Head and neck cancer: analysing the related risk factors, social determinants, and preventive measures

Somayyeh Azimi, DDS, MSc

This thesis is presented for the degree of Doctor of Philosophy of The University of Western Australia

School of Human Sciences
Anatomy, Physiology and Human Biology
2019
Dedication:
To the soul of my father
To my mother
To my husband
and
my daughter Setayesh
THESIS DECLARATION

I, Somayyeh Azimi, certify that:

This thesis has been substantially accomplished during enrolment in the degree.

This thesis does not contain material which has been submitted for the award of any other degree or diploma in my name, in any university or other tertiary institution.

No part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of The University of Western Australia and where applicable, any partner institution responsible for the joint-award of this degree.

This thesis does not contain any material previously published or written by another person, except where due reference has been made in the text and, where relevant, in the Declaration that follows.

The work(s) are not in any way a violation or infringement of any copyright, trademark, patent, or other rights whatsoever of any person.

The research involving human data reported in this thesis was assessed and exemption from ethics review was granted by the Human Research Ethics Committee at the University of Western Australia #: RA/4/1/8118.

Written patient consent has been received and archived for the research involving patient data reported in this thesis.

Parts of the work described in this thesis was funded by Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ir.sbmui.rds.rec.1394.93).

This thesis contains published work and/or work prepared for publication, some of which has been co-authored.

Signature:  

Signature: Somayyeh Azimi

Date: 05.11.2018
ABSTRACT

Worldwide, head and neck cancers, including malignant neoplasms of lip, oral cavity and pharynx, are one of the most common cancers, with the greatest incidence in the most deprived countries. New cases of oral cancer accounts for up to 4% (representing a considerable burden) of all cancers globally.

Age, tobacco, alcohol, unhealthy diet and human papilloma virus infection are proposed as the main risk factors for head and neck cancer. Socioeconomic status and inequality are also mentioned as major determinants in previous studies. Many of these risk factors might be preventable by increasing awareness about this debilitating disease; and early detection by effective screening may help to reducing the burden of disease.

The aims of this research were to investigate the distribution of head and neck cancer and related risk factors and socio-economic determinants. Part of the project was the comparative study between defined population from two different socio-economically countries (Iran and Australia). It also explored inequality in knowledge and awareness about oral cancer that might have an effect on early detection of this devastating disease. This research also looked into developing a risk factor based model for head and neck cancer screening. The cancer protective effect of nutrients in high-risk population has been investigated in an experimental study as a part of project as well.

The findings indicated the difference in head and neck cancer patterns in a defined population from two countries (Iran and Australia). Socio-economic inequalities are clearly presented in head and neck cancer developing and were reflected in the awareness and knowledge about signs, symptoms and risk factors of head and neck cancer in an Iranian population. The risk factor-based model of screening in individuals with high risk head and neck cancer showed risk factors other than diet and habits, including SES and lifestyle, are important in the prediction of this cancer in the Iranian population. Also, the effectiveness of green tea consumption in both the short- and long-term in salivary antioxidants enhancement has been found in smokers, as a high-risk individuals.

Based on the findings of this research, efforts should be made to increase the level of general awareness and knowledge of risk factors. Reducing the socio-economic gap in society may be effective in decreasing the development of head and neck cancer through increasing the awareness of behavioural risk factors: healthy diet, and equal access to health care. High-risk individuals should be encouraged to quit high-risk behaviours and to consume natural antioxidants, which may help to reduce the risks as well. Knowledge of signs and symptoms and screening, based on risk factors, may assist in early detection and in turn facilitate the timely treatment of this chronic devastating disease. These findings will be helpful to implement preventive and diagnostic programs for head and neck cancer, specifically for high-risk groups.
# TABLE OF CONTENTS

Title page........................................................................................................................................i
Dedication.........................................................................................................................................ii
Thesis declaration............................................................................................................................iii
Abstract...........................................................................................................................................iv
Table of contents.............................................................................................................................v
List of tables......................................................................................................................................xiv
List of figures....................................................................................................................................xvi
Acknowledgments............................................................................................................................xvii
Authorship declaration-co-authored publications .................................................................xviii
Publications arising from thesis......................................................................................................xxii
Conference presentation.................................................................................................................xxiii
Other publication that has been co-authored during the study ........................................xxiii
Chapter 1- Introduction and literature review .............................................................................1
  1-1-General introduction..............................................................................................................2
  1-2- Literature review..................................................................................................................3
  1-2-1- Cancer..............................................................................................................................3
  1-2-2- Head and neck cancer.......................................................................................................3
  1-2-2-1- Oral cavity and oropharyngeal cancer.........................................................................3
  1-2-2-2- Different types...............................................................................................................4
  1-2-2-2-1- Squamous cell carcinoma (SCC) .............................................................................4
1-2-2-6-4- Genetic causes .................................................................14
1-2-2-6-5- Other possible risk factors.............................................14
1-2-2-7- Diagnosis.................................................................14
1-2-2-7-1- Early detection..........................................................15
1-2-2-7-1-1- Conventional oral examination and cancer screening........16
1-2-2-7-1-2- Self-examination.....................................................17
1-2-2-7-2- Differential diagnosis .................................................17
1-2-2-7-3- Definitive diagnosis...................................................18
1-2-2-8- Management............................................................18
1-2-2-8-1- Prevention of oral cancer.............................................18
1-2-2-8-2- Available cancer treatment........................................20
1-2-2-8-2-1- Surgery.............................................................21
1-2-2-8-2-2- Radiotherapy.......................................................21
1-2-2-8-2-3- Chemotherapy.....................................................22
1-2-2-8-2-4- Other treatment options.........................................22
1-2-2-8-3- Head and neck cancer and quality of life.........................22
1-3-References...........................................................................22

Chapter 2- Aim and structure....................................................27
2-1- Aim.......................................................................................28
2-2- Structures............................................................................28
2-2-1- A ten-year study of head and neck origin cancers pattern in adults.................................28
2-2-2- Evaluation of oral cancer awareness in an adult population and relation with socioeconomic status.................................................................29
2-2-3- The association between components of socioeconomic status and head and neck cancer, and risk-factor model for oral cancer.................................................................29

2-2-4- Evaluation the effect of green tea on head and neck cancer prevention.................................30

Chapter 3- To analyse a decade of head and neck cancer patterns in Western Australia and in the West of Iran..................................................................................................................31

3-1- Orofacial cancers in the West of Iran- A 10-year study.................................................................32

3-1-1- Abstract...............................................................................................................................32

3-1-2- Introduction.........................................................................................................................32

3-1-3- Materials and methods.......................................................................................................33

3-1-4- Results..................................................................................................................................34

3-1-5- Discussion............................................................................................................................38

3-1-6- Conclusion...........................................................................................................................40

3-1-7- References..........................................................................................................................40

3-2- Pattern of the head and the neck cancer in two geographically and socioeconomically different countries .........................................................................................................................43

3-2-1- Abstract...............................................................................................................................43

3-2-2- Introduction..........................................................................................................................44

3-2-3- Materials and methods.........................................................................................................45

3-2-3-1- Ethics...............................................................................................................................45

3-2-3-2- Exclusion criteria..............................................................................................................46

3-2-3-3- Definitions.......................................................................................................................46

3-2-4- Results..................................................................................................................................46

3-2-5- Discussion............................................................................................................................51

3-2-6- References..........................................................................................................................53
Chapter 4- To evaluate oral knowledge and awareness of oral cancer in an adult population and relation with socioeconomic status.................................................................56

4-1- Population survey of knowledge about oral cancer and related factors in the capital of Iran..57

4-1-1-Abstract.................................................................57

4-1-2-Introduction..........................................................57

4-1-3-Methods..................................................................59

4-1-3-1-Ethics.................................................................59

4-1-3-2-Questionnaire.......................................................59

4-1-3-3-Sampling and participation.....................................61

4-1-3-4-Study design........................................................61

4-1-3-5-Outcome variables...............................................61

4-1-3-6-Independent variables.........................................62

4-1-3-7-Statistics..............................................................62

4-1-4-Results.................................................................62

4-1-5-Discussion.............................................................68

4-1-6- Conclusion............................................................71

4-1-7-References............................................................71

4-2- Disparities in oral cancer awareness: A population survey in Tehran, Iran.........................76

4-2-1- Abstract...............................................................76

4-2-2-Introduction..........................................................76

4-2-3-Methods.................................................................78

4-2-3-1-Sampling and design...........................................78

4-2-3-2-Study protocol.....................................................78
Does socioeconomic status influence oral cancer awareness: The role of public education...91

4-3-1-Abstract ................................................................. 91
4-3-2-Introduction ............................................................. 91
4-3-3-Methods ................................................................. 92
4-3-3-1-Ethics ................................................................. 92
4-3-3-2-Questionnaire ......................................................... 93
4-3-3-3-Sampling and participation ....................................... 93
4-3-3-4-Study design ......................................................... 94
4-3-3-5-Outcome variables .................................................. 94
4-3-3-6-Explanatory variables .............................................. 94
4-3-3-7-Covariates .......................................................... 95
4-3-3-8-Statistics ............................................................ 95
4-3-4-Results ................................................................. 95
4-3-5-Discussion .............................................................. 98
Chapter 5- To evaluate relation between various socioeconomic component and oral cancer and finding the risk factor model base for oral cancer screening…………………………………………………………….105

5-1-Socioeconomic determinants as risk factors for squamous cell carcinoma of the head and neck- a case-control study in Iran……………………………………………………………………………...106

5-1-1-Abstract……………………………………………………………………….106

5-1-2-Introduction……………………………………………………………………..106

5-1-3-Methods…………………………………………………………………………107

5-1-3-1-Patients………………………………………………………………………..107

5-1-3-2-Controls………………………………………………………………………..108

5-1-3-3-Protocol of the study…………………………………………………………108

5-1-3-4-Outcome variables………………………………………………………….108

5-1-3-5-Explanatory variables………………………………………………………..108

5-1-4-Results…………………………………………………………………………110

5-1-5-Discussion……………………………………………………………………….114

5-1-6-Conclusion……………………………………………………………………..117

5-1-7-References……………………………………………………………………..118

5-2-Development of a risk factor-based model for head and neck squamous cell carcinoma- A case-control study…………………………………………………………………………………………121

5-2-1-Abstract………………………………………………………………………..121
Chapter 6- To evaluate the effect of green tea on oral cancer prevention ........................................135

6-1- Does green tea consumption improve the salivary antioxidant status of smokers? .............136

6-1-1- Abstract .........................................................................................................................136

6-1-2- Introduction ................................................................................................................136

6-1-3- Methods and materials ..........................................................................................138

6-1-3-1- Ethics ..................................................................................................................138

6-1-3-2- Participants .........................................................................................................138

6-1-3-3- Experimental protocol ..................................................................................138

6-1-3-4- Saliva collection ..............................................................................................139

6-1-3-5- Total antioxidant capacity assay (TAC) .................................................................139

6-1-3-6- Statistical analysis .............................................................................................140

6-1-4- Results ..................................................................................................................140

6-1-5- Discussion ...........................................................................................................142

6-1-6- Conclusion ...........................................................................................................144
6-1-7-References.................................................................144

6-2- Is there any association between green tea consumption and the risk of head and neck squamous cell carcinoma- Finding from a case-control study.................................148

6-2-1-Abstract.................................................................148

6-2-2-Introduction............................................................148

6-2-3-Materials and methods...............................................149

6-2-3-1-Ethics ...............................................................149

6-2-3-2-Participation.........................................................150

6-2-3-3-Study protocol......................................................150

6-2-3-4-Variables............................................................150

6-2-3-5-Statistical analysis ...............................................151

6-2-4-Results .................................................................151

6-2-5- Discussion............................................................154

6-2-6-Conclusion...........................................................156

6-2-7-References............................................................156

Chapter 7- Discussion........................................................160

7-1- Preamble.................................................................161

7-2 Principal findings......................................................161

7-2-1-Difference in frequency of oral cancer in different location (chapter 3) ................161

7-2-2- Disparities and inequality in oral cancer knowledge and awareness (chapter 4) .....161

7-2-3- Socio-economic inequality in head and neck cancer development (Chapter 5) .......161

7-2-4- Developing a risk-factor model for HNSCC (Chapter 5) .................................162

7-2-5- Salivary antioxidant status improvement after green tea consumption in smokers (Chapter
6) Preventive effect of green tea consumption on head and neck squamous cell carcinoma (HNSCC) (Chapter 6) ……………………………………………………………………………………162

7-3 Implications, comparison and recommendations (What this study adds) ………………163

7-4-Strengths and limitations……………………………………………………………………166

7-5-Future research recommendation…………………………………………………………167

7-6-Conclusion……………………………………………………………………………………167

7-7-References……………………………………………………………………………………167

Appendices………………………………………………………………………………………170

List of tables:

Table 3-1-1- The frequency of orofacial cancers in different age groups.......................34

Table 3-1-2- The number of lesions and mean age…………………………………………35

Table 4-1-1- Demographic characteristics of participants…………………………………..64

Table 4-1-2- Level of knowledge about oral cancer risk factors and signs……………………64

Table 4-1-3- Multivariate analysis for sociodemographic factors and knowledge of oral cancer………………………………………………………………………………65

Table 4s-1- Post hoc test (Duncan), for difference in knowledge about oral cancer risk factors according to the occupation ………………………………………………………74

Table 4s-2- Difference in knowledge about oral cancer signs and symptoms according to occupation (post hoc test) ……………………………………………………………74

Table 4-2-1- Distribution of knowledge scores among socio-demographic groups……….82

Table 4-2-2- Distribution of response rate to each awareness question……………………83

Table 4-2-3-General linear model results of explanatory variables effect…………………..84

Table 4-2-4-Predictors of awareness of oral cancer among participants in Iran……………84
Table 4-3-1- The distribution of level of knowledge by socioeconomic (SES) groups............96
Table 4-3-2- Results from principal component analysis (PCA) for construction of wealth index..................................................................................................................................................97
Table 4-3-3- General linear model regression results by socioeconomic status (SES) ............98
Table 5-1-1- Socioeconomic composite scores based on categories of income and education level. Categories were based on their distribution among all patients........................................109
Table 5-1-2- The distribution of sociodemographic variables and risk factors in cases and control groups. Data are expressed as number (%)..................................................................111
Table 5-1-3- Association between risk factors and risk of squamous cell carcinoma of the head and neck..............................................................................................................................113
Table 5-1-4- Association between social determinants and risk of squamous cell carcinoma of the head and neck..............................................................................................................................114
Table 5-2-1- Frequency of significant predictors with related adjusted OR for age and gender.................................................................................................................................................................126
Table 5-2-2: Predictive performance of 4 risk score model analysis ........................................128
Table 6-1-1- Age of participants in smokers and no-smoker groups.................................141
Table 6-1-2- Comparison of the mean difference of salivary TAC at different times in each study group.................................................................................................................................................................141
Table 6-1-3- Comparison the mean difference of salivary TAC between smokers and non-smokers at different times.................................................................................................................................142
Table 6-2-1 -The distributions of different variables in case and control group ............152
Table 6-2-2- Result of logistic regression between groups..................................................153
Table 6-2-3- Regression analysis, before and after adjustment for risk factors...............154
Table 6s-2-1- Distribution of different HNSCC in case group..............................................159
List of figures

Figure 3-1- 1- The distribution of the lesions by site .........................................................36

Figure 3-1-2- Gender distribution according to type of cancer .................................37

Figure 3-2-1-(a) - The distribution of orofacial malignancy by location in Iran (M- male, F- Female, T- total). (b) The distribution of orofacial malignancy by location in Australia (10×difference in scale). ..........................................................................................................................47

Figure 3-2- 2-(a) - The distribution of orofacial malignancy by location in Australia (A) and Iran (I). (b) The distribution of orofacial malignancy in men according to its location in Australia and Iran. (c) The distribution of orofacial malignancy in women according to its location in Australia and Iran ...........................................................................................................................................48

Figure 3-2- 3- The distribution of orofacial malignancy in Australia and Iran among patients belonging to different age groups ........................................................................................................................................49

Figure 3-2-4-(a) -The distribution of orofacial malignancy by location in Australia and Iran (age 30–44 years). (b)The distribution of orofacial malignancy by location in Australia and Iran (age 45–59 years) (c)The distribution of orofacial malignancy by location in Australia and Iran (age >75 years) ........................................................................................................................................50

Figure 3-2-5-(a) - The distribution of orofacial malignancy by sex and age in Australia. (b) The distribution of orofacial malignancy according to sex and age in Iran ........................................................................................................................................51

Figure 4-1-1- Knowledge about oral cancer risk factor in each question .........................66

Figure 4-1-2- Knowledge about oral cancer signs in each question ................................67

Figure 4s-1- (a, b) - Mean and confidence interval of knowledge about signs and risk factors in different level of education ........................................................................................................................................75

Figure 5-2-1-(a-d)-ROC curve for 4 risk factor-based model score and the developing of HNSCC ........................................................................................................................................129

Figure 6-1-1- Salivary TAC in smokers and non-smokers in study period .........................141
This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

Firstly, I would like to express my sincere gratitude to all of my supervisors in the School of Human Sciences, at The University of Western Australia- Winthrop Professor Marc Tennant, Associate Professor Estie Kruger, and Emeritus Professor John McGeachie.

I would like to express my special appreciation to my coordinating supervisor W/Prof. Marc Tennant, firstly, for accepting me as a Ph.D. candidate, and for the continuous support of my Ph.D. study and related research. He is a tremendous mentor for me. He has always ear to hear and solve my problems!

My sincere thanks also goes to A/Prof. Estie Kruger for continuous encouragement and advice throughout my study.

I greatly appreciate the support of E/ Prof. John McGeachie. It is a great privilege for me to having his advice and supervision.

I would like to thank Dr. Zahra Ghorbani, Dr. Nasrin Rafieain for their precious support in conducting this research. Besides, I would like to thank the rest of my co-authors in published papers for their insightful comments.

I would also like to acknowledge the support of Shahid Beheshti University of Medical Sciences, and Imam Khomeini Hospital.

Last but not the least, I would like to thank my husband, my daughter and my mother for supporting me throughout my life.
This thesis contains work that has been published and under review for publication.

Details of the work-

Location in thesis-
Chapter 3, Part 1
Student contribution to work- Literature Search, Data acquisition, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (80%)

Co-author signatures and dates- Tennant M, Kruger E, Taheri J, Sehatpour M, Rezaei B

4th-January-2019

Details of the work-

Location in thesis-
Chapter 3, Part 2
Student contribution to work- Literature Search, Data acquisition, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (90%)

Co-author signatures and dates- Mortazavi H, Tennant M, Kruger E, Rezaei B, Taheri JB, Tarahhomi MR

4th-January-2019

Details of the work-

Location in thesis-
Chapter 4, Part 1
Student contribution to work- Literature Search, Data acquisition, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (90%)

Co-author signatures and dates- Mortazavi H, Tennant M, Kruger E, Rezaei B, Taheri JB, Tarahhomi MR

4th-January-2019
Details of the work-

Location in thesis-
Chapter 4, Part 2

Student contribution to work- Literature Search, Data acquisition, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (90%)

Co-author signatures and dates- Ghorbani Z, Ghasemi E, Tennant M, Kruger E.

4th-January-2019

Details of the work-

Location in thesis-
Chapter 4, Part 3

Student contribution to work- Literature Search, Data acquisition, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (90%)

Co-author signatures and dates- Ghorbani Z, Ghasemi E, Tennant M, Kruger E.

4th-January-2019

Details of the work-

Location in thesis-
Chapter 5, Part 1

Student contribution to work- Literature Search, Data acquisition, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (90%)

Co-author signatures and dates- Rafieian N, Manifar S, Ghorbani Z, Tennant M, Kruger E.

4th-January-2019
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location in thesis-</td>
<td>Chapter 5, Part 2</td>
</tr>
<tr>
<td>Student contribution to work-</td>
<td>Literature Search, Data acquisition, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (95%)</td>
</tr>
<tr>
<td>Co-author signatures and dates-</td>
<td>Rafieian N, Ghasemi E, Ghorbani Z, Tennant M, Kruger E.</td>
</tr>
<tr>
<td></td>
<td>4th-January-2019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location in thesis-</td>
<td>Chapter 6, Part 1</td>
</tr>
<tr>
<td>Student contribution to work-</td>
<td>Literature Search, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (75%)</td>
</tr>
<tr>
<td>Co-author signatures and dates-</td>
<td>Mansouri Z, Bakhtiari S, Tennant M, Kruger E, Rajabibazl M, Daraei A.</td>
</tr>
<tr>
<td></td>
<td>4th-January-2019</td>
</tr>
</tbody>
</table>
Details of the work-

Location in thesis-
Chapter 6, Part 2

Student contribution to work-
Student contribution to work- Literature Search, Data analysis, interpretation of data, Manuscript preparation, manuscript writing and editing (45%)

Co-author signatures and dates- Rafieian N, Manifar S, Julideh H, Mohammad Shirkoda

<table>
<thead>
<tr>
<th>Name</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rafieian N</td>
<td>4th-January-2019</td>
</tr>
</tbody>
</table>

Student signature-

Date- 4th-January-2019

I, Marc Tennant certify that the student statements regarding their contribution to each of the works listed above are correct

<table>
<thead>
<tr>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th-January-2019</td>
</tr>
</tbody>
</table>
Publications Arising from Thesis


Conference Presentation

Green tea consumption in smokers and the effects on total antioxidant capacity of saliva- Is this a pathway for oral cancer prevention? 12th congress of IADR, Iranian Division, 2016.


Oral cancer general awareness- A survey in Tehran, Iran, 57th Annual Scientific Meeting of IADR Australian & New Zealand Division, 2017.

Screening for Head and Neck Squamous Cell Carcinoma- Risk Factor-Based Models, 58th Annual Scientific Meeting of IADR Australian & New Zealand Division, 2018.

Other publication that has been co-authored during the study

Azimi S, Taheri JB, Tennant M, Kruger E, Molaei H, Ghorbani Z. Relationship between Mothers’ Knowledge and Attitude Towards the Importance of Oral Health and Dental Status of their Young Children. Oral Health & Preventive Dentistry, 2018, 16(3)-265-270


Taheri, J., Namazi, Z., Azimi, S., Mehdipour, M., Behrovan, R., Rezaei Far, K. Knowledge of Oral Precancerous Lesions Considering Years Since Graduation Among Dentists in the Capital City of Iran- a Pathway to Early Oral Cancer Diagnosis and Referral?. Asian Pacific Journal of Cancer Prevention, 2018;

Relation between ABO Blood Groups and Head and Neck Squamous Cell Carcinoma- A Case-Control Study (Accepted in Indian Journal of Cancer)
Chapter 1:

Introduction and Literature Review
1-1-General introduction:

Previous studies have found the burden of cancer will increase. It is expected that, more than 20 million cancer patients will be diagnosed annually by the year 2025. Cancer is a potentially lethal disease, with many other consequences. The increasing incidence would have a significant effect on healthcare status [1].

Worldwide, head and neck cancers are one of the most common cancers, with the greatest incidence in deprived countries. New cases of head and neck cancer account for up to 4% of all cancers globally. Cancer is the most important issue in oral healthcare, due to life threatening outcome which is an integral part of general health per se. Head and neck cancer not only affects the mouth, but potentially the jaws, neck, face, and adjacent anatomy. Cancers significantly affect patients’ quality of life, especially if diagnosed and treated late, while they are one of the preventable causes of disability and death worldwide [2-4]. Early diagnosis of oral cancer is critical for the successful treatment and long-term survival of this debilitating disease. Late diagnosis, due to a lack of routine screening, allows the disease to develop and progress into more advanced stages [5, 6].

The oral and oropharyngeal cancer incidence is increasing, and it is widely recognized and accepted that there is an urgent need for the rapid development of better awareness and knowledge amongst both public and health professionals. Considering the importance of equity in health in different societies, identifying socio-economic and other social risk indicators for head and neck cancer, and addressing inequality is vital. Therefore, preventive strategies focusing on reducing modifiable risk factors such as tobacco use, alcohol consumption, areca nut, and other similar habits, diagnosis and referral, care and after-care should be encouraged [1].

This project provides an overview of different aspects of head and neck cancer with the focus on inequality and prevention through different studies. Firstly, the incidence of head and neck cancer cases has been evaluated in a developing country (West of Iran) and compared with that of Western Australia. Secondly, public awareness about oral cancer has been examined. Thirdly, the association between socioeconomic status and risk for head and neck cancer has been investigated. Lastly, the cancer-protective effect of green tea in high-risk groups (smokers) and in head and neck patients has been assessed.
1-2-Literature review

Permeable: This chapter provides a general overview of head and neck cancers, especially oral and oropharyngeal cancer, and points to epidemiology, etiology, diagnosis and treatment.

1-2-1: Cancer

Cancers are one of the leading causes of death in the world [7]. Carcinogenesis is not a simple process. It is a multistep process that originates from abnormal oncogenic signals in different signaling pathways [8]. GLOBOCAN (global cancer) is an implementing project in the World Health Organization (WHO), with the goal of establishing data on prevalence, incidence, and mortality of almost all types of cancer, in adults (over 15 years) in 184 countries. It is estimated that the burden of cancer will increase over the next decades, especially in low and middle-income countries, and it is anticipated that there will be over 20 million new cancer cases annually in less than 10 years, by 2025[7]. The fifth version of GLOBOCAN in 2012 estimated that there were 14.1 million new cases of cancer; 36.2 million people were living with cancer, and 8.2 million died from this cause [9].

1-2-2: Head and neck cancer

Head and neck cancers are a heterogeneous group of malignant tumours that vary in their tissue of origin, primary anatomical sites, histopathology, and clinical presentations [7, 10]. They arise in the upper alimentary and respiratory tracts, including the oral cavity, lips, mouth, gums, alveolar ridge, two-thirds in front of the tongue, floor of mouth, hard palate and retromolar trigone, nasopharynx, oropharynx, hypopharynx and larynx. The median age at diagnosis is 50–59 years and the male: female ratio ranges from 2:1 to 4:1. Head and neck cancers have very high mortality and morbidity rates [7].

1-2-2-1: Oral cavity and oropharyngeal cancer

Cancers of the ‘oral cavity and oropharynx’, as classified in the WHO International Classification of Diseases (ICD), include cancers of the lip, tongue and oral cavity [ICD-10: C00-06], and oropharynx [ICD-10: C09- C10], but excludes the salivary glands [C07-08] and other pharyngeal sites [C11-13] [1].
From an anatomical aspect, the oral cavity and the oropharynx are distinct areas; however, there are some differences between these definitions in different databases and complete distinction between the oral cavity and the oropharyngeal cancer may not be possible [3, 11]. Cancers of the lateral border of the tongue are the most common intraoral malignancies, and collectively accounted for 60% of oropharyngeal cancers in 2010[11].

1-2-2-2: Different types of head and neck cancers

Malignant neoplasms are classified according to the tissue of origin and histopathology. Each differs in prevalence, incidence, and survival prognosis [7]. To facilitate communication between health-care providers, a classification system was established by the World Health Organisation (WHO) for oral cavity and oropharynx cancers including: epithelial origin cancer (squamous cell carcinoma, lympho-epithelial carcinoma); salivary gland cancer (salivary gland carcinoma, salivary gland adenoma); soft tissue cancer; hemato-lymphoid cancer and secondary tumors [12] plus mucosal malignant melanoma.

1-2-2-2-1: Squamous cell carcinoma (SCC)

Head and neck carcinomas are a biologically heterogeneous group of epithelial origin cancers from the mucosa of the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx. The most frequent group is the squamous cell carcinoma (SCC), accounting for 9 out of 10 neoplasias. The probability of occurrence increases with age, and the highest incidence is observed after the age of 40 [7, 10]. Due to poor prognosis and slow improvement in the five-year survival, head and neck squamous cell carcinoma (HNSCC) is an important health problem [13]. Significant drops in survival rate occur with metastasis to distant organs. The 5-year survival rate is estimated to be less than 10%, in late stage squamous cell carcinomas [5]. Recent evidence suggests that tumors originating at sites in the oral cavity (OC-SCC) are distinct from those originating in the oropharynx (OP-SCC) sites, and have different etiopathogenesis, and prognosis. [3]

1-2-2-2-1-1: Clinical presentation

The most common symptom that motivates patients to consult with a health professional is discomfort (up to 85%). Patients may complain of a sore in the mouth or on the lip. The most common clinical presentations, is ulceration, especially with fissuring or raised
exophytic margins, or rolled edges, and a granular floor which does not heal. The condition may also presents with white and red lesions, lumps with or without pain, tooth mobility, difficulty with tongue movement, chewing and swallowing [12]. Bleeding from the surface of the lesion is a characteristic of malignancy and would immediately raise a suspicion of neoplasia. Weight loss may occur with advanced disease [14].

In more detail, patients who present with nasal obstruction may have a lesion originating in the hard palate that has extended to involve the maxillary antrum or nasal cavity. An oral tumour that has infiltrated the structures of the oropharynx or has invaded the pterygoid muscles will usually cause malocclusion or trismus. Effusion in the middle ear is usually seen when a tumor has invaded the nasopharynx or the tensor veli palatini muscle. A lesion that invades the maxillary division of the trigeminal nerve (CN V) will interfere with the corneal reflex and a tumor that involves the mandibular division of the trigeminal nerve (CN V) will cause atrophy of the masseter or temporalis [14].

1-2-2-2-1-1-1: Frequency and appearance in site

The lower lip, the lateral borders of the tongue, and the floor of the mouth are three most common sites of oral cancer. Lip cancers mostly present as a chronic ulcer, small lump, or scabbed lesion. Intra-oral cancers are most common the middle third of the lateral borders of the tongue, and sometimes appear as an induration with an erythroplastic component. The second most common intra-oral site for cancer is the floor of the mouth and in this region is more frequently associated with leukoplakia (a potentially malignant disorder). The usual presentation in the anterior floor of the mouth is an indurated mass that soon ulcerates and slurring of speech is a common symptom. Almost 50% of carcinomas of the gingiva or alveolus invade the underlying alveolar bone even in the absence of radiographic changes. These cancers are often observed in the mandibular regions (premolar and molar), and present as an ulcer or lump. Adjacent teeth may be loose. Carcinomas of the buccal mucosa are often observed in the retromolar area or at the commissure. The majority present as lumps with ulceration, and some are associated with areas of become apparent in candidal leukoplakias. Carcinomas can also affect the palate or elsewhere [15].
1-2-2-3: Oral Potentially malignant disorders (OPMDs)

Some oral cancers are preceded by OPMDs. There is a number of OPMDs, each with different malignancy potentials. Erythroplakia has a very high risk of malignant transformation. Non-homogeneous leukoplakia and candidal leukoplakia are also common and carry a high risk of malignant transformation. Homogeneous Leukoplakia and Lichenoid lesions/lichen planus have less potential for malignant transformation. Although actinic cheilitis and submucous fibrosis have a high risk of transformation, these lesions generally are not common.

Early stage OPMDs are usually asymptomatic, solitary, small lesions. It is very difficult to differentiate them from early cancers and misdiagnosis is quite possible. Any symptoms in these lesions should increase the index of suspicion of malignant transformation [16].

1-2-2-4: Epidemiology

1-2-2-4-1: Incidence and mortality

The most recent publication of GLOBOCAN (in 2012), estimated that there are 529,500 cases of lip, oral cavity, and pharyngeal cancer and 292,300 deaths globally each year, accounting for about 3.8% of all cancer cases and 3.6% of cancer deaths. This figure includes a broad range of tumors with diverse etiologies by world region. Cancers of the oral cavity (31.14%) are the most common among oral and pharyngeal cancers, followed by cancers of the oropharynx (18.97%); nasopharynx (16.37%); hypopharynx (11.48%); parotid gland and other and unspecified major salivary glands (PGOSG) (7.57%); lip (4.47%); and other ill-defined cancers of the lip, oral cavity, and pharynx (2.98%). Each subsite has marked variation in relative contribution by world region, sex, and age [17].

For most countries, current five-year survival rates for treated oral and oropharynx cancers are around 50–60%. The best outcomes for overall five-year survival rates for treated mouth cancers are for cancer of the lip, at over 90% of patients. In general, prognosis decreases with advanced disease, low socio-economic status (SES), advanced age and continuing risky lifestyles [11].
1-2-4-1-1: Gender disparities

In 2012, around 70 percent of all newly diagnosed cases with lip, oral cavity, and pharyngeal cancer, (375,000) were in men and around 30 percent (154,400) in women. Although rates of oral cancer have traditionally been higher in men than in women, the ratio of males to females diagnosed with oral cancer has declined [11, 17]. However, the incidence by gender varies depending on the anatomic location, and is now about 1.5:1 for the mouth and about 2.8:1 for cancer of the oropharynx. Some reasons for changes in gender ratio are changing demographics and lifestyles, such as the changes in the prevalence of major risk factors, including heavy smoking and alcohol consumption, and increasing infection with the human papilloma viruses (HPV) as a consequence of changing behaviours [11, 14].

