and specificity of teledentistry in detecting lesions were high. Furthermore, it was observed that teledentistry was able to differentiate between malignant and non-malignant lesions.

In summary, the presentation of oral cancer at advanced stages had impacted the quality of life and prognosis of Malaysian oral cancer patients. In addition, we found that genetic changes could be a potential tool for prediction of prognosis. The general lack of awareness among the Malaysian public and the practice of multiple oral cancer risk habits suggests the need for educational intervention. As gender and ethnic differences were evident in the level of awareness and practice of these habits, interventional educational programs designed specifically to cater to the needs of each ethnic group would be most ideal. We also showed the potential of utilizing the concept of teledentistry as an alternative method for early detection of disease. However, at this point, our findings were unable to provide sufficient evidence to advocate the usage of MSE as a tool for early detection.

ABSTRAK

Kanser mulut adalah penyakit yang telah didapati berlaku lebih kerap di kalangan negara-negara membangun berbanding dengan negara maju. Prognosis pesakit adalah tidak memberansangkan, yang mana sebahagian besarnya adalah diakibatkan oleh pengesanan penyakit pada peringkat lewat. Kedudukan kanser yang terletak di bahagian kepala dan leher menyebabkan kanser tersebut jelas terlihat, dan ini memberi kesan kepada kualiti hidup pesakit-pesakit ini. Variasi di dalam pengamalan faktor risiko untuk kanser mulut di kawasan geografi yang berbeza juga telah didokumenkan. Malangnya, data berkaitan kanser mulut di kalangan penduduk Malaysia adalah sangat kurang. Menyedari kesan buruk kanser mulut, dan memandangkan ia tergolong di kalangan sepuluh kanser paling kerap berlaku di kalangan kaum India di Malaysia, maklumat terkini tentang senario kanser mulut di Malaysia amat diperlukan. Di dalam tesis ini, beberapa karya asal yang telah diterbitkan mengenai kanser mulut dalam konteks Malaysia dibentangkan. Kajian-kajian ini merangkumi spektrum yang luas, mulai dari i) sebelum permulaan penyakit, penilaian tahap kesedaran dan faktor-faktor risiko; ii) kesan penyakit, penilaian prognosis dan kualiti hidup pesakit; dan iii) pencegahan sekunder penyakit, penerokaan alat-alat yang berpotensi untuk digunakan untuk tujuan pengesanan awal.

Pertama sekali, tahap kesedaran masyarakat Malaysia mengenai kanser mulut telah dinilai. Didapati bahawa kesedaran adalah pada paras rendah, di mana hanya lebih kurang separuh daripada responden mengetahui tentang tabiat berisiko dan tanda-tanda kanser mulut. Menariknya, terdapat perbezaan dari segi jantina dan kaum terhadap tahap kesedaran di kalangan rakyat Malaysia. Walaupun media massa sering disarankan sebagai sumber utama untuk mendapatkan maklumat mengenai kanser mulut, namun kajian kami mendapati bahawa penyebaran maklumat melalui media massa tidak

memberikan peningkatan pengetahuan yang ketara di kalangan masyarakat mengenai tanda-tanda kanser mulut.

Berikutan ini, beberapa kajian mengenai faktor-faktor risiko penyakit kanser mulut telah dijalankan. Peranan merokok tembakau, meminum alkohol dan mengunyah sireh sebagai faktor risiko kanser mulut serta kesan sinergisnya telah disahkan dalam kajian kami. Hasil kajian ini menunjukkan terdapat perbezaan yang ketara dalam amalan tabiat risiko di kalangan setiap kaum. Analisis lanjut menunjukkan bahawa permulaan tabiat dipengaruhi oleh jantina, kaum dan gabungan amalan tabiat risiko yang lain, manakala pemberhentian tabiat ini dikaitkan dengan gabungan amalan dengan tabiat risiko lain, jenis rokok yang dihisap atau jenis sireh yang dikunyah. Penemuan mengenai peranan pengambilan makanan menunjukkan bahawa corak diet yang dicirikan dengan pengambilan daging, produk tenusu, makanan yang ditapai, minuman berkarbonat dan kafein yang banyak akan meningkatkan risiko kanser, manakala pengambilan buahan dan sayuran yang tinggi akan mengurangkan risiko kanser mulut.

Dari segi penilaian kesan penyakit, kami telah menentukan prognosis pesakit kanser mulut di Malaysia. Didapati bahawa kadar kelangsungan hidup lima tahun adalah lebih rendah berbanding kadar purata dunia. Tiada perbezaan kaum yang ketara didapati dalam prognosis pesakit-pesakit ini. Saiz kanser yang lebih besar, metastasis nodus limfa dan penyakit tahap lewat telah disahkan sebagai penunjuk prognosis yang baik. Selain daripada faktor klinikal, potensi petunjuk biologi sebagai penanda prognosis juga disiasat. Kajian kami mengenai gen *collagen triple helix repeat containing-1 (CTHRC1)* menunjukkan bahawa ekspresi *CTHRC1* yang tinggi membawa kepada kadar kelangsungan hidup yang lebih rendah, yang menunjukkan potensi petunjuk biologi sebagai satu kaedah untuk ramalan prognosis.

Selain itu, kesan kanser mulut terhadap kualiti hidup pesakit yang berkaitan dengan kesihatan (HRQoL) juga dinilai. Pada peringkat pra-rawatan, HRQoL pesakit dengan penyakit tahap awal diperhatikan lebih baik daripada pesakit dengan penyakit tahap lewat. Kemerosotan yang ketara dalam beberapa domain HRQoL sehingga tiga bulan selepas rawatan adalah jelas kelihatan bagi pesakit tahap lewat, manakala pesakit tahap awal pula tidak memperlihatkan sebarang kemerosotan HRQOL yang ketara pada peringkat tiga bulan selepas rawatan.

Di Malaysia, kebanyakan kanser mulut dikesan pada tahap lewat. Memandangkan telah didapati penyakit tahap lewat mempengaruhi prognosis pesakit dan kualiti hidup, keperluan untuk pengesanan awal tidak boleh diendah. Oleh itu, kami telah meneroka keberkesanan pemeriksaan mulut sendiri (mouth self-examintaion - MSE) sebagai alat yang berpotensi untuk pengesanan awal penyakit-penyakit mulut. Kebanyakan responden diperhatikan mengalami kesukaran dalam melaksanakan MSE. Walaupun kejituan MSE adalah tinggi, ketepatan MSE dalam mengesan lesi mulut adalah didapati rendah. Selain MSE, kami juga menilai potensi telepergigian sebagai salah satu kaedah pengesanan awal penyakit. Penemuan kami menunjukkan bahawa ketepatan dan kejituan telepergigian dalam mengesan lesi adalah tinggi. Tambahan pula, didapati bahawa telepergigian dapat membezakan di antara lesi malignan dan lesi bukan malignan.

Secara ringkasnya, pengesanan kanser mulut pada tahap lewat telah memberi kesan kepada kualiti hidup dan prognosis pesakit kanser mulut di Malaysia. Di samping itu, kami mendapati bahawa perubahan genetik mempunyai potensi untuk menjadi penunjuk prognosis. Kekurangan kesedaran di kalangan masyarakat Malaysia dan juga amalan tabiat berisiko yang berbilang menunjukkan keperluan untuk intervensi pendidikan. Memandangkan terdapat perbezaan jantina dan kaum yang jelas dalam tahap kesedaran dan amalan tabiat berisiko ini, program pendidikan intervensi yang

direka khusus untuk memenuhi keperluan setiap populasi adalah yang paling ideal. Kami juga telah menunjukkan potensi penggunaan konsep telepergigian sebagai kaedah alternatif untuk pengesanan awal penyakit. Walaubagaimanapun, pada masa ini, penemuan kami tidak dapat memberikan bukti yang mencukupi untuk menyokong penggunaan MSE sebagai salah satu alat untuk pengesanan awal penyakit.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ASIR	Age standardised incidence rate
ASMR	Age standardised mortality rate
Cm	Centimetres
COE	Clinical oral examination
CTHRC1	Collagen triple helix repeat containing-1
EBV	Epstein Barr Virus
ECS	Extracapsular spread
EORTC QLQ H&N	European Organization of Research Treatment Cancer Quality of Life Questionnaire for Head and Neck Cancer
FACT-H&N	Functional Assessment of Cancer Therapy–Head and Neck
FFQ	Food Frequency Questionnaire
GHQ	General Health Questionnaire
HAD	Hospital Anxiety and Depression scale
HBM	Health Belief Model
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HPV	Human Papilloma Virus
HRQoL	Health related quality of life
HSV	Herpes Simplex Virus
H&NCSQL	Head and Neck Cancer Specific Quality of Life
IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases
INHANCE	International Head and Neck Cancer Epidemiology
MD	Mediterranean Diet

Mm	Millimetres
MSE	Mouth self-examination
OPMD	Oral potentially malignant disorders
OSCC	Oral squamous cell carcinoma
PPV	Positive predictive value
PSS-HN	Performance Status Scale for Head and Neck
QL-H&N	Quality of Life Instrument for Head and Neck Cancer
QLQ	Quality of Life Questionnaire for Advanced Head and Neck Cancer
QoL	Quality of life
QOL-RTI/H&N	Quality of Life - Radiation Therapy Instrument Head & Neck Module
qPCR	quantitative polymerase chain reaction
SEA	South East Asian
SEER	Surveillance, Epidemiology and End Results Program
SES	Socioeconomic status
SF 36	Medical Short Form 36
TB	Toluidine blue
TV	Television
UWQOL	University of Washington Quality of Life Questionnaire
WHO	World Health Organization

LIST OF APPENDICES

SYNOPSIS OF PUBLISHED WORKS

Oral cancer is a debilitating disease that severely affects the sufferers and their caregivers. Availability of data regarding oral cancer in the Malaysian context is limited, as research conducted has been limited to certain areas/ topics. Therefore, a series of studies were undertaken to assess the oral cancer scenario in Malaysia, pertaining to awareness on oral cancer, etiological factors, prognosis of patients, impact on quality of life as well as potential early detection tools. This thesis contains research work from a total of twelve papers, which is the result of collaborative research with various researchers over the past eight years.

In the first paper, the level of awareness on oral cancer, its risk factors, signs and symptoms and preventive/ early detection method among the Malaysian public were assessed among adults sampled at strategically chosen shopping malls through a questionnaire survey. The majority were able to recognize smoking as a risk habit for oral cancer, however only half of them were able to recognize alcohol consumption and betel quid chewing as risk factors for oral cancer. Ethnic differences were observed in the knowledge on risk habits, whereby the Chinese were least aware that alcohol consumption increases oral cancer risk. Only about half of respondents were aware that red/ white spots and unhealed ulcers are early symptoms of oral cancer. Awareness was higher among Indians in which they were four times more likely to be able to recognize unhealed ulcers as a symptom. Awareness of mouth self-examination (MSE) as a preventive and early detection method was uniform across all the ethnic groups. The main source of information on oral cancer was mass media, followed by health campaigns and doctors/ dentists/ other health professionals. In summary, this study highlighted that there is a lack of in-depth oral cancer awareness with regards to risk habits, early signs and symptoms and early detection among this population.

As mass media was found to be the main source of information on oral cancer, we assessed the impact of a mass media campaign (television - TV) on awareness of signs and symptoms of oral cancer in the second paper. The mass media campaign consisted of i) a 20 second TV advertisement on oral cancer symptoms; and ii) two talk shows featuring an oral surgeon and an oral cancer survivor. Baseline awareness and impact of the campaign on awareness levels were measured using self-administered questionnaires sent via email. A significant increase in the proportion of those who had heard about oral cancer was observed. The increased awareness was more pronounced amongst females and the Chinese. However, there were no differences in the knowledge of the public on the signs and symptoms of oral cancer between the pre and post campaign. Ethnic differences were observed in terms of audience reach of this campaign. The Indians had the lowest reach at less than one-fifth, in contrast to the Malays where more than two-thirds were reached. In conclusion, a mass media campaign could be an effective medium to improve general awareness on oral cancer, however, a better strategy needs to be implemented to effectively disseminate in-depth knowledge on oral cancer.

In the third paper, we sought to validate the role of consumption of tobacco, alcohol and betel quid as risk factors for oral cancer. In this case-control study, data on smoking, alcohol consumption and betel quid chewing were collected using questionnaires from patients with cancers of the oral cavity as well as healthy controls recruited from seven hospital-based centers nationwide. A significant three-fold increased oral cancer risk was observed for those who were exclusively smoking, while betel quid chewers were six times at increased risk. A four to five fold increased risk was observed for those who were concurrently smoking and drinking and concurrently smoking and chewing. The practice of concurrent drinking and chewing showed an increased risk of 20 fold, while the highest risk was observed among those practicing all

three habits with an increased risk of up to 22 fold. Significant differences were observed in risk habits practiced by each ethnic group. The most common habit among the Malays was exclusively smoking, whereas concurrent smoking and drinking were the most common habits amongst the Chinese. Exclusive betel quid chewing was the most commonly practiced habit for the Indians and Indigenous people, while the ethnic group with the highest proportion of practicing all three risk habits was the Indigenous people. Betel quid chewing was the biggest attributable factor for oral cancer, accounting for almost one-fourth of the cases. In summary, smoking, alcohol consumption and betel quid chewing significantly increases oral cancer risk, with ethnic differences observed in the practice of these habits.

As smoking and betel quid chewing were established as risk factors for oral cancer, we investigated the factors associated with the initiation and cessation of these habits. For the fourth paper, data on smoking habit was obtained from a nationwide survey on prevalence of oral lesions among Malaysians. Males had a much higher prevalence of smoking than females. Ethnic variation was observed in smoking habits. Among the males, this habit is most prevalent among the Malays, whereas among females, it is most prevalent among 'Others' ethnic group. Smoking cessation most commonly occurred among those above 50 years old, and among Chinese. The quit rates were similar across the different durations (in years) of smoking and also the number of cigarettes smoked previously. Factors that were significantly associated with initiation of smoking habit were being male, Malay and being current betel quid and alcohol consumers. Smoking cessation was least likely to be found among Indians, current quid chewers and kretek users. In summary, smoking is a habit prevalent among Malay males. Factors associated with smoking initiation and cessation include gender, ethnicity, practice of other risk habits and type of tobacco used.

Using the same study population as in the fourth paper, data on the practice of betel quid chewing was extracted and analyzed in the fifth paper. Females had a higher prevalence of chewing habit than males. Indian females were found to have the highest prevalence of this habit, followed closely by the Indigenous females. Betel quid cessation rate was higher among males than females, with cessation being significantly more common among the Chinese. Females, those aged more than 40 years, Indian & Indigenous ethnic groups, and a history of smoking were factors found to significantly increase the likelihood of developing quid chewing habit. Females, those aged more than 40 years and those who included tobacco in their quid were less likely to quit the habit. In summary, betel quid chewing is most commonly practiced among the Indians and Indigenous females. The factors associated with the initiation and cessation of this habit were gender, age, ethnicity, smoking habit, type of quid and frequency of chewing.

Dietary intake has also been postulated to play a role in the development or prevention of cancer. In the sixth paper, we elucidated the association between dietary pattern and oral cancer risk. In this matched case-control study, dietary intake was measured using a Food Frequency Questionnaire (FFQ) that was developed and validated for the Malaysian population. Intake of the highest tertile of 'combination' diet pattern, which is loaded with intake of meat byproducts, dairy and fermented food conferred a three times increased risk for oral cancer. Similarly, intake of the highest tertile of a diet pattern loaded with intake of starches, carbonated beverages and caffeine conferred a two times increased risk. In this study, a diet pattern loaded with intake of fruits and vegetables were observed to confer a non-significant reduced oral cancer risk by about half. In summary, a diet characterized by high intake of meat byproducts, dairy, fermented food, carbonated drinks and caffeine increases the risk for oral cancer.

To further validate the association between dietary intake and cancer risk, we analyzed and compared the level of serum micronutrients (retinol, α-tocopherol and β-carotene) between oral cancer cases and controls using high performance liquid chromatography (HPLC) method in the seventh paper. The serum level of retinol and α-tocopherol were significantly lower among cases as compared to controls. High retinol levels were found to confer oral cancer protection of 50.0%, whereas high α-tocopherol levels were found to lower oral cancer risk by more than two-thirds. In conclusion, high levels of retinol and α-tocopherol confers protection against oral cancer risk, providing further evidence that these are promising chemoprevention agents for cancer of the oral cavity.

In the eighth paper, data on the 5-year overall survival and factors associated with patient outcome were analyzed in a cohort of patients with cancers of the oral cavity. In terms of patient outcome, less than half of the patients survived five years. When data was analyzed stratified by ethnicity, survival rate were similar for Malays, Chinese and Indians. Although the Indigenous people had lower survival rate compared to the other ethnic groups, the difference was not statistically significant. Among the clinical factors studied, tumor size of more than four cm, lymph node metastasis and late stage cancers were observed to be associated with poor prognosis. We attempted to elucidate differences in prognostic factors across the different ethnic groups, but could not find any evidence of a difference. In summary, the overall survival of Malaysian oral cancer patients is slightly lower than the reported world average. Tumor size, lymph node status and disease stage at presentation were significant prognostic factors, irrespective of ethnicity.

Recent technological advancements such as the gene/ exome sequencing technology has enabled the identification of potential biomarkers for the purpose of early detection and prediction of prognosis. Through a previous study, mutations in

chromosome 8q were identified in half of Malaysian oral cancer samples. One of the genes located at this region is collagen triple helix repeat containing-1 (*CTHRC1*). In the ninth paper, the potential of *CTHRC1* as a prognostic indicator for cancer of the oral cavity was assessed using the quantitative polymerase chain reaction (qPCR) and immunohistochemistry method. Significantly higher expression of *CTHRC1* was observed in oral cancer samples as compared to normal controls. Patients with high expression of *CTHRC1* were associated with significantly poorer survival outcomes than patients with low expression, whereby high expression of *CTHRC1* was found to confer a three times increased risk for mortality. In summary, *CTHRC1* is a potential biomarker to be used to predict prognosis of oral cancer patients.

Then, we proceeded to assess the changes in health-related quality of life (HRQoL) among early and late stage patients using a cross-culturally adapted and validated Malaysian version of the Functional Assessment of Cancer Therapy–Head and Neck (FACT-H&N) questionnaire in the tenth paper. Significant ethnic differences were seen at presentation. The Indigenous people presented with the highest proportion of late stage cancers, whereas the Chinese presented with the highest proportion of early stage cancers. At pre-treatment, except for social domain, the scores for late stage patients were significantly lower for all the HRQoL domains studied than for patients with early stage disease. At one month post-treatment, both early and late stage patients showed significant deterioration in functional and head and neck domains. At three months post-treatment, no more significant HRQoL deterioration was observed for early stage patients. In contrast, significant deterioration were seen among late stage patients for physical and head and neck domains. At six months post-treatment, no more significant HRQoL deterioration was observed for both early and late stage patients. Interestingly, emotional domain showed significant improvement at one month post-treatment for both early and late stage patients, and this positive change was

consistently noted at patients' subsequent visits. In summary, oral cancer patients with advanced disease stage have a poorer overall quality of life than those presenting early. The HRQoL domains most commonly affected were the functional, physical, and head and neck concerns.

As advanced disease stage has been shown to affect patients' quality of life, efforts towards secondary prevention in terms of early detection is warranted. In order to assess the potential of mouth self-examination (MSE) as a tool for early detection of oral cancers and oral potentially malignant disorders (OPMD), a study among a high risk Indigenous population comparing the detection of lesions between MSE and visual clinical oral examination (COE) was undertaken in the eleventh paper. Prior to data collection, respondents were provided with information on oral cancer including its risk habits and signs and symptoms. Respondents were also taught on how to perform MSE. About two-thirds of respondents showed high levels of difficulty, while less than one-tenth demonstrated high attention levels when performing MSE. Detection rate of lesions in the oral cavity using MSE by the respondents were lower than detection rate by COE by the specialist. Sensitivity of MSE in detecting OPMDs was poor, however specificity was high. Correspondingly, likelihood ratios for OPMDs were poor, while the negative predictive value was high. In summary, MSE was good at identifying absence of lesions, however it was not able to detect the presence of lesions. This study finding indicated that MSE is not an effective screening tool for early detection of OPMDs for this low socioeconomic population.

The twelfth paper aimed to assess the feasibility of teledentistry as an alternative method for early detection of oral cancers and OPMDs. In this study, the concordance in diagnosis of suspicious lesions using conventional COE was compared with the diagnosis using images from a mobile phone (teledentistry). For determination of presence of lesion, a strong concordance was recorded between COE and diagnosis

from images taken from the mobile phone with the highest resolution camera. The overall sensitivity and specificity in identifying the presence of lesions through teledentistry were high, whereby an increase in detection rates were observed with increased image resolution. In addition, the ability of teledentistry to discern lesions that are potentially malignant (OPMDs) from non-malignant and normal lesions were also examined. Similar with the ability to identify lesions, teledentistry showed a high sensitivity and specificity rate for identifying OPMDs, which increased as the image resolution increases. In summary, teledentistry can be used as an adjunctive tool for early detection of suspicious lesions, especially in a low resource setting, as it can provide a direct link between primary healthcare workers and specialists.

CHAPTER 1: INTRODUCTION

1.1 Background

An estimated 18.1 million new cancer cases and 9.6 million cancer deaths occurred worldwide in 2018. Of these, cancer of the oral cavity accounted for 355,000 new cases and 177,000 cancer deaths (Bray, Ferlay, Soerjomataram, Siegel, Torre et al., 2018). A variation in the incidence trend for oral cancer was observed. The age standardized incidence rate (ASIR) was reported to be higher in developing than developed countries. For both males and females, the geographical region with the highest ASIR is Melanesia, whereas the regions with the lowest ASIR are Western Africa and Eastern Asia (Bray et al., 2018).

In Malaysia, oral cancer is not among the top ten most commonly occurring malignancies. However, ethnic variation in incidence had been observed whereby cancer of the oral cavity was ranked as the eighth and fourth most commonly occurring cancer among Indian males and females respectively (Azizah, Nor Saleha, Noor Hashimah, Asmah, & Mastulu, 2016). The second most commonly identified ethnic group with an increased risk for oral cancer is the Indigenous population of East Malaysia (Zain, Ikeda, Razak, Axell, Majid et al., 1997).

Tobacco (smoke and smokeless) use, excessive alcohol consumption and betel quid chewing are lifestyle habits that have been established as attributable risks for oral cancer. A study amongst a population with high oral cancer incidence found that current smokers were 11 times at increased risk (Radoi, Paget-Bailly, Cyr, Papadopoulos, Guida et al., 2013). In addition, a dose-response relationship between smoking and oral cancer risk was also documented (Jayalekshmi, Gangadharan, Akiba, Koriyama, & Nair, 2011; Muwonge, Ramadas, Sankila, Thara, Thomas et al., 2008). Similar increased risk with dose-response relationship were observed for alcohol consumption (De Stefani, Boffetta, Deneo-Pellegrini, Ronco, Acosta et al., 2007; Lissowska,

Pilarska, Pilarski, Samolczyk-Wanyura, Piekarczyk et al., 2003) and betel quid chewing (Lee, Lee, Fang, Wu, Shieh et al., 2011; Muwonge et al., 2008).