1-2-2-4-1-2: Global and racial disparities

The prevalence and incidence rate of head and neck malignancies varies in different locations across the world, with a higher tendency in less developed regions [2, 12, 18].

Geographic location is a significant factor for the head and neck cancer development [19]. Two-thirds of cases occur in people from South Asia; Latin America; Papua New Guinea and other Pacific islands in Melanesia [8, 11]. It is highly prevalent in India, Pakistan, Brazil, France, Afghanistan, Bangladesh, Sri Lanka, Bhutan, Nepal, Iran and Maldives, considering different types of cancer occurrence in these countries [20, 21]. More than 50% of all cancers, in parts of India are oral cancer [8]. In South Asia, cultural habits, such as alcohol consumption, reverse smoking and most importantly betel quid chewing, as well as low socioeconomic status and a diet with low fruits and vegetables consumption contribute to this high prevalence. Unfortunately, in some parts of the world with high rates of oral cancer, data and evidence for the incidence and mortality are not available or not of high quality; therefore, the exact nature and extent of the problem is still unclear [9, 12].

Also, in developed countries, the incidence is generally higher in ethnic minorities and immigrants from high risk areas. In USA, African-Americans have a higher incidence, present with more advanced disease at presentation, and experience a generally greater mortality when compared with White Caucasians [11].
The incidence rates in Europe are higher in eastern parts compared with western, southern or northern parts. Although, there are unknown causes underlying these differences; it is likely to arise from various components such as quality of care, access to healthcare, diet, or even cultural beliefs [11,22].

**1-2-2-4-2- Australian head and neck cancer statistics**

**1-2-2-4-2-1: Incidence of head and neck cancer**

In Australia, head and neck cancer including malignant neoplasm of the lip, oral cavity and pharynx (C00–C14) and malignant neoplasms of the respiratory and intrathoracic organs (C30–3) remains the 7th most commonly diagnosed cancer in 2017, the same ranking as 2013.

In 2017, it was estimated that around 5000 new cases of head and neck cancer were diagnosed in Australia (more than 3500 males and around 1300 females) an increase compared with new cases of head and neck cancer diagnosed in 2013 (almost 4400, around 3100 males and 1200 females). The age-standardised incidence rate was estimated to be 27 for males and 9 for females and overall there were 18 cases (per 100,000 persons) in 2017, a slight increase from 2013, with 17 cases (26 for males and 9.3 for females) per 100,000 persons. Finally, it is estimated that 1 in 48 (1 in 32 males, and 1 in 92 females) individuals are at risk of being diagnosed with head and neck cancer by their 85th birthday [23].

**1-2-2-4-2-2: Deaths from head and neck cancer**

In 2014, there was around 1000 (766 males and 274 females) deaths from head and neck cancer in Australia. In 2017, it was estimated that there was more or less the same number of deaths (777 males and 249 females). It was estimated that it is the 18th most leading cause of death from cancer in 2017, compared with the 15th most common cause of cancer death in Australia in 2014. In 2017, it was estimated that the age-standardised mortality rate will be 3.5 (5.7 for males and 1.6 for females) deaths per 100,000 persons, which is lower than 2014, with the age-standardised mortality rate of 3.8 (6.1 for males and 1.9 for females) deaths per 100,000 persons.

It was estimated that the risk of an individual dying from head and neck cancer is 1 in
214 (1 in 132 males and 1 in 497 females) by their 85th birthday, in 2017. There were almost 4000 people living who had been diagnosed with head and neck cancer at the end of 2012, and more than 15000 people who had been diagnosed with head and neck cancer from 2008 to 2012. The proportion surviving for 5 years in individuals diagnosed with head and neck cancer, compared to their counterparts in the general Australian population in 2009–2013, was 69% (68% for males and 72% for females) [23].

1-2-2-5: Etiology and pathogenesis (Genetic/epigenetics)

The incidence of oral cancer increases with age. This may be a reflection of period of exposure to initiators or promoters, or time for the accumulation of genetic alteration, including physical/chemical irritants, or some viruses, and even hormonal changes and impaired immune systems. Most patients diagnosed with oral cancer are between 50 and 70 years however, it can occur in younger adults. In addition, oral cancer may develop as a consequence of impaired immune systems in individuals infected by HIV, patients with solid organ and hematopoietic stem cell transplantations, and patients undergoing chemotherapy [12].

Predisposing factors and external carcinogenic factors induced a great variety of genetic or epigenetic events that promote genomic instability and in turn the development of tumors.

Genetic changes and processes like loss of heterozygosity, DNA damage, segregation of chromosomes, as well as irreversible changes in DNA sequence, such as gene deletions, mutations and amplifications and other behaviours lead to defects in normal cellular process oncogene activation or tumor suppressing genes (TSGs) inactivation and development and progression of oral pre-malignancy and oral cancer[8]. A particular type of alteration in the genetic control of DNA repair, caused by different types of abnormalities in normal genetic processes, such as immortalization, apoptosis, invasion, proliferation, transcription factors, growth factor receptor, angiogenesis and signal transducers, appear in abnormal epithelium cells of the upper alimentary and respiratory tracts [8].

Epigenetic variations which change gene expression that are not encoded in the DNA sequence, like chemical modifications in DNA methylation, RNA mediated silencing of genes and histone modifications, might also be involved in oral cancer development [8,
Thus, new reports about epigenetic modifications may provide prophylactic, diagnostic and therapeutic benefits [24].

1-2-2-6: Possible risk factors

HNSCC has multifactorial pathogenesis. There are strong associations with the consumption of tobacco, alcohol and use of areca nut. This cancer also develops in association with viral, bacterial and fungal infections, immunosuppression, genetics, radiation, expression of oncogenes, deactivation of tumor suppression genes and malnutrition. The population-attributable risk of smoking and consuming alcohol for developing HNSCC 74% in general (80% for males, 61% for females) is estimated [7, 10].

1-2-2-6-1: Behavioural risk factors

1-2-2-6-1-1: Tobacco: (Smoking/ smokeless tobacco)

Smoking including cigars, cigarettes, or pipes; chewing tobacco; or snuff (powdered tobacco) are the most important risk factors for HNSCC. Also, passive smoking may contribute to HNSCC development. Consumers of smokeless snuff frequently develops OPMDs which may progress to carcinomas over time. Second primary tumor (second unrelated tumor which occurs in someone who has had any previous cancer) may develop significantly in active smokers as well [14].

Tobacco contains over 60 carcinogens. The most relevant for oral cancer are the tobacco-specific nitrosamines (TSNAs), N-nitrosamines; NNK [4-(methylnitrosoamo)-1-(3-pyridyl)-1-butanone]; NNN [N-nitrosonornicotine]; PAH [Polycyclic aromatic hydrocarbons, e.g. benzene and aromatic amines]; Aromatic amines; Heavy metals. There are more than 10^{15} free radicals in one “puff” of a smoke of cigarette. Free radical production triggers changes in various antioxidant enzymes (such as: superoxide dismutase, glutathione-S- transferase (GST), catalase and glutathione peroxidase, glutathione reductase). It has been reported that these alterations result in genetic variations in tumor suppressor genes (APC, p53), oncogene (Ras), proto-oncogenes (Myc), and genes for controlling normal cellular processes (EIF3E, GSTM1) [8, 25]. The associated risk of smoking seems to be dose-dependent and correlates with daily or cumulative cigarette consumption. [3]
Cessation of smoking, leads to a decline in OC-SCC and OP-SCC risk. The risk of oral cancer is around 30% lower in quit smokers than that of a current smoker, 1–4 years after quitting smoking, and for oropharynx/hypopharynx cancer, this risk reduces around 50%, 5–9 years after smoking cessation. Almost 20 years after cessation, the risk of oral cancer will be reduced to “never-smokers” [25].

1-2-2-6-1-2: Alcohol

Alcohol consumption is associated with an increased risk of oral and pharyngeal cancer among “never” smokers [22]. Several hypotheses have been proposed to explain underlying carcinogenic mechanisms. Firstly, ethanol is metabolized into carcinogenic acetaldehyde by epithelial cells and microflora. Secondly, these beverages may contain aldehyde and various carcinogenic contaminants, such as nitrosamines and polycyclic aromatic hydrocarbons. Heavy drinkers may have nutritional deficiencies that also increase the risk of SCC [3]. Cancer risk increases with the level and number of years of alcohol consumption. Every 1.5 units of alcohol consumed per day increases the risk of oral and pharyngeal cancer by 35% in men and 9% in women [26]. Many studies have found that there is a synergic effect of cigarette smoking, and alcohol consumption that, in heavy drinkers, compounds the risk to 30 to 36 times higher than for non-smokers and non-drinkers [14, 27].

1-2-2-6-1-3: Betel chewing and other agents

All three main products of ‘Betel’ (areca nut, betel and paan) without tobacco, contain the stimulant arecoline, which has nicotinic and muscarinic agonist properties. Arecoline, is the primary active ingredient, it is genotoxic and carcinogenic and has a role in the multistage progression of oral cancer.

Consumption of betel quid without tobacco is an isolated risk factor for oral cancer development. Betel quid chewed with tobacco increases the risk of oral cancer in those who neither smoke nor drink by around 7 times [26].

1-2-2-6-2: Infective agent

1-2-2-6-2-1: HPV

Human Papilloma Virus (HPV) is a double-stranded DNA virus with a special affinity
for the basal layer of squamous epithelial cells. The prototypic HPV16 and HPV 18 are capable of the malignant transformation of epithelial cells derived from both the ano-genital and upper alimentary and respiratory tracts [10]. Several studies investigated HPV as a causative factor for HNSCC. HPV infection is commonly transmitted by sexual practices. The role of HPV infection and oro-genital contact in causing HNSCC has been investigated in various studies. The history of oral sex, having multiple partners, high-risk sexual behaviour or being homosexual are strongly associated with tonsillar and oropharyngeal cancers [10, 16].

HPV-positive HNSCC is seen more commonly in the oropharynx, particularly the palatine and lingual tonsils and is least likely to appear in oral cavity [3]. It has a higher frequency in younger age groups, non-smokers and non-drinkers, and tends to have poor differentiation and frequent basaloid histology. HPV-positive HNSCC rarely metastasises to distant organs or has second primaries. Patients with HPV-positive HNSCC, despite presenting at an advanced stage of disease, have a better prognosis and survival than those with equally advanced HPV-negative HNSCC. Partners of women with cervical cancer or a history of cervical cancer have an increased risk of developing oral cancer. HPV transmission from women to men appears to be higher than from men to women. HPV sero-prevalence is considerably higher among women compared with men [10, 16]. HPV vaccination, currently approved for the prevention of uterine cervical carcinoma and ano-genital warts, may offer great promise in controlling the rise of OP-SCC in the future; however, studies so far have not yet yielded sufficient evidence for the indication of HPV vaccination for prevention of OP-SCC [3].

1-2-2-6-2-2: Other microorganisms

Other microorganisms may have potential carcinogenic effects. Dental plaque bacteria, may induce cell proliferation, inhibit apoptosis, interfere with cellular signaling, and cause mutagenic interaction with saliva. Bacteria associated with periodontal disease cause inflammatory reactions and proto-oncogenes. Viridans streptococci and Candida species may convert ethanol to acetaldehyde. Herpes simplex virus activates proto-oncogenes, and inactivates the p53 tumour suppressor gene [16].
1-2-2-6-3: Environmental risk factor

1-2-2-6-3-1: Dietary defects

Various studies have shown that diets low in fruit and vegetables and high in animal fats are associated with an increased risk of oral and oropharynx cancer. This may be due to the absence of zinc or other vitamins and minerals. Vitamin A deficiency could increase the risk of developing oral and oropharynx cancer. Poor diets and eating patterns are common in people who drink excess alcohol, and may help explain why alcohol increases the risk of some cancers. Diets high in some types of salted fish that may be eaten as part of a Chinese diet may increase the risk of nasopharyngeal cancer [28].

1-2-2-6-3-2: Sun light

Exposure to sun and associated ultraviolet light radiation is a risk factor for the development of cancer of the lip [27, 28].

1-2-2-6-3-3: Socio-economic factors

Oral cancer is more common in socioeconomically deprived populations. The significant increase in the incidence of head and neck cancer, including oral cancer, in people with low levels of education and lower incomes patients have been indicated in several studies. A strong association between smoking and alcohol consumption and socioeconomic status has been suggested, however, after adjusting for smoking and alcohol consumption, individuals with lower educational levels, lower occupational status/social class, those performing manual labour and those with lower income, still had a higher risk of contracting head and neck cancer, including oral cancer [27, 29]. The underlying aetiology of this is yet to be proved and the components and pathways of this socioeconomic effect have had limited attention. Possible explanations include limited access to health care and health information, increased exposure to environmental carcinogens, increased levels of behavioral risk factors, including higher tobacco and alcohol consumption and poor nutrition, and stresses caused by job insecurity or unemployment [27, 29-31].

It is speculated that efforts to reduce exposure to risk factors are unlikely to succeed unless they are accompanied by measures designed to improve socioeconomic circumstances.
and to decrease inequalities. Health professionals and policy makers must be taken into consideration advocating for socioeconomic change in addition to behavioral changes [29, 30].

1-2-2-6-4: Genetic causes

It has been suggested that there is a higher risk of developing a head and neck cancer if a first-degree relative has had these conditions. Environmental factors or exposure to common risk factors may have an effect in familial cases, some of which may be inherited. A family history of oral, pharyngeal and laryngeal cancer is a strong determinant of cancer risk, independent of tobacco and alcohol use. Reports have indicated that people who had a close relative with cancer of the larynx, have around a 3 times higher risk of developing oral and pharyngeal cancer. Also, a four-fold increasing the risk of oesophageal cancer has been found where a close relative had oral or pharyngeal cancer [28]. The risk of developing head and neck cancer may more than double if there is a family history, particularly if a sibling has had a diagnosis [28].

Occasionally genetics has been proven to have a notable role in cancer predisposition. There are rare inherited disorders, such as Fanconi anaemia, dyskeratosis congenital, ataxia telangiectasia, Bloom syndrome, and xeroderma pigmentosum, with a known association with primary malignancies, including mouth cancer [28].

1-2-2-6-5: Other possible risk factors

Other possible risk factors include: diseases such as chronic candidiasis, diabetes, discoid lupus erythematosus; HIV/AIDS, Plummer-Vinson syndrome, and primary carcinomas in the upper alimentary and respiratory tracts. Furthermore, scleroderma, medications such as anti-hypertensives and immunosuppressive drugs, and iatrogenic causes such as radiotherapy are other well established risk factors. Chronic irritation has also been postulated as a risk factor that may result from ill-fitting dentures, poor oral hygiene, poor dentition, and missing teeth [32]. However, the role of these conditions in oral cancer development is uncertain [28].

1-2-2-7: Diagnosis

Any single lesion that persists more than 3 weeks and cannot be wiped off the mucosa,
particularly if it is red in colour, ulcerated or a lump (the acronym RULE), especially if there is firmness on palpation (induration), should be regarded with suspicion. It needs a histopathological diagnosis by biopsy examination. Generally, individuals report to a clinician only in the later stages of malignancy, despite the oral cavity being accessible for examination, thus no improvement in survival rate for oral cancer has been observed over the decades [15, 19].

1-2-2-7-1: Early detection

Cancers are more likely to be cured using standard treatment protocols if detected at early stages; however, delayed diagnosis, can dramatically affect the treatment outcomes [33].

A lack of awareness among health care providers and the public that may result in delays in the recognition and diagnosis of oral cancer is a problem. Barriers in the health care system that hinder patients from seeking medical or dental care, result in delayed referral to the appropriate healthcare worker, especially in low- and middle-income countries [34]. Previous studies have indicated socioeconomic status, such as social marginalization, separated, divorced or widowed status, and tobacco/alcohol use as well as advanced age and being male are associated with late-stage diagnosis of oral cancer. Conversely, previous referral to a specialist physician, facilitated access to the specialist, and close contact with a health professional or a regular dentist was related to early-stage diagnosis [33, 35]. The level of education has also been related to late-stage diagnosis. Late-stage tumours are less prevalent in patients with higher levels of education, while illiterate patients and those with an incomplete education or education complete to primary school level only, presented with a higher proportion of late stage (T4 tumours) [15, 33, 36].

Previous studies found a low awareness regarding risk factors and common signs and symptoms of oral cancer among the general population in different countries. In a study where a group of healthy individuals examined images of oral lesions, higher risk lesions were less likely to be perceived as oral cancer or to make patients seek professional advice. High-risk patients were less aware about the appearance of oral cancer and less likely to take action if they noticed an oral lesion [33, 37]. Hence, increasing the awareness among the public as well as professionals, including dentists, physicians, oral hygienists and nurse practitioners, should be considered by health managers to avoid
delayed diagnosis. It seems that dentists with higher patient loads were less likely to conduct screening for the early detection of oral cancer, and it is not perceived to be as a priority in private clinics [15, 33].

1-2-2-7-1-1: Conventional oral examination and cancer screening

The best way to detect lesions of the upper alimentary and respiratory tracts is physical examination. This initial assessment often indicates the chronicity or severity of the disease. A comprehensive physical examination should be done with certain emphasis on the head and neck of each patient. This would include inspection, palpation supplemented by otoscopic, and neurological examinations, with emphasis on related cranial nerves and, when indicated, indirect laryngoscopy or nasopharyngolaryngoscopy [14].

Conventional oral examination should include the buccal and lingual mucosa, ventral tongue and labial mucosa, submental, submandibular and cervical lymph nodes. All areas should be scrutinized using a good light and retraction, which is best available in a dental office.

A screening test or screening examination is not diagnostic and must be specified from case finding or early detection. It is defined as the application of a test to people who are apparently free of disease, to identify those who may have the disease, from those who may not. In fact, it is intended to identify tissue changes that may indicate the likelihood of having or developing the disease in question. Screening is the continuous examining and referral of a defined population at periodic intervals, which is most often managed by a national or regional program. Oral cancer screening would involve the implementation of an oral examination with the objective of identifying changes, which may precede the development of oral cancer, or predict it with a high likelihood. Individuals identified as likely to have the disease, should be referred for more extensive examinations by specialists for a definitive diagnosis [38].

The advantage of conventional oral examination as a screening test for oral cancer is that is minimally invasive, has a high validity (in the case of experienced examiners), involves minimum examination time, has no morbidity, no need for special facilities, and it can
be undertaken as a part of a general or dental examination. However, the success of oral screening may depend on the quality of the examiner; it cannot distinguish between benign, malignant and OPMDs lesions, it is difficult to maintain a simple record, and the cost-effectiveness is uncertain. There are increasing concerns about over-diagnosis (false-positive results or lead time bias) that result in over investigation or over-treatment. These would be of no benefit to the patient and carry possible additional risks or costs [38].

According to a 2010 Cochrane review, there is not sufficient evidence to indicate that a screening program can assist in early detection of oral cancers, and they did not recommend screening of the general population either by using visual examination or adjunctive tools (such as brush biopsy, toluidine blue, fluorescence imaging) to decrease mortality from Oral Squamous Cell Carcinoma (OSCC). The regular screening by visual inspection by qualified healthcare providers for high-risk groups however is recommended [15, 33].

1-2-2-7-1-2: Self-examination

Although the oral cavity is an easily accessible site for visual inspection as part of routine care by health workers, the mouth self-examination (MSE) has also been suggested as an opportunity to detect early stages of oral cancer [33]. Nevertheless, the results compared to the clinical findings of a specialist, demonstrate the low sensitivity (0.43), specificity (0.44) and accuracy (0.43) of MSE for detection of oral cancer, due to insufficient performance of 75% of patients [33, 39]. A systematic review estimated sensitivity to range from 0.18 to 0.33, and specificity from 0.54 to 1.00 for the diagnostic accuracy of MSE for early detection of oral cancer or potentially malignant disorders. Therefore, the current evidence does not support the use of MSE as a strategy for screening of oral cancer [33].

1-2-2-7-2: Differential diagnosis

The differential diagnosis OSCC includes other malignant tumors such as minor salivary gland neoplasms, mesenchymal tumors (sarcomas), melanoma, and lymphoma; chronic infections, such as syphilis, tuberculosis, or histoplasmosis. Traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), aphthous ulcers, and other benign tumors of the oral cavity may mimic a SCC of the oral cavity. Occasionally, pyogenic
granulomas or similar less serious lesions such as necrotizing sialometaplasia can clinically and histologically mimic OSCC [15].

Clinical differentiation of OPMDs and OSCC from benign lesions can be challenging, even for highly trained professionals. OPMDs and OSCC may appear innocuous without any symptoms, and some can be overlooked. Less than one third of leukoplakias, a common OPMDs, are ever subjected to biopsy, and even biopsy can leave cancers undetected in OPMDs [14].

1-2-2-7-3: Definitive diagnosis

An incisional biopsy, which involves incising a thin slice of tissue from the area, is mandatory to confirm any diagnosis of cancer. It may be performed in the dental/specialist office or it can be done as outpatient surgery depending on patient preference and the anatomic site. The biopsy specimen should be large enough to include the suspect area and sufficient normal tissue, away from areas of obvious necrosis or excess keratinization. This provides the pathologist with an opportunity to make the diagnosis and not have to request an additional specimen. A non-representative biopsy may delay diagnosis. Ideally, scans to evaluate the primary site should be performed prior to biopsy to avoid the effect of upstaging from the oedema caused by biopsy trauma, but this is rarely feasible [14, 15].

1-2-2-8: Management

1-2-2-8-1: Prevention of oral cancer

Prevention is the best long-term strategy for cost-effective cancer control. The overall goal of prevention and control of cancer is to reduce incidence, morbidity and mortality, and to improve the quality of life of cancer patients and their families. In addition, it can be beneficial for the prevention of other chronic diseases with the common risk factors [27, 40].

Previous studies concluded that oral cancers could be avoided in three out of four cases by the elimination of unsafe behaviours such as cigarette smoking, and consumption of alcohol. Exposures to tobacco and/or alcohol or betel quid are very high risk factors for developing oral cancer in the majority of people. Currently approximately 1 billion men
and 250 million women smoke; 2 billion people consume alcohol; and 600-1,200 million people worldwide chew betel quid. Lifestyle modification to eliminate these risk factors could have a significant impact in reducing oral cancer rates. It is known that quitting smoking decreases the risk of oral cancers and that after 20 years of not smoking, the risk is reduced to the level of those who have never smoked [27].

Various tobacco control measures have been adopted to decrease the incidence of head and neck cancers. These include social awareness programs, effective legislation, restriction of sales to minors, increased taxes and product disclosure laws. After the implementation of such measures, several countries have seen a downward trend in smoking prevalence and a decline in head and neck cancer incidence correlating with a decline in tobacco use. However, some other countries have witnessed an increasing incidence of oropharyngeal and oral cavity cancers despite reduced in rates of smoking since the 1980s [41].

The role of health professionals in oral cancer surveillance is vital. It is probable that patients at high-risk for OC (such as the elderly, smokers and alcohol users) present to their general practitioner (GP) or dentist, which emphasises this role [22]. Dentists should encourage their patients to quit smoking and not abuse alcohol. However, some studies showed that primary care physicians confirmed that they would not question patients about the amount of tobacco and alcohol consumed or past tobacco and alcohol use history [33, 42]. Barriers to improving training of dentists included time constraints, competing priorities and reluctance to taking on the workload of dentists. Oral hygiene education and training and oral cancer detection can be improved by providing an e-learning, problem-based learning sessions and access to specialist tutors. Impressively, a large study reported around 75% of evaluated primary care dentists felt incapable of performing biopsies, almost 60% had never performed one, and only some of them were able to recognise potentially malignant lesions. This demonstrates that there might be a lack of training education or continuing education programs for general dentists focused on oral cancer for general dentists might exist [22, 33].

There is little awareness among health professional regarding HPV infection and its role in HNSCC. Patients lack information concerning the risks associated with HPV infection, and health professionals are reluctant to ask about sexual practices or counsel patients regarding oro-genital contact and HPV transmission because of the social stigma [10].
Several studies established the protective effects of a healthy diet. Consumption of fruit, vegetables, coffee, and dietary folate intake are certain factors protecting against developing oropharyngeal cancers [22].

A previous study indicated an inverse association between fruit and vegetable intake in total, and incidence of head and neck cancer. It has been reported that consumption of each portion of fruit and vegetables daily almost halves the risk of oral cancer, and people with the highest amount fruit intake have almost 50% reduction in the risk of head and neck cancer. The Mediterranean diets also, may be related with a decline in oral and pharyngeal cancer development. Studies have claimed that dietary vitamin C consumption (745 mg/week) and calcium supplements protect people from developing OPC, but a Cochrane review suggest the evidence is inconclusive [28]. Studies also suggest that the intake of vitamin A, carotene, and tocopherol may reduce the risk of developing oral cavity cancers [14].

There is an inverse association between consumption of tea and coffee and the risk of oral and pharynx cancer [28]. Tea polyphenols are strong antioxidants can scavenge the free radicals. This is a suggested potential mechanism for the chemo-preventive of some teas effect against carcinogenesis. However, controlled interventional and observational studies were not sufficient and evidence on possibility of cancer prevention by black or green tea were inconclusive [43, 44].

It seems that education about signs and symptoms as well as risk factors is a feasible approach for prevention of oral cancers. Raising public and professional awareness can help to reduce risk factors and improve early diagnosis.

1-2-2-8-2: Available cancer treatment:

The planning of cancer treatment is based on: tumour type; stage (size, nodal status and metastases) and grade; balance of benefit of a particular treatment and its potential adverse impact (such as the effect on appearance, speech, eating and swallowing). Co-existent medical conditions, general health and fitness; social circumstances; and most importantly, the wishes of the patient are important factors to consider [45].

OSCC is more common in older adults. Many of them have been exposed to tobacco and alcohol, or a combination, most of them are from poor income and low resources groups,
and are sometimes malnourished. Therefore, co-morbidities are common, such as cardiovascular disease, respiratory disease and hepatic disorders are common [45].

The most appropriate treatment will be recommended by the multidisciplinary team (MDT) and there may be choices between different treatment modalities [45]. A MDT made up of a surgical oncologist specializing in head and neck cancers, radiation oncologist, medical oncologist, plastic surgeons, dentist and prosthodontist, speech therapist, psychologist and social worker. The treatment option will consider expected survival of disease (due to stage at presentation); likelihood and severity of complications; the likelihood of mortality within the first year following treatment; treatment costs and quality of life. Many factors may adversely affect treatment [14, 45].

**1-2-2-8-2-1: Surgery**

For early or localized oral cancer, surgery may be the preferred treatment. These lesions can be removed with only minor changes to chewing, swallowing or speech and patients can often adapt quickly. With more advanced lesions, surgery may result in damage of structure and fibrosis, and this may have an influence on esthetic and function. Surgery is also indicated for tumors that have infiltrated bone when the side effects of surgery are less significant than radiation, lack of sensitivity to radiation in tumours, and for recurrent tumour in areas that have previously received radiotherapy. Surgery may also be used in palliative cases to reduce the bulk of the tumor and to promote drainage from a blocked cavity [12].

**1-2-2-8-2-2: Radiotherapy**

In difficult to reach areas, or where surgical removal might cause major damage to the tissue structure, radiotherapy may be administered as a single preferred treatment modality for cancers. It can also be as part of a combined radiotherapy, surgical and/or chemotherapy management, or for palliation. However, radiation therapy as a cure causes early and late toxicities. Radiation may provide symptomatic relief from pain, bleeding, ulceration, and oropharyngeal obstruction in palliative treatment. Hyper fractionation of radiation (usually twice daily dosing), is a strategy to increase the intensity of treatment for increased tumoricidal effects and results in more severe acute effects [12].
1-2-2-8-2-3: Chemotherapy

Chemotherapy may be used as induction therapy prior to local therapies. Concurrent Chemoradiotherapy (CCRT), and adjuvant chemotherapy may be indicated after local treatment [12].

1-2-2-8-2-4: Other treatment options

Other treatment options include: photodynamic therapy, gene therapy, and immunotherapy. A second opinion may be desirable to give more information and discuss different treatment options with patients. It usually helps them to feel more confident about the treatment plan [12].

1-2-2-8-3: Head and neck cancer and quality of life

Coping with a diagnosis of cancer, is challenging for all patients, both practically and emotionally. Patients need support as they are likely to feel confused, fearful, and lacking control. It is important for them to get the appropriate information about the type of cancer and how it is best treated. Comprehensive information about the cancer and management options would help patients to make informed decisions and cope with treatment. Treatment of oral cancer including surgery, radiotherapy and chemotherapy may have a detrimental effect on patients’ appearance and on functions such as swallowing or speech. These problems can have a massive negative influence on social integration, emotion, and well-being. Cancer patients also need practical support for concerns including financial issues and family matters. It can also be challenging for clinicians [45, 46].

1-3: References


3. Chi AC, Day TA, Neville BW. Oral cavity and oropharyngeal squamous cell


26. Kalavrezos N, Scully C. Mouth cancer for clinicians part 4: risk factors (traditional:
alcohol, betel and others). Dent Update. 2015;42(7):644-54.


Chapter 2

Aim and structure
Preamble: Against the background of the Literature Review, the importance of avoiding life-threatening and costly treatment of head and neck cancers, by prevention strategies, early detection, and implementing intervention, particularly in high-risk groups, was highlighted.

2-1-Aim

This thesis will explore head and neck cancers, especially squamous cell carcinoma, and attempt to identify prevention strategies and resolve some of the issues mentioned above, through extensive analysis of data from Iran (a developing, highly populated country, in Middle East), and Western Australian.

There were four primary objectives for addressing the questions raised about frequency, awareness, inequalities and prevention.

- Firstly, the project evaluated the head and neck cancer rate in a part of Iran (developing country), and compared that with that of Western Australia (developed country), through a retrospective study.
- Secondly, the main part of the thesis was an examination of the awareness of people about oral cancer, by conducting a cross-sectional survey and investigating the association between socioeconomic status and risk for head and neck cancer, through a case–control study.
- Thirdly, the risk-factor based model for oral cancer has been investigated.
- Finally, the cancer-protective effects of green tea in high-risk groups (smokers) and head and neck cancer patients were assessed through a preliminary interventional and case-control study.

2-2- Structures

In this section, each objective is briefly mentioned and in the following chapters, Chapters three to six, each of these are addressed individually.

2-2-1-A ten-year study of head and neck cancer in adults

The aim was to assess the incidence and prevalence of head and the neck cancer, in two different locations, with different socioeconomic situations. Data on all cases of head and
neck cancer (as a primary diagnosis) from April 2002 to March 2012 were collected from three major hospitals in the West of Iran, with the help of staff in the hospitals, and by information from medical records of patients. Age, sex, histopathological type, and the primary site of tumor were recorded according to the International Classification of Disease (ICD). Descriptive analysis was used to describe basic features and means (±SD) was reported and tests of significance were used as appropriate. Also, de-identified data on head and neck cancer for the period 2002–2012 were obtained from the Western Australian Cancer Registry, which was recorded according to ICD. The distribution of all types of head and neck cancer, diagnosed according to international cancer classification, between two similar sized populations, (in the West of Iran and Western Australia), was compared.

2-2-2- Evaluation of oral cancer awareness in an adult population and its association with socioeconomic status

The purpose of this study was to examine the levels of awareness of oral cancer, risk factors, signs and symptoms, and its association with socioeconomic status, as a main focus of this thesis, through a cross-sectional study in (Tehran) Iran. A questionnaire was designed, based on previous studies and validated. The samples included parents of public primary school students in Tehran (Capital city of Iran). Schools selected randomly from municipal regions and participants were invited from each school. Informed consent was obtained, and 1800 questionnaires were distributed among participants in the selected schools. Data were collected about awareness of risk factors, signs and symptoms of oral cancer, as well as demographic and individual socioeconomic backgrounds. Data were analysed with appropriate statistical methods (Descriptive statistics and Correlation analysis).

2-2-3- The association between components of socioeconomic status and head and neck cancer, and risk-factor model for oral cancer

In this study, the complex associations between various variables and risk for head and neck cancer through a case-control study in Iran were examined to find a successful way for future studies to reduce oral health inequality as well as planning for efficient screening programs.
Eligible adult patients with a definitive histopathological diagnosis of head and neck cancer were selected. Controls were matched by age and sex, and selected randomly from outpatients and healthy people who attended the hospital at the same time. After the participant’s informed consent, data were collected from around 400 participants getting through the structured questionnaire. The questionnaire included information about demographic characteristics, a brief medical and dental history, lifetime history of all types of smoking and consumption of alcohol, intake of selected foods, exposure to ultraviolet radiation, sexual behavior, social and occupational history. Data were analysed with appropriate statistical methods (Descriptive statistics and regression and multivariate analysis).

2-2-4- Evaluation the effect of green tea on head and neck cancer prevention

Firstly, the role of green tea, as a cancer protective agent, on the salivary antioxidant status in smokers was investigated, to find a way for cancer prevention in this group. Smokers and non-smoker participants were matched according to age and sex, participated after ethical approval and informed consent. They consumed two cups of green tea (2 g, each teabag) for 3 weeks, based on previous studies. On baseline, after 7 days and after 21 days salivary samples were collected; and salivary total antioxidant capacity (TAC) were measured accordingly. The results of salivary TAC at baseline and after green tea consumption (short-term and long-term) in two groups were compared. Also, the periodontal status of participants after consumption of green tea was defined as an accessory result. In second part of the study, the relationship between green tea drinking and the risk of developing head and neck squamous cell carcinoma (HNSCC) has been evaluated. HNSCC patients and matched controls completed a questionnaire about consumption of green tea in last two years. The risk of developing oral cancer in never consumers of green tea, after adjustment for other risk factors, were analysed.
Chapter 3

**To analyse a decade of head and neck cancer patterns in Western Australia and in the West of Iran**

This chapter is presented in two parts, which was published in the following articles:


3-1: Orofacial cancers in the West of Iran: A 10-year study

3-1-1-Abstract

Objectives: Orofacial cancer remains a substantial life-threatening disease in developing countries. Late diagnosis and treatment still lead to many avoidable deaths. The differences in incidence and prevalence between different geographical and ethnic groups remain an important issue for service planning and international action against cancer.

Methods: In this retrospective study, cancer of the orofacial region for the 10-year period (April 2002–March 2012) was evaluated in west of Iran. Age, sex, histopathological type, and the primary site of tumor were recorded according to the International Classification of disease for Oncology. Descriptive analyses were used to describe basic features, means (±standard deviation) were reported, and appropriate tests of significance were used.

Results: Squamous cell carcinoma was the most common malignancy (55.8%) followed by mucoepidermoid carcinoma (9.4%). The male to female ratio was 5:4 and the average age was 63 years. The most common site was lower lip (22%), followed by tongue (15%) and parotid salivary gland (13%).

Conclusion: Findings indicated, although squamous cell carcinoma is the most common cancer in this area, mucoepidermoid carcinoma has high rate which might be different from other areas. The lip was the most common location which is similar to most studies around the world. Considering the difference in incidence and mortality of head and neck cancer in less developed versus more developed regions, this kind of research in various populations provides better understanding of cancer for global programming in terms of prevention, detection, and treatment.

3-1-2-Introduction

One of the most significant causes of mortality is cancer [1]. The World Health Organization (2011) estimates that cancers cause more deaths than coronary heart disease or stroke. It is estimated that the burden of cancer will be increasing over the next decades, especially in low-and middle-income countries, and it is anticipated that there will be over 20 million new cancer cases annually in <10 years, by 2025. According to the GLOBACAN in 2012, estimates from 184 countries worldwide indicated 14.1 million
new cases of cancer and 8.2 million deaths [2]. Furthermore, in Iran, according to Mousavi et al., cancer is the third main cause of death and annually more than 30,000 deaths are reported as a result of cancer [3].

Cancers of the head and neck, include lip, oral cavity, oropharynx, hypopharynx, larynx, sinus and nasal cavities, and nasopharynx as well as the pharyngeal tonsils and salivary glands; and represent a considerable burden worldwide. The prevalence of head and neck malignancies differs (by up to twenty times) in different places across the world, with a higher tendency in less developed regions [1, 4-9]. However, data of incidence and mortality are not of high quality, and evidence is limited in developing countries; hence, the exact nature and extent of the problem remain unknown [4-9]. Considering the fact that regular observation of head and neck cancer incidence rates is required for global cancer control strategies, data of each specific region are important for understanding the burden of disease and evaluation of the extent of the problem. Moreover, these data are essential for the allocation of resources for prevention, diagnosis, treatment, and supporting services. The aim of this study was to determine the 10-year incidence of head and neck primary malignant tumors in Kermanshah, in the West of Iran.

3-1-3- Materials and methods

In this retrospective descriptive study, data were collected from pathology records registered in the laboratories of the three leading public hospitals in Kermanshah Metropolitan (West of Iran) from 2002 to 2012. This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences. This research has been conducted in full accordance with the World Medical Association Declaration of Helsinki. Patients' information remained confidential and data were anonymized and de-identified period to analysis.

A total of 3927 case records were evaluated and all cases with the definitive diagnosis of primary oropharyngeal cancer were extracted for the study. Recurrent, metastatic, and premalignant lesions were not included in the study. Age, gender, tumor location, and histopathological type were obtained from patients' records. Information regarding the lesions was registered in specific record sheets according to the International
Classification of Disease for Oncology. The anatomical origin was classified as follows: larynx, oral cavity (lip, tongue, floor of mouth, maxilla, mandible, gingival, and buccal mucosa), oropharynx, sinus and nasal cavities, and salivary glands. The data were analyzed with SPSS software version 18.0. Descriptive analysis was used to describe basic features and means (±SD) were reported and tests of significance were used as appropriate. Significance was set at a P value of 0.05.

3-1-4 Results

Overall 181 cases (4.6%) from 3927 patients were diagnosed with primary malignant head and neck cancers, by histopathological confirmation. The mean age of all patients was 63 years (range: 7–92 years). The mean age of males and females did not differ significantly and was 63.7 (±14.3) years and 62.3 (±16.2) years, respectively [Table 1], [Table 2]. The most common site of involvement was the lower lip (22%) followed by the tongue (15%) and parotid salivary glands (13%) [Figure 1].

Table 3-1-1: The frequency of orofacial cancers in different age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 years</td>
<td>4</td>
<td>2.2</td>
</tr>
<tr>
<td>20-40</td>
<td>11</td>
<td>6.1</td>
</tr>
<tr>
<td>40-60</td>
<td>57</td>
<td>31.5</td>
</tr>
<tr>
<td>&gt;60</td>
<td>109</td>
<td>60.2</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 3-1-2: The number of lesions and mean age

<table>
<thead>
<tr>
<th>Lesion</th>
<th>N</th>
<th>Percent</th>
<th>Mean age(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>101</td>
<td>55.8</td>
<td>65.83 ± 13.27</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>17</td>
<td>9.4</td>
<td>67.53 ± 14.12</td>
</tr>
<tr>
<td>Adeno carcinoma</td>
<td>6</td>
<td>3.3</td>
<td>64.00 ± 12.34</td>
</tr>
<tr>
<td>Adenoidcystic carcinoma</td>
<td>9</td>
<td>5.0</td>
<td>58.22 ± 8.10</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>3</td>
<td>1.7</td>
<td>50.67 ± 11.01</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>1</td>
<td>0.6</td>
<td>68.00 ± 0.0</td>
</tr>
<tr>
<td>Malignant mixed tumor</td>
<td>3</td>
<td>1.7</td>
<td>66.67 ± 3.21</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>2</td>
<td>1.1</td>
<td>53.00 ± 12.72</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>11</td>
<td>6.1</td>
<td>67.18 ± 16.72</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
<td>6</td>
<td>3.3</td>
<td>59.33 ± 9.07</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7</td>
<td>3.9</td>
<td>57.29 ± 8.20</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>8</td>
<td>4.4</td>
<td>44.88 ± 23.50</td>
</tr>
<tr>
<td>Chondro sarcoma</td>
<td>2</td>
<td>1.1</td>
<td>28.00 ± 12.72</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>1</td>
<td>0.6</td>
<td>47.00 ± 0.0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
<td>1.7</td>
<td>75.00 ± 5.56</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>1</td>
<td>0.6</td>
<td>12.00 ± 0.0</td>
</tr>
</tbody>
</table>
In the current study, 89% of cancers were of epithelial origin (with an average age of 66 years), from which most of them were from mucosa (62.3% squamous cell carcinoma (SCC) and 3.7% verrucous carcinoma) and the remainder were from salivary gland epithelium, 6% of bone origin, and 4% of lymphoid origin. SCC was the most common histological type, comprising 62% of epithelial cancers. In the oral cavity, the most affected site of SCC was the tongue (37%). SCC was the most common lesion type in both males and females [Figure 2].
For all malignancy cases (n = 181), 101 were male (56%) and 80 were female (44%); but for SCC cases (n = 101), 60 (59%) were male and 41 (41%) were female.

The most common malignancy of salivary glands was mucoepidermoid carcinoma (MEC), with 17 cases (38%) followed by adenoid cystic carcinoma with 9 cases (20%). The most commonly affected salivary gland was the parotid with 24 cases (54%) followed by minor and submandibular salivary glands. Osteosarcoma with 8 cases (66%) was the most common bone malignancy.

Figure 3-1-2: Gender distribution according to type of cancer
3-1-5- Discussion

In this descriptive study, 181 patients from the archives (n = 3927) of the Pathology Departments of the three main hospitals of Kermanshah, Iran, from 2002 to 2012 were reviewed. The mean age of cases was 63 years with 92% of patients more than 40 years old. These data compare to previous research from a close region (middle of Iran-Isfahan), where the mean age of cases was 52 years, and around one-third of cases (27%) occurred in patients younger than 40 years [10]. A separate previous study from Southeast of Iran in 2014, showed the average age of 53 years, with 18% under 41 years old. These reports of high rates of young cancer patients are more than reported by other studies worldwide [11]. The present findings are more consistent with international trends and may be a result of the larger number of cases in sample presented in this thesis.

The mean age of SCC patients in the present study was 65 years, which compares well with other studies: in Myers et al. and Schantz et al., the mean age at diagnosis for SCC was approximately 60 years [10],[12],[13], and Funk et al. reported 64 years as average [10],[14]. In this study, the mean age of males was slightly higher than females (63 vs. 62 years). Arotiba et al. in Nigeria, reported that males with SCC were relatively younger than females (mean 48 years versus 58 years) [15].

In this study, the male to female ratio in SCC was 1.2–1, and in overall malignancies was the same. Razavi et al. (Iran) reported a male to female ratio of 1.4–1 in Iran [10] and Larizade et al. in 2014 reported that most patients (73%) were male and the overall male to female ratio was 2.74:1 [11]. Moreover, time trend analysis of oral cancer in Iran highlighted disparities between oral cancer incidence trends in males and females over the 6 years from 2005 to 2010 [16]. It seems that not only the higher rates of smoking and alcohol consumption are vital issues, but also sex hormone differences may be the reason for male predilection [17]. However, recently, the incidence of head and neck cancer has increased significantly in women, changes in environmental exposure probably could explain this finding [11].

The greatest majority of malignancy types in this study were SCC (56%) followed by MEC (9%). This result was in accordance with Razavi et al.’s study in Iran, with the majority of SCC (60%) followed by MEC (8%), [10]. Rabiei et al. (2016) in the North of Iran reported that the most common type of cancer was SCC followed by basal cell
carcinoma [18]. Furthermore, in a UAE study (2014), the most prevalent malignant lesion was OSCC followed by MEC [19], however, in one study in Iran, lymphoma was the second most prevalent malignancy (9%) after SCC (77%). A systematic review on 25 articles from Iran showed that the range of SCC was different, from 38% to 97% in different studies; however, none of them were in the West of Iran [11].

In the present study, the most commonly involved site was the lip with more than one out of every four cancers. This finding is in agreement with other reports from Iran [1]. For instance, in 2016 in the North of Iran, Rabiei et al. reported that in the oral cavity (C00–C08), the most common cancers were on the lip (C00), followed by the tongue (C01, C02) [18].

The tongue was the most frequently involved site in the oral cavity (when the lip was excluded), and that was consistent with previous reports [20-22]. However, some studies also reported other sites (rather than the lip and tongue) to be the most involved sites. For example, the gingiva and larynx were reported as most commonly affected sites in recent studies in Iran [10],[11],[23]. Although in this study lip and tongue were most common site of involvement, considering various sites of distribution in different studies, the preventive plans need to focus on all sites of oral cavity. However, due to a considerable lack of understanding of the incidence of oral cancer incidence, especially in populated developing countries, such as Iran [16], the focus on screening for prevention and early detection of lip and tongue cancer is recommended due to its high rate of involvement.[1]

It is reported that about half of salivary gland neoplasms were in the parotid gland. The most common type was mucoepidermoid (38%) followed by adenoid cystic carcinoma (20%). These findings are confirmed by another study Iran (2014), which reported mucoepidermoid (35%) followed by adenoid cystic carcinoma (17%) as the most common types.[11]

Around 90% of all malignancies were epithelial cancers, 6% bony lesions (with majority of osteosarcoma), and 4% lymphomas in accordance with Andisheh Tadbir in Southeast Iran [4]. Furthermore, in the UAE, malignant neoplasms of epithelial origin occurred in 78% of cases followed by malignant neoplasms of glandular origin (13%) and malignant neoplasms of mesenchymal origin (8%).[19]
3-1-6-Conclusion

This kind of research in different populations and countries provides a better understanding of malignant lesions and these data are required for national and global programming in terms of prevention, early detection, and treatment. Oral health professionals should be educated on a comprehensive examination of the head and neck for screening of malignancy. Furthermore, educational programs for the population on the awareness about risk factors and signs of head and neck cancer are highly recommended.

3-1-7-References


3-2-Patterns of the head and the neck cancer in two geographically and socioeconomically different countries

3-2-1-Abstract

Objectives: Cancer distribution is different among the less developed and the more developed regions. This difference could be a barrier for service planning and international action against cancers of the head and the neck. This study compares the distribution of cancers of the head and the neck between two similar-sized populations from the West of Iran and Western Australia.

Materials and Methods: In this retrospective study, de-identified data were collected for a 10-year period from patients diagnosed with head and the neck cancers. Data were obtained from the Western Australia Cancer Registries and from major hospitals in the West of Iran. Rate, age at diagnosis, sex, and site code were included in the data sheet. Descriptive analysis was used to describe the basic features, means (±standard deviation) were reported, and tests of significance were used as appropriate.

Results: In Iran, cancer of the lip, followed by cancer of the major salivary gland, and cancer of the tongue were the three most frequent types of cancers, whereas in Australia, the most frequent types of cancer were the lip followed by the tongue and the tonsil. The distribution of malignancy by site among the patients belonging to different ages indicated that cancer of the lip was the most frequent in both Iran and Australia, except among the patients belonging to the age group of 60–74 years in Iran, where cancer of the major salivary gland had the highest frequency. Both men and women were susceptible to cancers of the head and the neck in the age range of 60–74 years in Iran, whereas in Australia, it was more frequent among men belonging to the age range of 45–59 years and in women above the age of 75 years.

Conclusion: This preliminary study defined differences in orofacial malignancy between Iran and Australia. Further studies in countries with different socioeconomic statuses are recommended.
3-2-2-Introduction

Cancer is a non-communicable disease with a high rate of disability and death, resulting as one of the diseases with the greatest disease burden in the world [1]. Recent global studies estimated an incidence of more than 14 million new cases of cancer in 2012. It is expected that by 2025, more than 20 million cancer patients will be diagnosed annually [1, 2]. Despite progress in prevention methods and treatment options, more than 8 million cancer deaths were reported in 2012 [1, 2]. The World Health Organization (WHO) reported that deaths from cancer have been overtaking all deaths from coronary heart disease or stroke [3]. This increase in the burden of cancer is not only because of lifestyle risk factors, but also because of aging of the global population [1, 4]. The increasing cancer incidence would have a significant effect on the healthcare status and the individuals’ quality of life [4].

Cancers of the head and the neck are a related group of cancers involving the lip and the oral cavity, the pharynx, and the larynx [5]. From an anatomic aspect, the oral cavity and the oropharynx are distinct areas; however, there are some differences between these definitions in different databases. Therefore, complete distinction between the oral cavity and the oropharynx may not be possible [6]. The fifth version of Global Cancer Incidence, Mortality and Prevalence (GLOBACAN) estimated more than 550,000 new cases of cancer of the head and the neck in 2012 that accounted for more than 4% of all the cancers. In addition, it was estimated that more than 300,000 people died worldwide from these types of cancers in that year [2, 7].

The incidence and mortality of each type of cancer varied widely in each region, including cancer of the head and the neck [8]. Recently, an evaluation by GLOBACAN found the highest age-standardized rate (ASR) for cancer of the lip/oral cavity and other pharyngeal cancers in the Southeast Asia region (6.4 and 3.6 per 100,000 people, respectively) and 4.6 and 1.1 ASR World (W), respectively, for the Eastern Mediterranean region; however, this rate was the lowest for the Western Pacific (2.0 and 0.8, respectively)[6].

According to the International Agency of Research on Cancer, the burden of cancer is greater in the low- and middle-income countries. In addition, there was a difference in incidence and mortality of cancer of the head and the neck in less developed versus more developed regions [1, 2]. This difference might be because of the acquisition of cancer-
related risk factors such as tobacco smoking, alcohol consumption, and diet, environmental and occupational risk factors, acquisition of human papillomavirus (HPV) infection, or generally different socioeconomic status [4, 9].

Epidemiological studies on cancer are limited, and some are not of high-quality (especially in developing countries). For example, Iran as a developing country has high-quality data for incidence, but the coverage is less than 10%, and there is no availability of mortality data. Conversely, Australia (a more developed region) has high-quality data with more than 50% coverage for incidence and high-quality vital registration for mortality data [2, 9].

Although many studies have shown wide variations in cancer rates across different parts of the world, to the best of current knowledge, no study has compared in detail the incidence, age, sex of patients, and the sites of head and neck cancer between patients in a developing country (Iran) versus a developed country (Australia), considering that these regions differ geographically, and in terms of climate, behavioral factors and healthcare systems [10-12].

The comparisons of cancer incidence/types across time and geographical areas could provide important insights into the relative burden and cause of disease as a first step toward finding or elucidating cancer pattern variation. This study compared the distribution of all types of cancers of the head and the neck according to the international cancer classification between two similar-sized populations of Western Iran and Western Australia.

3-2-3-Materials and methods:

3-2-3-1-Ethics

Ethical approval for this study was not required, because only completely de-identified data from cancer registries were used in the analysis. In this retrospective study, de-identified data on cancer of the head and the neck for a 10-year period (2002–2012) were obtained from the Western Australia Cancer Registries and from the major hospitals in the West of Iran.
3-2-3-2-Exclusion criteria
Only patients from metropolitan areas were included to eliminate the issue of remoteness from services. Recurrent, metastatic, and premalignant lesions were not included.

3-2-3-3-Definitions
Tumors were classified into the following subsites according to the International Classification of Diseases in Oncology: the tongue; tonsils; oropharynx; the gum and cheek; floor of the mouth; palate and other parts of the mouth; and the internal mucosa of the lip. The age at diagnosis, sex, and site code were included in the data sheet. Descriptive analysis was used to describe the basic features, means (±standard deviation) were reported, and tests of significance were used as appropriate.

3-2-4-Results
Totally, 2400 oral cancers evaluated in this study were from the registries in Western Australia and Iran [Figure 1]. In Iran, cancer of the lip followed by cancers of the major salivary glands and the tongue were the three most frequent cancers, whereas in Australia, cancer of the lip followed by cancers of the tongue and the tonsil were the three most frequent cancer sites [Figure 2]. The distribution of malignancy by site among the patients belonging to different ages indicated that cancer of the lip was the most frequent cancer in both Iran and Australia [Figure 3], except among the patients belonging to the age group of 60–74 years in Iran, where cancer of the major salivary glands had the highest frequency [Figure 4]. The results also showed that both men and women were susceptible for cancer of the head and the neck in the age range of 60–74 years in Iran, whereas in Australia, cancer of the head and the neck was more frequent in men aged 45–59 years, and in women above the age of 75 years [Figure 5].
Figure 3-2-1: (a) The distribution of orofacial malignancy by location of body in Iran (M: male, F: Female, T: total). (b) The distribution of orofacial malignancy by location in Australia (10× difference in scale)
Figure 3-2: (a) The distribution of orofacial malignancy by location in Australia (A) and Iran (I). (b) The distribution of orofacial malignancy in men according to its location in Australia and Iran. (c) The distribution of orofacial malignancy in women according to its location in Australia and Iran.
Figure 3-2-3: The distribution of orofacial malignancy in Australia and Iran among patients belonging to different age groups
Figure 3-2-4: (a) The distribution of orofacial malignancy by location in Australia and Iran (age 30–44 years). (b) The distribution of orofacial malignancy by location in Australia and Iran (age 45–59 years). (c) The distribution of orofacial malignancy by location in Australia and Iran (age >75 years)
Figure 3-2-5- (a) The distribution of orofacial malignancy by sex and age in Australia. (b) The distribution of orofacial malignancy according to sex and age in Iran

3-2-5-Discussion

This study showed the difference in the distribution of cancer of the head and the neck among patients in West of Iran and Western Australia over a 10-year period. It was estimated that the same trends for cancer of the head and the neck in these 10 years.

The results showed that there was a large difference in the distribution of orofacial malignancy by site among the patients in Iran and Australia. The most frequent cancer was cancer of the lip in both Iran and Australia; however, cancer of the lip had a much higher incidence in Australia than Iran (39 and 26% of the total cancers of the head and
the neck, respectively). In addition, this difference was higher in women (42 and 29% from total cancer incidence, respectively). It is speculated that the higher Ultra Violet (UV) index in Australia may cause this difference [10]. In a systematic review on the epidemiology of oral cancer in Iran, cancer of the lip was reported as the second most frequent cancer, just after cancer of the tongue [11].

Moreover, the analysis revealed that cancers of the major salivary glands and the gum were much more frequent in Iran. The difference in the incidence of the salivary gland malignancies might be because of differences in etiological factors. Although the contributing factors of the salivary gland neoplasms are not well recognized, it seems that smoking and alcohol consumption are not the major risk factors; low intake of some nutrients such as vitamin A and C and ionizing radiation might be affecting the development of the tumor [12-14].

This study found cancer of the tonsils to be reported much more frequently in Australia. Some studies reported an increase in incidence of head and neck squamous cell carcinoma (HNSCC) in Australia, especially of the oropharynx, despite a fall in the number of patients diagnosed with other smoking-related cancers. They concluded that the recent increase in HSNCC among younger patients has been attributed to the rising prevalence of HPV infection, and was hypothesized to reflect the changing sexual behaviors during the recent decades [15-18].

In terms of age, most affected people in Iran were in the age group of 60–74 years, whereas in Australia, most women were in the age group of above 75 years, and most men were in the age group of 45–59 years. This increase among younger patients might be attributed to the rising prevalence of HPV infection especially in the tonsils of nonsmoking patients. Recent studies in Australia reported that 63% of HPV-positive oropharyngeal squamous cell carcinomas were found in the age group of 50–59 years, and this was in line with the present studies. It was also reported that HNSCC tumors in men showed higher HPV prevalence than those from women [15].

According to a WHO report on the global tobacco epidemic 2015, Australia and Iran were among the countries with the highest level of achievement for the surveillance of effective tobacco use, strong smoke-free legislation, appropriate cessation support, health warning labels about the danger of tobacco, and anti-tobacco mass media campaigns. In addition,
both had an adult daily smoking prevalence (2013) of less than 15% [19]. However, there was a difference in smoking rates across the States and provinces in a vast country such as Australia or a populated country such as Iran. Moreover, other risk indicators such as socioeconomic disparities might contribute to the differences seen between Iran and Australia in terms of cancer of the head and the neck.

This study had some of the following limitations: data were not collected from all cancer patients in Iran but from only three major hospitals in the metropolitan area of Kermanshah province in the West of Iran because of the lack of availability of data.

Considering the fact that cancer of the lip and oral cavity ranked globally from 16 to 14 between 1990 and 2013 and cancer of the other pharynx from 21 to 18 in terms of absolute years of life lost is an indication that these conditions should be investigated [20].

It is concluded that differences exist in orofacial malignancy among the patients of Iran and Australia in terms of incidence, site of cancer, and age and gender. Further studies to identify the patterns of cancer of the head and the neck and ways for prevention are recommended.

3-2-6-References


Chapter 4

To evaluate oral knowledge and awareness of oral cancer in an adult population and relation with socioeconomic status

This Chapter includes three parts that have been published as the following articles:


4-1- Population Survey of knowledge about oral cancer and related factors in the capital of Iran

4-1-1-Abstract

Objectives: Knowledge about oral cancer risk factors and signs facilitates prevention and early diagnosis, and in turn, increases survival. In this population-based survey, knowledge about oral cancer was assessed in Iran.

Methods: A total of 1800 self-administered questionnaires (collecting sociodemographic data and questions regarding oral cancer risk factors and signs) were distributed through random sampling. Final scores ranged between 0 and 15 for the risk factors and 0–11 for the signs. Scores below the median indicated a low level of knowledge, scores representing the third quartile of correct answers indicated a moderate level of knowledge, and scores representing the upper quartile indicated a high level of knowledge. Statistical tests were used for analysis of knowledge level in different sociodemographic categories.

Results: A total of 1312 participants completed the questionnaires. The average of knowledge scores for risk factors was 5.3 ± 3.0 and for signs was 4.5 ± 2.9. Overall, 75 and 56% respectively were able to identify major risk factors (smoking and alcohol); 23.5% could not define any related signs and symptoms. Dividing scores into quartiles indicated that three out of four people had “low” knowledge about risk factors and 58% had “low” knowledge about signs and symptoms. Females and highly educated people had more knowledge of oral cancer. Significant differences were found between job and level of knowledge (P = 0.001). Conclusion: This survey revealed that public knowledge of oral cancer was not satisfactory in Iran. Efforts should be done to inform and educate people with risk factors, initial clinical presentation, and symptoms, in order to improve prevention and promote early diagnosis.

4-1-2-Introduction

Cancer is a major health problem with an estimation of over 14 million cases around the world, based on a recent international agency of research on cancer report [2] and an expectation to increase to 24 million cases by 2035 [1, 2]. Also, cancer is the third leading
cause of death in Iran [3]. Oral cancer cases (which affect the oral cavity, including the tongue, floor of the mouth, buccal mucosa, gingiva, palate, and lips) are estimated to be over 300,000, representing 2.1% of all new cancers in the latest data [1, 4]. In 2017, oral cavity and pharyngeal cancer has been estimated as the ninth leading cancer type in men in the USA, representing 4% of all new cases of cancers [5]. In recent global data, the incidence of lip and oral cavity cancers was 2.2 and 1.8 in 100,000 for males and females, respectively, and the mortality rate was estimated at 0.68/100000 in Iran [6].

Over 90% of oral cancers arise from the squamous epithelium that results in oral squamous cell carcinomas (OSCCs) [7], which are primarily linked to habits of tobacco, alcohol, and betel use. Other possible factors are human papillomavirus (HPV) infection, family history and genetic factors, diet, and immune-suppression; and ultraviolet light is implicated in lip cancer. Some reports also stated that socioeconomic status (SES) is influential [8, 9].

OSCC survival rates are about 80% if diagnosed at an early stage; however, it is less than 30% in cases with advanced stage diagnosis [10]. Although oral cancer examination can be performed without discomfort to patients due to the accessibility of the oral cavity, lesions are diagnosed at an advanced stage in more than two-thirds of patients; thus, the survival rate is low [11].

In Iran, the 5-year survival of oral cancer patients is less than 50%. This low survival has been thought to be due to the diagnostic delay: the mean time from the onset of symptoms to the final diagnosis, as reported by Sargeran (2015), which is at 7.2 months [12]. They indicated that this delay is higher than that reported in many other studies and suggested that the lack of, or insufficient knowledge about oral cancer, might be one of the reasons [12]. Other studies also mentioned the lack of public awareness of risk factors, signs, and symptoms associated with oral cancer as a potent barrier for the early detection of lesions [10].

Since lifestyle factors such as tobacco and alcohol consumption are also important risk factors, awareness of oral cancer risks might motivate individuals to change their behaviors and reduce their probability of having cancer [10, 13]. Previous studies about oral cancer knowledge in Iran have been conducted in defined groups of people, especially in patients attending dental clinics in different locations (North, Central, South
provinces) with inconsistent results [6, 14-17]. Little is known about public oral cancer knowledge in Iran, and to the best of the author’s knowledge, there is no population-based study in Tehran. The aim of this survey was to determine the public knowledge about oral cancer as a baseline data (in the capital city of Iran) to use for effective primary preventive programs in future.

4-1-3-Methods

This cross-sectional study was conducted in the capital city of Iran, Tehran, from 2016 to 2017 using self-administered questionnaires.

4-1-3-1-Ethics

The research project was approved by the Medical University Ethics Committee. The purpose of the study was fully explained in the questionnaire, and responses to the questions were on a voluntary basis. All participants were assured of anonymity and confidentiality.

4-1-3-2-Questionnaire

The questionnaire was designed with an adaptation of previous valid questionnaires of oral cancer knowledge [18, 19]. Some modifications were necessary in consideration of local cultural, environmental, and language environments. Psychometric properties were evaluated for the modified questionnaire. For face validity, an expert panel was set up consisting of six oral medicine and community oral health specialists for detecting any “ambiguity,” “difficulty,” and “irrelevancy” in phrases and changes applied. Then, the content validity ratio (CVR) and content validity index (CVI) were evaluated, using opinions of 10 experts in oral medicine and community oral health. Items with CVR scores more than 0.59 and CVI scores more than 0.79 were considered as acceptable items. Sixty volunteer participants (invited from patients attending the Dental School for routine dental checkups) completed the questionnaire once, and again 2 weeks later for test-retest reliability (Cronbach’s Alpha Coefficient was 0.81 and Intraclass Correlation Coefficient (ICC) was 0.88). Eventually, the final Persian language questionnaire fitted onto a double-sided plus one single A4 paper sheet stapled together. The purpose of the study and instructions were explained at the beginning of the questionnaire. Participants were requested to use their own knowledge, without any help from online resources. The
questionnaire included demographic and socioeconomic questions (age, gender, education, and employment status). Fifteen questions were about knowledge of risk factors and 11 questions about signs and symptoms of oral cancer, including positive and negative factors. All knowledge questions were close-ended with “yes,” “no,” and “do not know” options.

Box 1 shows the final questionnaire. For analysis of risk factors and signs’ knowledge scores, each correct answer was allocated a score of 1, and for incorrect answers, including “do not know”, zero was assigned. Thus, the final scores for each participant ranged between 0 and 15 for risk factor knowledge and between 0 and 11 for the “sign and symptom” knowledge. Scores were also divided into quartiles. Scores below the median indicate a low level of knowledge, scores representing the third quartile of correct answers indicated a moderate level of knowledge, and scores representing the upper quartile indicated a high level of knowledge [20].

<table>
<thead>
<tr>
<th>Knowledge of risk factors</th>
<th>Knowledge of signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Using tobacco (Smoking cigarettes, pipe, hookah or chewing (+))</td>
<td>1. White or red patches in mouth that do not go away (+)</td>
</tr>
<tr>
<td>2. Being over 60 years of age (+)</td>
<td>2. Non-healing ulcer in the mouth lasting more than a month (+)</td>
</tr>
<tr>
<td>3. Drinking alcohol almost every day (+)</td>
<td>3. Long-lasting swelling or growth in mouth (+)</td>
</tr>
<tr>
<td>4. Spending time in the sever sunlight (+)</td>
<td>4. Small ulcer that healing in two week (−)</td>
</tr>
<tr>
<td>5. Sexually transmitted virus Human papilloma virus (+)</td>
<td>5. Having difficulty or pain in swallowing (+)</td>
</tr>
<tr>
<td>6. Having a family member with mouth or throat cancer (+)</td>
<td>6. Mouth blisters that healing and recurring (−)</td>
</tr>
<tr>
<td>7. Eating spicy foods (−)</td>
<td>7. Hoarseness or change in voice that does not go away (+)</td>
</tr>
<tr>
<td>8. Eating and drinking hot foods (−)</td>
<td>8. Immediate weight loss (+)</td>
</tr>
<tr>
<td>9. Lip and cheek biting habit (−)</td>
<td>9. Discomfort and soreness in mouth that does not go away (+)</td>
</tr>
<tr>
<td>10. Long term using artificial teeth (−)</td>
<td>10. Tooth sensitivity to hot or cold (−)</td>
</tr>
<tr>
<td>11. Being overweight (−)</td>
<td>11. Long-lasting swelling in neck or sore throat that does not go away (+)</td>
</tr>
<tr>
<td>12. Pollution in the air (−)</td>
<td></td>
</tr>
<tr>
<td>13. Allergy to foods and medicine (−)</td>
<td></td>
</tr>
<tr>
<td>14. Not eating enough fruits and vegetables (+)</td>
<td></td>
</tr>
<tr>
<td>15. Untreated tooth caries (−)</td>
<td></td>
</tr>
</tbody>
</table>

Box 1: Final questions
4-1-3-3-Sampling and Participation

According to previous studies in Iran in recent years [6] that considered 16% the percentage of knowledgeable patients (with regard to the risk factors of oral cancer) for the sampling formula, it was estimated that 1000 participants should be sufficient for the survey. Additional sampling was added in order to compensate losses and refusals.