Prognosis for oral cancer patient is poor, with 5-year survival rate of approximately 50.0% (Listl, Jansen, Stenzinger, Freier, Emrich et al., 2013; Rogers, Brown, Woolgar, Lowe, Magennis et al., 2009; Warnakulasuriya, 2009b). This rate is lower compared to other more commonly occurring cancers such as breast cancer with rates ranging from 70.0-90.0% (Balduzzi, Bagnardi, Rotmensz, Dellapasqua, Montagna et al., 2014; Carey, Perou, Livasy, Dressler, Cowan et al., 2006; Cronin-Fenton, Kjaersgaard, Norgaard, Pedersen, Thomassen et al., 2017). One of the major causes of poor prognosis is delayed disease presentation. In developed countries, the proportion of oral cancer patients presenting with stages III and IV is about 50.0% (Carvalho, Singh, Spiro, Kowalski, & Shah, 2004; Seoane-Romero, Vazquez-Mahia, Seoane, Varela-Centelles, Tomas et al., 2012), whereas in developing countries, about two-thirds of oral cancer patients presented with advanced stage tumors (Carvalho et al., 2004; Iype, Pandey, Mathew, Thomas, Sebastian et al., 2001; Shenoi, Devrukhkar, Chaudhuri, Sharma, Sapre et al., 2012). The same scenario is seen in Malaysia, in which almost two-thirds of patients presented with stage III and IV tumors (Doss, Thomson, Drummond, & Raja Latifah, 2011; Vincent-Chong, Salahshourifar, Woo, Anwar, Razali et al., 2017). The effect of disease stage on prognosis is shown in a study among South Koreans, where the 5-year survival rate was reported to be at 95.0% for stage I tumors, however the rate was significantly less at only 45.5% for stage IV cancers (Geum, Roh, Yoon, Kim, Lee et al., 2013). Similar findings were also reported by other researchers (Jan, Hsu, Liu, Wong, Poon et al., 2011; Kademani, Bell, Bagheri, Holmgren, Dierks et al., 2005; Kim, Kim, Kim, Han, Jung et al., 2016; Listl et al., 2013; Massano, Regateiro, Januario, & Ferreira, 2006).

Apart from disease stage, several other factors have been identified as useful prognostic indicators for patient outcome. Cervical lymph node status is one such factor. The 5-year disease-specific survival rate was significantly lower at 58.3% for patients with lymph node metastasis than 93.2% for patients without metastasis (Kim et al., 2016). This finding of higher mortality risk among patients with lymph node metastasis concurs with results from other studies worldwide (McMahon, O'Brien, Pathak, Hamill, McNeil et al., 2003; Rogers et al., 2009; Suslu, Hosal, Aslan, Sozeri, & Dolgun, 2013). Other factors that have been hypothesized to influence prognosis includes surgical margin (Binahmed, Nason, & Abdoh, 2007; Chandu, Adams, & Smith, 2005; Jan et al., 2011; Rogers et al., 2009), histologic grade (Arduino, Carrozzo, Chiecchio, Broccoletti, Tirone et al., 2008; Kademani et al., 2005), tumor thickness (Massano et al., 2006; Suslu et al., 2013) and extracapsular spread (Chandu et al., 2005; Jan et al., 2011; Massano et al., 2006). Apart from clinical factors as mentioned above, literature has also documented ethnicity as a potential indicator for prognosis. Findings from the Surveillance, Epidemiology and End Results Program (SEER) database indicate that among US citizens, survival was poorest among the African-Americans with 40.0% higher mortality risk than Caucasians (Osazuwa-Peters, Massa, Christopher, Walker, & Varvares, 2016).

Oral cancer is a debilitating disease which carries a severe functional and psychosocial impact that compromises one's quality of life. This is because the disease itself and its treatment are often accompanied with diminished or loss of important daily functions, besides aesthetical changes to the face. Among the functions affected by oral cancer are speech, swallowing and chewing (Murphy, Ridner, Wells, & Dietrich, 2007; Rogers, Lowe, Fisher, Brown, & Vaughan, 2002; Schliephake & Jamil, 2002). Oral cancer also results in psychosocial issues, which are mostly attributed to the anatomic location of the disease, primarily the face, rendering the tumor and effect of treatment

clearly visible. Depression, social isolation, disfigurement and reduced self-image are some of the psychosocial effects inherent to this disease (Smith, Shuman, & Riba, 2017).

Health-related quality of life (HRQoL) has been described as a multi-dimensional concept that assesses the perceived physical, emotional, social and cognitive functioning, in addition to disease symptoms and side effects of treatment. Quality of life is a secondary outcome measure that could be used to assess therapeutic effectiveness. It has also been shown to be a significant predictor of duration of patient survival (Montazeri, 2009).

Oral cancer survivors experience a prolonged effect of this disease. A study among Brazilians found at one year after resection of tumor, the overall HRQoL remains significantly poorer as compared to quality of life at pre-treatment (Biazevic, Antunes, Togni, de Andrade, de Carvalho et al., 2010). Chewing, recreation, swallowing and shoulder function were among the severely affected functions (Biazevic et al., 2010). Another study carried out in a Swedish population found that even at three years after diagnosis, patients were still affected with significant functional limitations such as dry mouth, limited mouth opening and reduced senses (Hammerlid & Taft, 2001), whereas a ten year follow-up on a cohort of 22 patients found that half of the patients had serious swallowing issues and limited mouth opening (Kraaijenga, Oskam, van der Molen, Hamming-Vrieze, Hilgers et al., 2015).

HRQoL of patients can be influenced by several factors. Disease stage at presentation has been consistently shown to affect quality of life. Patients presenting with advanced stages of cancer were found to have significantly poorer functional status, especially in terms of swallowing, speech and disfigurement (Hassanein, Musgrove, & Bradbury, 2001). Poorer HRQoL status amongst patients with stages III and IV disease corroborates reports by other researchers (Chaukar, Walvekar, Das,

Deshpande, Pai et al., 2009; Dwivedi, St Rose, Chisholm, Youssefi, Hassan et al., 2012; Rathod, Livergant, Klein, Witterick, & Ringash, 2015; Schliephake & Jamil, 2002). Apart from disease stage, other factors that have been reported to affect HRQoL of oral cancer patients include age, gender and treatment modality (Chaukar et al., 2009; Dwivedi et al., 2012; Hassanein et al., 2001; Rathod et al., 2015).

Given the fact that the incidence and mortality rates are among the highest in South East Asian (SEA) countries, cancer of the oral cavity should be considered as one of the major health concerns in this region. This is especially true for Malaysia as the National Cancer Registry had documented that oral cancer is among the most commonly occurring cancers among the Indians. The high proportion of advanced stage disease presentation among Malaysians further emphasizes the importance of this disease. However, to date, evidence-based data on etiology, prognosis and quality of life of Malaysians affected by oral cancer is scarce, to the point of almost non-existent. Studies that have been carried out among Malaysians were mostly on oral cancer awareness levels (Al Dubai, Ganasegeran, Alabsi, Alshagga, & Ali, 2012; Awan, Khang, Yee, & Zain, 2014; Saleh, Kong, Vengu, Badrudeen, Zain et al., 2014) and genetic/ protein changes in oral cancer patients (Karsani, Saihen, Zain, Cheong, & Abdul Rahman, 2014; Kong, Zanaruddin, Lau, Ramanathan, Kallarakkal et al., 2015; Vincent-Chong et al., 2017).

This scenario highlights the need for additional information on the etiology of this disease, factors influencing prognosis, impact on patient's quality of life and potential tools for early detection that is inherent to this population. Thus, a series of studies were conducted over the last few years in an attempt to add to the body of knowledge, such that the data obtained can be used for the planning of preventive efforts, besides assisting clinicians in patient management and informed decision

making for the Malaysian setting. The findings of these studies are compiled and presented in this thesis.

1.2 Research questions

The research questions that this thesis aims to answer are as follows:

1. What is the awareness level of oral cancer among Malaysians?
2. What are the odds for oral cancer developing among Malaysians who practice known risk habits for oral cancer?
3. What are the factors that influence the initiation and cessation of these habits?
4. Does dietary intake play any role in modulating oral cancer risk?
5. What is the survival rate for oral cancer patients in Malaysia, and what are the clinical factors predicting prognosis?
6. Can genetic changes/ mutations act as a potential biomarker to predict prognosis?
7. How does oral cancer affect quality of life of Malaysian patients?
8. What is the feasibility of mouth self-examination as a tool for early detection?
9. Can teledentistry be utilized as a method for early detection?

1.3 Aims and specific objectives

This thesis aims to determine awareness level, etiological factors and prognostic indicators for Malaysian oral cancer patients. In addition, the impact of this disease on their quality of life is assessed, and potential tools for early detection are also explored.

The specific objectives of this thesis are as follows:

1. To assess the awareness level of oral cancer among Malaysians
2. To determine the risk for oral cancer among Malaysians practicing known risk habits for oral cancer (smoking and betel quid chewing)
3. To assess the factors that influence the initiation and cessation of these habits
4. To determine whether dietary intake is associated with oral cancer risk
5. To determine the survival rate for oral cancer patients, and clinical factors predicting prognosis
6. To explore whether genetic changes/ mutations has the potential to be used as a biomarker to predict prognosis
7. To assess the impact of oral cancer on quality of life of patients
8. To assess the feasibility of mouth self-examination as a tool for early detection of lesions
9. To assess the accuracy of clinical diagnoses made using teledentistry

1.4 Research progress linking the research papers

To answer the aforementioned specific objectives, a series of studies were undertaken over a period of eight years and the findings were published. These studies relate to the oral cancer scenario in Malaysia, encompassing five components; namely i) awareness; ii) etiology; iii) prognosis; iv) quality of life; and v) early detection. The research progress and linkage between these five components are shown in Figure 1.

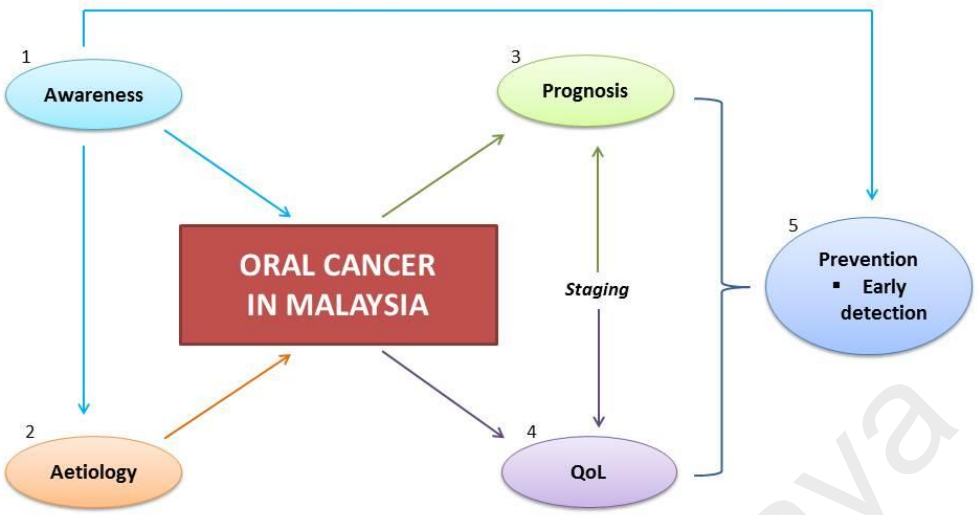


Figure 1.1: Conceptual framework showing progress and linkage of research papers

1.4.1 Awareness

Firstly, the level of awareness of oral cancer was assessed in a pilot study conducted among selected Malaysians sampled from selected shopping malls. Then, to obtain representativeness of data such that the findings can be generalized to the Malaysian population, a nationwide survey using a mass media approach was undertaken. These studies encompass awareness on etiology, signs and symptoms and early detection of oral cancer. In addition, an education intervention using mass media was also conducted to assess the feasibility of utilizing mass media as one of the methods to aid early detection of disease.

1.4.2 Etiology

Next, studies on etiological factors were conducted. Smoking, alcohol consumption and betel quid chewing has been established worldwide as risk habits for

oral cancer. However, data for the Malaysian population is scarce. To further validate the role of these risk habits as etiological factors for oral cancer, a case-control study was carried out to calculate the odds and attributable risks for the different ethnic groups in Malaysia. In addition, using a dataset from a previous nationwide survey, the prevalence of these risk habits and factors affecting the commencement and cessation of the habits were determined.

One of the hypothesized etiological factors for oral cancer is dietary intake. Numerous studies have investigated the role of diet in cancer development especially amongst Caucasians, however findings were contradictory and inconclusive. Furthermore, there is a vast difference in the types of foods consumed between Asians and Caucasians, thus not allowing findings to be inferred to the Malaysian population. As such, case-control studies assessing the association between dietary pattern and micronutrient levels and risk for oral cancer were undertaken.

1.4.3 Prognosis

Despite technological advancements in diagnosis, treatment and post-operative care, the survival and prognosis of oral cancer patients remains poor. In view of the non-availability of data on survival outcomes of Malaysian oral cancer patients, a study was conducted among patients treated at selected referral centers nationwide, to obtain data on 5-year overall survival rate. In addition, clinical factors that could predict prognosis of these patients were also identified.

The etiology of cancer has been shown to be multi-factorial, involving exogenous factors such as lifestyle habits, and endogenous factors, which are often studied in the form of changes or mutations at the cellular or molecular level. As the association between lifestyle risk habits with cancer development had been explored as

mentioned, an effort was then made to assess whether genetic changes/ mutations at the molecular level can be used as a biomarker to predict patient outcome.

1.4.4 Quality of life

Once the awareness level, etiology and prognosis of Malaysian oral cancer patients were determined, the need for assessment of the impact of this disease on patient's quality of life (QoL) was highlighted, as findings could be used to improve clinical decision making for better patient management. Although QoL studies amongst oral cancer patients are well documented worldwide, data on the effect of oral cancer on QoL amongst the Malaysian population is not sufficient. Thus far, there was only one published study that assessed the validity and discriminative ability of a QoL assessment tool that has been translated and cross-culturally adapted for use in the Malaysian context. Thus, a longitudinal study assessing changes in patient's QoL in terms of their physical, functional, social and emotional well-being, and head and neck concerns was conducted. As cancer staging has been shown to significantly affect prognosis, impact of oral cancer on QoL was analyzed separately between early and late stage patients.

1.4.5 Early detection

In view that most cases of oral cancer worldwide, including in Malaysia are currently being diagnosed at advanced stages, which ultimately affects prognosis and QoL of patients, the need for a method or tool for prevention, in terms of early detection of malignant and oral potentially malignant disorders (OPMD) is emphasized. Mouth self-examination (MSE) is a method that has been proposed for this purpose. However, due to the limited reported studies on MSE, evidence on its efficacy as a tool for early detection is lacking. Thus, the feasibility of MSE as a tool for early detection was tested

on a high risk Indigenous population with a high prevalence of tobacco and betel quid chewing practice.

An emerging method for early detection of lesions in the oral cavity is teledentistry, in which information technology and telecommunications provide a platform for exchange of dental information, digital imaging and health-related information using mobile devices. The high usage of mobile phones among Malaysians justifies the utilization of teledentistry to facilitate early detection. However, prior to advocating teledentistry as an effective method for early detection of lesions, accuracy in diagnosis made from teledentistry needs to be determined. As such, a study on the concordance in clinical diagnosis between conventional examination of the oral cavity and teledentistry was undertaken.

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology of oral cancer

2.1.1 Definition

The World Health Organization (WHO) defined cancer as 'a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs' (http://www.who.int/cancer/en/). Other frequently used terms to describe this disease include malignant tumor and neoplasm. It is a debilitating disease, which may affect anyone worldwide, not discriminating any particular population, age group or ethnicity.

To distinguish the difference between normal and cancerous cells, the concept of 'hallmarks of cancer' was proposed (Hanahan & Weinberg, 2011). This concept advocates that during the development of a tumor, cells acquire these biological traits: i) sustaining proliferative signaling; ii) evading growth suppressors; iii) resisting cell death; iv) enabling replicative immortality; v) inducing angiogenesis; and vi) activating invasion and metastasis (Figure 2.1) (Hanahan & Weinberg, 2011).

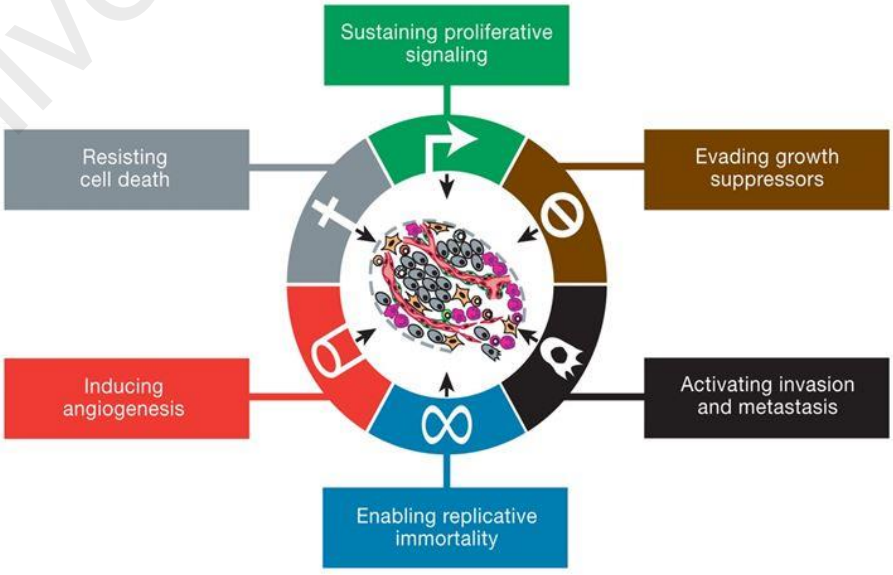


Figure 2.1: Hallmarks of cancer

Cancer can affect any parts of the body, including the oral cavity. Cancer of the oral cavity is a sub-set of a broader group of cancer, termed as head and neck cancer. Head and neck cancer is defined as a group of tumors arising at the mucosa of the upper aerodigestive tract (Lydiatt, Snehal, O'Sullivan, Brandwein, Ridge et al., 2017). Head and neck cancer comprises of cancer of the: i) lip and oral cavity; ii) parotid and salivary gland; iii) oropharynx; iv) hypopharynx; v) nasopharynx; and vi) larynx (Shield, Ferlay, Jemal, Sankaranarayanan, Chaturvedi et al., 2017), each with different etiologies. Table 2.1 shows the specific sub-sites of each type of cancer, according to the classification by the International Classification of Diseases, tenth edition (ICD-10) by the WHO.

Table 2.1: Sub-sites of head and neck cancers

Cancer	**Sub-site**	**ICD-10 Code**
Lip and oral cavity	Lip	C00
	Other and unspecified parts of tongue	C02
	Gum	C03
	Floor of mouth	C04
	Palate	C05
	Other and unspecified parts of mouth	C06
	Other and ill-defined sites in the lip, oral cavity and pharynx	C14
Parotid and salivary gland	Parotid gland	C07
	Other and unspecified major salivary glands	C08
Oropharynx	Base of tongue	C01
	Tonsil	C09
	Oropharynx	C10
Hypopharynx	Piriform sinus	C12
	Hypopharynx	C13
Nasopharynx	Nasopharynx	C11
Larynx	Larynx	C32

(Shield et al., 2017)

In the context of this thesis, oral cancer is defined as cancer of the lip and oral cavity (ICD-10 C00, C02-06, C14).

2.1.2 Types of oral cancer, including oral potentially malignant disorders (OPMDs)

The most commonly occurring cancer of the oral cavity is oral squamous cell carcinoma (OSCC), whereby it accounts for more than 90.0% of oral cavity cancers (Montero & Patel, 2015). OSCC is a cancer that occurs at the squamous cells, which can be found at the epithelial lining of the oral cavity. It is characterized by differentiation of squamous cells at varying degrees, with or without keratinization (Suciu, Morariu, Ormenisan, Grigoras, Bostan et al., 2014). Minor salivary gland tumors such as mucoepidermoid carcinoma, adenocarcinoma and adenoid cystic carcinoma accounts for less than 5.0% of oral cancer cases, while the remainder are the rarely occurring lymphomas, bony tumors such as osteosarcomas and malignant odontogenic tumors (Montero & Patel, 2015).

Oral cancer can arise independently on its own, or it can be preceded by a group of lesions termed as oral potentially malignant disorders (OPMD). The most commonly occurring OPMD is leukoplakia and erythroplakia, while oral submucous fibrosis is another OPMD that commonly occurs in South East Asia (Dionne, Warnakulasuriya, Zain, & Cheong, 2015).

Leukoplakia is defined as ‘a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer (Warnakulasuriya, Johnson, & van der Waal, 2007). Leukoplakia is categorized into homogenous and non-homogenous leukoplakia, based on surface color and morphological (thickness) characteristics. Homogeneous lesions are flat, thin and uniform white in color, whereas the varieties for non-homogenous leukoplakia are i)

mixed white and red lesion known as 'erythroleukoplakia' that may be either irregularly flat (speckled) or nodular, and ii) verrucous leukoplakia (van der Waal, 2009). Dysplasia is observed in 1.0-30.0% of leukoplakias (Dionne et al., 2015). The estimated malignant transformation rate is 3.5%, with non-homogenous types and higher grade of dysplasia being the factors associated with greater malignant potential (Warnakulasuriya & Ariyawardana, 2016).

Erythroplakia is defined as 'a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease' (Warnakulasuriya et al., 2007). Erythroplakia usually appears as flat or even depressed with a smooth or granular surface, and has been recognized as the lesion with the highest risk of malignant transformation (van der Waal, 2009). Dysplasia is present in nearly all erythroplakic cases (Dionne et al., 2015). Upon confirmation of mild or moderate dysplasia, the risk for malignant transformation is 10.3%, while severe dysplasia carries a transformation rate of 24.1% (Mehanna, Rattay, Smith, & McConkey, 2009).

Oral submucous fibrosis is a disorder that is characterized by fibrosis of the lining mucosa (Warnakulasuriya et al., 2007). It manifests as a burning sensation, blanching and stiffening of the oral mucosa and trismus, whereby in advanced stages, vertical fibrous bands appear in the cheeks, faucial pillars, and encircle the lips (van der Waal, 2009). It is strongly associated with the betel quid chewing habit, with an estimated malignant transformation rate of 0.5% per year (van der Waal, 2009).

2.1.3 Incidence and mortality

In 2018, there were an estimated 18.1 million total cancer cases, with age standardized incidence rate (ASIR) of 218.6 and 182.6 per 100,000 males and females respectively, whereas death from cancer were estimated to be at 9.6 million, with age standardized mortality rate (ASMR) of 122.7 and 83.1 per 100,000 males and females

respectively (Bray et al., 2018). Asia accounted for 48.4% of total cancer cases, as compared to 21.0% for US and 23.4% for Europe, whereas in terms of mortality, Asia ranks the highest at 57.3%, compared to the rates of 14.4% and 20.3% for US and Europe respectively (Bray et al., 2018).

Oral cancer (lip and oral cavity, excluding oropharyngeal cancer) ranked at 18th most common cancer worldwide, accounting for 2.0% of all cancers. In 2018, there were an estimated 246,420 new cases for males and 108,444 new cases for females, with corresponding ASIRs of 5.8 and 2.3 per 100,000 populations respectively (Bray et al., 2018). In terms of mortality, there were 119,693 and 57,691 oral cancer deaths among males and females, with corresponding ASMR of 2.8 and 1.2 respectively (Bray et al., 2018).

An earlier review documented that incidence rates are highest in South and Southeast Asian countries such as Sri Lanka, India, Pakistan and Taiwan, parts of West (France) and Eastern Europe (Hungary, Slovakia and Slovenia), Brazil, Uruguay and Puerto Rico from the Latin America and Caribbean region, and Papua New Guinea and Melanesia in the Pacific region (Warnakulasuriya, 2009b). Similar results were seen from the latest set of incidence data extracted from GLOBOCAN 2018. Incidence was found to be highest in Melanesia with ASIR of 21.2 per 100,000 males and 12.0 per 100,000 females, followed by South Central Asia, Australia/ New Zealand, Eastern Europe and Western Europe. The ASIR for SEA region was 3.2 and 1.8 per 100,000 males and females respectively (Bray et al., 2018).

Within the SEA region itself, variation is observed in the incidence and mortality of oral cancers. Table 2.2 shows the incidence and mortality rates for selected countries from this region. ASIR was reported to be the highest in Myanmar, Brunei and Timor-Leste with 6.2, 6.0 and 5.6 per 100,000 populations respectively, whereas mortality was highest for Myanmar (3.8/100,000), Timor-Leste (3.6/100,000) and

Cambodia (3.4/100,000) (Cheong, Vatanasapt, Yang, Zain, Kerr et al., 2017). Similarly, variation by gender was also observed across the countries, with ASIR ranging from 2.5 (Laos) to 8.6 (Myanmar) for males, and ASIR of between 1.6 (Vietnam) to 9.0 (Brunei) for females (Cheong et al., 2017).

Table 2.2: Incidence and mortality rates for selected SEA countries

Country	Incidence (per 100,000)			Mortality (per 100,000)		
	Male	Female	Total	Male	Female	Total
Laos	2.5	4.2	3.5	1.4	2.3	1.9
Malaysia	3.3	2.8	3.0	1.2	0.8	1.0
Vietnam	3.3	1.6	2.4	1.5	0.7	1.1
Brunei	4.5	9.0	6.0	1.1	2.0	1.4
Timor-Leste	5.9	5.3	5.6	3.8	3.4	3.6
Cambodia	7.1	5.2	3.8	4.1	2.9	3.4
Myanmar	8.6	4.1	6.2	5.3	2.5	3.8

(Cheong et al., 2017)

In Malaysia, there were an estimated 776 new oral cancer cases in 2012, with ASIR of 3.3 and 2.8 per 100,000 males and females respectively, whereas in terms of mortality, there were 253 deaths with ASMR of 1.2 and 0.8 per 100,000 males and females respectively (Cheong et al., 2017). An interesting observation is that there is a marked variation in the incidence of oral cancer among the different ethnic groups that constitute the Malaysian population. Data from the Malaysian National Cancer Registry documented that although oral cancer is not ranked within the top ten most common cancer among the total population, it was found to be within the top ten most common cancer among the Indians, a minority group which only constitute about 9.0% of the Malaysian population, with ASIR of 2.9 and 7.5 per 100,000 Indian males and females respectively (Azizah et al., 2016). In addition, an earlier nationwide study had

documented that apart from the Indians, the Indigenous population of East Malaysia was also found to be at an increased risk for cancer of the oral cavity (Zain et al., 1997). Based on the GLOBOCAN data, it was projected that oral cancer incidence among Malaysians will increase by 31.1%, while mortality will increase by 32.8% by 2020 (Cheong et al., 2017).

2.1.4 Gender, age, socioeconomic and site distribution

Globally, oral cancer is more predominant among males as compared to females, ranking within the top 13 most common cancers worldwide among men, compared to women where it was ranked as the 21st most common cancer (Bray et al., 2018). Additionally, a study in the US among a multi-racial population consisting of Caucasians, Blacks, Hispanics and Asians reported that oral cancer rates among men were two to four times higher than women for each ethnicity (Brown, Check, & Devesa, 2012).

In Asia, oral cancer is more common among males with ASIR of 5.2 per 100,000 as compared to ASIR of 2.5 for females (Ferlay, Soerjomataram, Dikshit, Eser, Mathers et al., 2015). Earlier studies had documented this preponderance for males in oral cancer incidence with a male to female ratio of 1.45:1 among Japanese (Ariyoshi, Shimahara, Omura, Yamamoto, Mizuki et al., 2008) and 2:1 among Indians (Aruna, Prasad, Shavi, Ariga, Rajesh et al., 2011). However, in some Asian populations especially from the South East Asia, oral cancer is found to be more prevalent among females. A study in Thailand found that in comparison to males, females had a higher incidence of oral cancer with ASIR of 6.2 compared to 3.9 per 100,000 population (Vatanasapt, Suwanrungruang, Kamsa-Ard, Promthet, & Parkin, 2011). Furthermore, the incidence in females was reported to be almost double the incidence amongst males in Laos with ASIR of 4.2 and 2.5 per 100,000 females and males respectively, whereas

the ASIRs for Brunei were 9.0 vs 4.5 for females and males respectively (Cheong et al., 2017). Gender differences in oral cancer incidence worldwide have been widely attributed to differences in the practice of established risk habits for oral cancer such as tobacco, alcohol and betel quid consumption.

Oral cancer usually occurs between the fifth and sixth decade of life. Alarmingly a shift towards a younger age at diagnosis has been observed in recent years. A review of 46 studies reported that the prevalence of younger cancers, defined as below 40 years old, was approximately 4.0-6.0% (Llewellyn, Johnson, & Warnakulasuriya, 2001). However, an increase in the figures is observed more recently. A study in Thailand reported that 12.5% of oral cancers occurred under 45 years old (Iamaroon, Pattanaporn, Pongsiriwet, Wanachantararak, Prapayasatok et al., 2004), whereas a study in India reported a prevalence of 7.5% of cancers under the age of 40 (Sherin, Simi, Shameena, & Sudha, 2008). A recent systematic review concluded that there is a rising trend in the incidence of oral cancers among younger people worldwide, especially in Western populations, with tongue being the most common site for this age group (Hussein, Helder, de Visscher, Leemans, Braakhuis et al., 2017).

Although rare, oral cancer also occurs among pediatric patients. A review reported that for the period of 1970-2005, there were 65 cases of pediatric cancer, in which four of these cases were diagnosed under the age of 12, with the majority of the cases occurring on the tongue (Stolk-Liefferink, Dumans, van der Meij, Knegt, & van der Wal, 2008). Moreover, there appears to be a rising trend of oral cancers among very young children, with the youngest case of gingiva cancer reported in a six year old boy from US (Sidell, Nabili, Lai, Cheung, Kirsch et al., 2009).

Oral cancer, unfortunately, has been recognized as a disease that has the affinity to affect individuals from the lower socioeconomic status (SES). A population-based study in Scotland reported that people living in the most deprived neighbourhoods and

those who were unemployed had a significantly higher risk, which was mostly attributed to the habit of smoking and alcohol consumption (Conway, McMahon, Smith, Black, Robertson et al., 2010). However, a study among Canadians found that after controlling for tobacco intake, cancer risk was higher among patients with lower income and education level (Johnson, McDonald, Corsten, & Rourke, 2010). Similarly, a study on a Brazilian population reported that SES was significantly associated with cancer risk even after controlling for tobacco and alcohol (Boing, Antunes, de Carvalho, de Gois Filho, Kowalski et al., 2011). A meta-analysis of 41 studies exploring socioeconomic inequalities reported that compared to populations with higher SES, oral cancer risk was significantly increased for those with the lowest strata of education level, social class and income (Conway, Petticrew, Marlborough, Berthiller, Hashibe et al., 2008). In addition, a recent study in British Columbia documented that the highest oral cancer incidence rates among men and women were observed in the most deprived SES group, in which this population was at 2.2 and 1.8 times higher risk respectively than the least deprived group (Auluck, Walker, Hislop, Lear, Schuurman et al., 2014).

Looking into the specific sub-sites of oral cancer, incidence is highest for the sub-sites of oral cavity, followed by oropharynx and nasopharynx (Shield et al., 2017). The incidence of each sub-site varies by geographical region, as shown in Table 2.3. South-central Asia is the region with the highest proportion of oral cavity and oropharyngeal cancers, accounting for 40.9% and 35.1% of cases respectively. Eastern and South-east Asia have the highest incidence of nasopharyngeal cancers, with China contributing 53.5% of the cases, whereas lip cancers, with a global ASIR of 0.3 per 100,000 populations, are most prevalent in Central and Eastern Europe (Shield et al., 2017).

Table 2.3: Incidence of head and neck cancer by sub-site

Sub-site	Global ASIR (per 100,000)	Most common world region	Proportion of total cases (%)
Lip	0.3	Central & Eastern Europe	19.2
Oropharynx	1.4	South Central Asia	35.1
Oral cavity	2.7	South Central Asia	40.9
Nasopharynx	1.2	Eastern & South East Asia	71.5
Hypopharynx	0.8	South Central Asia	48.2

(Shield et al., 2017)

Within the sub-site of oral cavity, site predilection according to geographical region is also observed. Tongue is the most common site among European and US populations, whereas in Asian populations such as Sri Lanka and India the most prevalent site is the buccal mucosa (Tandon, Dadhich, Saluja, Bawane, & Sachdeva, 2017; Warnakulasuriya, 2009b). Other less commonly occurring sites include the gingiva, floor of mouth, palate and lip.

These differences in the incidence and distribution of oral cancers worldwide have been attributed to the variation in etiological factors, particularly the practice of risk habits inherent in each population across the regions.

2.2 Etiological factors of oral cancer

2.2.1 Tobacco consumption

In most high income countries the consumption of tobacco has been reported to be stabilized or on the decline. On the other hand in many low and middle income countries which are home to 80.0% of the world's one billion smokers, tobacco use is observed to be on the rise (Chi, Day, & Neville, 2015). The role of tobacco in carcinogenesis has been extensively studied. Studies conducted in India, Taiwan and Papua New Guinea which are among the countries with the highest oral cancer

incidence in the world found that the consumption of tobacco, in the form of cigarette smoking conferred a two to five times increased oral cancer risk (Lin, Jiang, Wu, Chen, & Liu, 2011; Subapriya, Thangavelu, Mathavan, Ramachandran, & Nagini, 2007; Thomas, Bain, Battistutta, Ness, Paissat et al., 2007).

Similar findings, but with a more pronounced effect were noted for studies among Western communities. A review of epidemiological studies in US reported that smokers had an increased risk of between five to nine times, in which it increases up to 17 times for extremely heavy smokers of more than 80 cigarettes per day (Neville & Day, 2002), while studies in France (Radoi et al., 2013), Uruguay (De Stefani et al., 2007) and Spain (Moreno-Lopez, Esparza-Gomez, Gonzalez-Navarro, Cerero-Lapiedra, Gonzalez-Hernandez et al., 2000) reported that the increased risk for current smokers as compared to never smokers were between five to twelve fold.

Another type of tobacco commonly consumed through inhalation is *bidi*. *Bidi*, which is widely consumed in India, Pakistan and Sri Lanka is prepared by hand rolling dried tobacco flakes into dried *Temburni* leaves (Krishna Rao, Mejia, Roberts-Thomson, & Logan, 2013). Similar to cigarettes, *bidi* smoking had been found to be independently associated with a two to five times increased risk for oral cancer (Balaram, Sridhar, Rajkumar, Vaccarella, Herrero et al., 2002; Jayalekshmi et al., 2011; Muwonge et al., 2008; Subapriya et al., 2007).

A dose-response relationship was evident for the frequency and number of years smoking. An increased risk of 14 fold were observed for the highest number of cigarettes smoked per day (>30 sticks) and the longest duration of smoking (>50 years) (De Stefani et al., 2007). Similar dose-response observations were also reported by other studies (Jayalekshmi et al., 2011; Lissowska et al., 2003; Radoi et al., 2013; Subapriya et al., 2007; Thomas et al., 2007).

Apart from inhalation, another form of tobacco consumption is through mastication (smokeless tobacco). Tobacco chewing is a habit that is mostly practiced in Asian countries. Earlier studies among Indian populations had documented that tobacco chewers were at two to three times increased risk for oral cancer as compared to non-chewers (Jayalekshmi et al., 2011; Subapriya et al., 2007). Recently, a meta-analysis of 15 case control studies reported that tobacco chewing confers an increased oral cancer risk of up to seven times (Gupta & Johnson, 2014). In Western populations, tobacco is more commonly chewed or consumed in the form of snuff. Studies conducted on Swedish populations found that snuff consumption was not associated with an increased oral cancer risk (Luo, Ye, Zendehdel, Adami, Adami et al., 2007; Rosenquist, 2005), while a meta-analysis on US and European populations concluded that none or at most, a minimally elevated oral cancer risk were associated with consumption of snuff (Weitkunat, Sanders, & Lee, 2007).

2.2.2 Betel quid chewing

The International Agency for Research on Cancer (IARC) has classified betel quid (with or without tobacco) as a Group 1 carcinogen. It is estimated that betel quid is used by 600-1200 million people worldwide (Petti, 2009), with dependency rates varying between 2.8% in Taiwan to as high as 39.2% among Nepalese (Lee, Ko, Yen, Chu, Gao et al., 2012). Betel quid chewing is a habit that is predominantly practiced in Asian countries such as India, Pakistan and Taiwan, as well as Papua New Guinea, in the region of Oceania. This habit is also observed in Western countries, among migrant populations from South Asian countries (Gupta & Warnakulasuriya, 2002).

As the content of the quid is diverse from one population to the other, a workshop was held in Kuala Lumpur in 1996 in an effort to bring some uniformity in the reporting of betel quid chewing. The workshop formally defined quid as ‘a

substance, or mixture of substances, placed in the mouth or chewed and remaining in contact with the mucosa, usually containing one or both of the basic ingredient; tobacco and/or areca nut, in raw or any manufactured or processed form' (Zain, Ikeda, Gupta, Warnakulasuriya, van Wyk et al., 1999). Differences can be seen in the type of quid chewed across the different populations. In countries such as India, Pakistan and Sri Lanka, the quid or paan as it is known, consists of piper betel leaf, areca nut, lime, condiment, sweeteners, and sometimes tobacco (Merchant, Husain, Hosain, Fikree, Pitiphat et al., 2000), whereas in Taiwan, a quid typically consists of unripe areca nut, slaked lime and piper betel leaf/ inflorescence/ stem, without tobacco (Lee et al., 2011).

The habit of betel quid chewing, both with and without tobacco has been documented to increase the risk for oral cancer. A case-control study from India reported that chewing of betel quid or paan with tobacco increased likelihood of cancer by three fold (Subapriya et al., 2007). Similarly, other studies from various countries had documented the association between oral cancer risk with chewing tobacco added betel quid, with increased risks ranging between five to eight times (Amtha, Razak, Basuki, Roeslan, Gautama et al., 2014; Merchant et al., 2000; Muwonge et al., 2008). The effect of quid chewing was found to be more pronounced among females, whereby a study in India reported an odds ratio of 45.9 among women chewing paan with tobacco as compared to an odds ratio of 6.1 for men (Balaram et al., 2002).

The independent effect of betel quid chewing was also evidenced by findings of significant association between the chewing of quid without tobacco with oral cancer risk. A large cohort study among 10,657 Taiwanese reported that the odds for developing oral cancer was 12 times higher among those chewing betel quid than never chewers (Lin et al., 2011). In Papua New Guinea, betel chewing without tobacco was associated with a two times increased risk (Thomas et al., 2007). Similarly, studies from India and Pakistan reported increased risks of between three to nine fold for

consumption of tobacco-free quid (Merchant et al., 2000; Muwonge et al., 2008). Moreover, a recent meta-analysis concluded that betel quid without tobacco confers an independent positive association with the occurrence of oral cancer (Gupta & Johnson, 2014). It was reported that for every year of betel quid chewing cessation, head and neck cancer risk reduced by 2.9% (Wu, Yen, Hsiao, Ou, Huang et al., 2016). A dose-response relationship were observed in terms of frequency and duration of chewing, in which increasing number of quid chewed per day and increasing number of years chewing conferred a significantly increased oral cancer risk (Balaram et al., 2002; De Stefani et al., 2007; Muwonge et al., 2008; Subapriya et al., 2007).

2.2.3 Alcohol consumption

It was estimated that in 2016, alcohol was consumed by 32.5% of the world's population (Collaborators, 2018). A reported 2.8 million deaths occurred due to alcohol use, of which cancers accounted for 27.1% female deaths and 18.9% male deaths among populations aged 50 years and older (Collaborators, 2018). In relation to oral cancer, current drinkers were reported to have triple the risk than never drinkers. A dose dependent relationship was evident whereby the risk for the highest category of frequency and years of drinking were increased by seven and three times respectively (De Stefani et al., 2007). Similarly, a case-control study in India reported an odds ratio of 1.7 for current drinkers, with a significant trend of increasing risk with increasing frequency and duration of drinking (Subapriya et al., 2007). Additionally, consumption of more than 50 grams of alcohol per day was associated with a seven fold increased risk in a Spanish population (Moreno-Lopez et al., 2000). Similar observations of dose-response relationship were reported by studies conducted in Poland (Lissowska et al., 2003) and Sweden (Rosenquist, 2005). In a French area where oral cancer incidence is high, alcohol consumption was found to be associated with cancer risk only if it is

consumed for more than 4.5 glasses per day (Radoi et al., 2013). Analysis using data from the WHO global survey on alcohol and health estimated that 36.7% of oral cancer cases were attributable to consumption of alcohol (Praud, Rota, Rehm, Shield, Zatonski et al., 2016). However, on the other hand, studies by researchers in India (Balaram et al., 2002; Jayalekshmi et al., 2011; Muwonge et al., 2008) and Taiwan (Lin et al., 2011) did not find a positive association between consumption of alcohol alone with increased cancer risk, instead significant increased risk was only observed if the subjects consumed alcohol in conjunction with consumption of tobacco and/ or betel quid (Lin et al., 2011; Muwonge et al., 2008).

In view of the conflicting findings from the literature on the independent role of alcohol in oral carcinogenesis, a recent meta-analysis of 52 case-control and cohort studies was conducted (Bagnardi, Rota, Botteri, Tramacere, Islami et al., 2015). It was concluded that alcohol consumption is significantly associated with increased oral cancer risk, with evident dose-response relationship whereby a five times increase in risk was observed amongst those in the category of heavy drinkers. In addition, it was found that the effect of alcohol on oral cancer risk were found to be more pronounced among populations in Europe and US with increased risk of five times for the highest category of consumption as compared to the increased risk of three times for studies conducted among Asians (Bagnardi et al., 2015).

These lifestyle risk habits (smoking, drinking, chewing) are often practiced simultaneously. Although each habit may act independently to increase cancer risk, studies have documented that all these habits tend to trigger a synergistic effect when consumed together. A large cohort study among the Taiwanese documented an increased risk of 47 fold for concurrent smoker, drinker and chewer (Lin et al., 2011). Similarly, a case-control study from India also reported an increased risk of eight times for subjects who practiced all three habits (Kadashetti, Chaudhary, Patil, Gawande,

Shivakumar et al., 2015). Additionally, a meta-analysis has concluded that the interaction between smoking, drinking and betel quid chewing confers a pooled excess risk for oral cancer by 28 times (Petti, Masood, & Scully, 2013).

2.2.4 Diet and nutrition

Epidemiological studies have shown that diet plays an important role in many chronic diseases, including cancer. The association between dietary intake and occurrence of various cancers such as breast, esophagus, and colorectal has been studied extensively. Similarly, the role of diet in oral carcinogenesis has been widely described.

Numerous studies have established the protective effect of high intake of fruits and vegetables on cancer risk, including for oral cancer. Studies in Spain and the Netherlands reported an inverse association between oral cancer and consumption of vegetables and fruits with risk reduction by half (Maasland, van den Brandt, Kremer, Goldbohm, & Schouten, 2015; Sanchez, Martinez, Nieto, Castellsague, Quintana et al., 2003). Additionally, studies from other European populations have reported protective effect of the consumption of total vegetables and fruits in the highest tertile, with risk reduction of up to 80.0% and 60.0% respectively (Bravi, Bosetti, Filomeno, Levi, Garavello et al., 2013). Similar findings were also reported for studies conducted amongst Asians. A study in Southern India reported an oral cancer risk reduction of 50.0-60.0% for the frequent consumption of fruits and vegetables (Rajkumar, Sridhar, Balaram, Vaccarella, Gajalakshmi et al., 2003). A multi-center study from China on head and neck cancer patients, reported that cancer risk significantly decreased with higher intake of fruits and vegetables (Butler, Lee, Li, Li, Chen et al., 2017), while among the Taiwanese, failure to consume fruits and vegetables daily increased risk for head and neck cancers by two fold (Chang, Lee, Lee, Huang, Ou et al., 2017).

In contrast, significant positive associations were found for the frequent consumption of meat. An Indian study found that the consumption of processed meat such as ham and salami increases oral cancer risk of up to four times (Rajkumar et al., 2003). The Netherland Cohort study on 120,852 participants documented that subjects with high intake of processed meat had almost double the risk for oral cancer (Perloy, Maasland, van den Brandt, Kremer, & Schouten, 2017). Results from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium which pooled analysis of 22 case-control studies from Europe, North America, Latin America, India, Japan and Australia found that higher intake of meat products was associated with increased cancer risk, especially for the consumption of processed and red meat (Chuang, Jenab, Heck, Bosetti, Talamini et al., 2012).

Humans do not consume only one or two types of foods, thus the trend of dietary studies in relation to cancer risk in recent years has shifted towards the study of dietary pattern, instead of individual food items/ types. A study in Uruguay found that a dietary pattern loaded by intake of raw vegetables, fruits, liver and fish was observed to be associated with 70.0% reduction in oral cancer risk (De Stefani, Boffetta, Ronco, Correa, Oreggia et al., 2005). Similarly, findings from the Carolina Head and Neck Cancer Epidemiology Study reported that a dietary pattern characterized by high intake of fruits, vegetables and lean protein conferred a 55.0% reduced risk (Bradshaw, Siega-Riz, Campbell, Weissler, Funkhouser et al., 2012). Moreover, a diet pattern that is characterized by high intake of fruits, vegetables, fish, poultry, and whole grains had been observed to result in significantly lower mortality rates (Arthur, Peterson, Rozek, Taylor, Light et al., 2013). Another diet pattern that has been shown to offer protection against oral cancer is the Mediterranean Diet (MD), which is characterized by high intake of monounsaturated fatty acids from olive oil, vegetables, fruits, plant proteins, whole grains, fish, low-fat dairy and low red meat consumption. It was found that oral

cancer risk reduces between 40.0-80.0% with increasing adherence to MD (Filomeno, Bosetti, Garavello, Levi, Galeone et al., 2014; Giraldi, Panic, Cadoni, Boccia, & Leoncini, 2017). In addition, a recent systematic review concluded that high adherence to MD is associated with reduced head and neck cancer occurrence and mortality risk (Schwingshackl, Schwedhelm, Galbete, & Hoffmann, 2017).