The study population comprised adult people who were parents of public primary school students in Tehran, Iran. Tehran is the capital city with a population of 8,737,510, according to the Iran Census 2016 and is located in the North-central part of the country. The sampling method was a multi-stage stratified random technique. Firstly, from the 22 municipal regions in Tehran, and according to a geographic location in the South, East, West, and North, four regions were selected. Then, considering the average population, one or two schools were randomly selected from each region school list and the parents were invited from each school.

4-1-3-4-Study Design

After obtaining the necessary permits, a total of 1800 invitations were distributed to parents at the school to reach the best sample size. Participants were invited, and if willing to take part, signed the consent form for participation.

Participants were asked to return the filled questionnaire on the same day, but without any time restrictions. Illiterate persons were excluded due to the self-administered nature of the questionnaire. A brochure containing information about oral and lip cancer were provided to all parents in defined schools after finishing the study. This brochure was approved by the panel expert of community oral health and oral medicine specialists in Shahid Beheshti University of Medical Sciences, Tehran, Iran.

4-1-3-5-Outcome variables

Knowledge about oral cancer risk factors, signs, and symptoms were collected through a numerical scale. For each correct response for the components of the questionnaire, one point was assigned. The scores of each question in the risk factor category (ranging from 0 to 15) were summed and signs and symptoms category (ranging from 0 to 11).
4-1-3-6-Independent variables

Sex, age, educational attainment, and employment status were the independent variables. Educational attainment was recorded as years of study successfully completed and then categorized into groups according to the years of study of up to 11 (less than high school diploma), 12 years (high school diploma), or more than 12 years (greater than high school diploma). Age was recorded as date of birth, and then, it was categorized, similar to most of the previous studies [1, 10], to enable more accurate comparison and analysis. It was categorized into groups of 25-35, 35-45, and >45 years. Due to higher rates of oral cancer in older adults (>45), it was hypothesized that they might have different knowledge levels about oral cancer. We did not categorize elderly people were not categorized due to the limited number of participants in this category. Employment status was divided into three groups of unemployed, employed, and others (including students, housewives, and retirees). Then, the employed group were further subdivided into labor and related, employed (public or private), self-employed, and professionals.

4-1-3-7-Statistics

Data were coded and processed by SPSS (version 22) software. The distribution of demographic data and the correct responses to questions were analyzed and tabulated. Statistical tests, including ANOVA and independent sample t-test, and post hoc tests were used for analysis of the level of knowledge in different age groups, gender, education levels, and employment status. P<0.05 was considered statistically significant in the survey.

4-1-4-Results

Out of 1800 parents, 1312 completed questionnaires were returned (overall response rate 72.8%). Overly, 38% of participants were male and 62% were female with the average age of 37.8±9.02. More than 30% of participants had more than a high school diploma (12 years) education. Only 2.1% was unemployed at the time of the study. Table I shows the demographic background of participants. The average of knowledge scores for risk factors was 5.3±3.0 and for signs and symptoms was 4.5±2.9. Figure 1 indicates the frequency of responses for each question about risk factors of oral cancer, and Fig. 2 indicates the frequency of responses for each question about signs and symptoms of oral cancer separately. From all respondents, 75 and 56% of participants were able to
correctly identify two major risk factors (smoking and alcohol), respectively; and 47% mentioned both correctly. Knowledge about genetic, HPV, and fresh vegetables were in the next order. People were less informed about the risk of older age, and sunlight, and had a misconception about hot food and tooth caries as risk factors for oral cancer. Overall, 11.9% could not define any related risk factors. Out of all the participants, 23.5% could not define any related signs and symptoms of oral cancer. However, more than 50% of participants correctly defined mouth swelling, long-lasting ulcers, and white or red patches as a sign of oral cancer; the lowest knowledge was about the change in voice (28%). Also, the highest misconception about early signs of oral cancer was recurrent oral ulcers. The division of participants into quartiles, based on scores, is shown in Table 2. Three out of four people had “low” knowledge about risk, and 58.5% had “low” knowledge about signs and symptoms (less than 50% of the scores) (Table 2). The statistical test indicated that knowledge of oral cancer signs or risk factors was not significantly different between the different age categories. Male participants had less knowledge of oral cancer signs and risk factors (p<0.05). Statistical analysis showed knowledge of oral cancer signs and risk factors was more in highly educated people (P=0.001). In addition, there was a significant difference between different job categories in terms of level of knowledge about signs and risk factors (P=0.001). Post hoc tests (Duncan) showed differences between knowledge about oral cancer risk factors in unemployed and labour and related occupations, and other job categories. Also, the post hoc tests (Duncan) indicated differences between knowledge of signs and symptoms in public/private employed and professionals, and unemployed and labour. Also, the multivariable analysis (General linear models) was performed to test the associated sociodemographic characteristic associated with knowledge of risk factors and signs and symptoms. Initially, all variables are presented in the model. In each step of the variable that has the highest P value of exited and the model is done with other remaining variables. Finally, the last model is a model with keeping the variables with P value <0.25. It showed that the score of knowledge of oral cancer risk factors and signs and symptoms was lower in lower educated people after age and gender adjustment (less than high school diploma: risk factor knowledge (-1.89), signs and symptoms (-2.23); high school diploma: risk factor knowledge (-0.95), signs and symptoms (-1.44). However there were not any significant differences between different age groups (Table 3).
Table 4-1-1: Demographic characteristics of participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-35</td>
<td>318</td>
<td>28.2</td>
</tr>
<tr>
<td>35-45</td>
<td>644</td>
<td>57.1</td>
</tr>
<tr>
<td>&gt;45</td>
<td>165</td>
<td>14.6</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>489</td>
<td>38.3</td>
</tr>
<tr>
<td>Female</td>
<td>788</td>
<td>61.7</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school diploma</td>
<td>373</td>
<td>31.8</td>
</tr>
<tr>
<td>High school diploma</td>
<td>411</td>
<td>35.1</td>
</tr>
<tr>
<td>Greater than high school diploma</td>
<td>388</td>
<td>33.1</td>
</tr>
<tr>
<td><strong>Employment status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>26</td>
<td>2.1</td>
</tr>
<tr>
<td>Labor &amp; related</td>
<td>125</td>
<td>10.0</td>
</tr>
<tr>
<td>Self employed</td>
<td>495</td>
<td>39.6</td>
</tr>
<tr>
<td>Employed (public or private)</td>
<td>370</td>
<td>29.6</td>
</tr>
<tr>
<td>Professional</td>
<td>80</td>
<td>6.4</td>
</tr>
<tr>
<td>Others</td>
<td>155</td>
<td>12.4</td>
</tr>
</tbody>
</table>

Table 4-1-2: Level of knowledge about oral cancer risk factors and signs

<table>
<thead>
<tr>
<th>Knowledge level</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>963</td>
<td>317</td>
<td>11</td>
<td>1291</td>
</tr>
<tr>
<td>Percentage</td>
<td>(74.6%)</td>
<td>(24.6%)</td>
<td>(0.9%)</td>
<td>(100%)</td>
</tr>
<tr>
<td><strong>Sign</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>755</td>
<td>377</td>
<td>104</td>
<td>1236</td>
</tr>
<tr>
<td>Percentage</td>
<td>(58.5%)</td>
<td>(29.2%)</td>
<td>(8.1%)</td>
<td>(100%)</td>
</tr>
</tbody>
</table>
Table 4-1-3: Multivariate analysis for sociodemographic factors and knowledge of oral cancer

<table>
<thead>
<tr>
<th>Dependent variables</th>
<th>Independent Variables</th>
<th>B*</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Knowledge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bound</td>
<td>Bound</td>
</tr>
<tr>
<td>of risk factors</td>
<td>25-35</td>
<td>-.201</td>
<td>.538</td>
<td>-.843</td>
<td>.441</td>
<td></td>
</tr>
<tr>
<td></td>
<td>35-45</td>
<td>.257</td>
<td>.380</td>
<td>-.316</td>
<td>.829</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;45</td>
<td>0a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-.751</td>
<td>.000</td>
<td>-1.153</td>
<td>-.350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school diploma</td>
<td>-1.899</td>
<td>.000</td>
<td>-2.370</td>
<td>-1.428</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>-.956</td>
<td>.000</td>
<td>-1.380</td>
<td>-.532</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greater than high school diploma</td>
<td>0a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knowledge</td>
<td>25-35</td>
<td>-.358</td>
<td>.266</td>
<td>-.990</td>
<td>.274</td>
<td></td>
</tr>
<tr>
<td>of signs and</td>
<td>35-45</td>
<td>.139</td>
<td>.628</td>
<td>-.423</td>
<td>.701</td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td>&gt;45</td>
<td>0a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-.630</td>
<td>.002</td>
<td>-1.027</td>
<td>-.232</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school diploma</td>
<td>-2.230</td>
<td>.000</td>
<td>-2.696</td>
<td>-1.763</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>-1.444</td>
<td>.000</td>
<td>-1.862</td>
<td>-1.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td>greater than high school diploma</td>
<td>0a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig 4-1-1: Knowledge about oral cancer risk factor in each question
Figure 4-1-2: Knowledge about oral cancer signs in each question

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling in neck</td>
<td>458</td>
<td>189</td>
<td>526</td>
</tr>
<tr>
<td>Tooth sensitivity to hot or cold</td>
<td>127</td>
<td>552</td>
<td>452</td>
</tr>
<tr>
<td>Discomfort in mouth</td>
<td>580</td>
<td>143</td>
<td>436</td>
</tr>
<tr>
<td>Immediate weight loss</td>
<td>393</td>
<td>809</td>
<td>459</td>
</tr>
<tr>
<td>Change in voice</td>
<td>332</td>
<td>307</td>
<td>504</td>
</tr>
<tr>
<td>Recurrent mouth blisters</td>
<td>333</td>
<td>188</td>
<td>459</td>
</tr>
<tr>
<td>Swallowing problem</td>
<td>514</td>
<td>348</td>
<td>467</td>
</tr>
<tr>
<td>Small healing ulcer</td>
<td>120</td>
<td>656</td>
<td>362</td>
</tr>
<tr>
<td>Mouth swelling</td>
<td>783</td>
<td>78</td>
<td>928</td>
</tr>
<tr>
<td>Long lasting ulcer</td>
<td>672</td>
<td>160</td>
<td>349</td>
</tr>
<tr>
<td>White or red patches</td>
<td>639</td>
<td>89</td>
<td>463</td>
</tr>
</tbody>
</table>
4-1-5-Discussion

This cross-sectional study was conducted on 1312 parents of public primary school students. This group of people was chosen because, firstly, public primary schools are almost evenly distributed in Tehran and stratified sampling is logical and convenient; secondly, this group of people will potentially be engaged with the next-generation health. The results of the present study showed that the level of oral cancer literacy is not satisfactory in a defined population in Iran. However, regarding the two main risk factors for oral cancer: tobacco and alcohol consumption, three out of four people identified tobacco, and more than half of the population could define alcohol as risk factors. Little was known about aging and sun exposure association with oral cancer. In terms of signs and symptoms, participants were more informed about mouth swelling and long-lasting ulcers. Almost one out of four could not define any related signs and symptoms of oral cancer.

In Iran, most of the recent studies on awareness of oral cancer risk factors and signs were on dental patients in limited geographic locations, with different sample sizes ranging from 320 to 783 people. The most correct answer about risk factors in those previous studies was about tobacco, ranging from 51 to 79%, which is comparable with the present study [6, 14, 15, 17]. Only Pakfetrat et al. (2010) in the Northeast of Iran showed that about 16% of dental patients were aware of the link between oral cancers and smoking. It seems that this difference is due to the open-ended structure of Pakfetrat’s study questionnaire [16]. Acceptable knowledge of tobacco as a risk factor might be related to high levels of achievement in effective tobacco use surveillance and health warning labels about the danger of tobacco in Iran, according to the WHO report [21].

All studies in Iran indicated a relatively lower knowledge of alcohol, ranging from 43 to 69% [6, 14, 15], except in Pakfetrat’s study that reported around 7% awareness [16]. Questions about consumption of fruit and vegetables were only mentioned in two studies with 36–40% knowledge, the same as results [6, 17]. None of these studies in Iran mentioned HPV as a risk factor in the questionnaire, this may be due to restrictions against the cultural background, and just one study mentioned viral infection generally (correct answer = 48%) [17]. The results of this study indicated that 47% of participants were informed about this virus. The surveys mentioned poor knowledge of initial signs; however, according to the results of those surveys, it is obvious that people are more
informed about the association between chronic ulcers and oral cancer than white or red patches. For instance, Andishe Tadibar et al. in the South of Iran reported chronic ulcers without pain (56.7%) as the most correct answers about related signs of oral cancer [15]. Regarding the relation between early diagnosis and treatment, raising knowledge of initial signs of oral cancer in Iran is essential. Association between sex, age, and awareness was inconsistent in previous studies in Iran; but most studies reported the relation between education level and awareness similar to this study [15, 17]. In the current study, a difference was found in knowledge among different employment status. Pakfetrat et al. (2010) also reported significant differences among people with different jobs regarding knowledge about oral cancer [16]. However, in a recent study in Iran, Razavi et al. (2015) could not define a significant difference among jobs [6]. That might be due to the different categorization for employment in different study.

Also, previous studies in recent years indicated that knowledge levels of oral cancer were not high. However, greater public awareness of tobacco as a risk factor was reported compared with other potential risk factors, especially alcohol consumption [11, 22-24]. These results are relevant in developed countries like Australia as well. In Australia, Dost et al. (2016) evaluated knowledge of oral cancer risk factors among 1498 high-risk Australians and found that participants thought smoking (87.5%) to be the most common risk factors associated with oral cancer, while only half of the respondents were aware of the risk from alcohol consumption [8]. Also, public knowledge about preventable risk factors, like HPV, is considerably low. For instance, a study in Australia (2015) showed only 23% of participants were aware of HPV infection and oral cancer [1]. However, high HPV vaccine coverage in countries like Australia could potentially lower oral cancer prevalence, while there is no national immunization program for HPV in Iran.

Although most studies confirm the association between advanced stage oral cancer and mortality [12], most surveys from around the world reported low levels of public knowledge regarding the clinical presentation of oral cancer [23]. Hassona et al. in 2015 surveyed 1200 dental patients in Jordan and reported 24% of participants had no knowledge about any signs of oral cancer, and only around 44, 41, and 33% were able to correctly identify white/red patches, a long-standing swelling, and a non-healing ulcer, respectively, as possible signs of oral cancer [9]. In Australia (2015), the most recognized sign was non-healing ulcers (49%) and only around 20% agreed with the question oral
cancer may present as a lump in the neck [1]. Posorski et al. (2014) in a study on awareness of signs (among senior citizens in Illinois, USA) reported better results, but the study population was only 93 people. The most correct answer about early signs in that study was chronic ulcers (74%). Also, more than half of participants had knowledge of white patches and swelling in the throat or neck [18].

Education level was related to awareness in most surveys, in line with the current study [10, 18]. Hertramf et al. in a study in North Germany found differences in knowledge levels between people with different education levels and occupation, and concluded that education, employment, and income are intertwined indicators. It means that a higher level of education results in better employment and higher income [11]. However, some studies could not find any relation between education and awareness [9]. It might be due to the role of available online resources for general health learning.

Although attention to oral hygiene and caries prevention is important, misconception about the association to oral cancer could be scaremongering. Razavi et al. in 2015 reported about half of the studied population believes poor oral hygiene to be a risk factor for oral cancer in Iran [25]. Dost et al. in 2016 reported more than 60% of Australians mentioned poor oral hygiene as a risk factor for oral cancer, just after the danger from smoking [8]. They discussed that this misconception might be due to a belief that cleanliness is associated with good health. Although the questions were slightly different, in the current study, where more than 40% agreed with tooth caries as an associated risk factor for oral cancer. Also, people should be informed that any lesion in the oral cavity is not a sign of cancer. The present study showed more than one out of three participants thought recurrent blisters could be signs of oral cancer.

In this study, persons with limited literacy: people who are not able to read/write or they did not have any years of schooling were excluded. Only 11 people (< 0.01%) did not complete the questionnaire due to their limited literacy; therefore, it did not affect the results. Also, the sample selection was from parents of primary school students, so senior adults were not included in this study, and this was considered to be a limitation.

The focus of the present study was oral cancer. Although assessing other cancer knowledge is also important, assessing knowledge of all cancers in one study would need an extensive questionnaire and could thus result in much lower response rates and lower
accuracy. Also, knowledge about oral cancer signs is very important due to easy visualization by people, and that it is not matter of concern in most of the other cancers. However, further studies to assess other cancer knowledge and compare that with oral cancer knowledge are recommended.

The unsatisfactory level of knowledge in this study, which revealed public health policy makers in Iran, should conduct an active educational strategy for improving knowledge about cancer, such as the ability to recognize risk factors and clinical presentation of suspected lesions, promotion of preventive behaviors, and enhancement of early detection of cancer in primary care, along with global cancer education.

4-1-6- Conclusion

Considering the results of the present study, it is obvious that knowledge about tobacco is higher than other potential risk factors. It is a deficiency in knowledge about other risk factors of oral cancer and there is very low awareness of initial signs of oral cancer which is not acceptable in Tehran, the capital city of Iran. Education about oral cancer risk factors especially diet and HPV virus and as well as education about all signs of oral cancer is the first priority. It will be the most feasible approach for change, and efforts should include population-level education and information about habitual risk factors and initial signs and symptoms in order to promote early diagnosis.

4-1-7-References


15. Tadbir AA, Ebrahimi H, Pourshahidi S, Zeraatkar M (2013) Evaluation of levels of


**Supplementary tables and figures:**

Table 4s-1: post hoc test (Duncan), for difference in knowledge about oral cancer risk factors according to the occupation

<table>
<thead>
<tr>
<th>Occupation</th>
<th>N</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unemployed</td>
<td>26</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labor &amp; related</td>
<td>123</td>
<td>4.4</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>153</td>
<td>5.2</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Self employed</td>
<td>485</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed (public/private)</td>
<td>366</td>
<td></td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Professional</td>
<td>80</td>
<td></td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Sig</td>
<td></td>
<td>0.09</td>
<td>0.07</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Table 4s-2: Difference in knowledge about oral cancer signs and symptoms according to the occupation (post hoc test)

<table>
<thead>
<tr>
<th>Occupation</th>
<th>N</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unemployed</td>
<td>26</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Labor &amp; related</td>
<td>116</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>Self employed</td>
<td>466</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Others</td>
<td>143</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Employed (public/private)</td>
<td>351</td>
<td></td>
<td>5.0</td>
</tr>
<tr>
<td>Professional</td>
<td>78</td>
<td></td>
<td>5.1</td>
</tr>
<tr>
<td>Sig</td>
<td></td>
<td>0.07</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Figure 4s-1: (a, b): Mean and confidence interval of knowledge about signs and risk factors in different level of education.
4-2- Disparities in oral cancer awareness: A population survey in Tehran, Iran

4-2-1- Abstract

Oral cancer is a life-threatening disease with low survival rates, especially when diagnosed in an advanced stage. Lack of awareness about this cancer among the population is proposed as a possible reason for this diagnostic delay. The aim of this study was to evaluate oral cancer awareness, as well as its association with sociodemographic status in Tehran. In this cross-sectional population-based survey, 1800 self-administered questionnaires (collecting sociodemographic data, questions regarding oral cancer awareness and the source of information) were distributed through multistage stratified random sampling. Scores for questions ranged from 0 to 4, and totals were summed. The outcome of responses was also analyzed separately. In total, 1312 questionnaires (from 788 females and 489) were available for analysis (37.8 ± 9.02 years). Only 30% of the respondents were aware of oral cancer. The average score for awareness was 1.09 ± 1.6 with no significant differences between age groups and genders. Of the participants, 6.5% had complete awareness about oral cancer. A significant difference was found between mean scores in different levels of education and occupation (p = 0.0001). From 585 responses to the “source of information” question, “public media” was the most important source (almost 50%). Only 2% mentioned “dentists” as a source of information. This study indicated an alarming lack of oral cancer awareness and literacy in Tehran, Iran. Dentists should be obliged to practice their pivotal role in informing the public about oral cancer.

4-2-2- Introduction

Oral cancer, including malignancies of the tongue, floor of the mouth, buccal mucosa, gingiva, palate, and lips [1], represented more than 2% of all newly diagnosed cancers, and 1.8% of estimated cancer deaths in recent data [2]. In Iran, as a developing middle-income country, a recent WHO report (2012) showed oral cancer (CD00-08) incidence to be 2.2 and 1.8 age-standardized rate per population (ASR/P, per 100,000 population) for males and females respectively [3]. Consistent with global trends, previous research in Iran (based on national registry data), also reported an increasing age-standardized rate of head and neck cancer over time [4]. Squamous cell carcinomas (SCC) of the lip and
oral cavity comprise 90–95% of all of these malignancies [5], and tobacco, alcohol, and betel use known risk factors.

Oral cancer has poor prognosis and little improvement in the 5-year survival [6]. In fact, oral cancer has been reported to have one of the lowest 5-year survival rates of all cancers [7]. Generally, survival rates are decreasing with the advancement of the stage, and metastasis to distant organs in late stages of squamous cell carcinomas leads to drastic lowering of survival rates [8, 9]. Although the easy visual access to the oral mucosa theoretically contributes to early detection, the proportion of cases diagnosed at an early stage is still lower than 50% [1, 10]. Sargeran (2015) estimated that diagnostic delay; the mean time from onset of symptoms to the final diagnosis for oral cancer was 7.2 months in Iran which is high. This diagnostic delay might be due to general lack of awareness about this cancer, not only among the population, but also among health care professionals [11].

Previous reviews reported that the greatest burden of oral cancer falls upon people from the most deprived communities [2], and oral cancer risk indicators included low occupational social class, lower income, and low educational attainment [12]. This disparity might be associated with less access to health care, less probability of being insured, and more advanced stages at presentation in patients of lower socioeconomic class. A lack or insufficient knowledge of oral cancer could also be proposed as a possible reason for such outcome differences [11].

Public oral cancer literacy, especially awareness about the nature and the importance of early detection and prevention, is an important issue. People should be informed about small oral lesions pre-cursing oral cancer, and that early treatment of these lesions can prevent development into oral cancer, or improve the chances of cure [13, 14]. This awareness leads to seeking treatment at the early stages of the disease [9], reduces the rate of functional and cosmetic impairment of treatment, improves the prognosis, and reduces mortality and morbidity, and in turn has significant impact on the quality of life [9, 14].

There are multiple population-based and non-population-based studies assessing the levels of awareness and knowledge of symptoms and risk factors of oral cancer [8, 9, 14, 15]. Results of these studies vary widely, reflecting environmental, geographic, and sociodemographic differences. However, very few studies have examined the awareness
of early detection and prevention as important elements of oral cancer literacy [14]. A review of studies reporting oral cancer awareness and literacy in Iran are rare, and, were carried out among dental patients [16-19]. Although Tehran is the second-largest metropolitan area in the Middle East, no studies on this topic (carried out in this population) could be found. The recent study is about oral cancer signs and symptoms and risk factors in Tehran, Iran [20].

Against the background of recent recommendations to identify vulnerable groups in Iran (in order to reduce the burden of oral cancers) [4], the aim of this present study, following a previous study about oral cancer signs and symptoms and risk factors’ knowledge, was to assess the general awareness of oral cancer and associations with sociodemographic status in the Tehran population.

4-2-3-Methods

4-2-3-1-Sampling and design

This cross-sectional study was conducted in the capital city of Iran, Tehran, in 2016–2017 using self-administered questionnaires. A multistage stratified random sampling approach was used to select a representative sample of the target population. The target population was the parents of primary school students. This group was selected due to the even distribution of public primary schools in the city and is also seen as an important target group as they are parents of young children, and oral health awareness is vital. Firstly, the 22 municipal regions in Tehran were stratified according to geographical location (South, North, East, and West), and then 4 regions (1 from each geographical area) were randomly selected. Secondly, one or two schools were then randomly selected from each of the four regions. In each school, a grade was randomly selected and the invitation letter sent for all the parents in that grade. Resulting from this selection, a total of 1800 parents were invited to participate in the study. One invitation letter was sent home with each student, so both parents had a chance to see the letter.

4-2-3-2-Study protocol

Participants answered a self-completed questionnaire. The purpose of the study was fully explained in the questionnaire. All participants were assured of anonymity and
confidentiality and completion of questionnaires was on a voluntary basis. Included were questions on sociodemographic factors (age, gender, education, and occupation) as well as question about family history of cancer and four questions on oral cancer awareness (adopted from previous studies) [13, 14, 18]. A panel of experts in oral medicine and community dentistry confirmed the clarity of questions in the local language, prior to the onset of the study. The overall awareness of oral cancer was assessed by the responses to the following questions (with a dichotomous outcome, yes or no): “Have you ever heard of oral cancer?” and “Is oral cancer a contagious disease?” Two questions (also with a dichotomous outcome) to measure oral cancer literacy has been used: “Are you aware that a small lesion in your mouth can develop into oral cancer?” and “Are you aware that early treatment of oral lesions can prevent them from developing into oral cancer?” An open-ended question about the source of information was also added. Participants were requested to return all completed questionnaires on the same day, and were to answer all questions without seeking information from online resources. A pilot study was conducted before finalizing the questionnaire, on a random sample of 60 patients attending a dental school clinic, to ensure clarity and practicability of the questions. Measuring scale reliability of questionnaire showed Cronbach’s alpha coefficient was 0.81 (reliability coefficient of 0.70 or higher is considered” acceptable”). Participants mentioned the previous history of cancer excluded from the study (2 people).

4-2-3-3-Outcome variables

Scores were allocated to responses: for three questions, a score of 1 was allocated for “yes” and zero for “no.” However, the question on the contiguous nature of oral cancer had reverse scoring, with a score of 1 for “no” and zero for “yes.” These outcome variables were analyzed through a numerical scale. We summed the scores of all questions for each participant (ranging from 0 to 4.) The outcome of each question was also analyzed separately.

4-2-3-4-Explanatory variables

Socioeconomic status, including educational attainment and occupation, was the explanatory variable. Educational attainment was recorded as years of study successfully completed. Occupation was recorded as unemployed, employed, or others (including students, housewives, and retired). The employed groups were further subdivided into
labor and related, employed (public or private), self-employed, and managerial/professionals.

4-2-3-5-Covariates

Covariates included were gender and age. Age was recorded as year of birth.

4-2-3-6-Other variables

The source of information was also determined through an open-ended question, and based on responses, the following categories were created: public media, family and friends, medical group, dentists, self-study and others.

4-2-3-7-Statistical analysis

Firstly, descriptive data were analyzed and tabulated for demographic information and positive responses to outcome variables. Then, statistical tests, including chi-square test, ANOVA and independent sample t-test, post hoc test, and general linear model regression were used for analysis of variables in different sociodemographic groups. $P < 0.05$ was considered statistically significant in the survey. To investigate the hypotheses of the regression model, the studentized residual was calculated. The values ranged from -3 to +3, which indicated that there were no outliers. The Q-Q plot graph was plotted for studentized residual values indicating the approximate normality of the residuals. SPSS (version 22) software was used for data processing.

4-2-4-Results

A total of 1800 questionnaires were distributed. Of these, 1312 were available for analysis. The study population consisted of 788 female and 489 male participants with the average age of $37.8 \pm 9.0$. The sociodemographic characteristics of respondents are summarized in Table 1. The majority of participants had education up to high school diploma level. Although only 26 people were unemployed at the time of study, 469 (40%) had a history of unemployment in their career journey (Table 1).

Table 2 summarizes the response to each question separately. Only 30% of the respondents had heard about oral cancer, and gender and age had no significant
associations with this awareness (p = 0.11 and p = 0.59 respectively). Almost 30% of participants had a misconception about the non-communicable nature of the disease, with significant differences between genders and age groups: higher in females and age group 35–45 (p = 0.02, p = 0.01 respectively). Almost 85% of participants were not aware of the possibility of small oral lesions developing into oral cancer, but there was no significant difference between genders and age groups (p = 0.283, p = 0.336 respectively). However, around 60% of the study population stated that early treatment of oral lesions could prevent these from developing into oral cancer, and there were no significant differences between male and female participants (p = 0.12), but a significant difference was found in age group 35–45 (p = 0.01). More educated participants had higher awareness levels (p = 0.0001). Also, responses to the four questions were significantly different between employed and unemployed participants (p = 0.0001).

The mean score for awareness was 1.62 ± 1.09. Some 15% of participants did not answer correctly to any questions and had no knowledge about oral cancer; only 6.4% had complete awareness about oral cancer. There was no significant difference in mean score in gender and age groups; however, statistical tests indicated significant differences between mean scores in different levels of education and occupation (p = 0.0001) (Table 1). The post hoc test (Duncan) results for education showed the more the education the higher the score of oral cancer awareness. Also, the post hoc test showed people with managerial/professional jobs had more awareness about oral cancer, and unemployed and labor and related groups had significantly lesser knowledge. Using a general linear model for multivariate analysis demonstrated the significant effect of education and occupation (Table 3). Initially, all variables are presented in the model. In each step of the variable that has the highest P value of p, exited and the model is done with other remaining variables. Finally, the last model is a model with keeping the variables with P value < 0.25. The regression coefficient is shown in Table 4. Results showed that score of awareness about oral cancer was lower in lower educated people after age and gender adjustment. (less than high school diploma: (-0.46); high school diploma: (-0.37).

It is obvious that people with a university degree and employment (public or private) and managerial/professionals had more information about oral cancer after controlling other factors (Table 4). Summarized data about source of information indicated that more than half of participants stated that they did not have any information or left this question
blank. From 585 responses to this question, public media with 315 (51%) responses were most important source of information, followed by self-study (14.5%) and family and friends (12.3%). Only 5.8% mentioned that medical group and 2.5% mentioned that dentists were a source of their information.