On the other hand, a case-control study in Indonesia found that a dietary pattern characterized by the consumption of fast food, fermented food, canned food and snacks high in fat and sugar increases oral cancer risk by two times (Amtha, Zain, Razak, Basuki, Roeslan et al., 2009). Additionally, in Uruguay, subjects whose food consumption were characterized by frequent intake of red meat, beef and processed meat had almost triple the risk for head and neck cancers (Deneo-Pellegrini, Boffetta, De Stefani, Correa, Ronco et al., 2013).

2.2.5 Viruses

Human Papilloma Virus (HPV) has been postulated as one of the risk factors for head and neck cancers, including oral cancer. HPV prevalence in oral cancer ranges between 0.0-100.0% (Llamas-Martinez, Esparza-Gomez, Campo-Trapero, Cancela-Rodriguez, Bascones-Martinez et al., 2008), which has been attributed to differences in type of specimen used and methods used for HPV detection. A systematic review of 60 studies reported that the weighted HPV prevalence amongst oral cancers was 20.2% (Isayeva, Li, Maswahu, & Brandwein-Gensler, 2012). High risk HPV 16 was the most commonly detected genotype, accounting for up to 82.2% of HPV positive cases (Isayeva et al., 2012; Kreimer, Clifford, Boyle, & Franceschi, 2005; Ndiaye, Mena, Alemany, Arbyn, Castellsague et al., 2014).

A study in Spain reported a significantly higher detection of HPV amongst subjects with oral cancer (33.3%) as compared to normal controls (Llamas-Martinez et

al., 2008). Furthermore, a study in US reported that positive HPV status, together with heavy tobacco use confers a three times increased risk for oral cancer, while concurrent HPV positivity and heavy alcohol consumption confers an increased risk of up to ten times (Smith, Rubenstein, Haugen, Pawlita, & Turek, 2012). The role of HPV in oral carcinogenesis was further evidenced by a meta-analysis of 39 studies, which concluded that HPV infection is associated with a four times increased risk for oral cancer (Syrjanen, Lodi, von Bultzingslowen, Aliko, Arduino et al., 2011).

However, recent evidence has suggested that HPV is a major etiologic factor for only a subset of head and neck cancers, specifically oropharyngeal cancers. A review comparing prevalence of HPV between oropharyngeal and non-oropharyngeal sites reported that the fraction of oral cavity cancers with the presence of HPV was five times lower than that for oropharyngeal cancers (Combes & Franceschi, 2014). In a recent meta-analysis of 148 studies, HPV prevalence was reported to be highest for oropharyngeal cancers at 45.8%, compared to 24.2% for oral cavity cancers (Ndiaye et al., 2014). These figures correspond with an earlier figure of a review of 60 studies which also reported a significantly higher HPV prevalence for oropharyngeal (35.6%) than oral cavity cancers (23.5%) (Kreimer et al., 2005). An analysis of HPV prevalence by sub-sites of head and neck cancer is shown in Table 2.4. HPV detection was highest for tonsil (53.9%) followed by base of the tongue (47.8%), which are sub-sites of oropharyngeal cancer, while the lowest HPV rates were found amongst hard palate (6.2%) and mobile tongue (6.5%), sub-sites of the oral cavity (Ndiaye et al., 2014). Additionally, based on published reports, the estimated HPV attributable fraction for oropharyngeal cancers were found to be higher at 39.8%, than 16.3% for oral cavity cancers (Ndiaye et al., 2014). This finding concurs with a recent review which concluded that in contrast to oropharyngeal cancers, only a small proportion of oral

cavity cancers is associated with HPV infection (Mirghani, Amen, Moreau, & Lacau St Guily, 2015).

Table 2.4: HPV prevalence in selected sub-sites of head and neck cancer

Sub-site	Prevalence (%)
Tonsil	53.9
Base of tongue	47.8
Palate	42.6
Gum	39.9
Hypopharynx	21.9
Lip	19.2
Soft palate	11.7
Mobile tongue	6.5
Hard palate	6.2

(Ndiaye et al., 2014)

HPV positive oropharyngeal cancers have been associated with improved patient outcomes. The 3-year overall survival was found to be significantly better for HPV positive (82.4%) as compared to HPV negative (57.1%) cancers, with reduction in the risk of death of 58.0% (Ang, Harris, Wheeler, Weber, Rosenthal et al., 2010). Additionally, disease-specific and recurrence-free survival rates were also found to be significantly worse for HPV negative oropharyngeal cancers (Smith et al., 2012). However, the same was not observed for HPV positive oral cavity cancers. Although a trend of better survival for HPV positive cancers was reported, the finding did not achieve statistical significance (Kaminagakura, Villa, Andreoli, Sobrinho, Vartanian et al., 2012). Similarly, studies conducted in US and India found that survival rates were not statistically different between HPV positive and negative tumors (Elango, Suresh, Erode, Subhadradevi, Ravindran et al., 2011; Smith et al., 2012).

Apart from HPV, other viruses being studied for its potential association with head and neck cancers, but at a lesser magnitude, include Epstein Barr Virus (EBV) and Herpes Simplex Virus (HSV). The reported prevalence rate of EBV among European (Hungary, Sweden) and Asian (India, Thailand) communities range between 19.0-37.9% (Acharya, Ekalaksananan, Vatanasapt, Loyha, Phusingha et al., 2015; Jalouli, Ibrahim, Mehrotra, Jalouli, Sapkota et al., 2010; Kis, Feher, Gall, Tar, Boda et al., 2009; Sand, Jalouli, Larsson, & Hirsch, 2002), while the reported proportion of HSV infection was 15.0% (Jalouli, Jalouli, Sapkota, Ibrahim, Larsson et al., 2012). A multi-country study of eight different countries reported that EBV and HSV prevalence were significantly higher in industrialized countries such as Sweden, Norway, UK and US than developing countries like Sudan, India, Sri Lanka and Yemen (Jalouli et al., 2012).

2.2.6 Other factors

In addition to the risk factors mentioned above, several other factors have been studied by previous researchers at a lesser extent. Immunosuppression has been hypothesized as an emerging risk factor, whereby the use of immunosuppressive drugs such as azathioprine and cyclosporin has been associated with the risk for lip and tongue cancers (Warnakulasuriya, 2009a). Another emerging risk factor is mate drinking. The consumption of mate, an infusion of the herb *Ilex paraguariensis*, which is widely consumed in Latin American countries such as Argentina and Uruguay has been shown to be significantly associated with a two times increased risk (Dasanayake, Silverman, & Warnakulasuriya, 2010; Warnakulasuriya, 2009a).

Poor oral hygiene and dentition, as measured by the number of missing teeth, frequency of dental check-up and general oral condition have also been studied as potential risk factors for cancer of the oral cavity (Lissowska et al., 2003; Rosenquist, 2005). In addition, indoor air pollution has also been shown to be associated with oral

cancer, whereby daily exposure to carcinogenic compounds formed during cooking processes using oil, coal or wood had been reported to confer an increased risk (Warnakulasuriya, 2009a). Additionally, occupational exposure to high levels of solvents and metal/ wood/ cement dust were reported to be associated with increased risk (Chi et al., 2015). Other factors that has been studied but resulted in inconsistent evidence include hereditary and familial risk, cannabis use, khat chewing, nicotine replacement therapy, HIV infection and alcohol containing mouthwashes (Warnakulasuriya, 2009a).

2.3 Awareness of oral cancer

2.3.1 Awareness among general public

In a recent Adult Dental Health Survey conducted in the UK, a high proportion of respondents (81.0%) were found to have heard about oral cancer (Kawecki, Nedeva, Iloya, & Macfarlane, 2019). This finding concurs with an earlier study conducted in an area with high incidence of oral cancer, with awareness level of 84.0% (Amarasinghe, Usgodaarachchi, Johnson, Lalloo, & Warnakulasuriya, 2010). However, lower levels of awareness were reported by other populations. In a study conducted in Nepal, only 58.2% of the respondents had heard about oral cancer (Bajracharya, Gupta, Sapkota, & Bhatta, 2018), whereas awareness rates are even lower in Jordanian (45.6%) (Hassona, Scully, Abu Ghosh, Khoury, Jarrar et al., 2015) and Turkish (39.3%) (Peker & Alkurt, 2010) populations.

A high proportion of respondents (84.2%) were found to be able to identify smoking as a risk factor, however knowledge on the role of alcohol as a risk factor for oral cancer was poor at 58.8% (Kawecki et al., 2019). Similarly, high awareness on smoking and low awareness on alcohol consumption as risk factors for oral cancer were also reported by other researchers (Shimpi, Jethwani, Bharatkumar, Chyou, Gulrich et

al., 2018; Formosa, Jenner, Nguyen-Thi, Stephens, Wilson et al., 2015; Hassona et al., 2015; Hertrampft, Wenz, Koller, & Wiltfang, 2012). In populations that practiced betel quid chewing, awareness on betel quid and paan chewing as a risk factor were high at 68.0-79.0% (Formosa et al., 2015; Amarasinge et al., 2010; Elango et al., 2009).

Awareness on the signs and symptoms of oral cancer are less satisfactory. White or red patches were correctly identified by 43.8% of respondents, while only 32.9% agreed that unhealed ulcers were signs and symptoms for oral cancer (Hassona et al., 2015). In a study conducted among rural populations in India, only 7.8% correctly identified white patches as a sign for oral cancer, whereas awareness on red patches and unhealed ulcers were also low at 35.0% and 24.0% respectively (Sankeshwari, Ankola, Hebbal,,Muttagi, & Rawal, 2016). Similarly, awareness on signs and symptoms were found to be poor in studies conducted in Nepal (Bajracharya et al., 2018) and Turkey (Peker & Alkurt 2010).

2.3.2 Awareness among healthcare practitioners

A study comparing the level of awareness between medical and dental undergraduates found that dental students had a significantly higher knowledge on risk factors and signs and symptoms of oral cancer (Awan, Khang, Yee, & Zain, 2014). This finding concurs with an earlier study conducted among medical and dental students in the UK (Carter & Ogden, 2007a). In addition, dental students were reported to be more likely to counsel patients on risk habits for oral cancer (Awan et al., 2014; Carter & Ogden, 2007a).

Similar findings were observed among medical and dental practitioners. With regards to risk factors, although knowledge on smoking was comparable between medical and dental practitioners, knowledge on alcohol consumption was significantly

lower among medical practitioners (43.3%) as compared to dental practitioners (87.2%) (Carter & Ogden, 2007b). In addition, medical practitioners were reported to be less knowledgeable on signs and symptoms, and were less likely to advise patients on oral cancer risk habits.

Although awareness on oral cancer, with regards to risk factors and signs and symptoms were quite high, the majority of general dental practitioners admitted to needing further training on oral cancer screening (Hashim, Abo-Fanas, Al-Tak, Al-Kadri, & Abu Ebaid, 2018; Alaizari & Al-Maweri, 2014). Similarly, in Malaysia, it was reported that training of dentists on risk habit cessation and early detection of oral cancer would be beneficial (Saleh, Kong, Vengu, Badrudeen, & Zain et al., 2014). This highlights the importance of continuing education among medical and dental practitioners, as lack of knowledge among these healthcare professionals would lead to delayed diagnosis, which would have an adverse effect on prognosis of patients.

2.4 Prognosis of oral cancer

2.4.1 Survival

An earlier review reported that for most countries, the 5-year survival rate for cancers of the oral cavity was approximately 50.0%, with cancer of the lip having the highest survival rate of 90.0% (Warnakulasuriya, 2009b). However, in recent years, there seems to be a variation in the reported survival rates worldwide.

The prognosis for most European and some developed Asian countries were observed to be better than the reported 50.0%. Among the highest 5-year overall survival rates were reported for Italy with a rate of 76.8% (Arduino et al., 2008), followed by Korea with 75.7% (Geum et al., 2013), Taiwan with 71.0% (Jan et al., 2011), Spain with 68.5% (Gonzalez-Moles, Esteban, Rodriguez-Archilla, Ruiz-Avila, & Gonzalez-Moles, 2002) and Canada with 61.9% (Binahmed et al., 2007). It should be

noted, however that this higher survival rate could be attributed to the higher proportion of early stage cancers (stage I and II) in these studies. In line with earlier reports, a large study whereby data on 15,792 Germans collected from eleven population-based registries reported that the 5-year overall survival rate was 54.6% (Listl et al., 2013). Similar survival rates were reported for India at 54.1% (Bobdey, Sathwara, Jain, Saoba, & Balasubramaniam, 2018), Taiwan at 54.5% (Chen, Shieh, Ho, Tsai, Yang et al., 2007), UK at 56.0% (Rogers et al., 2009) and US at 50.0% (Dillon, Brown, McDonald, Ludwig, Clark et al., 2015). For disease-specific survival, the reported rate ranges from as high as 74.0% in Canada (Binahmed et al., 2007) and UK (Rogers et al., 2009), 66.7% among Japanese tongue cancers (Kurokawa, Zhang, Matsumoto, Yamashita, Tomoyose et al., 2005), to as low as 54.9% in India (Iype et al., 2001) and 42.0% in US (Dillon et al., 2015).

Data on the prognosis of Malaysian oral cancer patients is scarce. A small study on 86 oral cancer patients from a single institution reported that the 1 and 3-year overall survival rates were 72.7% and 61.5% respectively (Balasundram, Mustafa, Ip, Adnan, & Supramaniam, 2012), while another study in which 87.0% of the cases were stage III and IV cancers reported a very low 5-year survival rate of only 18.0% (Razak, Saddki, Naing, & Abdullah, 2010).

2.4.2 Clinical and histopathological factors affecting prognosis

Several clinical and histopathological factors have been identified to be significantly associated with prognosis of patients. These factors are summarized in Table 2.5.

Table 2.5: Clinical and histopathological factors affecting prognosis

Factor	Indication	Survival rates (5)
Cancer stage	Early Late	79.7 – 96.0 42.1 – 57.1
Lymph node metastasis	Negative Positive	59.8 – 93.2 20.0 – 58.3
Tumor size	≤4cm >4cm	66.2 - 75.2 22.2 - 55.2
Tumor thickness	≤3-5mm >3-5mm	85.7 – 95.0 30.4 – 57.0
Tumor site	No difference in prognosis	
Histologic grade	Well differentiated Moderately differentiated Poorly differentiated	49.1 – 94.7 59.0 25.0 – 51.0
Surgical margin	Clear Close Involved	65.0 – 69.0 58.0 38.0 – 48.0
Extracapsular spread	Negative Positive	70.0 – 71.5 15.6 – 33.0
Recurrence	Negative Positive	89.1 63.2

These factors are further explained in the following sections.

2.4.2.1 Cancer stage

Although cancer stage has been labeled as imperfect for prognostic purposes, its value in influencing the outcome of patients has been accepted by the vast majority of authors (Massano et al., 2006). The prognostic value of cancer stage at presentation has been established by numerous studies. Among 378 Taiwanese patients, those presenting with stage I cancers had a significantly higher 5-year survival rate than stage IV patients (Lo, Kao, Chi, Wong, & Chang, 2003). Similarly in Italy, among 245 patients who had their tumors surgically removed, the 5-year survival rate for stage I was 79.9% in comparison to the low survival rate of 42.1% for stage IV tumors (Garzino-Demo, Dell'Acqua, Dalmasso, Fasolis, La Terra Maggiore et al., 2006). Statistically significant differences in prognosis in relation to cancer stage were also reported by other studies. The survival rate for stage I cancer ranges between 88.2% to

96.0% while prognosis for stage IV patients were reported to be between 42.6% to 57.1%, in studies conducted among Koreans (Geum et al., 2013; Kim et al., 2016), Taiwanese (Jan et al., 2011) and Indians (Bobdey et al., 2018).

2.4.2.2 Lymph node metastasis

The role of lymph node metastasis in predicting prognosis has been established by numerous researchers. Among Koreans, those with node metastasis had a significantly poorer prognosis with 5-year survival rate of 58.3%, compared to those without node metastasis (93.2%) (Kim et al., 2016). Similarly, the prognosis of those with negative nodes were better (with survival rates of 65.8% and 59.8%) than survival rates of those with advanced nodal disease (only 20.0% and 28.5%) among the Taiwanese (Lo et al., 2003) and Indians (Iype et al., 2001) respectively. Correspondingly, the 5-year mortality rate was reported to be lowest for those without lymph node metastasis (12.9%) and highest among those with advanced node metastasis (71.3%) (Arduino et al., 2008), while a two to three times increased risk for mortality were observed among those with lymph node metastasis in studies conducted in Japan and the UK (Kurokawa et al., 2005; Rogers et al., 2009). Findings of significantly poorer prognosis among patients with lymph node metastasis compared to those without metastasis were also reported by other researchers (Bobdey et al., 2018; Jan et al., 2011; McMahon et al., 2003; Suslu et al., 2013).

2.4.2.3 Tumor size

Another clinical factor that has been shown to have the potential to be a prognostic indicator is tumor size. Patients with tumor size of more than four cm were reported to have a significantly lower survival rate (55.2%) compared to tumors measuring four cm and less (75.2%) (Jan et al., 2011). Similarly, other studies reported

worse survival rates of only 22.2% to 42.9% for tumors measuring more than four cm compared to the rates of 66.2% to 67.8% for tumors less than two cm (Bobdey et al., 2018; Lo et al., 2003). Correspondingly, the 5-year mortality rates for smaller sized tumors (T1-T2) were reported to be lower at 20.0% compared to mortality rates of bigger tumors (T3-T4) at 48.5% (Arduino et al., 2008).

2.4.2.4 Tumor thickness

Apart from the size of tumor, thickness of tumor has also been shown to be a potential prognostic factor. Among patients in the UK, those with tumor thickness of ≤5mm had a significantly better prognosis with survival rates of 95.0%, compared to 30.4% among those with tumor thickness of >5mm (Ocharoenrat, Pillai, Patel, Fisher, Archer et al., 2003). In a study among tongue cancers in Spain, tumor thickness was reported to be the most important factor influencing survival, whereby tumor thickness of ≤3mm were associated with a survival rate of 85.7% than 57.0% among those with tumor thickness of more than three mm (Gonzalez-Moles et al., 2002). A study among the Japanese found that tumor depth of ≥4mm was associated with three times increased risk for mortality (Kurokawa et al., 2005). Similar findings of worse prognosis among patients with deeper thickness of the tumor were also observed by other researchers (Al-Rajhi, Khafaga, El-Husseiny, Saleem, Mourad et al., 2000; Suslu et al., 2013).

2.4.2.5 Tumor site

A study in Italy reported that cancer located at the anterior part of the lateral border of tongue was associated with significantly better prognosis (5-year survival rate of 74.9%) than other sub-sites within the oral cavity (Garzino-Demo et al., 2006). However, other researchers did not find any evidence of the prognostic value of tumor site. Data analyzed on 11,134 patients captured from the SEER database comparing

prognosis of cancer of the buccal mucosa to the other sites, found that no difference in survival was evident between buccal and non-buccal sites upon controlling for potential confounding factors (Camilon, Stokes, Fuller, Nguyen, & Lentsch, 2014). Similar observations of no difference in prognosis of oral cancer patients in relation to tumor site was reported by other researchers (Kademani et al., 2005; Kim et al., 2016; Lo et al., 2003).

2.4.2.6 Histologic grade

A pathological factor that has been hypothesized to be associated with prognosis is histologic grade of the tumor, which is graded using the Broder's classification system. The 5-year survival rates were significantly different between the three histologic grades, with well differentiated tumors (Grade 1) having the highest survival rate at 74.0%, followed by moderately differentiated tumors (Grade 2) with 59.0% and poorly differentiated tumors (Grade 3) at 51.0% in a study among Caucasians (Garzino-Demo et al., 2006). The same finding was also observed among Asians whereby well differentiated tumors had a significantly better survival rate of 94.7% and 49.1% than the rate of 25.0% and 36.8% for poorly differentiated tumors among the Koreans (Geum et al., 2013) and Taiwanese (Lo et al., 2003) respectively. Similarly, in India survival was reported to be the worst for poorly differentiated tumors at only 20.6%, with a hazard ratio of 7.3 (Bobdey et al., 2018). Correspondingly, the 5-year mortality rate was found to be the lowest for well differentiated tumors at 9.3%, while the highest rate was reported for poorly differentiated tumors (40.8%) (Arduino et al., 2008).

2.4.2.7 Surgical margin

The status of surgical margin has also been postulated to be an important prognostic factor as this is the only factor that can be controlled by the surgeons during

resection of tumors. The 5-year survival rate for involved margin was reported to be 48.0%, than the better prognosis of clear margin with survival rate of 65.0% (Garzino-Demo et al., 2006). Similarly, patients with clear margins were reported to have a significantly better survival rate at 69.0% than the rates of 58.0% with close margin and 38.0% with involved margins (Binahmed et al., 2007). Significantly better prognosis for clear surgical margins were also observed by other researchers (Dillon et al., 2015; Woolgar, Rogers, Lowe, Brown, & Vaughan, 2003). An analysis of data obtained from a cancer registry in Canada estimated that the increased risk of mortality for oral cancer patients with involved surgical margins was as high as 90.0% (Binahmed et al., 2007). This finding of increased relative risk of mortality for patients with involved margins was also reported by other researchers (Chandu et al., 2005; Jan et al., 2011; Rogers et al., 2009).

2.4.2.8 Extracapsular spread (ECS)

Another pathological factor that has been hypothesized to be a good prognostic indicator is extranodal/ extracapsular spread (ECS) of cervical lymph node metastasis. The 5-year survival for patients with ECS were found to be significantly lower at 33.0% than survival rate of 70.0% in patients without ECS among patients in the UK (Woolgar et al., 2003). Similarly, positive ECS status were found to confer a worse prognosis with survival rate of only 15.6% and 28.0% than the high survival rate of 71.5% and 63.7% among patients with no evidence of ECS among the Taiwanese (Jan et al., 2011) and Indians (Bobdey et al., 2018) respectively. Moreover, patients with ECS were reported to have a two to seven times increased mortality risk (Bobdey et al., 2018; Chandu et al., 2005; Jan et al., 2011).

2.4.2.9 Recurrence

Some studies have shown that recurrence is associated with patient outcome. The 5-year survival rate for patients with recurrence were significantly lower at 63.2% than 89.1% for those without recurrence (Kim et al., 2016). Another study also reported an association between recurrence and prognosis, in which it was found that prognosis were significantly poorest among patients with regional recurrence, with survival rate of 24.1% and relative mortality risk of 6.9, than patients with local recurrence or without recurrence (Chandu et al., 2005).

2.4.3 Other factors affecting prognosis

Other factors that have been studied in relation to their potential role as prognostic factors include age, gender, ethnicity, socioeconomic status and practice of risk habits. In most studies, age and gender were not found to be associated with prognosis of patients (Bobdey et al., 2018; Geum et al., 2013; Kademani et al., 2005; Kim et al., 2016; Suslu et al., 2013). The same finding was observed for the practice of risk habits (Al-Rajhi et al., 2000; Arduino et al., 2008; Iype et al., 2001). However some studies did report a significant association between gender and risk habits. Females were observed to have a significantly better survival rate of 73.1% than males (57.3%) in a study among the Italians (Garzino-Demo et al., 2006). This finding was supported by data from the SEER database on a cohort of 22,162 US patients whereby females had a 9.0% reduced risk of cancer specific mortality than males (Osazuwa-Peters et al., 2016). With regards to the practice of risk habits, a study among the Taiwanese (where the habit of betel quid chewing is prevalent) reported that of all risk habits, only betel quid chewing was found to be related to survival, whereby survival for chewers (49.2%) were significantly poorer than non-chewers (63.1%) (Lo et al., 2003).

Data analyzed from the SEER database showed that ethnicity could potentially play a role in prognosis of patients. The 5-year survival rate for Whites was found to be significantly higher at 48.1% than 28.2% for African-Americans. In addition, African-Americans were observed to have a 40.0% increased risk for mortality than Whites (Osazuwa-Peters et al., 2016). This ethnic group was also found to have an increased risk for metastatic cancer (Shiboski, Schmidt, & Jordan, 2007). Another ethnic group that had been identified to have poorer outcomes are the American Indians (Dwojak, Sequist, Emerick, & Deschler, 2013). South Asians living in British Columbia were also found to have a significantly poorer prognosis than the native population (Auluck, Hislop, Bajdik, Hay, Bottorff et al., 2012). Socioeconomic status is another factor reported to be significantly associated with survival. Patients from a lower socioeconomic status were found to have a higher hazard of mortality than patients in the highest socioeconomic strata (Osazuwa-Peters et al., 2016).

Apart from the factors mentioned above, quality of life has also been postulated to be associated with prognosis of cancer patients (Dharma-Wardene, Au, Hanson, Dupere, Hewitt et al., 2004; Montazeri, Milroy, Hole, McEwen, & Gillis, 2001). In addition to the general issues of pain and fatigue faced by patients with cancers of other sites, patients with cancers of the oral cavity were postulated to experience a poorer quality of life as the disease affects daily functions such as chewing and swallowing (Hoxbroe Michaelsen, Gronhoj, Hoxbroe Michaelsen, Friborg, & von Buchwald, 2017) which in turn compromises their nutritional and immune status. In addition, oral cancer also results in psychosocial effects such as depression and social isolation due to aesthetic changes to their facial appearance (Smith et al., 2017). This highlights the urgent need to address and improve the quality of life of oral cancer patients and survivors.

2.5 Quality of life (QoL) of oral cancer patients

2.5.1 Definition

The WHO has defined quality of life (QoL) as an individual's perception of their position in life in the context of their culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. This is a broad ranging concept, affected in a complex way by a person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment (Petersen, 2003). QoL is considered to be an important parameter for cancer patients, as it does not only reflect the impact of the disease on the sufferers, it could also be used to measure the success or effectiveness of clinical patient management.

QoL is a multi-dimensional concept, which can be seen by the breadth of available QoL questionnaires. This had prompted researchers to develop questionnaires that focus on selective areas of their interest. Health related quality of life (HRQoL) has been defined as a subset of quality of life which focuses on function, symptoms, treatment side effects and performance (Rogers, Fisher, & Woolgar, 1999).

2.5.2 Assessment of HRQoL

In the past, HRQoL has been assessed by a few methods, for example observation by the clinician which is very subjective, semi-structured interviews and qualitative approaches. Patient completed questionnaires have now been accepted as the more practical, accurate and sensitive method (Ringash & Bezjak, 2001; Rogers et al., 1999). The assessment of HRQoL for oral cancer, which is a sub-site of head and neck cancer has been suggested to consist of four areas; 1) global and broader dimension which measures physical, psychological and social functions; 2) general cancer which measures symptoms and treatment side effects; 3) head and neck specific which

measures complications, side effects and functional problems inherent among head and neck cancers; and 4) head and neck performance which measures oral functions such as speech, swallowing and chewing (Rogers et al., 1999).

There are a variety of validated questionnaires that has been used to assess HRQoL of head and neck cancer patients such as the General Health Questionnaire (GHQ), Karnofsky Performance Status, Hospital Anxiety and Depression scale (HAD), Medical Short Form 36 (SF 36), Head and Neck Cancer Specific Quality of Life (H&NCSQL), Performance Status Scale for Head and Neck (PSS-HN), Quality of Life Instrument for Head and Neck Cancer (QL-H&N), Quality of Life Questionnaire for Advanced Head and Neck Cancer (QLQ) and Quality of Life - Radiation Therapy Instrument Head & Neck Module (QOL-RTI/H&N) (Ringash & Bezjak, 2001; Rogers et al., 1999). Among the available questionnaires, the three most commonly used among oral cancer patients in recent years are the European Organization of Research Treatment Cancer Quality of Life Questionnaire for Head and Neck Cancer (EORTC QLQ H&N), University of Washington Quality of Life Questionnaire (UWQOL), and Functional Assessment of Cancer Therapy Head and Neck (FACT-H&N) (Chandu, Smith, & Rogers, 2006; Rogers, Ahad, & Murphy, 2007). For the Malaysian population, the FACT-H&N had been translated and cross-culturally adapted with satisfactory construct validity and reliability (Doss et al., 2011), such that the questionnaire is deemed to be sensitive in detecting changes in HRQoL of patients. Brief descriptions of the three instruments are shown in Table 2.6.

Table 2.6: Commonly used questionnaires for the assessment of HRQoL among head and neck cancer patients

Instrument	Administration	Domains/ Items	Scoring
University of Washington Quality of Life Questionnaire (UWQOL)	Patient based, self-administered questionnaire Short instrument best suited to patients undergoing primary surgery, most common questionnaire used by clinicians Criticized for its minimal number of global questions, best administered in conjunction with general QoL instrument	15 questions: 12 disease-specific items on pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder problems, taste, saliva, mood, anxiety as well as three general items measuring global HRQOL, where patients rate which domain changes were most significant to them, plus a free text section allowing patients to address issues not contained within questionnaire	Each question is scored from 0 (worst) to 100 (best) using a Likert scale, maximum summary score of 900 The three global questions are scored individually
European Organization of Research Treatment Cancer Quality of Life Questionnaire for Head and Neck Cancer (EORTC QLQ H&N)	Patient based, self-administered questionnaire Used as a specific module in conjunction with the EORTC QLQ-C30, thus covering specific and global domains of HRQoL Developed not only by clinician and allied health input, but also includes input by patients from many cultures and language groups to ensure cross cultural validity Longer than other instruments, time consuming	35 questions in seven domains: pain, swallowing, senses, speech, social eating, social contact, and sexuality as well as 11 items inquiring about dental problems, problems with restricted mouth opening, sticky saliva, cough, feeling ill, analgesic use, nutritional supplement use, feeding tube, and loss or gain of weight	Scores are rated in Likert scale from 1 (not at all) to 4 (very much) Each subscale or single item is linearly transformed on a scale of 1–100. On the well-being subscales, a higher score reflects better QOL, while on the symptom scales, higher score indicate worse QOL

Table 2.6, continued

Instrument	Administration	Domains/ Items	Scoring
Functional Assessment of Cancer Therapy Head and Neck (FACT-H&N)	Patient based, self-administered questionnaire Comprises a core questionnaire called FACT-G, and a disease-specific subscale Developed using sound psychometric principles and input from patients	27 questions in four domains: physical, social/family, emotional, and functional as well as 11 head and neck specific items covering topics such as eating, swallowing, appearance, breathing, smoking, and alcohol habits	Scores are rated in Likert scale from 0 to 4 Scores are calculated separately for each domain, and an unweighted summary score is calculated for the FACT-G and the total FACT-H&N. The maximum score of 144 reflects the best possible QoL

(Chandu et al., 2006; Ringash & Bezjak, 2001)

A dramatic increase in studies assessing HRQoL of oral cancer patients were observed in recent years. Most of these studies focused on assessment of HRQoL predictors and HRQoL functional outcome following diagnosis and treatment (Rogers et al., 2007).

2.5.3 Impact of oral cancer and its treatment on HRQoL

Similar to other cancers, cancer of the oral cavity has been reported to exert a definitive impact on the HRQoL of the sufferer. A cross-sectional study among Indian patients who were followed up for 12 months after surgical removal of their tumors found that HRQoL domains most affected were financial difficulties (54.0%), appetite loss (36.0%), fatigue (33.0%), dry mouth (64.0%), dental problems (42.0%), sticky saliva (40.0%), cough (39.0%) and mouth opening (32.0%) (Chaukar et al., 2009), whereas in the UK, chewing difficulties, anxiety and swallowing problems were the predominant issues faced by patients (Dwivedi et al., 2012).

A number of longitudinal studies have been conducted to assess changes in HRQoL over time. At pre-treatment, HRQoL issues reported to be most prevalent were pain, chewing, swallowing, speech and anxiety (Biazevic et al., 2010; Gellrich, Schimming, Schramm, Schmalohr, Bremerich et al., 2002), whereas immediately after surgery, in addition to chewing and swallowing, patients also reported significant deteriorations in the areas of speech intelligibility, tongue mobility as well as mobility in the head, neck and shoulder region (Gellrich et al., 2002). Among Taiwanese patients currently undergoing radiotherapy, significant deterioration were observed between pre-treatment and during treatment for the domains of speech, social eating, social contact, dry mouth and sticky saliva (Fang, Liu, Tang, Wang, & Ko, 2004).

At the point of 12 months post-treatment, significant improvement were seen in relation to pain scores, anxiety and emotional function (Agarwal, Munjal, Koul, & Agarwal, 2014; Biazevic et al., 2010; Schliephake & Jamil, 2002), whereby continuous improvement in emotional functioning was consistently seen up to the 5-year follow up (Nordgren, Hammerlid, Bjordal, Ahlner-Elmqvist, Boysen et al., 2008). On the other hand, significant deteriorations were observed for appearance, social function and physical function such as swallowing, chewing, speech, taste, saliva, dry mouth and shoulder function (Agarwal et al., 2014; Biazevic et al., 2010; Hoxbroe Michaelsen et al., 2017; Schliephake & Jamil, 2002).

In a study comparing HRQoL between Swedish patients with the normal population, it was found that the impact of oral cancer was still evident even at three years after diagnosis, in which the scores for treatment-related side effects as well as H&N specific issues such as pain, swallowing, senses, social eating, teeth, mouth opening, dry mouth and mucous were significantly worse among oral cancer patients as compared to the normal population (Hammerlid & Taft, 2001). The debilitating impact of this disease was further demonstrated where significant deteriorations for physical

and role functioning, as well as senses, social contact, speech, teeth, mouth opening, dry mouth, sticky saliva and cough were still reported up until five and eight years post-treatment (Nordgren et al., 2008; Oskam, Verdonck-de Leeuw, Aaronson, Witte, de Bree et al., 2013).

Variations were documented in the pattern of HRQoL changes over time. The first pattern showed consecutive improvements at the first and third year follow-up, in which the domains involved were pain and emotional functioning. The second pattern was characterized by deterioration at the first year stage and improvement by the third year, and the domains involved were global QoL, physical functioning, role functioning, social functioning, financial problems, senses, social eating, social relationships, sexuality, mouth opening and intake of analgesics. In the third pattern, deterioration at both the first and third year follow-up were observed and this affected the domains of cognitive functioning, fatigue, constipation, diarrhea, deglutition, speech, dry mouth, sticky saliva, cough, feeling ill and weight gain (Infante-Cossio, Torres-Carranza, Cayuela, Hens-Aumente, Pastor-Gaitan et al., 2009).

Generally, HRQoL was observed to be the worst during the first three months after treatment, which then gradually improves over time with some domains reaching pre-treatment values (Hammerlid, Silander, Hornestam, & Sullivan, 2001; Mortensen & Jarden, 2016). Anxiety levels were at the peak before surgery, while the H&N specific issue of limited mouth opening was reported to be among the burdensome symptoms, affecting the ability to eat and communicate. Social eating deteriorated for the first few years, and the inability to speak affected relationships, social life as well as employment. Moreover, the inability to socialize with others was significantly associated with depression and anxiety, whereas disfigurement from surgical removal of their tumors led to social withdrawal and became a barrier for intimacy. In summary,

patients reported struggling with feelings of powerlessness, loss of independence, and low self-esteem (Mortensen & Jarden, 2016).

2.5.4 Factors affecting HRQoL

Stage of cancer at diagnosis has been established to be a significant factor influencing HRQoL. Overall HRQoL was significantly worse for patients presenting with late stage tumors, whereby they were significantly more affected in the domains of role and social functions, pain, fatigue, appetite as well as H&N specific items of swallowing, senses, speech, social eating, social contact, mouth opening, dryness of mouth, sticky saliva cough and mucous (Chaukar et al., 2009; Hammerlid et al., 2001; Hassanein et al., 2001; Infante-Cossio et al., 2009; Schliephake & Jamil, 2002). Correspondingly, patients with advanced stage tumors were found to have lower mean HRQoL scores as compared to patients in the early stages (Dwivedi et al., 2012).

Type of treatment modality is another factor found to influence patient's HRQoL. Patients who only had surgical removal of their tumors as their treatment modality were reported to have a significantly better overall HRQoL, as compared to those receiving radiotherapy only or a combined treatment modality. At 12 months post-treatment, patients who underwent surgery only, fared better in most domains. However the difference were most significant for role and cognitive functioning, pain, sleep and loss of appetite, and H&N specific items of swallowing, senses, speech, social eating, social contact, teeth and dryness of mouth (Chaukar et al., 2009). The impact of treatment modality on patient's HRQoL was further validated by other researchers. In longitudinal studies where patients were followed up until three and five years post-treatment, it was found that patients who only received surgical intervention had higher HRQoL scores at all time points, whereas patients treated with radiotherapy or multi-modal treatment scored significantly worse for physical and role function, dyspnea,

swallowing, senses, dry mouth, sticky saliva, mouth opening, speech and social issues with eating (Infante-Cossio et al., 2009; Nordgren et al., 2008).

Site of the tumor has also been postulated to affect HRQoL. Patients with oropharyngeal tumors were reported to have a worse overall HRQoL, and more prevalent symptoms of tiredness, nausea, loss of appetite, pain, dyspnea, higher intake of analgesics, speech problems, eating and social relationships as compared to oral cavity cancers (Infante-Cossio et al., 2009). This is in concordance with an earlier study whereby patients with oropharyngeal cancers were reported to have poorer HRQoL compared to the other sub-sites within the head and neck region (Hammerlid et al., 2001; Hassanein et al., 2001).

Age is another factor that has been hypothesized to affect HRQoL. In a study conducted in UK, younger patients (<60 years old) were found to fare significantly worse in the domains of swallowing, shoulder function and pain (Hassanein et al., 2001). Similarly, younger patients were reported to have significantly lower mean HRQoL scores than older patients (Dwivedi et al., 2012). In contrast, a study in which patients were followed up for three years found that the scores of younger patients were better for most of the HRQoL domains, with significant differences noted for physical functioning and nausea/ vomiting (Hammerlid et al., 2001).

Other factors that have been studied include SES and religious belief. HRQoL of patients with lower SES were found to be poorer, whereas religious beliefs were observed to confer a positive influence on HRQoL by helping patients to manage their emotions better (Mortensen & Jarden, 2016).

2.5.5 HRQoL as a predictor for survival

The potential role of HRQoL as a predictor for patient outcome in terms of survival has been studied previously. A meta-analysis of 30 randomized controlled trials

conducted on 11 types of cancers including head and neck, noted that HRQoL parameters of physical function, pain and appetite loss were significant predictors of survival (Quinten, Coens, Mauer, Comte, Sprangers et al., 2009).

With regards to oral cancer, a study among Taiwanese reported that pre-treatment fatigue scores were a significant predictor of survival, whereby a ten point increase in scores confer a 17.0% reduction in survival (Fang et al., 2004). A study conducted in the US found that only the physical component score (and not the mental component score) was associated with survival, in which a 14.0% reduction in mortality risk was estimated for every five unit increase in scores (Karvonen-Gutierrez, Ronis, Fowler, Terrell, Gruber et al., 2008). Correspondingly, the same study also reported that an increase in scores for the domains of pain, eating and speech, which indicate better HRQoL, were significantly associated with survival. Patients who had survived for up to five years post-treatment were observed to have a better HRQoL scores at diagnosis and at one year follow up compared to non-survivors (Nordgren et al., 2008). Additionally, another study reported that low HRQoL scores at one year after diagnosis confers a two times increased mortality risk (Mehanna & Morton, 2006).

However, some studies did not show any correlation between HRQoL scores with survival. A large study assessing pre-treatment HRQoL and patient outcomes in more than 1,000 patients with locally advanced cancer found that pre-treatment scores of the functional well-being domain is only a predictor of locoregional control, but not for overall survival (Siddiqui, Pajak, Watkins-Bruner, Konski, Coyne et al., 2008). Moreover, a recent review of studies conducted among head and neck cancer patients reported that four of eight studies did not show clear evidence of the role of HRQoL as a predictor for survival (Montazeri, 2009). Additionally, a previous review concluded that although there seemed to be an association between selected factors with survival, the evidence is neither strong nor proven (Mehanna, De Boer, & Morton, 2008).

Stage of cancer has been shown to not only affect the prognosis of patients, but is also an important factor influencing the quality of life of these patients (Dwivedi et al., 2012). Unfortunately, oral cancer patients tend to present themselves at late stages of their disease, especially in this part of the world with about two-thirds of patients presenting with stage III and IV disease (Vincent-Chong et al., 2017; Doss et al., 2011). This is baffling, as oral cancers primarily arise in the surface of the oral epithelium which is readily accessible for visual and tactile examination. Presentation at advanced stages which warrants a more complex treatment regime, coupled with limited access to healthcare services especially among the lower SES group further compounds the effect of this disease on the patient. Thus, it is of utmost importance that efforts towards early detection, especially in terms of identification of diagnostic aids be strongly advocated in order to reduce late presentation of disease.

2.6 Early detection of oral cancer

2.6.1 Importance of early detection

The primary reason for presentation of disease at late stages is delay in diagnosis. The time between the appearances of first symptom to diagnosis is influenced by multiple clinical, sociodemographic and psychosocial variables. On one side, there is the patient delay in which fear and lack of symptom recognition contributes to the delay (Smith, Pope, & Botha, 2005), whereas on the other hand there is the professional delay in diagnosing and treating the disease (Messadi, 2013). In Iran, it was reported that the median duration of patient delay was 45 days whereas professional delay was 86 days, giving a total delay of 20 weeks (Esmaelbeigi, Hadji, Harirchi, Omranipour, vand Rajabpour et al., 2014).

Early detection is a secondary prevention method, and it has been considered to be an important measure, as the primary prevention method of changing of lifestyle and

habits is slow and difficult to achieve. Clinicians can play a bigger role in improving patient outcomes if cancers are detected at an early stage, or if a premalignant lesion is identified and treated before malignant transformation (Messadi, 2013). The gold standard for oral cancer diagnosis is biopsy with histological assessment, but the disadvantage of this method is that it is invasive, painful and time consuming. Moreover, biopsy is only conducted upon presentation of patients to the clinic, by which time most of these lesions are already at an advanced stage.

Screening is one method that has been accepted for the early detection of cancers. Screening is defined as 'the application of a test or tests to people who are apparently free from the disease in question in order to sort out those who probably have the disease from those who probably do not' (Lingen, Kalmar, Karrison, & Speight, 2008). In essence, it is a method in which individuals are examined for the disease before the onset of symptoms. Screening is not a diagnostic method, rather its purpose is to identify abnormalities that requires referral for further investigation. Screening can be categorized into three types, i) population based screening - a population is assessed specifically for the purpose of detecting a specific disease; ii) opportunistic screening - patients attending a health care provider for another purpose are examined; iii) targeted screening - conducted among high risk individuals. Screening has been shown to be effective in reducing the morbidity and mortality rates for cancers such as breast with the mammogram and cervical with the Pap smear test.

2.6.2 Early detection methods/ techniques

Currently, several early detection methods are being utilized for purposes of screening for abnormalities. These methods are summarized in Table 2.7.

Table 2.7: Early detection methods/ techniques

Method	Features	Sensitivity (%)	Specificity (%)	Advantage/ Limitation
Clinical Oral Examination (COE)	Visual examination using normal incandescent light Current gold standard method for screening of the oral cavity	74 - 85	97 - 99	Unable to discriminate which lesion will progress to cancer
Brush biopsy	Evaluate suspicious lesion otherwise not subjected to biopsy	71 - 92	32 - 94	Unable to provide definitive diagnosis, positive findings from brush biopsy needs to be confirmed with scalpel biopsy
Toluidine blue staining	Vital dye that stains nucleic acid and abnormal tissues	78 - 100	31 - 100	Used to assist biopsy site selection Have the ability to determine lesion at risk of malignant progression
Chemiluminescence	Rinse with acetic acid solution prior to visual examination using blue white light	77 - 100	0 - 28	Unable to discriminate between keratotic, inflammatory or malignant lesion
VELScope	Portable handheld device Utilize concept of authoflourescence Visual examination using intense blue light	30 - 98	63 - 100	Unable to differentiate between dysplasia and benign inflammatory conditions

Table 2.7, continued

Method	Features	Sensitivity (%)	Specificity (%)	Advantage/ Limitation
Mouth Self Examination	Six step self examination method	18 - 43	44 - 100	Quick, non-invasive and inexpensive Can be done in the comfort of own home
Teledentistry	Combine information technology and telecommunication with dental care	91	91	Provide connectivity between primary care workers with specialists such that remote diagnosis were enabled

These early detection methods are further explained in the following sections.

2.6.2.1 Clinical Oral Examination (COE)

For oral cancer, clinical oral examination (COE) using normal incandescent light has been the mainstay method for screening. COE has been shown to be a beneficial method for the early detection of suspicious lesions. The sensitivity and specificity rates of a large screening program in the UK were reported to be 74.0% and 99.0% respectively (Lingen et al., 2008), indicating that COE has the ability to accurately distinguish between those with lesions (true positive) and those without lesions (true negative). A meta-analysis of studies using COE to screen for oral cancer and potentially malignant disorders reported a high pooled sensitivity of 85.0% and specificity of 97.0% (Downer, Moles, Palmer, & Speight, 2004). In addition, it was also found that trained healthcare auxillaries were able to use the COE and screen with a degree of accuracy that is similar to the dental practitioners.