Table 4-2-1- Distribution of knowledge score among socio- demographic groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Frequency N (%)</th>
<th>Knowledge score Mean(SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (n= 1277)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>489 (38.2%)</td>
<td>1.60±1.09</td>
<td>p=0.52</td>
</tr>
<tr>
<td>Female</td>
<td>788 (61.7%)</td>
<td>1.64±1.09</td>
<td></td>
</tr>
<tr>
<td><strong>Age (n= 1127)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-35</td>
<td>318 (28.2%)</td>
<td>1.60±1.07</td>
<td>p=0.41</td>
</tr>
<tr>
<td>35-45</td>
<td>644 (57.1%)</td>
<td>1.68±1.12</td>
<td></td>
</tr>
<tr>
<td>&gt;45</td>
<td>165 (14.6%)</td>
<td>1.59±1.01</td>
<td></td>
</tr>
<tr>
<td><strong>Education (n= 1172)</strong></td>
<td></td>
<td></td>
<td>p=0.001</td>
</tr>
<tr>
<td>Less than high school diploma</td>
<td>373 (31.8%)</td>
<td>1.36±0.97</td>
<td></td>
</tr>
<tr>
<td>High school diploma</td>
<td>411 (35.1%)</td>
<td>1.57±1.07</td>
<td></td>
</tr>
<tr>
<td>More than high school diploma</td>
<td>388 (33.1%)</td>
<td>1.97±1.17</td>
<td></td>
</tr>
<tr>
<td><strong>Occupation (n= 1251)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self employed</td>
<td>495 (39.6%)</td>
<td>1.59±1.00</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Employed(Public/Private)</td>
<td>370 (29.6%)</td>
<td>1.77±1.13</td>
<td></td>
</tr>
<tr>
<td>Labor &amp; related</td>
<td>125 (10%)</td>
<td>1.34±1.07</td>
<td></td>
</tr>
<tr>
<td>managerial and Professional</td>
<td>80 (6.4%)</td>
<td>2.11±1.20</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>26 (2.1%)</td>
<td>1.15±1.00</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>155 (12.4%)</td>
<td>1.46±1.16</td>
<td></td>
</tr>
</tbody>
</table>
Table 4-2: Distribution of response rate to each awareness question

<table>
<thead>
<tr>
<th>Outcome variables</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heard about oral cancer (n= 1280)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>394</td>
<td>30.7</td>
</tr>
<tr>
<td>No</td>
<td>886</td>
<td>69.2</td>
</tr>
<tr>
<td><strong>Is oral cancer contagious (n= 1132)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>362</td>
<td>32.0</td>
</tr>
<tr>
<td>No</td>
<td>770</td>
<td>68.0</td>
</tr>
<tr>
<td><strong>Awareness about lesions developing oral cancer (n= 1259)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>187</td>
<td>14.8</td>
</tr>
<tr>
<td>No</td>
<td>1072</td>
<td>85.1</td>
</tr>
<tr>
<td><strong>Awareness of early treatment prevent oral cancer development (n=1288)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>776</td>
<td>60.2</td>
</tr>
<tr>
<td>No</td>
<td>512</td>
<td>39.7</td>
</tr>
</tbody>
</table>
Table 4-2-3-General linear model results of explanatory variables effect

<table>
<thead>
<tr>
<th>Source</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Model</td>
<td>79.15(^a)</td>
<td>10</td>
<td>7.91</td>
<td>6.70</td>
<td>.0001</td>
</tr>
<tr>
<td>Intercept</td>
<td>838.69</td>
<td>1</td>
<td>838.69</td>
<td>710.80</td>
<td>.0001</td>
</tr>
<tr>
<td>Age</td>
<td>5.53</td>
<td>2</td>
<td>2.76</td>
<td>2.34</td>
<td>.09</td>
</tr>
<tr>
<td>Sex</td>
<td>3.57</td>
<td>1</td>
<td>3.57</td>
<td>3.03</td>
<td>.08</td>
</tr>
<tr>
<td>education</td>
<td>30.83</td>
<td>2</td>
<td>15.41</td>
<td>13.06</td>
<td>.0001</td>
</tr>
<tr>
<td>Occupation</td>
<td>13.44</td>
<td>5</td>
<td>2.69</td>
<td>2.28</td>
<td>.04</td>
</tr>
<tr>
<td>Error</td>
<td>1172.83</td>
<td>994</td>
<td>1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4057.00</td>
<td>1005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected Total</td>
<td>1251.98</td>
<td>1004</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) R Squared = .063 (Adjusted R Squared = .054)

Table 4-2-4-Predictors of awareness of oral cancer among participants in Iran

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B#</th>
<th>Std. Error</th>
<th>t</th>
<th>P.Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>1.83</td>
<td>.14</td>
<td>12.27</td>
<td>.0001</td>
<td>1.53 - 2.12</td>
</tr>
<tr>
<td>Age 25-35</td>
<td>-.14</td>
<td>.12</td>
<td>-1.20</td>
<td>.23</td>
<td>-.38 .09</td>
</tr>
<tr>
<td>Age 35-45</td>
<td>.02</td>
<td>.10</td>
<td>.23</td>
<td>.81</td>
<td>-.18 .23</td>
</tr>
<tr>
<td>Age &gt;45*</td>
<td>0*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>-.13</td>
<td>.07</td>
<td>-1.74</td>
<td>.08</td>
<td>-.28 .01</td>
</tr>
<tr>
<td>Female*</td>
<td>0*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>-.46</td>
<td>.10</td>
<td>-4.63</td>
<td>.0001</td>
<td>-.66 -.26</td>
</tr>
<tr>
<td>High school graduate</td>
<td>-.37</td>
<td>.08</td>
<td>-4.31</td>
<td>.0001</td>
<td>-.54 -.20</td>
</tr>
<tr>
<td>University degree*</td>
<td>0*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self employed</td>
<td>.14</td>
<td>.11</td>
<td>1.31</td>
<td>.19</td>
<td>-.07 .36</td>
</tr>
<tr>
<td>Public/ private employed</td>
<td>.24</td>
<td>.12</td>
<td>2.00</td>
<td>.04</td>
<td>.00 .48</td>
</tr>
<tr>
<td>labor &amp; related</td>
<td>.13</td>
<td>.15</td>
<td>.87</td>
<td>.38</td>
<td>-.164 .42</td>
</tr>
<tr>
<td>Professional</td>
<td>.56</td>
<td>.17</td>
<td>3.23</td>
<td>.001</td>
<td>.221 .90</td>
</tr>
<tr>
<td>unemployed</td>
<td>.02</td>
<td>.28</td>
<td>.07</td>
<td>.94</td>
<td>-.53 .57</td>
</tr>
<tr>
<td>Others*</td>
<td>0*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) This parameter is set to zero because it is redundant.

*: reference #Coefficient of estimate
4-2-5-Discussion

In the current study, oral cancer general awareness in a defined population was evaluated in Iran. Results indicated that general awareness of oral cancer is unsatisfactory. Only a minority of the population had complete awareness of oral cancer and only one third had heard about oral cancer. Most importantly, only 15% of the population was aware of the development of oral cancer from small oral lesions, that in turn could result in late diagnosis. One third of respondents had misconceptions about the non-communicable nature of oral cancer that might affect the quality of life of cancer patients. Education and occupation had a direct relation to oral cancer awareness.

This study has some limitations. The parents of private primary school students were not included in the sampling. However, around 85% of students in Tehran are in public schools; therefore, sampling from these schools is quite representative of this target population. Also, private schools are not homogenously distributed in the city (there are quite a few private school in a limited area), and it was considered that these are not a good representation of the community, due to the different socioeconomic status. Adults who do not have primary school children and those more at risk for oral cancer would be older adult, were not included, as this cancer is strongly associated with age. It should be noted that accessing a representing sample of adults for these kinds of studies is very difficult. However, the sampling design somewhat allowed the generalizability of the results to Tehran middle-aged adults, and middle-aged people are the majority of the population in Iran [21], and parents having children have a more influential effect on community health. They not only influence their own health, but also that of their children. The other limitation of the present study was the exclusion of illiterate people as a result of using self-administered questionnaires. However, only 11 people did not participate due to illiteracy. Also, there is no information about non-responders considering the volunteer-based design of study.

In a recent study in the central part of Iran in 2015, more than half of patients were aware about mouth cancer, which is higher than the current study. However, they included adult patients who had attended public and private dental clinics, and that might affect the results [22]. In addition, they reported that 34% learned from mass media and almost 8% reported doctors and dentists as the sources of information, which is almost similar to the
current study [22]. In another study in Iran, results indicated that 69% believed that early
detection and diagnosis of oral cancer would lead to better prognosis or improvement;
that is comparable with the current results as presented in this thesis. Pakfetrat et al. also
asked about contagiousness of oral cancer, but unfortunately, they did not report separate
results for this question [18]. In a large study with almost 800 participants attending a
dental school in the southern part of Iran, results revealed only 32% of participants had
heard about oral cancer, similar to the current results. They also reported 54% of those
aware of oral cancer, learned from public media, the same as the current study. They
reported around 15% learned from their dentist; that is very different from this study. It
seems that the closed-ended nature of this question in Andishe Tadibar study versus open-
ended question in this study affects the results [17]. However, the medical and dental
group altogether was about 9% of source of information. The reason why dentists did not
inform their patients might be due to low levels of knowledge about oral cancer in Iranian
dentists [23]. Razavi et al. reported that only 34% of dentists in the central part of Iran
were knowledgeable about oral cancer [24]. Sarabadani et al. reported around 60% of
dentists in the northeast of Iran believed that they had acquired the essential skills for oral
cancer screening, and only about half of them claimed that their knowledge of oral cancer
is up to date [25].

Al-Maweri et al. in 2015 in the neighbouring country of Saudi Arabia used four questions
for assessing general awareness of oral cancer, almost the same as the current study, and
reported 53% of participants heard about oral cancer, which is better than the results than
the current study, but still showed a low level of awareness. Also, regarding
misconceptions about the contagious nature of oral cancer, they reported only 43% of the
population knew that oral cancer is non-communicable. In addition, their results showed
that more than half of participants learned from the media, which is the same as the current
study. Dentists were as low as 12% of source of information in the Al-Maweri study [13].

In a multicultural deprived area in East London Al-Kabbi et al. in 2015, surveyed oral
cancer literacy in an adult population through multistage stratified random sampling and
revealed that around 26% of the population was aware that a small lesion in the mouth
can develop into oral cancer. They confirmed the significant association between
educational attainment and socioeconomic position and level of awareness, even after
adjusting for age, gender, and ethnicity [14]. Also, they reported around 40% were aware
that early treatment could prevent a lesion from developing oral cancer. Those in professional and managerial occupations were more informed, even after adjustment for other demographic items. In the current study, results showed that only 15% of participants was aware about oral lesions developing into cancer; that showed less awareness in the population of the present study [even compared to people in a deprived area in London). However, almost 60% of the population had awareness about early treatment, and that is comparable with the UK study. Also, occupation and education were associated with this awareness in the current study, confirming the findings from the UK [14]. However, the results of regression analysis were shown. R square and adjusted R square are very small, so the model should be used with caution for prediction.

In a study in Australia in 2016, low levels of awareness [around 50%) have been reported (among people attending a dental hospital) [9]. Although some studies around the world reported higher levels of awareness in their populations [26], these low levels of awareness of oral cancer in developed countries like the UK and Australia, as well as developing countries like Iran, emphasize the importance of the British Dental Association’s guidelines to increase awareness as a cost-effective approach to reducing the population burden of oral cancer [14, 27].

Media resources were reported as the most important source of information in most studies [9, 13, 21]. These findings give special importance to mass media in education of health issues to public. Although the evidence from this study might not be sufficient to arrive at a strong conclusion about the role of dentists in oral cancer awareness, due to open-ended design of the question, as well as the frequency of participants’ dental visits, the low influential role of dentists should be addressed, with emphasis on an improvement in professional knowledge and awareness of oral cancer. Also, detection of oral cancer should be a highly recommended on continuing education topic for professionals accordingly [9].

4-2-6-Conclusion

Bearing in mind the limitations of this study, an alarming lack of oral cancer awareness in Tehran, the capital of Iran, provides a valuable baseline of data for more comprehensive research to be undertaken. Considering the increasing trend of head and neck cancer cases in recent reports and high diagnostic delays in oral cancer in Iran [11], efforts should
be made, not only for enhancement of the awareness (through freely accessible displayed oral cancer education material in public places), but dentists should be obliged to practice their pivotal role in informing the public about oral cancer.

4.2.7-References


3. http://globocan.iarc.fr/ia/World/atlas.html. Available at 5th of Sep/ 2017


4-3- Does socioeconomic status influence oral cancer awareness: The role of public education

4-3-1-Abstract

The objective was to investigate whether an association exists between socioeconomic status and oral cancer awareness.

Methods: A multi-stage random sample of adults in Tehran, Iran, was investigated (n = 1800). The outcome was awareness of oral cancer and knowledge of risk factors and signs and symptoms. The main exposures were self-reported socioeconomic status of indicators of the family’s assets and economic situation.

Results: The mean (± SD) age was 37.8 (± 9.02), and about 60% were female (response rate=73%). The average score for awareness was (1.09 ± 1.6, out of 4), for risk factors was (5.3 ± 3.0, out of 15), and for signs and symptoms was (4.5 ± 2.9, out of 11). Awareness and knowledge were significantly lower among the poorest participants, controlling for age/ gender (P<0.001).

Conclusion: Inequalities have been observed in oral cancer awareness. Conducting educational programs might reduce this gap, and diminish the oral cancer burden.

4-3-2-Introduction

The association between socio-economic status (SES) and different health outcomes is widely documented in previous studies [1]. Evidence of inequalities in oral health has been repeatedly illustrated between and within countries [2]. Oral cancer, including cancer of the lip and oral cavity [3] is not an exception, and recent global data have shown differences in incidence and mortality in different countries [4]. Associations between oral cancer risk and low SES [5], and the relationship between survival and mortality of oral cancer and both individual and area deprivation have been determined previously [6]. Despite some theoretical explanations for the disparity in health, public health researchers still debate of how SES relates to impaired health [1, 2, 7].

More advanced stages of oral cancer at first presentation in patients of lower socioeconomic class, have been proposed as a possible association with disparity in oral cancer burdens [8]. Moreover, a lack of or insufficient knowledge of oral cancer has been
suggested as an effective factor in late diagnosis [8]. Therefore, it could be proposed that socio-economic position has an effect on awareness and knowledge about oral cancer, and in turn will facilitate advanced stage diagnosis.

Previous studies have used various single or combined indicators to measure SES, mostly focused on occupation, education and income [9-12]. However, unavailable or unreliable results have been mentioned for income and occupation especially in developing countries [13]. Ghorbani et al developed an asset-based SES index using principal component analysis (PCA), as a method for determining weights for components of a wealth index from a set of variables, for exploring oral health inequalities in the Iranian population. They suggested that household assets could be a good indicator of assessment ‘long-run’ economic status [13].

There are multiple international studies assessing the levels of awareness and knowledge of symptoms and risk factors of oral cancer [14-16], however, most used sociodemographic measures such as age, gender and education as attributing factors. Also, a review of the relevant literature found that studies reporting oral cancer awareness in Iran are rare with inconsistent results about sociodemographic factors [17-20]. To the best of current knowledge, there is no study associating wealth status and the level of knowledge about oral cancer, in a developing country. The aim of this study was to investigate the association between individual wealth (by determining SES) and its association with awareness about oral cancer in Iran.

4-3-2-Methods

This cross-sectional study is follow-up of an oral cancer knowledge study [21] that was conducted in the capital city of Iran, Tehran in 2016-2017 using self-administered questionnaires.

4-3-2-1-Ethics

The research project was approved by the Shahid Beheshti University of Medical Sciences, Tehran, Iran Ethics Committee. The purpose of the study was fully explained in the questionnaire and responses to questions were on a voluntary basis. All participants were assured of anonymity and confidentiality.
4-3-2-2-Questionnaire

The questionnaire assessed the awareness and knowledge of risk factors and symptoms of oral cancer as well as socio-economic status. It included demographic questions (sex, age), four yes/no questions about oral cancer awareness (heard about cancer, non-communicable nature, early diagnosis and treatment); 15 questions about knowledge of risk factors (tobacco, alcohol, sunlight, diet, genetics, age and Human Papilloma Virus). It also included 11 questions about signs and symptoms (ulcers, red or white patches, swelling, difficulty swallowing, and discomfort, changes in voice and weight loss) [21]. Oral cancer knowledge questions were closed-ended positive and negative questions with "yes", "no", "do not know" options [22, 23]. Questionnaires were designed by slightly modifying previous valid questionnaires considering the local cultural, environmental, and language environment [22, 23]. For assessment of SES, an eight-item composite wealth index was used by adapting the existing validated asset questions [13] including house ownership (own/rent); and yes/no questions about having a car, personal computer, dishwasher, steam-cleaner (a device to clean surfaces), microwave; and questions about income satisfaction: (How satisfied are you with your current household income - Highly satisfied, satisfied, dissatisfied, highly dissatisfied?). Also questions were asked about financial management: Do you have the ability to manage expenditure with the available monthly income - can’t make ends meet, manage to get by, have enough money plus some extra, money was not a problem? The above questions were done in consideration of previous studies [22, 24, 25].

A pilot study was conducted before finalising the questionnaire, on a random sample of 60 patients attending a dental school clinic, to ensure clarity and practicability of the questions (α= 0.81). The purpose of the study and instructions were explained at the beginning of the questionnaire.

4-3-2-3-Sampling and participation

According to previous studies in Iran in recent years [19], that considered 16% as the percentage of knowledgeable patients (with regard to the risk factors of oral cancer) for the sampling formula, it was estimated that 1000 participants should be enough for the survey. Additional sampling was added in order to compensate for losses and refusals.

The study population comprised of adults who were parents of public primary school
students in Tehran. The sampling method was multi-stage stratified random technique. Firstly, from the 22 municipal regions in Tehran and according to a geographic location in South, East, West, and North, four regions were selected. Then, one or two schools were randomly selected from each region’s school list. In each school, a grade was randomly selected and the invitation letter sent for all the parents in that grade. One invitation letter was sent home with each student, so, both parents had the chance to see the letter.

4-3-2-4-Study design

A total of 1800 invitations were distributed to parents at the school to reach the best sample size. Resulting from this selection, 1800 parents were invited to participate in the study. Participants were invited, and if willing to take part, signed the consent form.

Participants were requested to return the filled questionnaire on the same day, without any time restrictions and to use their own knowledge, without seeking information from online resources. Illiterate persons, who were not able to write/read, were excluded due to the self-administered nature of questionnaire. A brochure containing information about oral and lip cancer were provided to all parents in defined schools after finishing the study. This brochure was approved by the panel expert of community oral health and oral medicine specialists in Shahid Beheshti University of Medical Sciences, Tehran, Iran.

4-3-2-5-Outcome variables

Awareness about oral cancer and knowledge of risk factors and signs and symptoms were collected through a numerical scale. Each correct answer was allocated a score of 1, and for incorrect answers, including "do not know", zero was assigned. The final scores for each participant were summed up separately, ranged between 0-4 for awareness, 0-15 for risk factor knowledge, and between 0-11 for knowledge of signs and symptoms.

4-3-2-6-Explanatory variables

The main explanatory variable was a composite wealth index as the socioeconomic status proxy. The PCA was applied to indicator variables and the samples classified into five equal wealth quintiles, which the first quintile represented the poorest 20% of the sample.
4-3-2-7-Covariates

Self-reported age was recorded in date of birth and was categorised into groups of 25–35, 35–45, and >45 years. Self-reported sex also recorded.

4-3-2-8-Statistics

PCA was used to develop wealth index using STATA 11.1. Because the items included both binary and continuous variables, polychoric correlations were applied in the principal factor analysis correlation matrix. Then, the SES classification to five quintiles, was conducted by cluster analysis using the data-driven approach. Descriptive and univariate analyses were used to explore the distribution of oral cancer knowledge and awareness by SPSS (version 22) software. Statistical tests, including ANOVA and post hoc tests and general linear regression were used for analysis of the level of knowledge and awareness among socio-demographic groups. P < 0.05 was considered statistically significant in the survey.

4-3-3-Results

Out of 1800 adults, 1312 completed questionnaires were returned (72.8% response rate). In total, 62% of participants were female and 38% were male with the average age of 37.8 ± 9.02. Mean±SD score for awareness was 1.09 ± 1.6 (out of 4), for risk factors knowledge was [5.3 ± 3.0] (out of 15), and for sign and symptoms knowledge was [4.5 ± 2.9] (out of 11). Analyses indicated that oral cancer awareness and knowledge of oral cancer signs or risk factors was not significantly different between the different age categories. Male participants had less knowledge of oral cancer signs and risk factors (p<0.05), however awareness was not different between males and females. (Table 1)

The PCA revealed one component with consideration of an Eigen-value > 1; the first one covered 84% of variance. All variables included in the factor 1 had positive factor scores, and were associated with higher socioeconomic status. Factor loading and scoring coefficients are presented in Table 2. Income management, with a weight of 0.72, had the highest contribution to the composite wealth score, and house ownership had the lowest impact on the combined index (Table 2).

Table 1 also demonstrates the relation between SES and level of knowledge and
awareness. Statistical tests indicated the significant difference between level of awareness and knowledge of oral cancer risk factors and signs and symptoms in different socioeconomic groups ($p<0.001$). The post hoc test results showed the higher the wealth index, the higher the score of oral cancer knowledge and awareness. Table 3 shows general linear model analysis. Results of this analysis revealed after controlling age and gender the level of wealth remained significantly associated with knowledge and awareness of oral cancer. It means that poorest quantile had (-0.69 (CI:0.91—0.46)) lower score in general awareness, (-1.58 (CI:-2.19—0.96) lower score in knowledge of risk factors and (-1.34 (CI:-1.96—0.72)) lower score in knowledge of signs and symptoms of oral cancer than the richest quantile.

Table 4-3-1: The distribution of level of knowledge by socioeconomic (SES) groups

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency (%)</th>
<th>General awareness(±SD)</th>
<th>Knowledge of risk factors(±SD)</th>
<th>Knowledge of signs (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>489(38.2%)</td>
<td>1.60(1.09)</td>
<td>4.90(2.92)</td>
<td>4.21(2.96)</td>
</tr>
<tr>
<td>Female</td>
<td>788(61.7%)</td>
<td>1.64(1.01)</td>
<td>5.60(3.00)</td>
<td>4.70(2.88)</td>
</tr>
<tr>
<td>P-value</td>
<td>$p^a=562$</td>
<td>$p^a&lt;0.001$</td>
<td>$p^a&lt;0.001$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Frequency (%)</th>
<th>General awareness(±SD)</th>
<th>Knowledge of risk factors(±SD)</th>
<th>Knowledge of signs (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-35</td>
<td>318(28.2%)</td>
<td>1.60 (1.07)</td>
<td>5.26(3.00)</td>
<td>4.38(2.88)</td>
</tr>
<tr>
<td>35-45</td>
<td>644(57.1%)</td>
<td>1.68 (1.1)</td>
<td>5.44(3.08)</td>
<td>4.68(2.99)</td>
</tr>
<tr>
<td>&gt;45</td>
<td>165(14.6%)</td>
<td>1.59 (1.0)</td>
<td>5.17(2.83)</td>
<td>4.26(2.88)</td>
</tr>
<tr>
<td>P-value</td>
<td>$p^b=0.4$</td>
<td>$p^b=0.50$</td>
<td>$p^b=0.16$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Socioeconomic status</th>
<th>Frequency (%)</th>
<th>General awareness(±SD)</th>
<th>Knowledge of risk factors(±SD)</th>
<th>Knowledge of signs (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th ( Richest)</td>
<td>204(17.5%)</td>
<td>1.92(1.12)</td>
<td>6.23(2.82)</td>
<td>5.09(2.98)</td>
</tr>
<tr>
<td>4th</td>
<td>258(22.2%)</td>
<td>1.72(1.03)</td>
<td>5.85(2.87)</td>
<td>4.88(2.92)</td>
</tr>
<tr>
<td>3rd</td>
<td>207(17.8%)</td>
<td>1.72(1.07)</td>
<td>5.45(3.05)</td>
<td>4.60(3.01)</td>
</tr>
<tr>
<td>2nd</td>
<td>262(22.5%)</td>
<td>1.54(1.07)</td>
<td>4.95(2.95)</td>
<td>4.35(2.83)</td>
</tr>
<tr>
<td>1st (Poorest)</td>
<td>233(20.0%)</td>
<td>1.30(1.02)</td>
<td>4.69(2.97)</td>
<td>3.91(2.68)</td>
</tr>
<tr>
<td>P-value</td>
<td>$p^b &lt;0.001$</td>
<td>$p^b &lt;0.001$</td>
<td>$p^b &lt;0.001$</td>
<td></td>
</tr>
</tbody>
</table>

a=independent sample t test, b=ANOVA test
Table 4-3-2: Results from principal component analysis (PCA) for construction of wealth index

<table>
<thead>
<tr>
<th>Factor</th>
<th>Eigenvalue</th>
<th>Variance proportion</th>
<th>Cumulative Variance proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor1</td>
<td>3.15</td>
<td>0.84</td>
<td>0.84</td>
</tr>
<tr>
<td>Factor2</td>
<td>0.84</td>
<td>0.22</td>
<td>1.06</td>
</tr>
<tr>
<td>Factor3</td>
<td>0.23</td>
<td>0.06</td>
<td>1.13</td>
</tr>
<tr>
<td>Factor4</td>
<td>0.06</td>
<td>0.01</td>
<td>1.14</td>
</tr>
<tr>
<td>Factor5</td>
<td>-0.03</td>
<td>-0.01</td>
<td>1.139</td>
</tr>
<tr>
<td>Factor6</td>
<td>-0.12</td>
<td>-0.3</td>
<td>1.10</td>
</tr>
<tr>
<td>Factor7</td>
<td>-0.17</td>
<td>-0.04</td>
<td>1.05</td>
</tr>
<tr>
<td>Factor8</td>
<td>-0.21</td>
<td>-0.05</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Observed Variable (wealth index)</th>
<th>Weight for factor 1</th>
<th>Scoring Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal Computer</td>
<td>0.57</td>
<td>0.11</td>
</tr>
<tr>
<td>Dishwasher</td>
<td>0.63</td>
<td>0.14</td>
</tr>
<tr>
<td>Steam cleaner</td>
<td>0.70</td>
<td>0.26</td>
</tr>
<tr>
<td>Microwave</td>
<td>0.62</td>
<td>0.15</td>
</tr>
<tr>
<td>Car</td>
<td>0.55</td>
<td>0.10</td>
</tr>
<tr>
<td>House</td>
<td>0.50</td>
<td>0.08</td>
</tr>
<tr>
<td>Financial management</td>
<td>0.72</td>
<td>0.28</td>
</tr>
<tr>
<td>Income satisfaction</td>
<td>0.67</td>
<td>0.18</td>
</tr>
</tbody>
</table>
Table 4-3-3: General linear model regression results by socioeconomic status (SES)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B*</th>
<th>Std. Error</th>
<th>t</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>General awareness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (Poorest)</td>
<td>-0.692</td>
<td>0.114</td>
<td>-6.083</td>
<td>.000</td>
<td>-0.915</td>
</tr>
<tr>
<td>2nd</td>
<td>-0.450</td>
<td>0.113</td>
<td>-3.985</td>
<td>.000</td>
<td>-0.672</td>
</tr>
<tr>
<td>3rd</td>
<td>-0.270</td>
<td>0.117</td>
<td>-2.304</td>
<td>.021</td>
<td>-0.500</td>
</tr>
<tr>
<td>4th</td>
<td>-0.237</td>
<td>0.112</td>
<td>-2.123</td>
<td>.034</td>
<td>-0.457</td>
</tr>
<tr>
<td>5th (Richest)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knowledge of risk factor 1st (Poorest)</td>
<td>-1.580</td>
<td>0.315</td>
<td>-5.017</td>
<td>.000</td>
<td>-2.198</td>
</tr>
<tr>
<td>2nd</td>
<td>-1.434</td>
<td>0.311</td>
<td>-4.606</td>
<td>.000</td>
<td>-2.045</td>
</tr>
<tr>
<td>3rd</td>
<td>-0.845</td>
<td>0.323</td>
<td>-2.612</td>
<td>.009</td>
<td>-1.480</td>
</tr>
<tr>
<td>4th</td>
<td>-0.393</td>
<td>0.308</td>
<td>-1.278</td>
<td>.202</td>
<td>-0.997</td>
</tr>
<tr>
<td>5th (Richest)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knowledge of signs 1st (Poorest)</td>
<td>-1.348</td>
<td>0.315</td>
<td>-4.276</td>
<td>.000</td>
<td>-1.967</td>
</tr>
<tr>
<td>2nd</td>
<td>-0.837</td>
<td>0.311</td>
<td>-2.694</td>
<td>.007</td>
<td>-1.447</td>
</tr>
<tr>
<td>3rd</td>
<td>-0.595</td>
<td>0.322</td>
<td>-1.845</td>
<td>.065</td>
<td>-1.227</td>
</tr>
<tr>
<td>4th</td>
<td>-0.329</td>
<td>0.309</td>
<td>-1.064</td>
<td>.288</td>
<td>-0.936</td>
</tr>
<tr>
<td>5th (Richest)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. This parameter is set to zero because it is redundant.

*Coefficient of estimate

All analysis adjusted for age and gender

4-3-4-Discussion

4-3-4-1-Main finding of this study

The findings of the current study indicate that, although awareness and knowledge of oral cancer is insufficient in Iran, there is a significant difference between population SES and
level of knowledge. A created wealth index was used in this study as a combined index for better assessment of SES in the study population.

4-3-4-2-What is already known on this topic

Multiple studies evaluated the association between various sociodemographic indices, such as age, gender, education, and occupation and level of knowledge of oral cancer [26, 27]. Different studies reported inconsistent results in relationships between the level of knowledge and sex and age. In Iran, in terms of occupation, only Pakfetrat et al (2010) reported significant differences in knowledge among people with different occupations [18]. Occupation could not be a good indicator of SES due to the existence of income inequalities within one occupation, as well as high rates of women without formal occupations in developing countries. In Iran, Pakfetrat (2010), Tadibar (2013), and Golami (2016) et al reported the higher the level of education, the higher the score of oral cancer knowledge [17, 18, 20]. Although education is a good predictor of SES, it is not a sole indicator of it. Income has been used as an indicator of SES in oral cancer knowledge studies previously [12, 27]. However, there are high non-response rates on items directly measuring income especially in developing countries due to cultural factors [13, 28].

An asset-based approach, with collecting information on ownership of a range of durable assets, is an alternative to traditionally monetary indicators, such as consumption expenditure or income, to measuring SES [1, 2]. Gorbani et al created an asset-based wealth index for measuring oral health inequality in Tehran and demonstrated the low level of oral health in the poorest quantile [2]. Also, Islami et al in North Iran constructed asset-based wealth index for assessing SES and oesophageal cancer and reported the protective effect of high wealth scores in the group with the highest wealth status (Top 20%) [28].

4-3-4-3-What this study adds

In the present study, a wealth-index was developed using asset items, as well as two indirect monetary questions about financial management and income satisfaction. Previous studies have shown that people refuse to discuss their income information with
others, and it is treated as sensitive or confidential, however, income satisfaction questions dealt with the emotional self-evaluation of income considering past or current income, or standard income relative to one’s own merits and qualifications. Miething argued that it could be an indicator of perceived inequality as well as a non-income-based exogenous measurement of income inequality [24]. Also, financial management as the self-rated ability to manage with the available monthly income has been used as a component of measuring SES in previous studies [25].

In the current study, PCA was for weighting to construct a wealth index, and results show the first component explained more than 80% of original variables. The criteria for the selection of variables for PCA are not well defined, and the number of selected components is arbitrary [29]. Gorbani et al in Iran, used PCA methods for measuring socioeconomic inequalities. They used the first component factor scores with coverage of 34% of variance. Also, they classified the samples into five equal wealth quintiles, similar as in this study [13]. Krefis et al, in 2010, used PCA asset-based wealth index for SES assessment with 20% coverage of first component and argued that combined SES indicators using PCAs provides a quantification and classification of individual SES levels and enable the present author to use the resulting score for risk analyses [25].

4-3-4-4-Limitations of this study

Although a well-designed PCA analysis has been set up as a suitable tool for assigning weights to the indicators in this study, all information on asset measures are based on self-reports of participants, and were not confirmed by direct observations, and this was considered to be a limitation. However, the present author asked questions about easily recalled ownership or appliances, which reduce the possibility of recall bias. In addition, prices are not taken into consideration in asset ownership, so, the appropriateness of the wealth index may differ between regions. However, most previous studies used this approach for construction of a wealth index [13, 30]. Also, as an outcome of this study, a brochure about oral cancer risk factors and signs and symptoms was handed out in primary schools after the study, which can help parents as well as children acquire oral cancer related knowledge.

In conclusion, the results of this study demonstrate the advantage of multiple variables rather than a single indicator of SES. The inverse association between combined indictors
of SES and all components of oral cancer knowledge (general awareness, knowledge of risk factors and signs and symptoms) has been confirmed in the present study. Although improvements in SES are not achievable without changing the general economy, dental public health policy makers should conduct active educational programs, especially for the most deprived parts of the population, to reduce the gap in the burden of oral cancer.

4-3-5-References


Chapter 5

To evaluate the relationship between various socioeconomic components and oral cancer, and finding the risk-factor model base for oral cancer screening

This Chapter includes two parts that have been published as the following articles:


Part 2- Development of a risk factor-based model for head and neck squamous cell carcinoma: A case-control study (under review)- Presented in 58th IADR congress, Perth, Australia
5-1-Socioeconomic determinants as risk factors for squamous cell carcinoma of the head and neck: a case-control study in Iran.

5-1-1-Abstract

Objectives: The aim was to assess the association between different components of sociodemographic status and the risk of developing squamous cell carcinoma (SCC) of the head and neck, after adjusting for the influence of the known behavioural risk factors of smoking and drinking alcohol.