A landmark study for the effectiveness of screening programs, as measured by survival and mortality rates would be the Kerala randomized controlled trial (Sankaranarayanan, Ramadas, Thara, Muwonge, Thomas et al., 2013; Sankaranarayanan, Ramadas, Thomas, Muwonge, Thara et al., 2005). In that study, 191,872 individuals were recruited and assigned to either an intervention (screened) or a control group. The intervention group was exposed to repeated rounds of screening via COE and was followed up for 15 years. A significantly reduced mortality risk of 24.0% was documented for tobacco and/or alcohol users in the intervention group after four rounds of screening. Moreover, a 38.0% reduction in oral cancer incidence were reported amongst tobacco and/ or alcohol users adhering to four screening rounds (Sankaranarayanan et al., 2013).

However, although COE has been accepted as the gold standard method for screening, its utility still remains controversial as there have been reports that COE might have limited ability in detecting malignant lesions at an early stage. While COE may be able to detect clinical lesions, a study has suggested that some premalignant lesions may appear as clinically normal (Thomson, 2002), thus reducing the efficacy of COE in detecting suspicious lesions with normal mucosal appearance. Moreover, COE has been observed to not have the ability to discriminate which premalignant lesions will progress to cancer and which will not (Lingen et al., 2008). A meta-analysis of trials concluded that there is limited evidence for the efficacy of COE as a method for early detection, as reduced mortality risk is only evident amongst individuals with high risk habits (Brocklehurst, Kujan, O'Malley, Ogden, Shepherd et al., 2013). However, cost-effectiveness analyses found that opportunistic screening among high risk individuals by primary care practitioners (Speight, Palmer, Moles, Downer, Smith et al., 2006) or targeted screening among high risk populations (Dedhia, Smith, Johnson, & Roberts, 2011) may be beneficial.

Apart from COE, knowledge and technological advancements over the years have encouraged and led to the development of other adjunctive tools that can aid in the early detection of oral cancers, which are reviewed in the following section.

2.6.2.2 Brush biopsy

The brush biopsy was designed for the evaluation of lesions that otherwise would not be subjected to biopsy due to the low level of suspicion for carcinoma (Lingen et al., 2008). When an abnormal result is reported, it is to be followed by a scalpel biopsy of the lesion, as brush biopsy is unable to provide a definitive diagnosis.

Among a sample of 243 patients that were found to have abnormal brush biopsy results, 93 of them showed dysplasia or cancer upon histological evaluation, yielding a calculated positive predictive value (PPV) of 38.0%. Additionally, the brush biopsy technique was reported to have a sensitivity of 92.0% and specificity of 94.0% in detecting dysplasia and oral cancer (Svirsky, Burns, Carpenter, Cohen, Bhattacharyya et al., 2002). Similarly, high sensitivity and specificity rates of 92.3% and 94.3% were reported by another researcher (Scheifele, Schmidt-Westhausen, Dietrich, & Reichart, 2004). A study conducted among patients referred to an oral medicine clinic reported a lower sensitivity and specificity rates of 71.0% and 32.0% respectively (Poate, Buchanan, Hodgson, Speight, Barrett et al., 2004). However, one weakness of this study is that the patient cohort (individuals already with suspicious lesions) was not consistent with the type of patients this technique was intended for.

In summary, the brush biopsy has shown potential as an effective early detection technique. However, the major weakness in these studies was that the gold standard (scalpel biopsy) was mostly only conducted among positive brush biopsy results, which could majorly impact the evaluation of efficacy in terms of sensitivity and specificity rates. This is enhanced by a study which discovered that of 15 cases with negative brush

biopsy, six of them did in fact have dysplasia or carcinoma upon being evaluated by scalpel biopsy (Poate et al., 2004). Thus, more studies need to be conducted with sufficient sample size in which both brush and scalpel biopsy are performed on all participants to validate the effectiveness of brush biopsy as an effective early detection technique (Lingen et al., 2008).

2.6.2.3 Toluidine blue (TB) staining

Toluidine blue is a vital dye that stains nucleic acids and abnormal tissues. It has been used as a means of identifying clinically occult lesions in patients whose oral mucosa may otherwise be normal (Lingen et al., 2008) as it is a practical, rapid and inexpensive tool. TB staining has been recommended as an adjunctive method for early detection of oral cancer and premalignant lesions, to assist biopsy site selection, for assessment of margins and for determining premalignant lesion at risk of progression to carcinoma (Epstein & Guneri, 2009).

A study on patients presenting with oral mucosal lesions reported sensitivity and specificity rates of 95.0% and 71.4% respectively for the detection of premalignant or malignant lesions (Pallagatti, Sheikh, Aggarwal, Gupta, Singh et al., 2013). This finding is in concordance with another study that reported a similar sensitivity and specificity rates of 96.2% and 77.7% respectively (Allegra, Lombardo, Puzzo, & Garozzo, 2009). In a study among 100 patients with premalignant lesions that were followed up for an average of 44 months, TB was found to stain lesions with higher degrees of dysplasia. More importantly, TB was also found to have the ability to predict risk and outcome of lesions with little to no microscopic evidence of dysplasia, whereby a six fold increased cancer risk was observed for TB positive lesions, with positive staining in 12 of 15 lesions that progressed to cancer (Zhang, Williams, Poh, Laronde, Epstein et al., 2005).

Overall, there is some evidence that TB staining is a useful adjunct to clinical examination for the identification of potentially malignant and malignant lesions with sensitivity rates of 78.0%-100.0% and specificity rates of 31.0%-100.0% (Lingen et al., 2008). However, it should be noted that the usefulness of TB staining has only been evaluated in a secondary care environment among specialists, and not in primary care settings.

2.6.2.4 Light-based detection systems

Currently, there are two light-based systems that are being studied for the early detection of lesions in the oral cavity, namely chemiluminescence (reflective tissue fluorescence) and VELScope (narrow emission tissue fluorescence) (Lingen et al., 2008).

Chemiluminescence, which has long been used as an adjunct in the examination of the cervical mucosa, has been adapted for use in the oral cavity. In this method, patients will rinse with a 1.0% acetic acid solution before being subjected to a visual examination of the mouth using a blue-white light source. Under this illumination, normal epithelium will appear lightly bluish whereas abnormal epithelium will appear as a distinctly white spot (Lingen et al., 2008).

In a study on 40 patients with a previous history of oral cancer, the sensitivity and specificity rates for chemiluminescence were reported to be 100.0% and 14.0% respectively (Ram & Siar, 2005). However, one weakness of this study was that one-third of the lesions did not undergo the gold standard test (scalpel biopsy), thus the accuracy of the sensitivity and specificity cannot be determined. In a multi-center study, three out of 138 lesions identified by COE were not detected by chemiluminescence, which was later proven to be non-malignant (Epstein, Gorsky, Lonky, Silverman, Epstein et al., 2006). However, chemiluminescence was able to detect two lesions not

detected by COE, in which one was diagnosed as recurrent cancer while the other was of benign nature. In a study on patients with a history of tobacco consumption, chemiluminescence detected 61.0% of lesions identified to be suspicious of malignancy by COE (Kerr, Sirois, & Epstein, 2006). In this study, lesions illuminated under chemiluminescence appeared significantly sharper compared to under incandescent light. In another study among patients referred for white lesions in which patients were subjected to chemiluminescence followed by scalpel biopsy for definitive diagnosis, chemiluminescence enhanced the visibility of 47.0% of the lesions (Farah & McCullough, 2007). However, it was found that chemiluminescence was not able to discriminate between keratotic, inflammatory or malignant lesions, thus providing little benefit for this method to be used as an early detection tool. Another study conducted in the US also supported the conclusion that chemiluminescence did not improve the overall detection rate, in fact it was reported that this method produced reflections that made visualization in the oral cavity more difficult (Oh & Laskin, 2007). A systematic review documented that the sensitivity for chemiluminescence ranged between 77.0%-100.0%, while specificity was low between 0.0%-28.0% (Nagi, Reddy-Kantharaj, Rakesh, Janardhan-Reddy, & Sahu, 2016). It was also noted that chemiluminescence increases the brightness and margins of lesions, particularly for white lesions, however it may fail to spot red patches.

Visually Enhanced Lesion Scope (VELScope) is a portable device that was developed based on the concept that autofluorescence of tissue could potentially be used for cancer detection (Lingen et al., 2008). Under intense blue excitation light emitted by this device, areas of normal mucosa will appear as pale green autofluorescence (retain of autofluorescence), whereas areas with tissue abnormalities will appear as dark (loss of autofluorescence).

In a study among patients who had a history of malignancy, VELScope demonstrated a high sensitivity of 98.0% and specificity of 100.0% for discriminating malignant and premalignant lesions from normal mucosa when compared against histological diagnosis (Lane, Gilhuly, Whitehead, Zeng, Poh et al., 2006). Another study among patients with suspicious premalignant lesions reported that examination using VELScope yielded a higher sensitivity rate of 97.9% compared to 75.9% rate of COE (Hanken, Kraatz, Smeets, Heiland, Assaf et al., 2013). However, it should be noted that these studies were carried out among high risk populations in which some of them had already had a history of malignancy, thus the results cannot be generalized to screening in a general population. On the other hand, in a study among patients referred for potentially malignant lesions, although VELScope were found to enhance visibility of lesions and identified five clinically undetected lesions, the sensitivity and specificity rates of VELScope on its own were low at 30.0% and 63.0% respectively (Farah, McIntosh, Georgiou, & McCullough, 2012). One study investigated the efficacy of VELScope in determining surgical tumor margins. Of 20 cases, 95.0% of them demonstrated loss of autoflourescence that extended to as much as 25mm beyond the clinically visible tumor, in which 89.0% of biopsied samples from these areas were proven to be malignant (Poh, Zhang, Anderson, Durham, Williams et al., 2006). This finding suggests that VELScope might have the ability to identify lesions that were not detected by COE. A recent systematic review concluded that VELScope is useful in assisting clinicians to detect premalignant lesions, however the disadvantage is that it was found to be unable to differentiate between dysplasia and benign inflammatory conditions (Nagi et al., 2016).

2.6.3 Other emerging early detection aids

2.6.3.1 Mouth self-examination (MSE)

All early detection aids developed so far were targeted to be used by either clinicians or trained healthcare workers. Moreover, these aids need to be administered repeatedly at regular intervals on high risk individuals in order to effectively detect cancers at an early stage, which is deemed not practical in terms of feasibility and cost-effectiveness (Sarode, Sarode, & Karmarkar, 2012). As such, methods of self-examination were recommended to be prioritized for early detection of cancers. Self-examination has been found to effectively improve early detection of other cancers such as breast (Hacihasanoglu & Gozum, 2008) and skin (Oliveria, Chau, Christos, Charles, Mushlin et al., 2004). Mouth self-examination (MSE) is a quick, non-invasive, inexpensive and simple technique of self-screening for abnormalities in the mouth, which can be utilized by the general population in the comfort of their own home.

In a large study in India where 34,766 high risk individuals were sampled, 216 cases of potentially malignant lesions and three cases of oral cancers were detected (Elango, Anandkrishnan, Suresh, Iyer, Ramaiyer et al., 2011). The concordance of lesion detection between oral cancer specialists and trained healthcare workers was 100.0%, while the concordance between healthcare workers and MSE done by the study population was 72.0%. In this study, MSE was observed to have a low sensitivity rate of 18.0%, whereas the specificity is very high at 99.9%. In UK, a study on the efficacy of MSE conducted among patients with smoking habit attending a general practitioner's clinic reported a low sensitivity and specificity rate of 33.0% and 54.0% respectively (Scott, Rizvi, Grunfeld, & McGurk, 2010). Similarly, in a study among patients with Fanconi Anemia which was associated with a high risk of development of head and neck cancers, detection of lesions via MSE gave low sensitivity and specificity rates of 43.0% and 44.0%, when compared against the gold standard in which diagnoses was

made by an oral medicine specialist (Furquim, Pivovar, Cavalcanti, Araujo, Sales Bonfim et al., 2014).

In contrast, a study among 2,257 male prisoners in India with high prevalence of tobacco habits reported very high sensitivity and specificity rates of 92.2% and 96.6% respectively (Chaudhari, Hegde-Shetiya, Shirahatti, & Agrawal, 2013). The contrasting results between this study with the others could be explained by the method of information giving. In the study among prisoners, participants were educated face-to-face on the ill effects of tobacco with the help of photographs showing premalignant conditions, however in the other studies, information was only disseminated through leaflets or brochures. This emphasizes the importance of proper strategies of education, especially so as oral cancers have been established to occur predominantly among the lower SES group. Moreover, a previous study established that one of the barriers in performing MSE is that they were not sure where to look and what signs to look for (Scott, Weinman, & Grunfeld, 2011).

In a study based on the Health Belief Model, it was found that patients who perceived themselves to be susceptible, realized the severity of the disease and believed that preventive measures would give benefits were significantly more likely to perform MSE (Jornet, Garcia, Berdugo, Perez, & Lopez, 2015). This suggests that the content and delivery of educational intervention is a crucial step in the effort to detect cancers at early stages, as increased awareness could encourage them to actively and routinely conduct self-examination.

2.6.3.2 Teledentistry

Teledentistry is a new technique that combines telecommunication with dental care. It is defined as ‘the use of information technology for communication, to exchange information on dental records, digital imaging, and health related information using

mobile devices' (Daniel & Kumar, 2014). Research on the usefulness of teledentistry was conducted mostly for education purposes, followed by diagnosis, consultation and treatment planning (Marino & Ghanim, 2013). Most of these studies were conducted in the US, and to date, no studies from developing countries were reported. A recent systematic review reported that the most convincing evidence regarding the efficacy of teledentistry was provided by studies on pediatric dentistry, orthodontics and oral medicine, and that teledentistry can be cost-saving when compared to conventional consultation (Estai, Kanagasingam, Tennant, & Bunt, 2018).

Recently, a large study was conducted to assess the effectiveness of a mobile phone-based remote oral cancer screening program connecting primary care dental practitioners and frontline health care workers with oral cancer specialists. It was reported that in targeted screening in rural villages, the concordance of lesion detection between frontline health workers and specialists were low at 45.0%, however at opportunistic screening in a dental clinic, the concordance between primary care dental practitioners and specialists were very high at 100.0%. Of the patients who were referred and underwent biopsy for a definitive diagnosis of their lesions, 90.0% were confirmed to have malignant or potentially malignant lesions (Birur, Sunny, Jena, Kandasarma, Raghavan et al., 2015). Furthermore, in a survey conducted among patients at high risk for oral cancer, a sensitivity rate of 91.0% and specificity rate of 90.5% were recorded for diagnoses by trained examiners who diagnosed lesions based on images and videos from mobile phones, when compared against the gold standard diagnosis using COE (Gomes, Bonan, Ferreira, de Lucena Pereira, Correia et al., 2017). Another study among frontline healthcare workers also reported similar findings of the efficacy of a mobile phone based application, in which the use of the application had empowered them to identify lesions and provided connectivity with the specialists such that remote diagnosis by specialists were enabled (Desai, Birur, Bajaj, Shubhasini,

Bhanushree et al., 2015). These findings suggest that teledentistry could be used as a potential diagnostic aid for early detection of oral cancers in underserved populations and in a resource constrained setting.

Overall, there is growing evidence supporting the efficacy of teledentistry. However, a recent systematic review concluded that the evidence on its effectiveness and economic benefits (cost-saving) is not conclusive as most of the available literature leaned towards assessing the efficacy of the application of teledentistry, rather than assessing the effectiveness of teledentistry itself (Estai et al., 2018). Well-designed studies are warranted before teledentistry can be advocated for use in clinical settings.

CHAPTER 3: PUBLISHED WORKS

In this chapter, 12 original works pertaining to research in various aspects of oral cancer are presented, in which the PhD candidate is the principal author for six of these works. All of these works have been published, and are presented in the original published format of the respective journals. Each work presented here is preceded by a declaration of the contributions of all co-authors.

3.1 Publication 1

Oral Cancer Awareness and its Determinants among a Selected Malaysian Population

3.1.1 Contribution of co-authors

WMN Ghani was involved in the conception of study design, monitoring of data acquisition, data analysis and interpretation and drafted the manuscript. JG Doss was involved in conception of study design, data interpretation and critical revision of manuscript. M Jamaluddin was involved in data analysis and interpretation and critical revision of manuscript. D Kamaruzzaman was involved in the conception of study design, acquisition of data and critical revision of manuscript. RB Zain was involved in the conception of study design, provided resources and critical revision of manuscript. All authors read and approved the final manuscript.

3.1.2 Consent from corresponding author

24th February 2019

To whom it may concern,

Consent to include published article as part of PhD requirement:

Ghani WMN, Doss JG, Jamaluddin M, Kamaruzaman D, Zain RB. Oral Cancer Awareness and its Determinants among a Selected Malaysian Population. Asian Pacific Journal of Cancer Prevention. 2013;14(3):1957-63

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,

Associate Professor Dr Jennifer Geraldine Doss
Department of Community Oral Health & Clinical Prevention
Faculty of Dentistry, University of Malaya

3.2 Publication 2

Promoting Oral Cancer Awareness and Early Detection using a Mass Media Approach

3.2.1 Contribution of co-authors

A Saleh was involved in conception and design of the project, data collection and drafted the manuscript. YH Yang was involved in data analysis and interpretation and critical revision of manuscript. WMN Ghani was involved in drafting of data collection questionnaire, providing materials for the mass media campaign and critical revision of manuscript. N Abdullah, JG Doss, NA Talib and RB Zain were involved in study design and critical revision of manuscript. R Navonil was involved in data collection and coordination of the pre and post campaign survey. ZA Abdul Rahman and SM Ismail were involved in the conduct of the mass media campaign and critical revision of manuscript. SC Cheong conceived and supervised the study, obtained funding and revised the manuscript. All authors read and approved the final manuscript.

3.2.2 Consent from corresponding author

24th February 2019

To whom it may concern,

Consent to include published article as part of PhD requirement:

Saleh A, Yang YH, Ghani WMN, Abdullah N, Doss JG, Navonil R, Abdul Rahman ZA, Ismail SM, Talib NA, Zain RB, Cheong SC. Promoting Oral Cancer Awareness and Early Detection using a Mass Media Approach. Asian Pacific Journal of Cancer Prevention. 2012;13(4):1217-24

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,

Professor Dr Cheong Sok Ching
Senior Group Leader,
Head and Neck Cancer Research Team
Cancer Research Malaysia

3.3 Publication 3

Multi-ethnic variations in the practice of oral cancer risk habits in a developing country

3.3.1 Contribution of co-authors

WMN Ghani was involved in conception of study design, data analysis and interpretation and drafting of manuscript. IA Razak was involved in conception of study design, data interpretation and critical revision of manuscript. JG Doss was involved in conception of study design, data interpretation and critical revision of manuscript. YH Yang was involved in data analysis and interpretation and critical revision of manuscript. ZAA Rahman, SM Ismail, MT Abraham, WMW Mustafa, KK Tay were involved in acquisition of data and critical revision of manuscript. RB Zain was involved in conception of study design, data interpretation and critical revision of manuscript. All authors read and approved the final manuscript.

3.4 Publication 4

Factors affecting commencement and cessation of smoking behaviour in Malaysian adults

3.4.1 Contribution of co-authors

WMN Ghani was involved in conception of study design, data interpretation and drafted the manuscript. IA Razak, NA Talib and N Abdullah were involved in conception of study design and critical revision of manuscript. YH Yang was involved in data analysis and interpretation and critical revision of manuscript. N Ikeda was involved in acquisition of funding, conception of study design and critical revision of manuscript. PC Gupta was involved in conception of study design, sampling estimation and critical revision of manuscript. T Axell and Y Handa were involved in conception of study design and critical revision of manuscript. RB Zain was involved in conception of study design, coordination of the research group, ensuring quality control of data and critical revision of manuscript. All authors read and approved the final manuscript.

3.4.2 Consent from corresponding author

24th February 2019

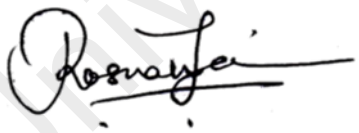
To whom it may concern,

Consent to include published article as part of PhD requirement:

Ghani WMN, Razak IA, Yang YH, Talib NA, Ikeda N, Axell T, Gupta PC, Handa Y, Abdullah N, Zain RB. Factors affecting commencement and cessation of smoking behaviour in Malaysian adults. BMC Public Health. 2012;12:207

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,



Professor Dr Rosnah Mohd Zain
Dean,
Faculty of Dentistry, MAHSA University

3.5 Publication 5

Factors affecting commencement and cessation of betel quid chewing behaviour in Malaysian adults

3.5.1 Contribution of co-authors

WMN Ghani was involved in conception of study design, data interpretation and drafted the manuscript. IA Razak, NA Talib and N Abdullah were involved in conception of study design and critical revision of manuscript. YH Yang was involved in data analysis and interpretation and critical revision of manuscript. N Ikeda was involved in acquisition of funding, conception of study design and critical revision of manuscript. PC Gupta was involved in conception of study design, sampling estimation and critical revision of manuscript. T Axell and Y Handa were involved in conception of study design and critical revision of manuscript. RB Zain was involved in conception of study design, coordination of the research group, ensuring quality control of data and critical revision of manuscript. All authors read and approved the final manuscript.

3.5.2 Consent from corresponding author

24th February 2019

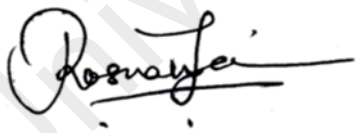
To whom it may concern,

Consent to include published article as part of PhD requirement:

Ghani WMN, Razak IA, Yang YH, Talib NA, Ikeda N, Axell T, Gupta PC, Handa Y, Abdullah N, Zain RB. Factors affecting commencement and cessation of betel quid chewing behaviour in Malaysian adults. BMC Public Health. 2011;11:82

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,



Professor Dr Rosnah Mohd Zain
Dean,
Faculty of Dentistry, MAHSA University

3.6 Publication 6

Dietary pattern and oral cancer risk – a factor analysis study

3.6.1 Contribution of co-authors

LC Helen-Ng was involved in conception of study design, data acquisition, data analysis and interpretation and drafted the manuscript. IA Razak was involved in conception of study design, monitoring of data acquisition, interpretation of data and critical revision of manuscript. WMN Ghani was involved in conception of study design, data acquisition, interpretation of data and critical revision of manuscript. J Marhazlinda was involved in data analysis and interpretation and critical revision of manuscript. AT Norain, ZAA Rahman, N Abdullah were involved in data acquisition and critical revision of manuscript. RL Raja Jallaludin and RB Zain were involved in conception of study design, interpretation of data and critical revision of manuscript. All authors read and approved the final manuscript.

3.6.2 Consent from corresponding author

24th February 2019

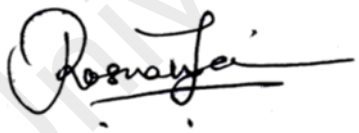
To whom it may concern,

Consent to include published article as part of PhD requirement:

Helen-Ng LC, Razak IA, Ghani WMN, Marhazlinda J, Norain AT, Raja Jallaludin RL, Rahman ZA, Abdullah N, Zain RB. Dietary pattern and oral cancer risk - a factor analysis study. Community Dentistry & Oral Epidemiology. 2012; 40:560-66

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,



Professor Dr Rosnah Mohd Zain
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3.7 Publication 7

High Serum Level of Retinol and α-Tocopherol Affords Protection Against Oral Cancer in a Multiethnic Population

3.7.1 Contribution of co-authors

V Athirajan was involved in conception of study design, data and material acquisition, performing experiments, data analysis and drafted the manuscript. IA Razak was involved in conception of study design, monitoring of data acquisition, interpretation of data and critical revision of manuscript. N Thurairajah was involved in designing and supervising experiments. WMN Ghani, LC Helen-Ng and RB Zain were involved in conception of study design, interpretation of data and critical revision of manuscript. YH Yang and LP Karen-Ng were involved in interpretation of data and critical revision of manuscript. ZAA Rahman, WMW Mustafa, MT Abraham, KK Tay, KM Yuen and N Jalil were involved in data and material acquisition and critical revision of manuscript. All authors read and approved the final manuscript.

3.7.2 Consent from corresponding author

24th February 2019

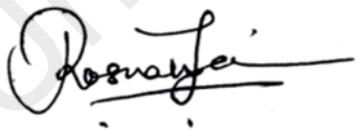
To whom it may concern,

Consent to include published article as part of PhD requirement:

Vimmitra A, Ishak AR, Thurairajah N, Ghani WMN, Helen-Ng LC, Yang YH, Karen-Ng LP, Rahman ZAA, Mustafa WMW, Abraham MT, Tay KK, Yuen KM, Jalil N, Zain RB. High serum level of retinol and α-tocopherol affords protection against oral cancer among a multiethnic population. Asian Pacific Journal of Cancer Prevention. 2014; 15(19): 8183-9

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,



Professor Dr Rosnah Mohd Zain
Dean,
Faculty of Dentistry, MAHSA University

3.8 Publication 8

Survival of oral cancer patients in different ethnicitie

3.8.1 Contribution of co-authors

WMN Ghani was involved in conception of study design, data acquisition, data analysis and interpretation and drafted the manuscript. A Ramanathan and SS Prime were involved in conception of study design, data interpretation and critical revision of manuscript. YH Yang was involved in data analysis and interpretation and critical revision of manuscript. IA Razak and JG Doss were involved in data interpretation and critical revision of manuscript. ZAA Rahman, MT Abraham, WMW Mustafa, KK Tay, TG Kallarakkal and AZ Bustam were involved in data acquisition and critical revision of manuscript. SC Cheong and RB Zain were involved in conception of study design and critical revision of manuscript. All authors read and approved the final manuscript.

3.9 Publication 9

Collagen Triple Helix Repeat Containing-1 (CTHRC1) Expression in Oral Squamous Cell Carcinoma (OSCC): Prognostic Value and Clinico-Pathological Implications

3.9.1 Contribution of co-authors

CE Lee was involved in conception of study design, data and material acquisition, performing experiments, data analysis and drafted the manuscript. VK Vincent-Chong and LP Karen-Ng were involved in conception of study design, designing experiments, data interpretation and critical revision of manuscript. A Ramanathan and TG Kallarakkal were involved in data acquisition and critical revision of manuscript. WMN Ghani was involved in data acquisition, data interpretation and critical revision of manuscript. ZAA Rahman, SM Ismail, MT Abraham, KK Tay and WMW Mustafa were involved in data and material acquisition and critical revision of manuscript. SC Cheong and RB Zain were involved in conception of study design and critical revision of manuscript. All authors read and approved the final manuscript.

3.9.2 Consent from corresponding author

24th February 2019

To whom it may concern,

Consent to include published article as part of PhD requirement:

Lee CE, Vincent-Chong VK, Ramanathan A, Kallarakkal TG, Karen-Ng LP, Ghani WMN, Rahman ZA, Ismail SM, Abraham MT, Tay KK, Mustafa WM, Cheong SC, Zain RB. Collagen Triple Helix Repeat Containing-1 (CTHRC1) Expression in Oral Squamous Cell Carcinoma (OSCC): Prognostic Value and Clinico-Pathological Implications. International Journal of Medical Sciences. 2015;12(12):937-45

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,

Professor Dr Rosnah Mohd Zain
Dean,
Faculty of Dentistry, MAHSA University

3.10 Publication 10

Changes in health-related quality of life of oral cancer patients treated with curative intent: experience of a developing country

3.10.1 Contribution of co-authors

JG Doss was involved in conception of study design, data interpretation and critical revision of manuscript. WMN Ghani was involved in conception of study design, data acquisition, data analysis and interpretation and drafted the manuscript. IA Razak was involved in conception of study design, data interpretation and critical revision of manuscript. YH Yang was involved in the quality control of data, data interpretation and critical revision of manuscript. SN Rogers and RB Zain were involved in conception of study design and critical revision of manuscript. All authors read and approved the final manuscript.

3.10.2 Consent from corresponding author

24th February 2019

To whom it may concern,

Consent to include published article as part of PhD requirement:

Doss JG, Ghani WMN, Razak IA, Yang YH, Rogers SN, Zain RB. Changes in health-related quality of life of oral cancer patients treated with curative intent: experience of a developing country. International Journal of Oral Maxillofacial Surgery. 2017;46(6):687-98

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,

Associate Professor Dr Jennifer Geraldine Doss
Department of Community Oral Health & Clinical Prevention
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3.11 Publication 11

Mouth self-examination as a screening tool for oral potentially malignant disorders among a high-risk Indigenous population

3.11.1 Contribution of co-authors

WMN Ghani was involved in conception of study design, monitoring of data acquisition, data analysis and interpretation and drafted the manuscript. IA Razak was involved in conception of study design, monitoring of data acquisition, data interpretation and critical revision of manuscript. JG Doss was involved in conception of study design, data interpretation and critical revision of manuscript. A Ramanathan was involved in conception of study design, data acquisition and critical revision of manuscript. Z Tahir, NA Ridzuan and S Edgar were involved in data acquisition and critical revision of manuscript. RB Zain was involved in conception of study design and critical revision of manuscript. All authors read and approved the final manuscript.

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3.12 Publication 12

Mobile Phone Imaging in Low Resource Settings for Early Detection of Oral Cancer and Concordance with Clinical Oral Examination

3.12.1 Contribution of co-authors

N Haron was involved in data collection, data analysis and interpretation and drafted the manuscript. RB Zain was involved in study design, and critical revision of manuscript. WMN Ghani was involved in data collection, data interpretation and critical revision of manuscript. A Saleh was involved in conception of study design, and critical revision of manuscript. TG Kallarakkal, A Ramanathan and SH Sinon were involved in data collection and critical revision of manuscript. IA Razak was involved in study design and critical revision of manuscript. SC Cheong conceived and supervised the study, obtained funding and revised the manuscript. All authors read and approved the final manuscript.

3.12.2 Consent from corresponding author

24th February 2019

To whom it may concern,

Consent to include published article as part of PhD requirement:

Haron N, Zain RB, Ghani WMN, Saleh A, Kallarakkal TG, Ramanathan A, Sinon SH, Razak IA, Cheong SC. Mobile Phone Imaging in Low Resource Settings for Early Detection of Oral Cancer and Concordance with Clinical Oral Examination. Telemedicine Journal E Health. 2017;23(3):192-9

As the corresponding author of the abovementioned article, I allow for Wan Maria Nabillah bt Wan Abdul Ghani to include this published article as part of her collection of published work, to be submitted for her PhD (prior publication mode) at University of Malaya, Kuala Lumpur.

Yours sincerely,

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CHAPTER 4: DISCUSSION & CONCLUSION

4.1 Introduction

Cancer of the oral cavity, as with other cancers brings forth a multitude of impacts, ranging from physical, psychological and economic (Foster, Wright, Hill, Hopkinson, & Roffe, 2009; Stein, Syrjala, & Andrykowski, 2008). Moreover, these life changing impacts are not only confined to the sufferer, it also affects their family members and caregivers (Girgis, Lambert, Johnson, Waller, & Currow, 2013; Terro & Crean, 2017). These impacts do not only originate from the disease itself, they could also manifest as a consequence of the management of the disease.

Oral cancer is thought to exert an even more pronounced impact, due to the very central location of the tumour, which is on the face. The visibility of the tumour as well as the effects of treatment, as compared to other cancers such as lung and colorectal, imparts a major psychological impact to the sufferers (Smith et al., 2017; Terro & Crean, 2017). Furthermore, as the cancer is located at one of the most important anatomical structure which is the mouth, functions such as mastication and swallowing are often affected (Biazevic et al., 2010; Dwivedi et al., 2012), which then affect the nutritional intake of patients. This puts a further strain on the already compromised immune status of these patients. A recently published systematic review has identified that depression, anxiety and malnutrition are the main issues that exert a significant impact on patient's overall quality of life (Moore, Ford, & Farah, 2014).

Oral cancer is not among the top ten most commonly occurring cancers among the general Malaysian population, however it is ranked within the top ten cancers among ethnic Indians (Azizah et al., 2016). Although cancer of the oral cavity is relatively easy to detect due to the ease of access to the tumour site, ironically more than two-thirds of the cases were diagnosed at advanced stages. In view of the debilitating impact of this disease, it is of importance that the oral cancer scenario in Malaysia be evaluated such

that the information gained could be used to aid efforts in oral cancer control in Malaysia. Realizing the lack of data concerning oral cancer in the Malaysian setting, studies on various aspects of oral cancer were undertaken over the last decade, which have contributed to the current body of knowledge. A summary of the findings of these studies are presented and discussed in the following section.

4.2 Contribution to the body of knowledge

From all of the studies that have been undertaken, three important areas of oral cancer in the Malaysian context have been addressed, namely risk factors, prognosis and early detection. Thus, the following discussion has been grouped under these subheadings.

4.2.1 Risk factors of oral cancer

In tandem with findings from other populations worldwide (Lin et al., 2011; Muwonge et al., 2008; Radoi et al., 2013; Thomas et al., 2007), our study has further validated that tobacco smoking, alcohol drinking and betel quid chewing are important risk factors for oral cancer (Ghani, Razak, Doss, Yang, Rahman et al., 2019a). Furthermore, this work has shown for the first time that betel quid chewing is the biggest attributable factor for oral cancer in the Malaysian population. This finding concurs with studies from India (Balaram et al., 2002; Muwonge et al., 2008), which is not surprising as in Malaysia, oral cancer prevalence is the highest among ethnic Indians (Azizah et al., 2016).

Additionally, this work has formally established that there are distinct ethnic differences in the practice of these habits (Ghani et al., 2019a). Betel quid chewing is the habit most prevalent among the Indians and Indigenous people, the Malays have the highest affinity for smoking whereas concurrent smoking and drinking are risk habits

most commonly observed among the Chinese. The reasons for these apparent differences are not clear, however it can be attributed to the social, cultural and religious beliefs of each ethnic group. For example, the habit of alcohol consumption is largely absent among the Malays mostly due to their Muslim faith which prohibits alcohol consumption, whereas it is widespread among the Chinese, Indians and the Indigenous people as it is considered a social norm. A previous study in Malaysia had reported that alcohol consumption was between 23.0-32.0% among the Chinese and the Indians, whereas it was very prevalent at 78.0% amongst the *Ibans*, one of the tribal groups of the Indigenous people (Kortteinen, 2008). Meanwhile, the habit of betel quid chewing among the Indians and Indigenous people could be due to cultural practices inherited from their ancestors. Studies have documented that betel quid chewing is more prevalent in rural than urban areas (de Silva, Hanwella, & Gunawardena, 2009) and is common among tea plantation workers and lorry/bus drivers in Sri Lanka (Selvananthan, Subramanium, Vairavanathan, Rajendra, & Shanmugarajan, 2018). A similar situation is observed here in Malaysia where traditionally, the Indians had lived in rural parts of the country, whereas the Indigenous people still do. Traditionally, Indians had mainly resided and worked in rubber plantations. Being a psychoactive substance, betel quid chewing had been documented to facilitate concentration and heightens alertness, prevents hunger and produces a sense of euphoria (Chu, 2001; Selvananthan et al., 2018), besides the perceived effect of relaxation and increased work capacity (Tan, Rosman, Ng, & Ahmad, 2000). These effects could have further promoted the practice of this habit among these specific ethnic groups.

Knowledge of the factors associated with the initiation and cessation of these risk habits is necessary to aid the planning of preventive efforts. Our findings further reiterate that ethnicity is an important determinant in the initiation of these risk habits, whereby being a Malay increases the likelihood of smoking initiation (Ghani, Razak,

Yang, Talib, Ikeda et al., 2012), whereas Indian and Indigenous people are more likely to develop the chewing habit (Ghani, Razak, Yang, Talib, Ikeda et al., 2011).

Apart from ethnicity, we found that gender is also an important determinant for the initiation of these habits. Smoking is much more common among males (Ghani et al., 2012), whereas betel quid chewing is more likely among females (Ghani et al., 2011). Male predominance in tobacco smoking had been established (Mackay & Amos, 2003; Sieminska & Jassem, 2014). However, it should be noted that in recent years, the number of females indulging in this habit is on the increase and is projected to further rise, especially in developing countries (Goel, Tripathy, Singh, & Lal, 2014; Mackay & Amos, 2003). Reasons associated with smoking among women include tension reduction, relaxation (Berlin, Singleton, Pedarriosse, Lancrenon, Rames et al., 2003) and weight concerns (Kaufman & Augustson, 2008). In addition, the weakening of social and cultural constraints (due to modernization of society and aspirations for gender equality) in recent years that had previously prevented women from smoking could also be a major contributor to this scenario (Sieminska & Jassem, 2014). As for betel quid chewing, our study findings of females being more likely to initiate this habit concurs with findings from other South East Asian populations such as Indonesia, Cambodia and Thailand (Gupta & Warnakulasuriya, 2002; Lee et al., 2012) but contrasts with other populations such as Taiwan, China, Sri Lanka and Solomon Islands (Lee et al., 2012; Tovosia, Chen, Ko, Tu, Tsai et al., 2007). Gender differences in the practice of this habit across the various geographic regions could be influenced by the social and cultural practices inherent to each region.

A pertinent observation in our study is that women were less likely than men to stop the habit once they have initiated it, which concurs with findings from previous studies (Lin, Wang, Chen, Chang, Yang et al., 2006; Yap, Ho, Kuo, & Yang, 2008). The lack of self-efficacy to stop the habit and peer pressure, particularly among Indian

and Indigenous females to conform to social norms of betel quid chewing could be other reasons that prevent them from stopping the habit.

Among Malaysians, cessation of these habits was found to occur most likely amongst the Chinese (Ghani et al., 2012; Ghani et al., 2011). One of the postulated reasons of higher cessation rates among the Chinese would be the higher levels of cancer awareness among them than the other ethnic groups, as reported by a previous study (Abdul Hadi, Hassali, Shafie, & Awaisu, 2010). This could be due to a higher general health consciousness among the Chinese. Previous studies found them to be less likely to become obese (Tan, Dunn, Samad, & Feisul, 2011), more likely to exercise frequently (Teh, Tey, & Ng, 2014) and more likely to consume fruits on a daily basis (Yen & Tan, 2012) than other ethnic groups. In addition, their sense of self-efficacy is another reason to practice healthy behaviours. An earlier study had documented that Chinese were more likely to perceive themselves as having good health than other ethnic groups (Teh et al., 2014). This higher positive outlook and self-efficacy level could act as strong motivators for them to quit their habit successfully.

Our study findings highlighted an association between the practice of various risk habits, which had impacted the initiation and cessation of these habits. For smokers, cessation were found to be least likely among betel quid chewers (Ghani et al., 2012) while among chewers, the habit of smoking significantly influences chewing initiation (Ghani et al, 2011). This is not surprising as tobacco and areca nut (the main component of betel quid) are quoted to be the second and fourth most commonly used psychoactive substance in the world (Gupta & Ray, 2004), whereby usage of these substances on its own has been shown to lead to addiction and dependence (Benegal, Rajkumar, & Muralidharan, 2008; Bhat, Blank, Balster, Nichter, & Nichter, 2010). Thus, it is physiologically plausible that usage of one substance would encourage the initiation of another substance (as has been found in our study), whereas the use of both these

products simultaneously would further increase the dependence and addiction rate, making cessation virtually impossible. Additionally, the ill effects of nicotine are further demonstrated in our studies. For smokers, cessation were observed to be least likely among *kretek* users (Ghani et al., 2012), whereas for betel quid chewers, cessation were least likely among those who included tobacco in their quid (Ghani et al., 2011). *Kretek* has been shown to have a higher nicotine yield compared to conventional cigarettes (Malson, Lee, Murty, Moolchan, & Pickworth, 2003; Roemer, Dempsey, & Schorp, 2014), thus long term usage of this product could lead to nicotine addiction. Likewise, the addition of tobacco in the quid further promotes nicotine addiction, thus making cessation extremely difficult.

One of the most non-invasive methods that can be utilized in preventing oral cancer, as well as a host of other chronic diseases is to advocate a change in dietary intake. Our papers on the association between dietary intake and oral cancer risk further add to the current body of knowledge and reiterate that dietary intake is an important factor in both the prevention and causation of cancer. A dietary pattern characterized with high intake of meat and its byproducts, dairy food, fermented food, carbonated beverages and caffeine was shown to increase the likelihood of developing cancer (Helen-Ng, Razak, Ghani, Marhazlinda, Norain et al., 2012). However, surprisingly, a dietary pattern loaded with intake of fruits and vegetables was found to confer only a non-significant reduction in oral cancer risk. This finding is in stark contrast to numerous other studies (Bravi et al., 2013; Butler et al., 2017; Maasland et al., 2015) which have firmly established the protective effect of high consumption of fruits and vegetables. We propose that this non-significant effect is attributed to the way vegetables are consumed in this population. Cooking of vegetables and some fruits, for example pineapple under high temperatures (wok frying/blanching/boiling) or in abundance of water (soup based) for a prolonged period could alter, dissolve or degrade

many of the water/fat soluble vitamins/ micronutrients/ phytochemicals, thus affecting the protective mechanism offered by these nutrients (Amtha et al., 2009; Jaiswal, Gupta, & Abu-Ghannam, 2012). Indeed, studies had shown that raw vegetables offered a higher nutritional value as compared to their cooked counterparts (Faller & Fialho, 2009; Zhang & Hamauzu, 2004).

To validate our assumption that the non-significant effect of fruits and vegetables consumption could have been attributed to the degradation of these nutrients caused by the method of food preparation/ cooking, we analysed and compared the bioavailability of retinol, α-tocopherol and β-carotene (micronutrients which can be found abundantly in fruits and vegetables) in the body between oral cancer patients and healthy controls (Athirajan, Razak, Thurairajah, Ghani, Ching et al., 2014). The finding of this study supports our assumption, in which we showed that high serum levels of retinol and α-tocopherol conferred a significant protection against oral cancer, which is in tandem with other studies that have reported the beneficial effect of these micronutrients through its antioxidant properties (Das Gupta & Suh, 2016; Iqubal, Khan, Kumar, Kumar, & Ajai, 2014).

4.2.2 Prognosis

Oral cancer imparts a huge impact on the prognosis of the sufferer. Data on prognosis, in terms of patient outcome of oral cancer patients in Malaysia is scarce, with only two published studies thus far (Balasundram et al., 2012; Razak et al., 2010). The drawback of these studies is the small sample size, and that patients were recruited from only one hospital-based centre for each study, therefore the results might not be generalizable to the Malaysian population. Thus, we evaluated the outcome of Malaysian oral cancer patients using data obtained from seven hospital-based government centres nationwide. Similar to other populations worldwide (Bobdey et al.,

2018; Chen et al., 2007; Dillon et al., 2015; Listl et al., 2013), prognosis for oral cancer patients in Malaysia in terms of patient outcomes was poor whereby less than half of the patients would attain the 5-year survival milestone (Ghani, Ramanathan, Prime, Yang, Razak et al., 2019b). This finding can be mostly attributed to the high proportion of late stage disease presentation (>65.0%) among Malaysians that was apparent in this study, as well as in earlier studies done on this population (Doss et al., 2011; Kong et al., 2015).

We also attempted to elucidate if there was any significant difference in patient outcome between the different ethnicities that co-exist in Malaysia (as we had earlier established that there are significant differences in their practice of risk habits). Although the Indigenous people (the most disadvantaged group in terms of SES) appeared to have a poorer outcome compared to the other ethnic groups, the difference was not statistically significant (Ghani et al., 2019b). This finding is in contrast to studies conducted in the West in which clear differences were seen in patient outcome between ethnicities, namely the Whites and African Americans (Gourin & Podolsky, 2006; Tomar, Loree, & Logan, 2004). The small sample size of Indigenous people recruited in this study (a study limitation) could have been a possible explanation for this non-significant finding. Further studies with larger sample sizes for each ethnic group are needed to elucidate if ethnicity has any influence on survival. Noteworthy, we observed that females have a poorer prognosis than males (Ghani et al., 2019b). Although most studies did not find any association between gender and prognosis, our study findings are in contrast to data from the SEER database, which indicated a reduced mortality rate among females (Osazuwa-Peters et al., 2016). Differences in findings could be due to various reasons, such as differences in gender equality, access to healthcare and socioeconomic status between a developed and developing country. Nevertheless, this study further validated that size of tumour, lymph node status and

disease stage at presentation are significant predictors of prognosis (Ghani et al., 2019b), in tandem with earlier study findings (Jan et al., 2011; Kim et al., 2016; Lo et al., 2003).

Cancer has been postulated as a disease that results from the accumulation of multiple alterations or mutations at the molecular level (Hanahan & Weinberg, 2011; Jurel, Gupta, Singh, Singh, & Srivastava, 2014). These changes alter the normal functions of oncogenes and tumour suppressor genes, and can deregulate normal cell activities (Krishna, Singh, Kumar, & Pal, 2015). Previous studies had identified several genes that are strongly implicated in oral cancers such as *EGFR*, *cyclin D1*, *k-ras*, *c-myc*, *p53* and *p16* (Krishna et al., 2015; Ram, Sarkar, Kumar, Konwar, Bhatt et al., 2011). An earlier study on a sample of Malaysian patients found that genetic mutations occur quite commonly in chromosome 8q (Vincent-Chong, Anwar, Karen-Ng, Cheong, Yang et al., 2013). Thus, we proceeded to assess whether changes in the expression of *CTHRC1*, one of the genes located at chromosome 8q could be utilized as a biomarker to predict patient outcome. Our study illustrated that over-expression of *CTHRC1* was significantly associated with poorer prognosis (Lee, Vincent-Chong, Ramanathan, Kallarakkal, Karen-Ng et al., 2015), which concurs with studies conducted on other types of cancer (Gu, Liu, Zhong, Bai, Sui et al., 2014; Tan, Liu, Liu, Hu, Liu et al., 2013). Moreover, expression of *CTHRC1* was observed to also have the ability to predict lymph node metastasis (Lee et al., 2015). This is an important finding, as lymph node metastasis has been established to be strongly associated with patient outcome (Jan et al., 2011; Kim et al., 2016). This finding lends further evidence to the hypothesis that genetic changes are good biomarker for prediction of patient outcome.