Methods: A group of 146 patients with histopathologically confirmed SCC of the head and neck were selected, and matched for age and sex, with 266 healthy controls for this case-control study. Personal details, occupation, socioeconomic status, smoking, and alcohol consumption were recorded. The association of sociodemographic variables with oral cancer was evaluated both separately and with a composite socioeconomic index. Chi squared tests, adjusted odds ratios (OR), and 95% CI were computed using logistic regression to estimate the effect.

Results: There was a significant difference between the two groups in the composite socioeconomic index (p < 0.001). The group with “low” socioeconomic status had the highest risk of oral cancer (OR = 3.89, 95% CI 1.28 to 11.82). Better-educated people with higher incomes had a lower risk of SCC of the head and neck after controlling for behavioural risk factors. However, marital and employment status and place of residence were not significantly associated with risk.

Conclusion: The findings confirm that some socioeconomic determinants were associated with the development of oral cancer in this study group.

5-1-2-Introduction

The prevalence of cancers of the head and neck (including the lip, oral cavity, and nasopharynx, pharynx, and larynx) has been estimated to be more than 5.5 million globally [1, 2], and squamous cell carcinoma (SCC) is the most common. Smoking, chewing tobacco, drinking alcohol, HPV, and a poor diet have been proposed as risk factors [3, 4].

Many studies have suggested that oral cancer is more common in socioeconomically
deprived populations, but the underlying aetiology of this is yet to be proved [2]. In addition, there has been no general agreement in previous studies about measures of socioeconomic status in which its relation to the epidemiology of cancer has been studied, and results are inconsistent [2, 5, 6].

The variation in geographical and regional incidences of oral cancer suggests that cultural, demographic, and social factors could have an important role in carcinogenesis [7, 8]. While each country certainly shares common socioeconomic characteristics, there may be differences in the distribution of components of socioeconomic status. This is particularly the case in developing countries, because of unavailable or unreliable data about levels of income, and difficulties in the evaluation of occupation (noticeably where formal occupations are less common among women) [6]. The accessibility (including availability and affordability) of healthcare in each country could also be an important factor that contributes to the association between socioeconomic status and the prevalence of SCC of the head and neck.

The aim of this study was to investigate the association between confirmed SCC of the head and neck and indicators of socioeconomic status (occupation of the head of the family, level of income, education and place of residence) in a developing country, Iran.

5-1-3-Methods

This matched case-control study was conducted at the Imam Khomeini Hospital Complex, Tehran, Iran, during 2016–17. The Medical Oncology Department (Cancer Institute) of this hospital treats patients from both rural and urban areas from all around Iran.

The research project was approved by the Iranian Medical University, Ethics Committee. The purpose of the study was fully explained to all participants, and informed consent was obtained from all. All participants were assured of anonymity and confidentiality.

5-1-3-1-Patients

Patients aged 18 years or over, with cancers of the head and neck with a histologically confirmed SCC were identified from the records of the hospital’s outpatient dental clinic. Patients were referred from the Medical Oncology Department and given pretreatment
dental clearance. Those who had had cancer previously, or who had any other malignancy, were excluded. The sample size was calculated to include 150 patients, according to the formula for comparing two qualitative proportions in two independent populations (power = 80%, $\alpha = 5\%$, 10% loss of participation).

5-1-3-2-Controls

Controls matched by age and sex were selected from the same hospital, from people in waiting rooms and outpatient clinics, during the same period as the patients with SCC, to ensure the same exposure patterns in the source population. The selection criteria for controls were: 18 years old or more, not diagnosed with any cancer, and not complaining of memory loss. Eligible controls were approached in random order (to avoid selection bias) until one agreed to participate. Some cases had one matched control, but most had two. All the control participants were examined to make sure that they did not have oral cancer.

5-1-3-3-Protocol of the study

Information was collected from cases and controls using a self-administered structured questionnaire, which included: personal and socioeconomic characteristics (age, sex, marital status, education, occupation of the head of the family, place of residence, and satisfaction with income), smoking and alcohol consumption, a brief medical history, and family history of cancer. Questions that were easy to recall were used, to avoid recall bias. A trained interviewer was available for assistance and response to any questions participants might have had.

5-1-3-4-Outcome variables

The outcome was diagnosis of SCC of the head and neck (lip and oral cavity, nasopharynx, pharynx, and larynx), confirmed by histopathological examination.

5-1-3-5-Explanatory variables

Patients who smoked or had smoked were recorded as current or ex-smokers; the rest as non-smokers. Other types of tobacco, and consumption of alcohol, were recorded as “yes” or “no”. A simple “yes/no” question was used to record a family history of cancer.
Marital status was recorded as married, single, or other (including divorced and widowed), place of residence as urban or rural, and educational attainment as years of study successfully completed. It was then subdivided into three sub-groups: less than high school diploma, high school diploma, further than high school diploma [9]. Employment was recorded as: unemployed, employed, or other (including students, housewives, and retired people). The employed group was further subdivided into labour and related, employed (public or private), self-employed, and managerial/professional [9]. Participants were also requested to state who was the head of the family in employment, when different from their own. The head of the family’s employment was used for analysis. Income satisfaction was recorded as highly dissatisfied, dissatisfied, satisfied, and highly satisfied. Only four people stated that they were “highly-satisfied” with their income, so this group was combined with the “satisfied” group for the regression analysis.

Also, a composite score for socioeconomic status (SES) was created based on the method described by Dahlstrom et al (Table 1) [10]. For this purpose, the combination of two score education categories and income satisfaction categories was used to define SES. Participants divided into three categories of low, middle, and high SES accordingly[10].

The statistical analysis was conducted using IBM SPSS Statistics for Windows (version 21, IBM Corp, Armonk, NY, USA). Statistical tests, including the chi squared or Fisher’s exact test, were used to compare the significance of differences between the case and control groups (probabilities of less than 0.05 were accepted as significant). The significance of the multivariate associations of risk factors with SCC of the head and neck were tested using binary logistic regression analysis to calculate unadjusted and adjusted odds ratios (OR) for potential confounders and corresponding 95% CI for each variable. The Hosmer–Lemeshow test was used for goodness of fit for logistic regression models.

Table 5-1-1: Socioeconomic composite index based on income satisfaction and education level.

<table>
<thead>
<tr>
<th>Income Education</th>
<th>Highly dissatisfied</th>
<th>Dissatisfied</th>
<th>Satisfied</th>
<th>Highly satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 years</td>
<td>Low</td>
<td>Low</td>
<td>mid</td>
<td>mid</td>
</tr>
<tr>
<td>12 years</td>
<td>Low</td>
<td>mid</td>
<td>mid</td>
<td>High</td>
</tr>
<tr>
<td>More than 12</td>
<td>mid</td>
<td>mid</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>
5-1-4-Results

A total of 148 completed questionnaires in the case group and 266 in the control group were available for analysis. Table 2 gives the personal and clinical details of the patients, and indicates the distribution of sociodemographic variables and risk factors in the two groups.

Logistic regression was used to calculate adjusted and unadjusted OR (age and sex) and corresponding 95% CI for behavioural risk factors (Table 3). The model was further adjusted in significant variables comprising the socioeconomic component (education, employment, and satisfaction with income). Logistic regression was also used to calculate unadjusted and adjusted OR (age and sex) and corresponding 95% CI for each significant variable in the socioeconomic indicator (education, income, and composite index of socioeconomic status) (Table 4). The model has been further adjusted for behavioural risk factors (smoking, other types of tobacco consumption, and alcohol).
Table 5-1-2: The distribution of sociodemographic variables and risk factors in cases and control groups. Data are expressed as number (%).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case (148)</th>
<th>Control (266)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male n=216</td>
<td>80 (54.1)</td>
<td>136 (51.1)</td>
<td>P= 0.568</td>
</tr>
<tr>
<td>Female n=198</td>
<td>68 (45.9)</td>
<td>130 (48.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=20 n=12</td>
<td>4 (2.7)</td>
<td>8 (3.0)</td>
<td></td>
</tr>
<tr>
<td>21-30 n=12</td>
<td>4 (2.7)</td>
<td>8 (3.0)</td>
<td></td>
</tr>
<tr>
<td>31-40 n=24</td>
<td>8 (5.5)</td>
<td>16 (6.0)</td>
<td></td>
</tr>
<tr>
<td>41–50 n = 70</td>
<td>24 (16.4)</td>
<td>46 (17.3)</td>
<td></td>
</tr>
<tr>
<td>51–60 n =93</td>
<td>35 (24.0)</td>
<td>58 (21.8)</td>
<td></td>
</tr>
<tr>
<td>61-70 n =99</td>
<td>35 (24.0)</td>
<td>64 (24.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;71 n= 102</td>
<td>36 (24.7)</td>
<td>66 (24.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural n =10</td>
<td>4 (2.8%)</td>
<td>6 (96.8%)</td>
<td>P=1.0</td>
</tr>
<tr>
<td>urban n =320</td>
<td>141(97.2%)</td>
<td>179(3.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school diploma n= 225</td>
<td>105 (70.9)</td>
<td>120 (45.1)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>High school diploma n=126</td>
<td>32 (21.6)</td>
<td>94 (35.3)</td>
<td></td>
</tr>
<tr>
<td>More than high school diploma n=63</td>
<td>11 (7.4)</td>
<td>52 (19.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>5 (3.6)</td>
<td>9 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Labour &amp; related</td>
<td>16 (11.7)</td>
<td>23 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Self- employed</td>
<td>62 (45.5)</td>
<td>89 (36.0)</td>
<td>P=0.07</td>
</tr>
<tr>
<td>Public- private employed</td>
<td>34 (25)</td>
<td>79 (31.9)</td>
<td></td>
</tr>
<tr>
<td>Professional</td>
<td>1 (0.7)</td>
<td>15 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>18 (13.2)</td>
<td>32 (12.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Income satisfaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly satisfied n=4</td>
<td>0 (0.0)</td>
<td>4 (1.5)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Satisfied n=65</td>
<td>22 (15.0)</td>
<td>43 (16.1)</td>
<td></td>
</tr>
<tr>
<td>Dissatisfied n=277</td>
<td>86 (58.9)</td>
<td>191 (71.8)</td>
<td></td>
</tr>
<tr>
<td>Highly dissatisfied n=66</td>
<td>38 (26.0)</td>
<td>28 (10.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married n =310</td>
<td>107 (73.3)</td>
<td>203 (76.3)</td>
<td>P=0.76</td>
</tr>
<tr>
<td>Unmarried n = 35</td>
<td>14 (9.6)</td>
<td>21 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>Others n = 67</td>
<td>25 (17.1)</td>
<td>42 (15.8)</td>
<td></td>
</tr>
<tr>
<td>Variables</td>
<td>Case (148)</td>
<td>Control (266)</td>
<td>P-value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------</td>
<td>---------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td></td>
</tr>
<tr>
<td>Family history of cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes n=4</td>
<td>3 (2.1)</td>
<td>1 (0.4)</td>
<td>P=0.13</td>
</tr>
<tr>
<td>No n=408</td>
<td>143 (97.9)</td>
<td>265 (996)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never n= 342</td>
<td>115 (79.3)</td>
<td>227 (85.3)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Current-Smoker n=31</td>
<td>3 (2.1)</td>
<td>28 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Ex-Smoker n=38</td>
<td>27 (18.6)</td>
<td>11 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever n=10</td>
<td>0 (0.0)</td>
<td>10 (3.9)</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Never n=366</td>
<td>139 (100.0)</td>
<td>247 (96.1)</td>
<td></td>
</tr>
<tr>
<td>Other-tobacco</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever n= 22</td>
<td>13 (9.7)</td>
<td>9 (3.6)</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Never n=362</td>
<td>121 (91.3)</td>
<td>241 (96.4)</td>
<td></td>
</tr>
<tr>
<td>SES composite index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low n= 212</td>
<td>95 (65.0)</td>
<td>116 (43.6)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Middle n= 178</td>
<td>47 (32.1)</td>
<td>131 (49.2)</td>
<td></td>
</tr>
<tr>
<td>High n= 23</td>
<td>4 (2.7)</td>
<td>19 (7.1)</td>
<td></td>
</tr>
</tbody>
</table>
Table 5-1-3: Association between risk factors and risk of squamous cell carcinoma of the head and neck.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude OR (95%CI)</th>
<th>Model 1 OR*(95%CI)</th>
<th>Model 2 OR**(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Current- Smoker</td>
<td>0.21 (0.06-0.71)</td>
<td>0.20 (0.06-0.70)</td>
<td>0.12 (0.32-0.48)</td>
</tr>
<tr>
<td>Ex-Smoker</td>
<td>4.85 (2.32-10.11)</td>
<td>4.69 (2.18-10.08)</td>
<td>5.47 (2.24-13.38)</td>
</tr>
<tr>
<td>P-Value</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Nagelkerke R Square</td>
<td>0.206</td>
<td>0.247</td>
<td></td>
</tr>
<tr>
<td><strong>Other-tobacco status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Ever</td>
<td>2.87 (1.19-6.91)</td>
<td>2.85 (1.16-7.00)</td>
<td>2.03 (0.74- 5.57)</td>
</tr>
<tr>
<td>P-Value</td>
<td>P=0.01</td>
<td>P= 0.02</td>
<td>P= 0.16</td>
</tr>
<tr>
<td>Nagelkerke R Square</td>
<td>0.024</td>
<td>0.180</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>0.001 (0.001-)</td>
<td>0.001 (0.001-)</td>
<td>-</td>
</tr>
<tr>
<td>P- value</td>
<td>0.99</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age and gender

** Adjusted for age, gender, education, employment and income satisfaction
Table 5-1-4: Association between social determinants and risk of squamous cell carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude OR (95%CI)</th>
<th>Model 1 OR*(95%CI)</th>
<th>Model 2 OR**(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than high school diploma</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>High school diploma</td>
<td>1.60 (0.74-3.45)</td>
<td>1.90 (0.85-4.24)</td>
<td>1.76 (0.69-4.47)</td>
</tr>
<tr>
<td>less than high school diploma</td>
<td>4.13 (2.05-8.34)</td>
<td>5.87 (2.67-12.8)</td>
<td>6.73 (2.75-16.49)</td>
</tr>
<tr>
<td>P-value</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Nagelkerke R Square</td>
<td>0.107</td>
<td>0.223</td>
<td></td>
</tr>
<tr>
<td><strong>Income satisfaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfied</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>0.96 (0.54-1.69)</td>
<td>0.96 (0.54-1.71)</td>
<td>1.09 (0.57-2.09)</td>
</tr>
<tr>
<td>Highly dissatisfied</td>
<td>2.89 (1.43-5.85)</td>
<td>2.85 (1.39-5.83)</td>
<td>4.47 (1.96-10.18)</td>
</tr>
<tr>
<td>P-Value</td>
<td>P&lt;0.001</td>
<td>P=0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Nagelkerke R Square</td>
<td>0.051</td>
<td>0.181</td>
<td></td>
</tr>
<tr>
<td><strong>SES composite index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Middle</td>
<td>1.70 (0.55-5.26)</td>
<td>1.67 (0.53-5.23)</td>
<td>2.98 (0.64-13.91)</td>
</tr>
<tr>
<td>Low</td>
<td>3.89 (1.28-11.82)</td>
<td>4.19 (1.35-12.94)</td>
<td>8.32 (1.81-38.23)</td>
</tr>
<tr>
<td>P-Value</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Nagelkerke R Square</td>
<td>0.067</td>
<td>0.190</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age and gender
** Adjusted for age, gender, smoking, other-tobacco, and alcohol

5-1-5-Discussion

An association was found between indicators of socioeconomic status and the risk of SCC of the head and neck in a defined randomly selected group in Iran, after controlling for various confounding variables.

Conway et al concluded in a meta-analysis that the risks of developing oral cancer were higher for those with low socioeconomic status (SES) than for those who were better off [11]. However, they stated the diversity of reporting oral cancer in papers that included definitions such as oral or oropharyngeal cancer, or both, or cancer of the head and neck
or upper alimentary and respiratory tracts, and these types of cancer might have causes

different from those of SCC of the head and neck. They also did not include any studies

from the Middle-East, except one unadjusted study from Turkey [11]. In this study, which

was in the Middle-East region, cases with only head and neck SCC diagnosis had been

included. The results indicated the similar outcome as the Conway et al study.

Participants with low SES measuring with composite socioeconomic index almost 4 times

had a higher risk for SCC.

The role of sociodemographic background in SCC of the head and neck in Iran has

previously been evaluated in retrospective studies [7,12]. Islami et al found a strong

association between socioeconomic status and oesophageal SCC in a case-control study

in the North of Iran, [13], but the present author knows of no available study that

investigated the association of social determinants with oral cancer in Iran.

The sampling design, with cases from the largest cancer hospital in Tehran, and randomly

selected matched controls, allowed for the generalisability of the results. A self-

administered questionnaire was used, rather than face-to-face interviews, as it was

thought that people would be more likely to participate. A trained interviewer was present

to answer questions and fill in the questionnaire for people who were illiterate. The

information about the stage at diagnosis was not recorded for the patients with cancer,

and that could be a limitation. It was also not possible to find two matched controls for

each case.

Education has been used as a marker of social status in various studies, and the collection

of information about educational standard is unlikely to be affected by recall bias, and is

not influenced by health status in old age.5. It could also have an influence on the

patient’s position in society, occupation, income, access to health care and health

information, as well as an influence on risky behaviours [11].

The results indicate the adverse effect of the degree of education on SCC of the head and

neck, and most previously published studies have indicated the same association with oral

cancer [5, 6, 14, 15]. In a recent retrospective study in Iran, a strong correlation was

found between lower educational level and risk of SCC of the head and neck [7].

However, Conway et al mentioned some studies that suggested that better education was

associated with an increased risk of oral cancer [11].
Previous research used income as an indicator of socioeconomic status [6, 15] because of its impact on housing, living environment, access to health care and social facilities, and quality of food [11]. However, unavailable or unreliable data on income (particularly in developing countries) has been mentioned as a complicating factor in detecting associations [16]. Conway et al [16] also indicated that a low monthly income had a significantly greater effect on the risk of oral cancer in developed, compared with undeveloped countries. In their study on socioeconomic status and risk of oral SCC in Iran, Islami et al mentioned that the participants were not questioned about their income because a pilot study had given unreliable results [13]. Despite the refusal to discuss income, questions about satisfaction with income are a self-evaluation of past or current income, or standard income, relative to one’s own merits and qualifications [17]. Participants were asked to self-evaluate their satisfaction with income, and results showed the inverse relation between that satisfaction and SCC of the head and neck.

Occupation could be a good indicator of social position, particularly in developed countries. A low social class occupation may reflect not only exposure to harmful physical environments, but also be associated with harmful psycho-logical or social environments that increase the risk of oral cancer [11]. However, inequalities in income exist within one occupation: for example, between sex, age, and place of residence. In addition, there is difficulty in the classification of some groups (homemakers and retirees), particularly in developing countries where women are less likely to have a formal occupation [13, 16, 18].

The employment of the head of family was analysed, and housewives and retirees were recorded as “others” in employment categories, and found no significant association between the head of the family’s employment and SCC of the head and neck. However, though some previous studies have used the head of the family’s occupation as an indicator, others have argued that the husband’s occupation might be not a good indicator of the socioeconomic status of a housewife [13, 19]. Some studies have reported significant differences between social occupational class and risk of oral cancer [20]. However, Islami et al reported that none of the occupation categories was associated with the risk of oral SCC in Iran [13]. A recent retrospective study in Iran reported a correlation between outdoor occupations and SCC, but they did not mention occupational social class [7].
Socioeconomic status was evaluated with the composite index, in most cases of SCC had “low” socioeconomic status compared with “middle” status in the control group. It seems that the combination of education and satisfaction with income is a good indicator for the socioeconomic status of this study group, and a higher socioeconomic status had a protective effect for SCC of the head and neck after adjustment for other variables. Previous studies also created another type of scale for socioeconomic status by combining education and occupation [14], or by weighting the three variables: education, occupation, and per capita income [21]. Occupation was not included in the composite score, because the results in this study were not significant, and previous studies in Iran had dealt with inconsistent categories.

The results also showed that smoking had a significant effect in the development of SCC of the head and neck (after controlling for social determinants). However, other types of tobacco consumption had no significant effect (after similar adjustments). It could be proposed that socioeconomic status might be modifying the effect of other types of tobacco consumption in developing risk of SCC of the head and neck.

The results of alcohol consumption are also inconsistent in this study. Only a small group of people mentioned a history of drinking alcohol, because it is illegal in Iran. However, in a recent study, Gupta et al found no significant associations between alcohol and oral cancer [22].

5-1-6-Conclusion

The results indicated that in this study group in Iran, the component of socioeconomic status, including education and income satisfaction, had an association with a risk of head and neck SCC. The effect of age, gender, cigarette smoking, other types of tobacco consumption and alcohol consumption was adjusted for better estimation. Results showed that people with less education (lower than a high school diploma) had almost 7 times higher risk of developing SCC. Also people who were highly dissatisfied with their income had almost 4.5 times, higher risk of developing SCC. Creating a composite index of SES using the two components of education and income satisfaction showed people with low SES were almost 8 times more in risk of developing SCC.
5-1-7-References


11. Conway DI, Petticrew M, Marlborough H, et al. Socioeconomic inequal- ities and


5-2-Development of a risk factor-based model for head and neck squamous cell carcinoma: A case-control study

5-2-1-Abstract

Objectives: This study explores the effects of various risk factors in the development of head and neck squamous cell carcinoma (HNSCC) and investigates a screening model using risk scores, to identify individuals at high risk in an Iranian population.

Methods: A total of 148 newly diagnosed HNSCC patients, and 266 age and gender-matched healthy controls participated in this case-control study. All data about potential predictors of HNSCC were collected using structured questionnaire. Adjusted odds ratios were calculated for significant risk factors. Risk score was defined based on the adjusted odds ratio for each of the predictors. Standard receiver operator characteristic (ROC) curve was plotted for significant predictors. The optimal cut-off (criterion) value was determined as the one with a suitable area under the ROC curve and simultaneously maximal sensitivity and specificity (Youden’s Index).

Results: From all potential predictors: habit (tobacco other than cigarette smoking), diet (fruits, raw and cooked vegetables), socio-economic status (SES) (economic status, education), oral health behaviours (brushing and flossing), lifestyle habit (lip sunscreen, weekly exercise), Rh +/- status, and green tea consumption were significantly different between the two groups. Total risk score for each individual ranged from 0 to 51. Four models were plotted to find the most accurate risk factor based model. Three out of 4 models had reasonable predictive ability (AUC > 0.7). The combination of all significant risk factors had the highest sensitivity (91.89), however the highest specificity (79.70) was indicated in the combination of habit, diet and SES (model 2).

Conclusion: The possibility of a risk factor-based model of screening in individuals with high risk HNSCC was investigated in the Iranian population. The results indicated that habits and diet alone could not predict HNSCC in this population.
5-2-2- Introduction

Head and neck squamous cell carcinoma (HNSCC) is a chronic devastating disease [1, 2]. The aetiology of HNSCC is multi-factorial; however, habits of tobacco and alcohol consumption are established as prominent modifiable risk factors with extensive research [3, 4]. Diet is also a significant risk factor for this cancer. Furthermore, socio-economic determinants such as occupation, education, income, and housing status have been considered as markers for HNSCC [1, 5].

HNSCC is difficult to manage and has poor survival rates when diagnosed late [6]. Delay in diagnosis is mostly because of late presentation and sometimes due to failure to subsequent follow-up of initial examination by professional workers [6].

Survival rates could improve with early diagnosis and timely treatment. It also, reduces the economic and psychologic burden of disease on the patients and their families as well as reduced physical disability [1, 6]. In countries with high proportions of the population living in a remote area, a screening program is more likely to be cost effective, when targeted on well-identified high-risk groups. In fact, inadequate guidelines, especially those related to identification of individuals to be screened have been determined as one of major obstacles to reliable and effective oral cancer screening [4, 6].

High-risk people could be identified by using risk score evaluation as a model. Risk scores are used to estimate an individual’s relative risk of disease on the basis of history of exposure to established risk factors, to improve professionals’ compliance for screening [6]. This risk scores model has been used to detect high-risk populations for colorectal and prostate cancers [7-9]. There is a similar model was also developed for identifying oral potentially malignant disorders (OPMDs) in high risk individuals [4]; and few predictive tools have been developed for the upper respiratory and digestive tracks (UADT) cancers [6]. Krishna Rao et al (2016), in a study to develop a screening model for UADT cancers in an Indian population, using risk scores to identify people at high risk, found risk scores ranged from 0 to 28 (sensitivity (0.928) and specificity (0.603)) with satisfactory predictive ability to screen for individuals with high risk of UADT. They recommended validation of this model in other populations to detect subgroups to be directed towards comprehensive clinical evaluation [6]. Also, in a recent case-control dietary risk score modeling of oral cancer in southeast China, results indicated the dietary
risk-score ranged from 0 to 66, and a plotted receiver operating characteristic (ROC) curve to evaluate the predictive accuracy of this dietary risk score, showed an area under the curve (AUC) of 0.682 [10].

A recent national study reported an increasing trend in age-standardised rates of cancer of head and neck in Iran [11], and recommended the identification of vulnerable groups and risk factors in order to reduce the burden of these cancers [11]. Finding high-risk people using risk score evaluation models can be helpful in screening and early diagnosis of HNSCC in a high populated country like Iran, especially in remote and regional areas; where people did not have access to high quality health care systems. Considering the lack of information and study in this population, this study provides a risk factor-based model for HNSCC, using various risk indicators, in an Iranian population.

5-2-3-Methods

This matched case-control study was conducted in the Medical Oncology Department (Cancer Institute) of Imam Khomeini Hospital Complex, Tehran, Iran, during 2016-2017, which comprised of patients from both urban and rural areas from all around the country. The Ethics Committee of the Iranian Medical University approved the project. Informed consent was obtained from all participants after an explanation of the purpose of the study. All participants were assured of anonymity and confidentiality.

5-2-3-1-Participant recruitment

A total of 150 newly diagnosed head and neck malignancy cases, aged ≥18 years, participated in this study. The number of cases was determined by sample size calculations (power=80%, α=5%, 10% loss of participation). The participants’ characteristics and recruitment was described in detail elsewhere [12]. One or two matched age and sex controls for each case were selected from people in outpatient clinics and waiting rooms at the same hospital, in the same period as the case group. The selection criteria were: age ≥18 years, not diagnosed with any cancer, and not suffering from memory loss. For avoiding selection bias, eligible controls were approached in a random order, until one agreed to participate. They were orally examined for clearance from oral cancer.
5-2-3-2-Study protocol

Information regarding all predictors, including risk factors and indicators of HNSCC based on a literature search [1, 6, 10, 13, 14], were collected from participants using a self-administered structured questionnaire. Information was obtained regarding demographic and socio-economic characteristics including: gender, age, marital status, education, employment, place of residency, assets, income satisfaction and financial management, life-course smoking, second hand smoking (in childhood and adulthood), and other types of tobacco and alcohol consumption, fruit and vegetable (raw, cooked) diet and oral hygiene practices (brushing and flossing), weekly exercise, lip sunscreen usage, history of oral sex, family history of cancer and brief medical history. The ABO and RH blood groups in both groups were recorded from medical history or identification documents, whenever possible and otherwise defined with slide agglutination and a blood group test. The easy to recall questions were used to avoid recall bias. The participants were requested to restrict the information to the time point before the onset of symptoms of oral cancer. A trained interviewer was available for response to the participants’ queries and assistance.

5-2-3-3-Variables

The outcome was diagnosis with HNSCC (oral cavity and lip, nasopharynx, other pharynx and larynx), confirmed by histopathology.

Predictors were dichotomized into broad categories so that questions could be easily administered for risk scoring, by adapting the previous study [6, 10]. A composite wealth index was created by adapting the existing validated asset questions (house ownership, car, computer, and utensils) and financial status (income satisfaction and financial management) using principal component analysis as an economic status proxy [15-18]. Then it was dichotomized considering the median.

5-2-3-4-Statistical analysis

SPSS (version 21), and STATA 11 software were used for data processing. Chi-square or Fisher’s exact test, were used to compare the case and control groups (P< 0.05 significant level). Statistically significant predictors at the bivariate level were included in the multivariable logistic regression. The multi-variate associations of risk factors with
HNSCC were tested using binary logistic regression analysis and adjusted odds ratios (ORs) for potential confounders. The Hosmer–Lemeshow test was used for goodness of fit for logistic regression models (P>0.05). In the forward method, first, there were no variables inside the equation, and at each stage the significant variables were entered into regression, until any significant variables did not remain outside the equation.

A risk score was defined by rounding off to the nearest whole number each predictor’s corresponding adjusted OR. ROC curves were plotted to examine the accuracy of the final model and risk scores cut-offs [19]. The ROC curve was plotted considering significant variables risk scores to find the best model for prediction. The optimal cut-off (criterion) value was defined as the one with good area under ROC curve (between 0.5 - 1.0) and simultaneously maximal sensitivity and specificity (Youden’s index).

4-2-4-Results

A total of 148 head and neck cancer patients and 266 randomly selected healthy people completed questionnaires. The cases and controls were matched in terms of age and gender. Self-reported age in years was matched between cases (58.91 ±15.59) and controls (58.41 ±15.94), ranging from 18–80 (P=0.75). The gender distribution was also the same in cases (Male: 80 (%54), Female: 68 (%46) and controls (Male: (136 (51%), Female: 130(49%) (p=0.56). From all predictors that has been dichotomized into broad categories: habit (other type of tobacco), diet (fruits, raw and cooked vegetables), socio-economic status (SES), (economic status, education), oral health practice (brushing and flossing), lifestyle habit (lip sunscreen, weekly exercise), Rh +/- status, and green tea consumption were significantly different between the two groups. Smoking status was not significant between the two groups when it dichotomized that to ever and never categories. Although ABO blood group was significantly different between the two groups, it was not included in risk analysis, due to inability to dichotomize the variable. Table 1 indicates the distribution of significant predictors of HNSCC with related adjusted OR (% 95 CI), as well as risk scores for the predictors. The total risk score determined ranged from 0 to 51 for each individual.

Youden’s Index and the associated criterion value was used to examine the accuracy of the multivariate model to predict the most common risk predictors for HNSCC to distinguish between two groups. Four models were used considering the significant
predictors including: 1-Diet and habit, 2-Diet, habit, SES, 3-Diet, habit, SES, oral health practice and lifestyle 4-all significant factors to find the most accurate risk factor based model for oral cancer prediction. Figure 1(a-d) illustrates the ROC curve indicating area under curve (AUC) for each category of predictors. (Model 1: AUC 1: 0.67, 95% CI = 0.62–0.72, standard error = 0.02, z-statistic = 6.33, P < 0.0001); (Model 2: AUC 2: 0.72, 95% CI = 0.67–0.76), standard error = 0.02, z-statistic = 8.40, P < 0.0001); (Model 3: AUC 3: 0.75, 95% CI = 0.71–0.79), standard error = 0.02, z-statistic = 10.55, P < 0.0001); (Model 4: AUC 4: 0.75, 95% CI = 0.70–0.79), standard error = 0.02, z-statistic = 10.48, P < 0.0001). Table 2 summarizes the predictive performance of this study risk-factor based model analysis.

Table 5-2-1: Frequency of significant predictors with related adjusted OR for age and gender.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%) in cases</th>
<th>Number (%) in controls</th>
<th>Total number (%)</th>
<th>Adjusted OR</th>
<th>P-Value</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Economic Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>43 (21.18)</td>
<td>160 (78.82)</td>
<td>203 (49.75)</td>
<td>Ref</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>100 (48.78)</td>
<td>105 (51.22)</td>
<td>205 (50.25)</td>
<td>3.83 (2.42-6.06)</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 12 years</td>
<td>11 (17.45)</td>
<td>52 (82.54)</td>
<td>63 (15.22)</td>
<td>Ref</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>less than 12 years</td>
<td>137 (39.03)</td>
<td>214 (60.97)</td>
<td>351 (84.78)</td>
<td>3.46 (1.65-7.24)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td><strong>Other tobacco</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>121 (33.43)</td>
<td>241 (66.57)</td>
<td>362 (94.27)</td>
<td>Ref</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>13 (59.09)</td>
<td>9 (40.91)</td>
<td>22 (5.73)</td>
<td>2.85 (1.61-7.00)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td><strong>Fruit consumption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 and more daily</td>
<td>109 (31.14)</td>
<td>241 (68.86)</td>
<td>350 (86.63)</td>
<td>Ref</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Less than 2 daily</td>
<td>38 (70.37)</td>
<td>16 (29.63)</td>
<td>54 (13.37)</td>
<td>5.20 (2.77-9.80)</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>1 and more weekly</td>
<td>Less than 1 weekly</td>
<td>1 and more daily</td>
<td>Less than 1 daily</td>
<td>Brushing</td>
<td>Flossing</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------</td>
<td>--------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Raw vegetable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and more weekly</td>
<td>70 (29.17)</td>
<td>170 (70.78)</td>
<td>240 (58.39)</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 1 weekly</td>
<td>77 (45.03)</td>
<td>94 (54.97)</td>
<td>171 (41.61)</td>
<td>2.04 (1.34-3.10)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Cooked vegetable</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and more weekly</td>
<td>55 (24.89)</td>
<td>166 (75.11)</td>
<td>221 (53.90)</td>
<td>Ref</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Less than 1 weekly</td>
<td>91 (48.15)</td>
<td>98 (51.85)</td>
<td>189 (46.10)</td>
<td>2.77 (1.81-4.23)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Brushing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and more daily</td>
<td>27 (20.77)</td>
<td>103 (79.23)</td>
<td>130 (31.78)</td>
<td>Ref</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Less than 1 daily</td>
<td>116 (41.58)</td>
<td>163 (58.42)</td>
<td>279 (68.22)</td>
<td>3.08 (1.83-5.18)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Flossing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 and more daily</td>
<td>7 (6.73)</td>
<td>97 (93.23)</td>
<td>104 (25.43)</td>
<td>Ref</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Less than 1 daily</td>
<td>140 (45.90)</td>
<td>165 (54.10)</td>
<td>305 (74.57)</td>
<td>14.48 (6.3-33.3)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Green tea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>31 (21.68)</td>
<td>112 (78.32)</td>
<td>143 (34.88)</td>
<td>Ref</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>116 (43.45)</td>
<td>151 (56.55)</td>
<td>267 (65.12)</td>
<td>2.92 (1.81-4.71)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than 1 weekly</td>
<td>33 (25.98)</td>
<td>94 (74.02)</td>
<td>127 (31.36)</td>
<td>Ref</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Less than 1 weekly</td>
<td>111 (39.93)</td>
<td>167 (60.07)</td>
<td>278 (68.64)</td>
<td>2.08 (1.28-3.40)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Lip sunscreen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td>11 (11.70)</td>
<td>83 (88.30)</td>
<td>94 (22.98)</td>
<td>Ref</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>135 (42.86)</td>
<td>180 (57.14)</td>
<td>315 (77.02)</td>
<td>6.84 (3.37-13.8)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Rh</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>133 (38.89)</td>
<td>209 (61.11)</td>
<td>342 (82.81)</td>
<td>Ref</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>
Table 5-2-2: Predictive performance of 4 risk score model analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Criterion</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
<th>+ LRφ</th>
<th>-LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk 1*</td>
<td>&gt;3</td>
<td>55.78</td>
<td>47.4 - 64.0</td>
<td>71.05</td>
<td>65.2 - 76.4</td>
<td>1.93</td>
<td>0.62</td>
</tr>
<tr>
<td>Risk 2^</td>
<td>&gt; 9</td>
<td>53.06</td>
<td>44.7 - 61.3</td>
<td>79.70</td>
<td>74.4 - 84.4</td>
<td>2.61</td>
<td>0.59</td>
</tr>
<tr>
<td>Risk 3#</td>
<td>&gt;25</td>
<td>91.16</td>
<td>85.4 - 95.2</td>
<td>49.62</td>
<td>43.5 - 55.8</td>
<td>1.81</td>
<td>0.18</td>
</tr>
<tr>
<td>Risk 4@</td>
<td>&gt;28</td>
<td>91.89</td>
<td>86.3 - 95.7</td>
<td>49.25</td>
<td>43.1 - 55.4</td>
<td>1.81</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* Risk 1: Diet and habit
^ Risk 2: Diet, habit, SES
# Risk 3: Diet, habit, SES, oral health practice and lifestyle
@ Risk 4: Diet, habit, SES, oral health practice, lifestyle and Rh and green tea drinking
φ Likelihood ratio
Figure 5-2-1(a-d): ROC curve for 4 risk factor-based model score and the developing of HNSCC
Discussion

Results of this matched age and gender case-control study provides the draft for a new approach to screening of high-risk populations to enable timely detection of HNSCC. The information has been obtained from patients and matched controls about all established risk factors, as well as possible risk factors and indicators, as identified in previously published literature. All significant variables considered as predictors in this risk-factor model for screening of HNSCC included: other type of tobacco, fruits, raw and cooked vegetables, economic status, education, brushing and flossing, lip sunscreen, weekly exercise, green tea consumption and Rh (+/-) status. The easy to recall questions were used to avoid bias, however, recall bias is inevitable because of the nature of the study design.

The dichotomized system according to previous studies were used [1, 4, 6] for convenience risk scoring. Questions about smoking and second-hand smoking in childhood and adulthood were asked from the study population, but these variables were not included in the model due to insignificant results in dichotomized categories (ever and never) that was not in accordance with most previous studies [1, 6, 10, 20]. The results of this study also showed no significant difference in alcohol consumption between healthy and cancer patients. Only a small group of participants in this study mentioned a history of alcohol consumption, (due to the illegal use of alcohol in Iran); but Gupta et al could not find statistical significant associations between oral cancer and alcohol [21]. A study amongst high-risk Chinese also failed to show that smoking and/or drinking alcohol were associated with risk of UADT cancers among women [3, 22]. However, the validity of self-reported exposures to tobacco and alcohol always raises concerns, especially due to pressure to quit or social embarrassment in societies [3].

Gupta et al, in their study, included the non-significant predictors at the bivariate level, but which was an established risk factor according to the previous studies. In the multivariable model, however, it seems that it is not necessary, and did not have a meaningful effect on the final results [6].

To find the best predictor model, a different set of significant risk factors in this society has been plotted. AUC > 0.7 represents reasonable predictive ability and AUC > 0.8 represents strong predictive ability [25]. In this study, the risk factor-based model had
reasonable predictive value in 3 out of 4 models. Results showed that the combination of all significant risk factors had a strong AUC with high sensitivity (91.89), however the highest specificity (79.70) which indicated, in combination of habit, diet and SES (model 2). Gupta et al (2016) in India reported an AUC 0.9 with optimal sensitivity (93.5%), and specificity (71.1%) for prediction of UADT in their model, including smoking, chewing tobacco, Mishri use, second hand exposure to tobacco smoke, drinking alcohol, spices in food, type of housing and Body Mass Index [1]. Krishna Rao et al (2016) reported the AUC (0.866) with the sensitivity (0.928) and specificity while specificity (0.603) for prediction of UADT in their model including smoking, chewing tobacco, fruit consumption, rinsing mouth with water after eating/chewing, and family history of UADT cancer in India [6]. Chen et al (2017) in China reported AUC (0.682), for the risk of dietary intake including meat, seafood, fish, leafy vegetables, other vegetables, fruit, milk and dairy products and eggs in oral cancer development. However, they did not mention sensitivity and specificity of their model [10].

Plotting ROC curves for individual risk factors and combined scores for the risk factors of UADT cancer have been previously studied in different countries including Sri Lanka, Taiwan, and India [1, 4, 6, 23]. Two of these studies were based on oral potentially malignant disorders (OPMDs) [4, 23] and only one was matched for age and gender (potential confounding) [1]. In addition, the dietary risk score for oral cancer with a generating ROC curve has been studied in a Chinese population. However, predictors included in these studies were different from the ones involved in the present study [10].

As mentioned in previous studies [12, 24], SES may influence the risk of developing oral cancer as well as a delay in diagnosis; however, there are controversies in components. Education and wealth index (measuring with assets and financial questionings) was used as a SES proxy in this study. Employment status was evaluated as a separate variable as well, but it was not included in the risk score model due to insignificant results.

In addition, oral health practice in detail (brushing and flossing) and lifestyle habits (lip sunscreen and weekly exercise) has been evaluated. The results show a high risk-score in both of them. This is an indication that people neglectful about their oral health and healthy behaviors might be more prone to developing cancer.

These results indicated that although previous studies focused more on smoking and
alcohol as risk factors of oral cancer, other variables including oral health behaviour and economic status should be considered in defining the risk of these cancers. Designing a new approach to enable early diagnosis of HNSCC based on screening of high-risk populations is necessary.

This risk-factor based screening model does not deny the importance or need for visual screening, but offers an initial screening of high-risk people. This is especially relevant in large population groups, or in remote areas with limited resource infrastructure and diagnostic facilities in a simple manner with data collection approach for following visual oral examination by trained healthcare workers for further investigation. On the other hand, a vast group of individuals with exposure to risks will be required to undergo extensive clinical oral examination when they may not have oral cancer or OPMDs. This will be a cause of anxiety as well as cost implications. More information from different parts of the world is necessary to develop a good risk score for indicating oral cancer [1].

In conclusion, a high sensitivity rate for HNSCC in this study has been reported by a combination of various risks. Habits and diet alone could not predict HNSCC in this population. Considering risks other than smoking and alcohol are recommended for risk-model screening of HNSCC.

5-2-6-References


Chapter 6

To evaluate the effect of green tea on oral cancer prevention

This chapter has been published as the following article:


Part 2- Is there any association between green tea consumption and the risk of head and neck squamous cell carcinoma: Finding from a case-control study. (Appendix G)
6-1- Does green tea consumption improve the salivary antioxidant status of smokers?

6-1-1-Abstract

Objective: Considering the higher rate of oral cancer, and reduction in salivary antioxidants in smokers as indicated in previous studies, antioxidant-containing nutrients such as green tea, seem to be beneficial in counteracting against oxidative stress in this group. This study assessed the salivary total antioxidant alteration in smokers compared to nonsmokers, after short-term (7 days) and long-term (3 weeks), green tea drinking.

Methods: In this experimental study, 20 volunteer moderate-to-heavy male smokers, and 20 matched healthy non-smokers were selected to participate, according to the inclusion criteria. Participants were instructed to drink two cups of green tea per day, by dissolving 2 grams of green tea in 150 ml of hot water for each cup. After saliva collection, antioxidant capacity of saliva was measured at baseline, after 7 days, and after 21 days. Statistical evaluation was done by SPSS 21, using paired sample T-tests, one-way ANOVA and Bonferroni tests.

Results: At day zero, nonsmokers had a higher antioxidant capacity than smokers (686.6 ± 62.22 Vs. 338.8 ±69.9) mM/50 µL, P< 0.001). There was also a significant difference between two groups in salivary total antioxidant capacity after one week and three weeks of green tea consumption (P<0.001). However, there was an upward trend in both smokers and non-smokers over the study period (after tea drinking). In addition, a significant difference was found in total antioxidant capacity alteration in smokers compared to non-smokers from baseline to day 21.

Conclusions: Results support the effectiveness of green tea consumption in salivary antioxidants enhancement in smokers, in both the short- and long-term.

6-1-2-Introduction

Tea prepared from the leaves of Camellia Sinensis, is a mixture of a large number of bioactive compounds including catechins, flavonols, lignans, and phenolic acids. Differences in processing of leaves result in different types of tea. Fresh tea leaves steamed immediately after harvesting in processing green tea (GT), result in minimal
oxidation of the naturally occurring polyphenols [1, 2]. Tea polyphenols are strong antioxidants and radical scavengers that are a potential mechanism for the chemopreventive effect against carcinogenesis.

Smoking is a serious global public health problem; cigarette smoke contains numerous compounds that generate reactive oxygen species (ROS), which trigger oxidative damage to DNA and cellular components, thereby contributing to carcinogenesis [4,5]. Due to the popularity of cigarette smoking and tea drinking, several experimental studies have explored the possible inhibitory effects of tea on cancer formation induced by cigarette smoking [5]. In human experiments, Schwartz, Baker, Larios, and Chung (2005) [6] and Hakim et al. (2003) [7] have shown that GT treatment lead to reducing DNA damage in smokers. These findings demonstrated the antioxidative property of GT in anticarcinogenesis [2]. Moreover, two small trials in patients with premalignant oral lesions demonstrated that the administration of tea resulted in a reduced risk of oral cancer [8-10] however, it is not known whether tea has a role in the primary prevention of oral cancer, or the effect of tea on oral cells might be different in smokers than non-smokers [8]. In an intervention study on the ingestion and topical application of green tea significantly decreased the size of oral lesions in comparison to the untreated controls [9].

Saliva is the first biological medium encountered during inhalation of cigarette smoke and first line of defense against oxidative stress. The antioxidant system of saliva has protective effects against microorganisms, toxins and oxidants, so may play a role in the anti-carcinogenic effect [11]. Based on the previous studies, oxidant-antioxidant balance of saliva is degraded in favour of oxidants in smokers, and this per se, may contribute to oral hygiene deterioration and oral cancer development in smokers [12, 13].

Carcinogenesis is a multistage process [14]. Constant and direct attacks of smoking on the oral epithelial cells gradually accumulates and leads to stepwise malignant transformation [15]. Thus it has many phases for prevention and intervention. Green tea is an ideal agent for a chemoprevention study because it has a low cost and toxicity and is readily available. Considering the inconclusive outcome about the protective effects of green tea consumption against the development of oral cancers in humans [14], and given the high performance of saliva in demonstrating the negative impact of smoking both locally and systematically [5], the aim of the present study was to evaluate the effect of short-term (after 7days) and long-term (after 3 weeks) green tea consumption on total
salivary antioxidant capacity (TAC) in smokers, to determine the rate of change in TAC, with the daily intake of green tea.

6-1-3-Methods and materials

6-1-3-1-Ethics

The study was conducted according to the principles of the “Declaration of Helsinki”; and approved by the Ethics Committee of the local Medical University (IR.SBMU.RIDS.REC.1394.76). All participants signed an informed consent document prior to the study.

6-1-3-2-Participants

In this experimental study, 40 healthy male moderate to heavy cigarette smokers (CS) and non-smokers (NCS) were studied. The sample size was determined with power and sample size calculation software, version 3.0.43 (power 80%), considering 20% potential loss of participants. Twenty moderate to heavy CS; (defined as those who ever smoked 100 cigarettes, smoked daily in the past 30 days, and smoked more than 10 cigarettes/day) [16]; and 20 matched control NCS; (who were self-reported of having never smoked); were selected through a convenience sampling method. The participants were recruited from attendees to the oral medicine department, Shahid Beheshti University of Medical Sciences, Tehran, Iran for routine dental checkups, and who met the inclusion criteria, during a 2-month period. Adult healthy Persian males were included (considering the case definition), who: had at least 20 teeth; without any surgical or non-surgical periodontal therapy in the past 6 months; and, did not drink more than one cup of green tea, or 3 cups of black tea or coffee daily. Also, participants were examined for clearance from oral lesions before inclusion in the study. Subjects with a history of any systemic diseases, regular users of mouthwash, medications or vitamin supplements within the past 3 months, those who had special dietary requirements, or alcohol and drug abusers were excluded from the study.

6-1-3-3-Experimental protocol

All participants were asked to consume a total of two cups of green tea per day between breakfast and lunch and between lunch and dinner for the period of three weeks. Every
cup was prepared by infusing 2 grams of GT in 150 ml of hot water (80°C) for 3 min. To reduce variation in consumption of GT, all packages of green tea from the same brand (Golestan brand) with the same production date and batch types were purchased. GT was supplied in small tea bags after careful weighing with a digital scale. Also, the same glasses for each participant were provided for equalizing the amount of heated water. They could add sugar to the tea, but the addition of milk was not allowed. The bags of tea were labeled with each subject’s number, and they were asked to stick their labels in a daily diary as a compliance check. The subjects were instructed to adhere as closely as possible to their normal eating habits during the experiment. Moreover, they were not allowed to consume more than 2 oranges or 2 glasses of fruit juice per day or to drink more than one cup of black tea in order to match the amount of antioxidants among participants as much as possible [17,18].

6-1-3-4-Saliva collection

Whole unstimulated saliva was collected at baseline, after 1 week and after 3 weeks of tea consumption. After rinsing the mouth with 15 ml of distilled water, subjects had to spit almost 2 ml of their saliva into falcon tubes in an upright position, between 9 and 12 o’clock in the morning. They had been requested to avoid eating, drinking or smoking at least 1 h before the saliva collection. The samples were immediately centrifuged at 3000 rpm at 4°C for 15 min; then was stored at 70°C until analysis. The trained senior students and the technician were blind about the participants.

6-1-3-5-Total antioxidant capacity assay (TAC)

TAC was measured by the ferric reducing ability of plasma (FRAP) method. This is a valid method for measuring antioxidant capacity, based on the ability of plasma to reduce FeIII to FeII in the presence of TPTZ (Tripyridyltriazine). After reaction, samples were read with the spectrophotometer at maximum absorbance in 593 nm [19]. This method has previously been used for measuring salivary TAC [20]. In this study, all samples were measured at the same time with one solution, and results were read with one calibrated spectrophotometer (SHIMADZU). Also, one experienced technician (who was blind about cases) completed all procedures, under supervision of a clinical biochemistry specialist.
6-1-3-6-Statistical analysis

Results are expressed as differences between groups were assessed by paired sample T-tests, One-way ANOVA and Bonferroni tests. Statistical significance was set at 95% (P < 0.05). SPSS software (Version 21) was used for statistical analyses.

6-1-4-Results

In the present study, 20 moderate-to-heavy CS males and 20 NCS males participated. The age of the CS group was 31.3 ± 6.7, and the NCS group was 31.8 ± 7.3, without any significant differences (P = 0.97). Table 1 provides the details of age in two groups.

A statistical test (paired t-test) was used to assess the difference between smokers and non-smokers in terms of salivary antioxidant capacity. The salivary TAC of each group at different times is indicated in Table 2 and Fig. 1.

At day zero the NCS group had higher salivary total antioxidant capacity (P<0.001). There was a significant difference between the two groups (CS and NCS) in average TAC after one week and three weeks of green tea consumption (P<0.001), with higher amounts of salivary TAC in the NCS group. However, a Bonferroni test showed a significant difference in alteration of salivary TAC in each group during the time, from baseline to day 21 (Table 2). Also, one-way ANOVA (Welch) tests showed a significant difference in total antioxidant capacity alteration in smokers compared to non-smokers, from baseline to day 7, and from day 7 to day 21 (Table 3).
Figure 6-1-1: Salivary TAC in smokers and non-smokers in study period.

Table 6-1-1: Age of participants in smokers and no-smoker groups

<table>
<thead>
<tr>
<th>Age</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS group</td>
<td>23</td>
<td>46</td>
<td>31.30</td>
<td>6.7</td>
</tr>
<tr>
<td>NCS group</td>
<td>23</td>
<td>45</td>
<td>31.80</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Table 6-1-2: Comparison the mean difference of salivary TAC in different time in each group of study

<table>
<thead>
<tr>
<th>Group name</th>
<th>Compare between different times</th>
<th>Mean difference (± SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>Baseline-day 7</td>
<td>8.95 (3.24)</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>Baseline-day 21</td>
<td>16.5 (3.47)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Day 7-day 21</td>
<td>7.55 (2.49)</td>
<td>0.021</td>
</tr>
<tr>
<td>CS</td>
<td>Baseline-day 7</td>
<td>112.45 (14.77)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Baseline-day 21</td>
<td>145.90 (14.07)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Day 7-day 21</td>
<td>33.45 (6.99)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Table 6-1-3: Comparison the mean difference of salivary TAC between smokers and non-smokers in different time

<table>
<thead>
<tr>
<th>Time period</th>
<th>Mean difference (± SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline-day 7</td>
<td>103.50 (15.12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Day 7-day 21</td>
<td>25.90 (7.42)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

6-1-5-Discussion

This study compared salivary TAC after 4 g GT consumptions (Total amount of daily tea ingestion) between CS and NCS. This amount of GT is in accordance with previous studies and is non-toxic [20]. Results indicated the positive potential of GT in increasing salivary TAC in both smokers and non-smokers. Participants were clear of mucosal oral lesions, but might have had dental conditions such as periodontitis and dental caries. Although it is valid to state that the salivary antioxidants are varied in different dental and periodontal conditions, the alteration of total antioxidant capacity during the time, after green tea consumption has been reported. Considering the fact that participants did not undergo any periodontal or dental treatment during the study, and they were asked to adhere to their previous dietary intake, these dental conditions did not change the results. Regarding the role of ROS in mediating apoptosis in various cancer cells, antioxidants with free radical scavenging action could protect cells from further cellular damage and in turn cancer prevention [7, 18, 20].

There are limited studies that investigated the role of GT on salivary antioxidant activity. Tavakol et al. (2013) evaluated the protective effects of green tea (in 30 Persian chemical laboratory workers) on salivary antioxidative biomarkers in a cross-sectional study after 28 days, and concluded that daily consumption of one cup GT (3 g GT, in 300 ml hot water) can reduce several parameters indicative of salivary oxidative stress such as TAC [20]. They reported the same results about the protective effect of GT in saliva with the same method for measuring TAC in accordance with this study; however, they did not consider smokers in their study. Although they used one cup of GT the amount of hot water was the same as this study and the amount of GT was almost the same of the present study. In an interventional, crossover trial in elderly subjects, Narotzki, Reznick, Mitki,
Aizenbud, and Levy (2014) reported salivary TAC was improved by 1.5g of GT drinking. However, no changes were observed in oral peroxidase enzymes [21].

Results of the present study demonstrated that, although the average TAC was always higher in the NCS group, the rate of change in TAC was significantly higher from baseline to day 7 and from day 7 to day 21 in CS group. These results support the more beneficial effects of green tea in smokers.

There are quite a few studies that reported the difference in antioxidant activity of smokers and non-smokers. However, there is a lack of evidence on the effect of GT on salivary TAC in smokers.

Previous studies evaluated the effect of tea on cigarette induced oxidative damage with inconsistent results [1, 17, 22-24]. Al-Awaida et al. in 2014, exposed the albino rat model to cigarette smoke and reported that oxidative stress, inflammation and tissue damage could be prevented by supplementation of Chinese green tea. They indicated that cigarette smoke exposure caused a significant decrease in catalase specific activity, but after GT administration in combination with cigarette smoke exposure, the catalase specific activities were significantly increased compared to smoke exposed rats given water as a drink [1].

In the present study, the time-relation of GT consumption on CS was evaluated. The results showed a significant difference in trend of TAC in each group over time. Although it has been demonstrated that plasma total antioxidant activity increased a few hours after the intake of single doses of GT [18], controversial results are reported about the effect of regular tea consumption [25, 26]. Erba et al. (2005) reported that a dietary long-term (42days) intervention with a moderate amount of GT (two cups a day), could improve plasma total antioxidant activity and antioxidant status [18]. They concluded that, after regular GT drinking, the mean plasma polyphenol concentration reaches a steady state that is significantly higher than baseline level, and remains for at least 12 h after the last ingestion [18]. In this study, the short-term (after 7 days) and long-term (after 3 weeks) effect of GT on CS and NCS was evaluated. The results indicated that there is a time-relation between GT consumption and salivary TAC. In addition, this finding supports the better effectiveness of GT on smokers in time period. In this experiment tea bags
were used for the intervention, and based on the availability of the other products, further study to compare them is recommended.

6-1-6-Conclusion

The level of total antioxidant capacity was always lower in smokers than non-smokers in the experimental period; however, there was a big difference in the amount of salivary antioxidant capacity in smokers post green tea consumption. Therefore, it seems that drinking green tea could partially compensate for the harmful effects of smoking by increasing the salivary antioxidant components, which has a significant role in the repair of cellular damage and per se might prevent oral cavity cancer. Nonetheless, since antioxidant components are not the only markers for oral pathologies, there is still a need for more clinical and biological interventions to identify guidelines for green tea consumption as part of prevention or treatment of oral conditions in smokers.

6-1-7-References


6-2- Is there any association between green tea consumption and the risk of head and neck squamous cell carcinoma? Findings from a case-control study.

6-2-1-Abstract

Objective: Green tea consumption has been shown to reduce the incidence of head and neck Squamous cell Carcinoma (HNSCC) in experimental animal models, however the results from human studies are inconclusive. The aim of this study was to evaluate the relationship between green tea consumption and the risk of HNSCC.

Methods: The study utilised a standardised questionnaire to investigate the relationship between green tea consumption and HNSCC experience. Data about the amount of green tea consumption was recorded from 147 patients with HNSCC and 263 age and gender matched controls. The results were analyzed with SPSS statistical software Version 21 using Chi-square test, and Logistic Regression (with a 95% confidence interval). Significance levels were set at 95% and p-values less than 0.05 were considered significant.

Results: Statistical analysis indicated significant differences between different groups of tea consumers in terms of HNSCC risk (P<0.001). The risk of developing oral cancer those who consume <1 cup of green tea daily was (OR= 0.29 (0.16-0.52) and for the group of >=1 cup green tea consumers was 0.38(0.17- 0.86) of those who never consume green tea (Reference point) after adjustment for other risk factors.

Conclusions: The findings support that green tea consumption may reduce the risk of HNSCC. To confirm the efficacy of green tea intake in preventing the development of HNSCC in humans further investigation is needed.

6-2-2-Introduction

Cancer is a leading cause of death world-wide. Some 90% of oral cancers are squamous cell carcinomas arising from the squamous epithelium [1, 2]. The cause of HNSCC is multifactorial. Approximately one in three head and neck cancer-related deaths are linked to lifestyle factors that include the consumption of alcohol, tobacco products, poor diet, and physical inactivity [3, 4].
The oral cavity is the entry point to the digestive tract for many carcinogens and anti-cancer substances [3, 5]. Dietary factors may play an important role in the development or prevention of oral cancer [2, 4]. Tea is the second most popular beverage consumed world-wide. It is derived from the leaves of the Camellia Sinensis plant [6], and includes a large number of bioactive substances such as catechins, flavonols, lignans, and phenolic acids [7]. Tea polyphenols are strong antioxidants and radical scavengers [3, 7, 8]. The mechanism of anti-oxidative activity of polyphenols includes the neutralization of free radicals in the body, the reduction or inhibition of ROS generation, cell division and apoptosis [4, 8]. Also, polyphenols inhibit angiogenesis, proliferation, invasion, and metastasis of cancer cells [4].

Green tea contains high levels of polyphenols. In the process of making green tea, fresh tea leaves are steamed or heated immediately after harvest, so that there is minimal oxidation of polyphenols [7]. Previous studies have indicated that green tea consumption may protect against various oral diseases including oral malignancy [3, 7]. Green tea may reduce DNA damage and increase total antioxidant capacity in smokers [7]. It may also reduce the risk of oral cancer in patients with premalignant oral lesions [7, 9].

The cancer-preventing effect of green tea has been demonstrated in laboratory studies [9-11], but results from human studies are limited and inconclusive [12] (Yuan 2013). Two previous case-control studies reporting the anti-carcinogenic effect of green tea, collected data using a standard questionnaire and interviews regarding tea consumption (frequency, duration, and type) [4, 13].

The aim of this study was to evaluate the relationship between green tea drinking and the risk of developing HNSCC, in Tehran, the capital of Iran.

6-2-3-Materials and methods

6-2-3-Ethics

The study was conducted according to the principles of the “Declaration of Helsinki”; and approved by the Ethics Committee of the Iranian University of Medical Sciences (code number: Abzums.Rec.1395.97). All participants signed an informed consent document prior to the study. Data were de-identified to protect patient confidentiality.
6-2-3-2-Participation

This study builds on the previous case-control study on HNSCC [14]. The participants’ characteristics and recruitment were described in detail in that study [14]. In that study, 147 patients in the case group and 263 individuals in the control group completed questionnaires about green tea consumption (2016-17). The case group consisted of patients (over age 18 years) newly diagnosed with histologically confirmed primary HNSCC in a major medical center in Tehran, Iran. Exclusion criteria were those who had cancer previously, or who had any other malignancy. The control group was randomly selected from people in waiting rooms and outpatient clinics at the same hospital, throughout the same period as the case group, to ensure the same exposure patterns in the source population. Controls were frequency-matched to the cases on age and gender, which was difficult due to older adults in the case group; however, it partly overcame by choosing the study group from a leading medical center in Tehran (a city with a population of more than 10 million), with large attendance numbers of referral patients. People with a history of any cancers or pre-cancerous lesions (leukoplakia and erythroplakia) were excluded from control group. All participants were visually examined for oral cancer clearance.

6-2-3-3-Study protocol

Information was collected from case and controls using a self-administered structured questionnaire that included demographic and socio-demographic characteristics (age, gender), smoking and alcohol consumption, a brief medical history, family history of cancer, and green tea consumption. The questions were structured for ease of recall to avoid recall bias. A trained interviewer was available to assist and respond to participants questions.

6-2-3-4-Variables

Outcome Variables:

The outcome was diagnosis with HNSCC, confirmed by histopathology. Details of HNSCC patients are provided in a supplementary table. (Table 1’)

Explanatory Variables:

Age was recorded as the date of birth. Cigarette smoking was recorded as either a current smoker, ex-smoker, or non-smoker. Alcohol and other tobacco consumption (smokeless and water-pipe) were recorded as ever and never consumption. A yes/no question was used to record family history of cancer. Daily consumption of green tea in the previous two years was recorded as never, <1 cup, between 1-2 cups and >2 cups.

6-2-3-5-Statistical analysis

Data were analyzed using SPSS statistical software, Version 21. Chi-square tests, Fisher tests and Logistic Regression (with a 95% confidence interval) were used to analyze the relation between drinking green tea and HNSCC. Significance levels were set at 95%, and p-values less than 0.05 were considered significant.

6-2-4-Results

In this study 147 adults (77 female and 70 male) with HNSCC and 263 controls (130 female and 133 male) were evaluated. The mean (±SD) age of the case group was (58.91 ±15.59) years and for the controls, (58.41 ±15.94) years. Age and gender were matched in two groups (p=0.76 and p=0.56 respectively). Table 1 presents the distributions of oral cancer according to the amount of tea consumption (never, <1 cup, between 1-2 cups vs >2 cups daily). Based on a Chi-Square Test, there was a significant difference between green tea consumers and the development of oral cancer (P<0.001). Only 10 people, all in control group mentioned alcohol consumption. In the case group: 3 people were current cigarette smokers, 27 people were ex- cigarette smokers, and 13 people used other types of tobacco. In the control group, there were 28 current cigarette smokers, 11 ex-cigarette smokers, and 9 users of other types of tobacco.
Table 6-2-1: The distributions of different variables in case and control group

<table>
<thead>
<tr>
<th>Variables</th>
<th>HNSCC (N=147)</th>
<th>Control group (N=263)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cigarette smokers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>3 (2.04)</td>
<td>28 (10.64)</td>
<td></td>
</tr>
<tr>
<td>Ex</td>
<td>27 (18.36)</td>
<td>11 (4.18)</td>
<td>0.001</td>
</tr>
<tr>
<td>Never</td>
<td>117 (79.59)</td>
<td>224 (85.17)</td>
<td></td>
</tr>
<tr>
<td><strong>Other tobacco</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>13 (8.84)</td>
<td>9 (3.42)</td>
<td>0.01</td>
</tr>
<tr>
<td>Never</td>
<td>134 (91.15)</td>
<td>254 (96.57)</td>
<td></td>
</tr>
<tr>
<td><strong>Tobacco overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>32 (21.76)</td>
<td>42 (15.96)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>115 (78.23)</td>
<td>221 (84.03)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>0 (0)</td>
<td>10 (3.80)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>147 (100)</td>
<td>253 (96.19)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Green tea consumption</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>116 (78.91)</td>
<td>151 (57.41)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 cup</td>
<td>20 (13.60)</td>
<td>81 (30.79)</td>
<td></td>
</tr>
<tr>
<td>1-2 cups</td>
<td>7 (4.76)</td>
<td>25 (9.50)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt;2 cups</td>
<td>4 (2.72)</td>
<td>6 (2.81)</td>
<td></td>
</tr>
</tbody>
</table>
Logistic regression analysis indicated significant differences between different groups of tea consumers in terms of HNSCC risk (P<0.001) (Table 2). This table provides the information regarding crude odds ratio (OR) and confidence interval (CI) of each tea consumption group. Only 10 participants mentioned that they consume more than 2 cups of green tea daily that might affect the results; therefore this group has been merged with the 1-2 cups group for further analysis. The results of logistic regression analysis OR with 95% CI before and after adjustment of other risk factors are presented in Table 3. The adjustment has been provided in 3 different models and the results indicated significant differences between case and control groups after adjustment for all confounders, including the smoking (cigarette and other types) and alcohol to overcome the effects of these variables. The risk of developing HNSCC in never consumers of green tea was 3.1 and 2.2 times higher than <1 cup daily consumers and >=1 cup daily consumers respectively.