Previous studies have shown that oral cancer, and its related treatment modality also affects prognosis of patients in terms of their health related quality of life (HRQoL) (Biazevic et al., 2010; Hoxbroe Michaelsen et al., 2017). However, in Malaysia thus far

there has been only one published study on HRQOL of oral cancer patients, reporting the validity of a cross-culturally translated and adapted quality of life measure (Doss et al., 2011). Previously, as part of a PhD thesis, HRQoL changes over time among oral cancer patients had been assessed (Doss, 2011), however the sample size was small and patients were followed only up to three months post-treatment. Building upon this, we undertook a study assessing the impact of oral cancer on HRQoL of Malaysian patients on a larger sample size and longer follow up time (Doss, Ghani, Razak, Yang, Rogers et al., 2017). Additionally, as disease stage has been shown to affect HRQoL, these impacts were analysed according to their disease stage at presentation.

At the point of diagnosis, it was shown that patients with advanced disease have a significantly poorer HRQoL than patients diagnosed with early stage disease (Doss et al., 2017), which concurs with findings from previous studies (Chaukar et al., 2009; Dwivedi et al., 2012). Furthermore, we showed that this pattern of better HRQoL among early stage patients was also observed consistently up till six months post-treatment. Significant deteriorations in HRQoL ceased at the point of three months post-treatment for the early stage patients, whereas advanced stage patients continued suffering significant impacts on their HRQoL well until six months post-treatment (Doss et al., 2017). This finding is not surprising, as patients presenting with advanced stage disease normally require more aggressive and complex multi-modal treatment, which more often than not result in significantly compromised functions (Chaukar et al., 2009; Sanderson & Ironside, 2002).

Our study indicated that the HRQoL domains most affected by oral cancer were the physical, functional and head and neck concerns (Doss et al., 2017), affecting patients in terms of disturbances in swallowing, speech, dry mouth, mouth opening and sleep. This concurs with findings from other populations worldwide (Biazevic et al., 2010; Dwivedi et al., 2012; Hammerlid & Taft, 2001). However, the social and

emotional impact arising from oral cancer is not clearly seen among our patients, unlike findings from other studies (Fang et al., 2004; Gellrich et al., 2002; Oskam et al., 2013). This lack of social and emotional impact could be explained by the strong family support system and religious beliefs of Asian patients, which are major sources of social and emotional support (Ahmad, Muhammad, & Abdullah, 2010). However, cultural differences could also play a role here. In the developing world particularly among Eastern cultures, matters relating to feelings and emotions are rarely explored or discussed openly as they are deemed to be 'sensitive'. This could have explained the non-apparent emotional and social impacts in our study, in which patients could have felt uncomfortable discussing or expressing these impacts, as compared to the Western or developed populations.

4.2.3 Early detection

It is noteworthy that awareness of Malaysians on oral cancer is poor. Only about half of the respondents were able to recognize the risk habits and signs and symptoms of oral cancer (Ghani, Doss, Jamaluddin, Kamaruzaman, & Zain, 2013; Saleh, Yang, Ghani, Abdullah, Doss et al., 2012). This figure is lower than other populations previously studied (Elango, Sundaram, Gangadharan, Subhas, Peter et al., 2009; Monteiro, Salazar, Pacheco, & Warnakulasuriya, 2012).

Our study findings revealed differences in awareness levels between ethnic groups. The Chinese were least aware of alcohol being a risk factor, whereas the Indians were most aware that an unhealed ulcer is an early sign of oral cancer (Ghani et al., 2013). Higher awareness among the Indians with regards to unhealed ulcers could be due to the fact that in Malaysia, oral cancer is highest among the Indian ethnic group (Azizah et al., 2016) and as such, they could have heard about early signs/ symptoms of this disease from their family or friends. In Malaysia, alcohol drinking has always been

associated with diseases other than cancer, thus low levels of knowledge regarding the association between alcohol and cancer is not surprising. The reasons as to why this knowledge is especially poor among the Chinese, is not fully understood. However, it could be related to their health beliefs. It has been postulated that if a person indulges in a certain habit, they are more likely to deny its adverse effects on health. Previous studies have shown that alcohol drinkers were more prone to 'unrealistic optimism', defined as the mistaken belief that their risk is lower than others (Dillard, Midboe, & Klein, 2009). A study in France where the alcohol consumption is among the highest in the world, found that among the French general population, beliefs associated with denial of alcohol's health risks were common (Bocquier, Fressard, Verger, Legleye, & Peretti-Watel, 2017). In addition to risk denial, they also relativize the risk, in which they compare the risk of interest to other risks, for example eating hamburgers are as harmful to health as drinking alcohol. These researchers had also established that higher levels of risk denial/ relativization were associated with increased probability of engaging in alcohol behaviour.

Additionally, we found that there were gender differences in awareness levels, whereby females were more aware of the signs and symptoms of oral cancer than their male counterparts (Ghani et al., 2013). The traditional social and cultural norm with regards to gender identity, has directed women to assume the role of caregiver for their family, especially in terms of healthcare. Previous studies have documented that women had accepted that caregiving is a natural role to be assumed by them, and that caring for family members are a moral obligation on their part (Friedemann & Buckwalter, 2014; Ruiz & Nicolas, 2018). This naturally assumed role, could explain the higher level of awareness among women, as this role would consciously or subconsciously direct them to be more attentive in matters relating to health.

In view that most patients present at late stages, and as oral cancer awareness among Malaysians is poor, apart from educating the Malaysian public on oral cancer, the need to identify effective methods for early detection cannot be overemphasized. Thus, efforts towards this direction were initiated. Firstly, as our paper had identified that mass media is the main source of knowledge of oral cancer, we tested the feasibility of using mass media (TV) to educate the public on signs and symptoms of oral cancer, such that it could facilitate early detection of diseases. Our findings indicated that dissemination of information through mass media (TV) was only useful in increasing the proportion of the Malaysian public who had heard about oral cancer, however it was not an effective method for the dissemination of in-depth knowledge such as the signs and symptoms of oral cancer (Saleh et al., 2012). This could probably be attributed to the fact that the permitted advertisement time exposure was too short. Moreover, only still images were used to educate the public on symptoms of oral cancer. This could also play a major role, as the images used might not be clear enough to educate and enable the viewers to correctly identify these symptoms. Furthermore, differences in the reach to audience were found between ethnicities, whereby the Indians were the least reached group (Saleh et al., 2012). This is unfortunate, as in Malaysia, the ethnic group most at risk for oral cancer, are in fact the Indians. This study finding is in contrast to other studies which reported that mass media campaigns could increase knowledge on cancer (Dixon, Pratt, Scully, Miller, Patterson et al., 2015; Eadie, MacKintosh, MacAskill, & Brown, 2009; Martin, Buykx, Shevills, Sullivan, Clark et al., 2018). A possible reason for this could be the variation in media coverage/ reach, intensity and duration of campaign as well as effectiveness of materials used between the aforementioned studies.

Subsequently, we assessed the feasibility of mouth self-examination (MSE) as a potential method for early disease detection among a low SES population at increased risk for oral cancer. Our study findings indicated that MSE was not an effective method

for early detection of diseases as it was not able to detect the presence of lesions in the oral cavity (Ghani, Razak, Doss, Ramanathan, Tahir et al., 2019c). This finding is in concordance with other studies which reported that the ability of MSE to detect lesions were quite poor/ limited (Elango, Anandkrishnan, et al., 2011; Scott et al., 2010).

However, we propose that the non-effectiveness of MSE as observed in the present study could also be due to other factors. Poor sensitivity of MSE in this study could be due to the poorer level of knowledge uptake among this low SES population as compared to knowledge uptake among populations with higher SES level. Perhaps, a different result would be seen with improvements to the program, particularly in relation to the content and method of delivery of the educational intervention to cater to the needs of a low SES population. A previous PhD study had utilized a structured, theory-based intervention module, modelled after the Health Belief Model (HBM) among an Indigenous population in Malaysia (Maling, 2016). This newly developed intervention module consisted of structured health education messages in a sequential flow, using a delivery of theory-based health education in small groups and respondent empowerment via step-by-step MSE demonstration, counselling and referral as well as a subsequent re-enforcement of oral cancer messages. It was observed that the level of improvement in oral cancer awareness and MSE uptake was significantly higher among respondents receiving the structured intervention based on HBM than those receiving the conventional method of intervention (Maling, 2016). Additionally, as discussed in the publication, limitations such as suitability of the venue (an open hall/space) to conduct an educational program as well as to perform MSE could have affected the outcome of this study. In future studies, particular attention should be given to the selection of venue, especially for performing MSE such that it offers enough privacy for the respondents to be able to perform MSE comfortably and without any reservation.

In order to facilitate early detection efforts, we also assessed the feasibility of using information and telecommunication technology. We found a strong concordance between the diagnoses made with conventional clinical oral examination (COE) and diagnoses made with teledentistry in detecting abnormalities in the mouth (Haron, Zain, Nabillah, Saleh, Kallarakkal et al., 2017). This finding concurs with other studies in the medical field that have shown teledentistry/ telemedicine to be a good adjunctive tool in detecting/ screening diseases (Estai, Kanagasingam, Huang, Checker, Steele et al., 2016; Quinley, Gormley, Ratcliffe, Shih, Szep et al., 2011). As such, this finding would be particularly useful for low and middle income countries such as Malaysia, where pockets of underserved populations exist due to lack of resources. Noteworthy was that with the use of teledentistry, a diagnosis of malignant and non-malignant lesions was differentiated (Haron et al., 2017). This is imperative as inability to discriminate malignant lesions (which require further treatment) from benign lesions (not needing active treatment) could lead to over-referral that would burden the healthcare system, besides triggering unnecessary fear among the patients.

Cumulatively, all of the aforementioned studies have contributed to the database of knowledge on various aspects of oral cancer, particularly within the Malaysian context. The information gained is important as it could serve as a basis for the planning of future oral health policies, and could guide researchers towards gaps in knowledge that needs to be addressed. Data obtained from these studies and its implications are summarised in the following section.

4.3 Cumulative effect of studies

The findings of all of the studies above are synthesized, and the following conclusions are derived:

Awareness level (Objective no 1)

1. Although general awareness on oral cancer among Malaysians is high, in-depth knowledge on risk habits and signs and symptoms are lacking.
2. There are significant gender and ethnic differences in awareness levels, which include the following:
    i. Females are more aware of signs and symptoms of oral cancer than males
    ii. Chinese are the least aware of alcohol as a risk factor, whereas Indians are most aware about unhealed ulcers being a symptom for oral cancer
3. Mass media is the main source of information on oral cancer. However, the effectiveness of a mass media campaign via TV on knowledge dissemination is not validated.

Risk habits (Objective no 2)

4. Identified lifestyle risk factors of oral cancer for the Malaysian population are namely:
    i. tobacco smoking
    ii. alcohol drinking
    iii. betel quid chewing
5. Malays mostly smoked, whereas Chinese mostly practiced concurrent smoking and drinking. In contrast, betel quid chewing is most prevalent among Indians and Indigenous people.
6. The habit of betel quid chewing confers the highest risk for oral cancer.
7. Synergistic effect of multiple practice of risk habits is observed.

Risk habit initiation and cessation (Objective no 3)

8. There are significant gender and ethnic differences in the initiation and cessation of risk habits, which include the following:
    i. Females are more inclined towards the habit of betel quid chewing, whereas males have a higher affinity for smoking
    ii. Females are less likely to quit smoking and betel quid chewing habit than males, once they have initiated the habit
    iii. Cessation of smoking and betel quid chewing habits are most likely to occur among the Chinese than the other ethnic groups
9. Apart from gender and ethnicity, habit initiation and cessation are also significantly associated with the concurrent practice of another risk habit and type of cigarette or betel quid consumed.

Dietary intake (Objective no 4)

10. High intake of meat and meat by products, dairy foods, fermented foods, carbonated beverages and caffeine increases cancer risk.
11. High intake of fruits and vegetables reduces cancer risk.

Prognosis of patients (Objective no 5)

12. Oral cancer significantly affects prognosis in terms of patient outcome whereby less than half of Malaysian oral cancer patients will surpass the 5-year survival milestone.
13. Although there are no significant differences in terms of prognosis between different ethnic groups in Malaysia, the Indigenous people are the most at risk ethnic group. They have the lowest survival rates, the highest proportion of late stage disease and the highest proportion of concurrently

practicing all three risk habits. Moreover, in Malaysia this ethnic group has the lowest SES.

14. Predictors of prognosis include size of the tumour, regional lymph node metastasis and disease stage at presentation.

Genetic changes as a biomarker for prognosis (Objective no 6)

15. Genetic changes at the cellular/ molecular level could be used as a biomarker to predict patient outcome.

Impact on quality of life (Objective no 7)

16. Disease stage at presentation is an important predictor of HRQoL.
17. Malaysian oral cancer patients' most affected HRQoL are in their physical, functional and head and neck domains.

MSE as a tool for early detection (Objective no 8)

18. MSE was not found to be an effective method to facilitate early detection of disease.

Accuracy of diagnosis using teledentistry (Objective no 9)

19. Teledentistry is a method that has the potential to be utilized for the purpose of early detection of oral cancers.

4.4 Recommendations

Based on the aforementioned findings, the following recommendations are made:

1. In view that more than two-thirds of oral cancers are diagnosed at late stages and that lack of knowledge on risk habits and signs and symptoms have been observed in our studies, an intensive educational intervention program on oral cancer needs to be developed and conducted by the relevant government authorities such that it could lead to prevention and early detection of oral cancer. The content, target group, delivery method, assessment of effectiveness and coverage of this proposed interventional program is suggested as the following:

    i. Content: This educational program should be comprehensive and include aspects of risk habits, signs and symptoms, impact of oral cancer on quality of life, importance of early detection and MSE. In addition, as gender and ethnic differences have been demonstrated in the practice of oral cancer risk habits, the impact of this educational/ interventional program would be more apparent if its development is tailored specifically for each ethnic group/ gender, giving emphasis on specific habits practiced by that particular ethnic group/ gender

    ii. Target group: At initial stages, in the interest of cost and for the purpose of assessment of its effectiveness, this intervention should be targeted to the high risk ethnic groups, for example the Indigenous people

    iii. Delivery method: As shown by a preliminary study (Maling, 2016), the intervention program needs to be developed in a structured manner, whereby delivery of its contents is done interactively in a sequential flow and in small groups to enable higher level of knowledge uptake among this population

iv. Assessment of outcome: The next phase is the assessment of the effectiveness of this educational intervention program. Effectiveness should be measured in terms of knowledge uptake and risky behavioral change. If found to be effective, this program should then be advocated nationwide, targeting areas with high prevalence of risk habits

v. Coverage: In addition, this educational program should also be expanded to target school-going children as it has been shown that the practice of oral cancer risk factors such as tobacco and alcohol consumption commences during adolescence

2. The majority of patients are still presenting at advanced disease stage, contributing to poor quality of life and prognosis, thus the importance of early detection is emphasized. In addition to advocating increased awareness and behavioral change of the public through the conduct of interventional programs, mobilizing action towards detection of cancers at an early stage by healthcare professionals is of equal importance. In view that the accuracy of diagnoses made from teledentistry has been established, it is recommended that teledentistry be introduced as one of the screening methods, and be integrated into the secondary prevention action plan by the Ministry of Health to aid in detection of oral cancer at early stages. This method would be especially beneficial in areas where there are underserved population due to the lack of clinical expertise and resources. However, it should be noted that a referral system pathway needs to be in place, such that at-risk patients identified through this method can be properly referred, followed up and clinically managed.

4.5 Suggestions for future research

1. Although the findings of this current study did not show a favorable impact of MSE in terms of its sensitivity, further research on the efficacy of MSE is recommended as its high specificity and accuracy rates indicated that MSE can potentially be utilized as an inexpensive, non-invasive self-screening tool. However, an improved method of the delivery of educational intervention is warranted to effectively determine the usefulness of MSE in promoting early detection of diseases.
2. As studies on the association between self-efficacy level with behavioral change among multi-ethnic Malaysia is scarce, thus it is suggested that a study assessing the intention and attempt to quit risky habits and self-efficacy levels among the different ethnic groups be conducted to validate the relationship between self-efficacy and behavior change, and to assess if there is a difference in self-efficacy levels among the different ethnic group.
3. The Indigenous people are prone to practicing multiple risk habits simultaneously. Their limited access to healthcare services further places this particular ethnic group at a disadvantage. Thus, it is suggested that an intensive oral cancer educational and cessation intervention program be developed specifically for this ethnic group, and a longitudinal study be conducted to assess whether this cessation intervention program could induce sustained behavioural change among this high risk population, such that their oral cancer risk could be reduced.
4. Although genetic changes have been shown to have the ability to predict outcome of patients, further research is needed to validate the accuracy of its prognostic ability. Furthermore, a cost-effectiveness analysis needs to be

conducted before screening patients for genetic changes can be advocated in routine clinical management as a method for prediction of patient outcome.

5. Patient's quality of life is the lowest during the period of active treatment and immediately after treatment. One of the effects of treatment, especially radiotherapy is the significantly reduced nutritional status of the patients due to treatment side effects such as mucositis, xerostomia and nausea. Previous studies have indicated a beneficial impact of nutritional intervention on nutritional status, physical functions and overall quality of life of patients, however these studies are mainly conducted in Western countries. As such, a nutritional intervention study among patients undergoing active radiation therapy is suggested to determine its efficacy in improving nutritional status, quality of life and prognosis of Malaysian oral cancer patients. If proven to be effective, nutritional intervention could be integrated as part of routine clinical management of patients.
6. Oral cancer and its associated treatments have been shown to impart psychological effect on the patients as well as their caregivers. A previous study on a Malaysian population has identified that there are unmet supportive needs among oral cancer survivors. To date, there are no published studies on the impact of supportive care activities such as emotional support through peer support group, physical and functional support through exercise, physiotherapy or speech therapy, as well as spiritual support through activities such as yoga or religious activities on patients' well-being. Thus, a study assessing the impact of supportive care activities on the well-being of oral cancer patients as well as their caregivers is advocated.

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APPENDIX A: LIST OF PUBLICATIONS

Twelve original research articles presented in this thesis are as the following:

1. **Ghani WMN**, Doss JG, Jamaluddin M, Kamaruzaman D, Zain RB. Oral Cancer Awareness and its Determinants among a Selected Malaysian Population. Asian Pacific Journal of Cancer Prevention. 2013;14(3):1957-63
2. Saleh A, Yang YH, **Ghani WMN**, Abdullah N, Doss JG, Navonil R, Abdul Rahman ZA, Ismail SM, Talib NA, Zain RB, Cheong SC. Promoting Oral Cancer Awareness and Early Detection using a Mass Media Approach. Asian Pacific Journal of Cancer Prevention. 2012;13(4):1217-24
3. **Ghani WMN**, Razak IA, Doss JG, Yang YH, Rahman ZAA, Ismail SM, Abraham MT, Mustafa WMW, Tay KK, Yuen KM, Zain RB. Multi-ethnic variations in the practice of oral cancer risk habits in a developing country. Oral Diseases. 2019;25(2):447-455.
4. **Ghani WMN**, Razak IA, Yang YH, Talib NA, Ikeda N, Axell T, Gupta PC, Handa Y, Abdullah N, Zain RB. Factors affecting commencement and cessation of smoking behaviour in Malaysian adults. BMC Public Health. 2012;12:207
5. **Ghani WMN**, Razak IA, Yang YH, Talib NA, Ikeda N, Axell T, Gupta PC, Handa Y, Abdullah N, Zain RB. Factors affecting commencement and cessation of betel quid chewing behaviour in Malaysian adults. BMC Public Health. 2011;11:82
6. Helen-Ng LC, Razak IA, **Ghani WMN**, Marhazlinda J, Norain AT, Raja Jallaludin RL, Rahman ZA, Abdullah N, Zain RB. Dietary pattern and oral

cancer risk - a factor analysis study. Community Dentistry & Oral Epidemiology. 2012; 40:560-66

7. Vimmitra A, Ishak AR, Thurairajah N, **Ghani WMN**, Helen-Ng LC, Yang YH, Karen-Ng LP, Rahman ZAA, Mustafa WMW, Abraham MT, Tay KK, Yuen KM, Jalil N, Zain RB. High serum level of retinol and α-tocopherol affords protection against oral cancer among a multiethnic population. Asian Pacific Journal of Cancer Prevention. 2014; 15(19): 8183-9
8. **Ghani WMN**, Ramanathan A, Prime SS, Yang YH, Rahman ZAA, Ismail SM, Abraham MT, Mustafa WMW, Jalil N, Tay KK, Yeun KM, Kallarakkal TG, Doss JG, Cheong SC, Razak IA, Narayanan P, Bustam AZ, Zain RB. Survival of oral cancer patients in different ethnicities. Cancer Invest. 2019; 37(7):275-287.
9. Lee CE, Vincent-Chong VK, Ramanathan A, Kallarakkal TG, Karen-Ng LP, **Ghani WMN**, Rahman ZA, Ismail SM, Abraham MT, Tay KK, Mustafa WM, Cheong SC, Zain RB. Collagen Triple Helix Repeat Containing-1 (CTHRC1) Expression in Oral Squamous Cell Carcinoma (OSCC): Prognostic Value and Clinico-Pathological Implications. International Journal of Medical Sciences. 2015;12(12):937-45
10. Doss JG, **Ghani WMN**, Razak IA, Yang YH, Rogers SN, Zain RB. Changes in health-related quality of life of oral cancer patients treated with curative intent: experience of a developing country. International Journal of Oral Maxillofacial Surgery. 2017;46(6):687-98
11. **Ghani WMN**, Razak IA, Doss JG, Ramanathan A, Tahir Z, Ridzuan NA, Edgar S, Zain RB. Mouth self-examination as a screening tool for oral potentially malignant disorders among a high risk Indigenous population. J Public Health. 2019; Mar 8. doi: 10.1111/jphd.12313. [Epub ahead of print]

12. Haron N, Zain RB, **Ghani WMN**, Saleh A, Kallarakkal TG, Ramanathan A, Sinon SH, Razak IA, Cheong SC. Mobile Phone Imaging in Low Resource Settings for Early Detection of Oral Cancer and Concordance with Clinical Oral Examination. Telemedicine Journal E Health. 2017;23(3):192-9

APPENDIX B: LIST OF PAPERS PRESENTED

1. **Ghani WMN**, Razak IA, Doss JG, Yang YH, Ismail SM, Abraham MT, Jalil N, Tay KK, Yuen KM, Mustafa WMW, Zain RB. Variation in the practice of oral cancer risk habits among different ethnicities in Malaysia. 16th Annual Scientific Meeting of IADR Malaysian Section, South East Asian Division. Hotel Armada, Petaling Jaya. 18th March 2017
2. Razak IA, **Ghani WMN**, Doss JG, Ramanathan A, Tahir Z, Ridzuan NA, Edgar S, Zain RB. Mouth self-examination (MSE) as a screening tool for oral potentially malignant disorders among a high-risk Indigenous population with a low socioeconomic status. World Cancer Congress. Kuala Lumpur Convention, Centre (KLCC), Kuala Lumpur. 1st – 4th October 2018