<table>
<thead>
<tr>
<th>Green Tea</th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% C.I. for EXP(B)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>19.813</td>
<td></td>
<td></td>
<td>3</td>
<td>.000</td>
<td>.321</td>
<td>.186</td>
<td>.555</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>-1.135</td>
<td>.279</td>
<td>16.604</td>
<td>1</td>
<td>.000</td>
<td>.364</td>
<td>.152</td>
<td>.872</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>-1.099</td>
<td>.445</td>
<td>5.142</td>
<td>1</td>
<td>.023</td>
<td>.391</td>
<td>.152</td>
<td>.872</td>
<td></td>
</tr>
<tr>
<td>&gt; 2</td>
<td>-.142</td>
<td>.657</td>
<td>.047</td>
<td>1</td>
<td>.829</td>
<td>.868</td>
<td>.239</td>
<td>3.147</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>-.264</td>
<td>.123</td>
<td>4.562</td>
<td>1</td>
<td>.033</td>
<td>.768</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 6-2-3: Regression analysis, before and after adjustment for risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR (CI 95%)</th>
<th>Model1* OR (CI 95%)</th>
<th>Model 2* OR (CI 95%)</th>
<th>Model3* OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Green tea &lt;1 cup</td>
<td>0.32 (0.18-0.55)</td>
<td>0.31 (0.17-0.54)</td>
<td>0.29 (0.16-0.52)</td>
<td>0.30 (0.16-0.56)</td>
</tr>
<tr>
<td>Green tea &gt;=1 cup</td>
<td>0.46 (0.22-0.95)</td>
<td>0.42 (0.19-0.90)</td>
<td>0.38 (0.17-0.86)</td>
<td>0.44 (0.18-1.04)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age and gender
** Adjusted for age and gender and cigarette smoking
*** Adjusted for age and gender and cigarette smoking, alcohol, other types of tobacco

6-2-5-Discussion

In this case-control randomly selected study, an increased risk of HNSCC in participants that never consumed green tea after adjusting for other variables such as age, gender, cigarette smoking, alcohol and other types of tobacco consumption has been observed. The very small number of people in the group with 2 or more cups of green tea consumption was not surprising due to the low popularity of green tea consumption in Iran, therefore, this group has been merged with the 1-2 cups of green tea consumption group.

In present study “cups” used as the measurement of green tea consumption adapting by previous studies [3, 4, 13]. Although laboratory studies on the cancer chemopreventive activities of green tea have shown that polyphenols may prevent oncogenesis by inducing apoptosis and inhibiting angiogenesis [4, 7], in clinical studies the dose-response effect has been emphasized. Previous studies used quantity of consumption (cups per day) for evaluation of the association between green tea and head and neck cancer [4]. Also, in a clinical trial authors concluded that determining the formulation and dosage of green tea for oral cancer prevention is essential [4].

These results support the findings of the meta-analysis published by Zhang et al (2014). The authors reported that tea consumption is inversely associated with the incidence of
oral cancer [3]. They also reported an inverse association between oral cavity cancer and tea consumption in a population-based case-control study conducted with face-to-face interviews and standardized questionnaires [13]. In a 2014 study, Huang found a reduced risk of HNSCC associated with green tea (for those who consumed 3 or more cups per day). This association was especially significant for pharyngeal cancer, although it was also present for oral cancer. Huang reported that the reduced risk of head and neck cancer associated with tea drinking was observed only among regular alcohol drinkers but not among occasional alcohol drinkers or those who abstain from alcohol [4]. However, the study findings show that after adjusting for the effect of alcohol, green tea did reduce the risk of HNSCC. One case–control study by Franceschi et al (1992) found a reduced risk of “mouth” (including gum, floor of the mouth and other unspecified parts of the mouth) cancer related to quantity of tea drinking [15]. In a case-control study from China comparing 723 oral cancer cases and 857 controls, Fu et al (2013) reported that black tea was not associated with the risk of oral cancer while green tea was associated with a reduced risk of oral cancer. In their study approximately 95% of study subjects were men [16], while the effect of gender has been adjusted in this study. Finally, Wang et al, (2014), in a meta-analysis, reported that tea consumption, especially green tea, may have a protective effect on oral cancer,(0.798 (0.673–0.947). These associations were significant in both Asian and Caucasian populations [6].

The results of some studies were inconsistent with these findings. For example, in a hospital-based case-control study from China, Zheng et al (1993) could not find any significant association between green tea drinking and reduced risk of oral cancer (OR=0.85, 95% CI: 0.32–2.31). However, the amount of green tea consumption in their study was low (only 7.4% of study subjects drinking 1 or more cups of green tea per month) [17]. Ide et al (2007) reported a non-significantly reduced risk of oral cancer associated with green tea consumption in a cohort study of 20,550 men and 29,671 women from Japan with an HR of 0.44 (95% CI: 0.19, 1.04). In their 10-year longitudinal study, only 37 participants were diagnosed with oral cancer. So the study was underpowered because of relatively small number of cancer cases (n=37) [18]. In addition, one study reported a significant positive association between risk of oral cancer and green tea consumption [19].
Overall, the results of epidemiologic research on anti-cancer effect of green tea are inconsistent. The different findings between studies in humans can be explained, at least in part, by the following: firstly, the amount of tea drinking by individuals in human studies is relatively low compared to the relative amount of tea that is used in vitro and in vivo experimental studies [12]. Also, the information about the amount of green tea consumed in various studies is not always documented [4]. Secondly, in some regions people are accustomed to drinking hot tea. The high temperature of tea would mask or alter the anti-cancer effect of tea across different populations. Thirdly, cigarette smoking and alcohol consumption have confounding effects and may contribute to the varying results among different studies [12]. The present study adjusted age, gender, cigarette smoking, alcohol, and other tobacco between groups. Fourthly, in a hospital-based case-control study, it is difficult to ensure that cases and controls are drawn from the same source population [4]. However, the effect of this variable was limited. Subjects were recruited from a major medical center located in Tehran City and all were Iranian ethnicity. Finally, according to population-based analysis, the plasma concentration of green tea catechins following a standardized consumption of green tea differs between individuals. This could be a further reason for the variability of the anti-cancer effect of green tea between individuals [20]. Although the overall duration of green tea consumption in the questionnaire did not ask, participants to report on their consumption during the previous two years.

6-2-6-Conclusion

The current study showed an inverse association between HNSCC cancer and green tea consumption, after adjusting other variables. It is necessary to do clinical trials or cohort studies with large numbers of patients to confirm the efficacy of green tea intake against the formation of oral cancer in humans. If the anticancer property of green tea is proven, it may offer as a cheap, popular, natural anti-cancer substance to reduce the occurrence of HNSCC.

6-2-7-References


Supplementary table:

Table 6s-2-1: Distribution of different HNSCC in case group

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>48 (32.21)</td>
</tr>
<tr>
<td>Lip</td>
<td>18 (12.08)</td>
</tr>
<tr>
<td>Vestibule</td>
<td>12 (8.05)</td>
</tr>
<tr>
<td>Cheek</td>
<td>2 (1.34)</td>
</tr>
<tr>
<td>Retromolar</td>
<td>8 (5.36)</td>
</tr>
<tr>
<td>Floor of the mouth</td>
<td>5 (3.35)</td>
</tr>
<tr>
<td>Gum max</td>
<td>9 (6.04)</td>
</tr>
<tr>
<td>Gum man</td>
<td>4 (2.68)</td>
</tr>
<tr>
<td>Palate</td>
<td>9 (6.04)</td>
</tr>
<tr>
<td>Tonsil</td>
<td>2 (1.34)</td>
</tr>
<tr>
<td>Larynx</td>
<td>3 (2.01)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>8 (5.36)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>3 (2.01)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>3 (2.01)</td>
</tr>
<tr>
<td>Middle ear</td>
<td>4 (2.68)</td>
</tr>
<tr>
<td>Max sinus</td>
<td>2 (1.34)</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>3 (2.01)</td>
</tr>
<tr>
<td>Parotid</td>
<td>1 (0.67)</td>
</tr>
<tr>
<td>Sub mandibular gland</td>
<td>2 (1.34)</td>
</tr>
<tr>
<td>Ill-defined site</td>
<td>3 (2.01)</td>
</tr>
</tbody>
</table>
Chapter 7

Discussion
7-1- Preamble

This chapter provides principal results from all studies as the new knowledge gained from this thesis as well as implications and comparisons with previous studies, limitations and strengths of this research and recommendations for future studies.

7-2 Principal findings

7-2-1-Difference in frequency of head and neck cancer in different location (Chapter 3)

The three most common sites of head and neck cancer in Iranian Province were lower lip, tongue and major salivary gland compared with Western Australia, that were lip, tongue and the tonsil. In Western Australia, these malignancies were more frequent among men in the age range of 45–59 years, and in women above the age of 75 years, compared to Iran where both men and women were in the age range of 60–74 years.

7-2-2- Disparities and inequality in head and neck cancer knowledge and awareness (Chapter 4)

Investigation of a defined population in Tehran revealed that one third of the respondents were aware of oral cancer, three quarters had a low knowledge about risk factors, and more than half had a low knowledge about signs and symptoms of head and neck cancer. Participants were more informed about tobacco and alcohol as risk factors; and mouth swelling and long-lasting ulcers as signs and symptoms of oral cancer. A significant difference was found between knowledge and awareness scores in different levels of education and occupation. A created wealth index revealed significantly lower knowledge and awareness among the poorest participants, controlling for age/ gender. Public media was mentioned by almost half of responders as a source of information. Only a slim percent mentioned that dentists were a source of information. These findings indicate insufficient awareness and knowledge about head and neck cancer in Tehran with large inequalities in the socioeconomic disadvantaged population.

7-2-3- Socio-economic inequality in head and neck cancer development (Chapter 5)

Evaluation of risk factors of head and neck cancer, and demographic and socioeconomic status of HNSCC patients in a case-control study revealed there was a significant
difference between the two groups in the composite socioeconomic index (including education and income satisfaction). Better-educated people with higher income satisfaction had a lower risk of HNSCC. No-significant association has been found in employment status and place of residency.

7-2-4- Developing a risk-factor model for HNSCC (Chapter 5)

Developing a risk factor-based model for HNSCC, based on significant risk indicators including habits (other type of tobacco), diet (fruits, raw and cooked vegetables), SES (economic status, education), oral health practice (brushing and flossing), lifestyle habit (lip sunscreen, weekly exercise), Rh +/- status, and green tea consumption on HNSCC cases and matched healthy control revealed that the total risk score for each individual ranged from 0 to 51. Results show that the combination of all significant risk factors had a strong area under the curve (AUC=0.75) with high sensitivity (92%).

7-2-5- Salivary antioxidant status improvement after green tea consumption in smokers (Chapter 6)

Significantly lower salivary TAC in smokers than non-smokers has been shown in the beginning of this study that suggested the effect of smoking on oxidation system. After green tea drinking, there was an upward trend in salivary TAC in both smokers and non-smokers over the study period. Although a lower amount of salivary total antioxidant capacity in smokers revealed, even after one week and three weeks of green tea consumption, a significant difference in TAC alteration in smokers compared to non-smokers from baseline to day 21.

7-2-6- Preventive effect of green tea consumption on head and neck squamous cell carcinoma (HNSCC) (Chapter 6)

Significant lower HNSCC risk has been indicated in consumers of green tea (less than 1 to 2 or more cups daily compared to never consumers in a case-control study on HNSCC after adjustment for other risk factors.)
7-3-Implications, comparison and recommendations (What this study adds)

The first part of this study looked into the patterns of the head and the neck malignancy in a province in Iran, and compared the findings with a more or less similar population in metropolitan Western Australia.

In recent report of WHO (2015), cancer is the in the top four leading causes of death (age 0-69) in 113 of 172 countries around the world. It has been mentioned that the reason behind this might be related to aging, change in distribution and prevalence of risk factors and association with socioeconomic measure [1].

Australia ranked between countries in which cancer is the first cause of death; Iran ranked in between the countries in which cancer is the third cause of death, with different top ranking cancer incidence and mortality between two countries [1, 2]. Although the WHO has global planning through GLOBACAN for monitoring all types of cancers, the details about the patterns of head and neck cancer in each country are not clear [1, 2]. The only information is age standardized incidence rates per 100 000 population for lip and oral cavity cancer have been reported as 12.9 for males and 4.5 for females in the South Central Asia region (Including Iran), and 9.4 for males and 3.7 for females in Australia/New Zealand region. Results of the current study defined on a ten years retrospective data indicated differences in site, age and gender between these two locations. These may be due to differences in exposure to traditional risk factors such as smoking or alcohol, or modern risk factors such as HPV or socioeconomic differences. The WHO report showed the age standardize prevalence of current tobacco smoking among aged 15 years and older is different between two countries: 16.7 in Australia compared to 21.5 in Iran [3]. Also, the WHO report on global consumption of alcohol indicated 10.6 total alcohol per capita (+15) consumption in Australia versus 1.0 in Iran. However, accuracy of the alcohol data may be influenced by legislation of prohibition of alcohol use in Iran[4]. The recent report on the burden of cancer attributable to HPV by site and country showed age standardized incidence rates (per 100,000) of head and neck cancer cases (oropharynx, oral cavity and larynx cases) attributable to HPV in 2012 was 0<1 in Iran and 0.75-1.25 in Australia. However, the quality and coverage of data in Iran was lower than Australia [5]. From a socioeconomic aspect Australia mapped among countries with very high human development index (HDI), Iran is among countries with a high human development index (HDI) [1].
Although there was a limitation in data collection in the Iranian Province (which is relatively deprived according to the classification of indicators of health development) [2, 6], these kinds of studies are necessary for evaluating cancer patterns, investigate the determinants of these cancer patterns to enable future global planning in cancer prevention. Survival rates are also an important part of evaluation of cancer patients; however, there were no data available on survival rates in Iranian province.

One of the main focal points of this project was the association between socioeconomic status and knowledge, awareness and risk of head and neck cancer development. To directly examine the relationship between the individuals’ SES and HNSCC knowledge, awareness and risk, considering previous studies [7, 8] the major component of socioeconomic variables, including education, employment and labour force status, as well as wealth status has been reviewed. Various combinations of these possible indicators as a proxy of SES, such as composite index of education and income satisfaction, and composite wealth index were investigated. The wealth index comprised of assets (house ownership, car, computer, and utensils) plus income satisfaction and financial management [7–9]. Information on net income was not obtained from participants in this study due to the economic complexity in Iran that would have affected the reliability of responses. Although a wealth index using principal component analysis has previously been used to find the relationship between economic status and some diseases [10] this has, to the best of the author’s knowledge, not been used before in HNSCC.

The findings showed inequalities in risk of HNSCC in socio-economically disadvantaged individuals. However, evaluating the role of SES will be complicated by the influence of any carcinogenic exposure, poor diet or risky behaviours, along with a low socioeconomic background [11,12]. Also, different health beliefs in people with lower social and economic conditions might exert a significant influence on health-seeking behaviours [11, 13]. The model has been further adjusted for behavioural risk factors (smoking, other types of tobacco consumption, and alcohol). The final model showed people with low SES had almost 8 times a higher risk of developing HNSCC. This result emphasised the social gradient in health. Similar results have been indicated by other studies, however, measuring the SES can be different in different countries and developing a specified SES index was a strong aspect of this current study.
In addition, the data for evaluating knowledge and awareness about HNSCC have been collected. Although results indicated that the knowledge of risk factors and signs and symptoms of oral cancer was relatively low in these groups of people; participants with less than high school diploma education had almost 2 times less knowledge about signs and symptoms of oral cancer. Also, differences in knowledge about oral cancer risk factors has been found in unemployed and labour and related occupations, and other job categories. This emphasises the role of education and employment status as a part of individual SES in this study group. In this part of the study, were collected from different municipal areas of to investigate the area- based SES; however, no conclusive results were found.

Moreover, this project looked into developing a risk factor-based model for HNSCC. These types of risk analyses will help to identify at-risk people for a proper screening program. Various combinations of significant dichotomized risk factors have been examined to find the best modeling for risk of HNSCC. High levels of sensitivity (>90%) were obtained for predicting cancer, for the following variables: diet, habit, SES, oral health practice and lifestyle. This model could not however, identify healthy people (poor specificity). The combination of the indicators diet, habit, and SES provided good specificity (almost 80%). These results indicated that variables other than smoking and alcohol should be considered for defining the risk of HNSCC. There is no previous study for which identifies HNSCC patients. Efforts should be made to find a standard model for early diagnosis of cancer patients and reduce the burden of disease.

The results of the study on HNSCC patients and matched controls showed no significant difference in smoking and alcohol consumption between healthy and cancer patients in a dichotomized category (“ever, never”), and this was not in accord with most previous studies [14-16]. Although the exact reason for this difference is not obvious, it assumed that many participants did not mention their situation properly due to social and legal restrictions in Iran, especially in public hospitals. The other reason in terms of an insignificant difference in smoking may be contributed to the major exposure to carcinogens from air pollution in Tehran, with an air pollution index of (85.84) [17]. That may mask the effect of smoking. However, the data have been reported accurately and this area may need more investigation in future studies.
A growing body of preclinical and epidemiological evidence points to multiple anticancer characteristics of herbs and spices [18]. However, not only are there controversies regarding their cancer preventive effects, moreover, the mechanisms of their effects are also unclear [18, 19]. The potential cancer protective mechanism of green tea in smokers (traditionally regarded as high-risk patients) has been examined as a part of the current study. The preliminary results confirmed the effect of green tea on enhancing the salivary antioxidant level, which has protective effects against microorganisms, toxins and oxidants. That may be a pathway for oral cancer prevention. Also, the preventive effect of green tea consumption on head and neck cancer has been investigated through a case-control study. The results indicated risk of developing HNSCC in never consumers of green tea was almost 3 and 2 times higher than < 1 cup daily consumers and ≥ 1 cup daily consumers respectively. These results support the preventive effect of green tea on HNSCC, that may provide a cheap, popular, natural anti-cancer substance to reduce the occurrence of HNSCC. These types of studies attempt to find a way to prevent oral cancer development, by suggesting the use of nutrients and healthy diets; however, it does not deny the role of behavioural changes, such as smoking cessation, and the pivotal role of dentists in such programs.

7-4-Strengths and limitations

The strengths and limitations of each study have been discussed in the relevant parts of this thesis. In this section, the strengths and limitation as a whole are briefly discussed.

The major strength of this work was to investigate various aspects of head and neck cancer by designing different types of studies. Although most of the studies were carried out amongst an Iranian- population, the Australian-population was also included. The results of each study were compared with that of international studies in the Discussion sections of each part of the thesis to provide an overview of this global problem.

However, the project had some limitations; firstly, the quality and reliability of hospital admissions data and diagnosis depends on the accuracy of clinicians and the data capture system. Secondly, collecting data from questionnaires always has limitations and depends on the accuracy of participant response. However, validated structured questionnaires were used, based on easy-to-recall questions, to avoid bias.

Also, direct questions were used for assessing individual social, demographic and
economic status of participants, as a good proxy of the SES. These types of questions however, are sensitive, especially in the Iranian study population due to financial and political situations.

7-5-Future research recommendation

In this thesis, oral cancer survival was not investigated. Future research may investigate survival data and its associations with the various socio-economic variables as identified by the presented research. It would also be valuable to examine the quality of life of cancer patients, considering the socio-economic variables, through a qualitative study. Further research could also be directed to extensive interventional studies to assess the cancer protective effect of nutrients.

7-6- Conclusion

Based on the findings of this project, there was a difference between distribution of head and neck cancer in defined populations in two different socioeconomically and geographically countries (Iran/ Australia). Also, the gap has been defined among different socio-economic groups in society in developing head and neck cancer. The results of this project defined the lower knowledge and awareness of head and neck cancer signs and risk factors among people with lower SES (including wealth, education, employment), therefore, efforts should be made to increase the level of general awareness which may be effective in decreasing the development of head and neck cancer. Also, screening based on risk factors may assist in early detection and in turn facilitate timely treatment of head and neck cancer. People, especially high-risk individuals should be encouraged to acquire healthy behaviours and, healthy diet practices. Using natural antioxidants like green tea may help to reducing the risks as well. These findings will be helpful to implement preventive and diagnostic programs for head and neck cancer, specifically for high-risk groups.
7-6-References


3. https://www.who.int/gho/tobacco/use/en/[access available on May 2019]


Appendices
Appendix A
Orofacial cancers in the West of Iran: A 10-year study

Somayyeh Azimi, Marc Tennant, Estie Kruger, Jamileh Bigom Taheri, Marziye Sehatpour, Babak Rezaei

International Research Collaborative - Oral Health and Equity, School of Anatomy, Physiology and Human Biology, University of Western Australia, Perth, Australia, 'Department of Oral Medicine, Dental School, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Orofacial cancer remains a substantial life-threatening disease in developing countries. Late diagnosis and treatment still lead to many avoidable deaths. The differences in incidence and prevalence between different geographical and ethnic groups remain an important issue for service planning and international action against cancer. Methods: In this retrospective study, cancer of the orofacial region for the 10-year period (April 2002–March 2012) was evaluated. Age, sex, histopathological type, and the primary site of tumor were recorded according to the International Classification of disease for Oncology. Descriptive analyses were used to describe basic features, means (±standard deviation) were reported, and appropriate tests of significance were used. Results: Squamous cell carcinoma was the most common malignancy (55.8%) followed by mucoepidermoid carcinoma (9.4%). The male to female ratio was 5:4 and the average age was 63 years. The most common site was lower lip (22%), followed by tongue (15%) and parotid salivary gland (13%). Conclusion: This 10-year retrospective study analyzed frequency of orofacial malignancies. Considering the difference in incidence and mortality of head and neck cancer in less developed versus more developed regions, this kind of research in various population provides better understanding of cancer for global programming in terms of prevention, detection, and treatment.

Key words: Epidemiology, head and neck, malignancy, prevalence, retrospective study

INTRODUCTION

One of the most significant causes of mortality is cancer.[1] The World Health Organization (2011) estimates that cancers are now leading to more deaths than coronary heart disease or stroke. It is estimated that the burden of cancer will be increasing over the next decades, especially in low- and middle-income countries, and it is anticipated that there will be over 20 million new cancer cases annually in <10 years, by 2025. According to the GLOBACAN in 2012, estimates from 184 countries worldwide indicated 14.1 million new cases of cancer and 8.2 million deaths.[2] Furthermore, in Iran, according to Mousavi et al., cancer is the third main cause of death and annually more than 30,000 deaths are reported as a result of cancer.[3]
Cancers of the head and neck include lip, oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract, and nasopharynx as well as the pharyngeal tonsils and salivary glands;\(^4\) and represent a considerable burden worldwide. The prevalence of head and neck malignancies differs (by up to twenty times) in different places across the world, with higher tendency in less developed regions.\(^1\)\(^-\)\(^9\) However, data of incidence and mortality are not of high quality, and evidence is limited in developing countries; hence, the exact nature and extent of the problem remain unknown.\(^4\)\(^-\)\(^9\) Considering the fact that regular observation of head and neck cancer incidence rates is required for global cancer control strategies, data of each specific region are important for understanding the burden of disease and evaluation of the extent of the problem. Moreover, these data are essential for the allocation of resources for prevention, diagnosis, treatment, and supporting services. The aim of this study was to determine the 10-year incidence of head and neck primary malignant tumors in Kermanshah, in the West of Iran.

**MATERIALS AND METHODS**

In this retrospective descriptive study, data were collected from pathology records registered in the laboratories of the three leading public hospitals in Kermanshah Metropolitan (West of Iran) from 2002 to 2012. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences. This research has been conducted in full accordance with the World Medical Association Declaration of Helsinki. We confirm that patients’ information remained confidential and data were anonymized and de-identified period to analysis.

A total of 3927 case records were evaluated and all cases with the definitive diagnosis of primary oropharyngeal cancer were extracted for the study. Recurrent, metastatic, and premalignant lesions were not included in the study. Age, gender, tumor location, and histopathological type were obtained from patients’ records. Information regarding the lesions was registered in specific record sheets according to the International Classification of Disease for Oncology. Anatomical origin was classified as follows: larynx, oral cavity (lip, tongue, floor of mouth, maxilla, mandible, gingival, and buccal mucosa), oropharynx, sinonasal, and salivary glands. The data were analyzed with SPSS software version 18.0. Descriptive analysis was used to describe basic features and means (±SD) were reported and tests of significance were used as appropriate. Significance was set at a \( P \) value of 0.05.

**RESULTS**

Overall 181 cases (4.6%) from 3927 patients were diagnosed with primary malignant head and neck cancers by histopathological confirmation. The mean age of all patients was 63 years (range: 7–92 years). The mean age of males and females did not differ significantly and was 63.7 (±14.3) years and 62.3 (±16.2) years, respectively [Table 1, 2 and Figure 1]. The most

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>20-40</td>
<td>11 (6.1)</td>
</tr>
<tr>
<td>40-60</td>
<td>57 (31.5)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>109 (60.2)</td>
</tr>
<tr>
<td>Total</td>
<td>181 (100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion</th>
<th>n (%)</th>
<th>Mean age±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>101 (55.8)</td>
<td>65.83±13.27</td>
</tr>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>17 (9.4)</td>
<td>67.53±14.12</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>6 (3.3)</td>
<td>64.00±12.34</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>9 (5)</td>
<td>58.22±8.10</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>3 (1.7)</td>
<td>50.67±11.01</td>
</tr>
<tr>
<td>Salivary duct carcinoma</td>
<td>1 (0.6)</td>
<td>68.00±0.00</td>
</tr>
<tr>
<td>Malignant mixed tumor</td>
<td>3 (1.7)</td>
<td>66.67±3.21</td>
</tr>
<tr>
<td>Undifferentiated carcinoma</td>
<td>2 (1.1)</td>
<td>53.00±12.72</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>11 (6.1)</td>
<td>67.18±16.72</td>
</tr>
<tr>
<td>Verrucous carcinoma</td>
<td>6 (3.3)</td>
<td>59.33±9.07</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7 (3.9)</td>
<td>57.29±8.20</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>8 (4.4)</td>
<td>44.88±23.50</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>2 (1.1)</td>
<td>28.00±12.72</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>1 (0.6)</td>
<td>47.00±0.00</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3 (1.7)</td>
<td>75.00±5.56</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>1 (0.6)</td>
<td>12.00±0.00</td>
</tr>
</tbody>
</table>

SD: Standard deviation

Figure 1: Frequency of lesions according to type of cancer
common site of involvement was the lower lip (22%) followed by the tongue (15%) and parotid salivary glands (13%) [Figure 2].

In the current study, 89% of cancers were of epithelial origin (with average age of 66 years), from which most of them were from mucosa (62.3% squamous cell carcinoma (SCC) and 3.7% verrucous carcinoma) and rests of them were from salivary gland epithelium, 6% of bone origin, and 4% of lymphoid origin. SCC was the most common histological type, comprising 62% of epithelial cancers. In the oral cavity, the most affected site of SCC was the tongue (37%). SCC was the most common lesion type in both males and females [Figure 3].

For all malignancy cases (n = 181), 101 were male (56%) and 80 were female (44%); but for SCC cases (n = 101), 60 (59%) were male and 41 (41%) were female.

The most common malignancy of salivary glands was mucoepidermoid carcinoma (MEC) with 17 cases (38%) followed by adenoid cystic carcinoma with 9 cases (20%). The most commonly affected salivary gland was the parotid with 24 cases (54%) followed by minor and submandibular salivary glands. Osteosarcoma with 8 cases (66%) was the most common bone malignancy.

DISCUSSION

In this descriptive study, 181 patients from the archive (n = 3927) of the pathology department of the three main hospitals of Kermanshah, Iran, from 2002 to 2012 were reviewed. The mean age of cases was 63 years with 92% of patients more than 40 years old. These data compare to previous research from a close region (middle of Iran-Isfahan) where the mean age of cases was 52 years, and around one-third of cases (27%) occurred in patients younger than 40 years. A separate previous study from Southeast of Iran, in 2014 showed the average age of 53 years, with 18% under 41 years old. These reports of high rate young cancer patients are more than reported by other studies worldwide.[11] Our findings are more consistent with international trends and may be a result of the larger number of cases in our sample.

The mean age of SCC patients in the present study was 65 years, which compares well with other studies: in Myers et al. and Schantz et al., the mean age at diagnosis for SCC was approximately 60 years,[10,12,13] and Funk et al. reported 64 years as average.[10,14]

In this study, the mean age of males was slightly higher than females (63 vs. 62 years). Arotiba et al. in Nigeria reported that males with SCC were relatively younger than females (mean 48 years versus 58 years).[15]

In this study, the male to female ratio in SCC was 1.2–1, and in overall malignancies was the same. Razavi et al. (Iran) reported a male to female ratio of 1.4–1 in Iran[10] and Larizade et al. in 2014 reported that most patients (73%) were male and the overall male to female ratio was 2.74:1.[11] Moreover, time trend analysis of oral cancer in Iran highlighted disparities between oral cancer incidence trends in males and females over the 6 years from 2005 to 2010.[16] It seems that not only the higher rate of smoking and alcohol consumption is a vital issue but also sex hormone differences may be the reason for male predilection.[17] However, recently, the incidence of head and neck cancer has increased significantly in women, changes in environmental exposure probably could explain this finding.[11]

The greatest majority of malignancy types in this study were SCC (56%) followed by MEC (9%). This result was in line with Razavi et al.’s study in Iran, with the majority of SCC (60%) followed by MEC (8%).[10] Rabiei et al. (2016) in north of Iran reported that the most
common type of cancer was SCC followed by basal cell carcinoma. Furthermore, in a UAE study (2014), the most prevalent malignant lesion was OSCC followed by MEC. However, in one study in Iran, lymphoma was the second most prevalent malignancy (9%) after SCC (77%). A systematic review on 25 articles in Iran showed that the range of SCC was different from 38% to 97% in different studies; however, none of them was in the West of Iran.

In the present study, the most commonly involved site was the lip with more than one out of every four cancers. This finding is in agreement with other reports in Iran. For instance, in 2016 in the north of Iran, Rabiei et al. reported that in the oral cavity (C00–C08), the most common cancers were lip cancer (C00) followed by tongue cancer (C01, C02). The tongue was the most frequently involved site of oral cavity (when lip was excluded), and that was consistent with previous reports. However, some studies have also reported other sites (rather than lip and tongue) to be the most involved sites. For example, the gingiva and larynx were reported as most commonly affected sites in recent studies in Iran. Considering various sites of distribution, it seems logical that preventive plans will be focus on all sites with potential of oral cancer. However, due to considerable lack of understanding of oral cancer incidence, especially in populated developing countries, such as Iran, focus on screening for prevention and early detection of lip and tongue cancer is recommended due to its high rate of involvement.

We report that about half of salivary gland neoplasms were in the parotid gland. The most common type was mucoepidermoid (38%) followed by adenoid cystic carcinoma (20%). These findings are confirmed by another study in Iran (2014), which reported mucoepidermoid (35%) followed by adenoid cystic carcinoma (17%) as the most common types.

Around 90% of all malignancies were epithelial cancers, 6% bony lesions (with majority of osteosarcoma), and 4% lymphomas in accordance with Andisheh Tadbir in Southeast of Iran. Furthermore, in the UAE, malignant neoplasms of epithelial origin occurred in 78% cases followed by malignant neoplasms of glandular origin (13%) and malignant neoplasms of mesenchymal origin (8%).

CONCLUSION

This kind of research in different populations and countries provides a better understanding of these lesions and these are required for national and global programming in terms of prevention, early detection, and treatment. Oral health professionals should be educated on comprehensive examination of head and neck for screening of malignancy. Furthermore, educational programs for awareness of people about risk factors and signs of head and neck cancer are highly recommended.

Acknowledgment

Dr. Azimi acknowledges the funding of postgraduate award from the University of Western Australia. This project was done with close cooperation of Oral Medicine department of Shahid Beheshti University of Medical Sciences.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

Appendix B
Pattern of the Head and the Neck Cancer in Two Geographically and Socioeconomically Different Countries

Abstract

Context: The differences in frequency of cancer among the less developed and the more developed regions continue to remain as an important problem for service planning and international action against cancers of the head and the neck. Aim: This study compares distribution of cancers of the head and the neck between two similar-sized populations from the west of Iran and Western Australia. Setting and Design: In this retrospective study, de-identified data were collected for a 10-year period from patients diagnosed with head and the neck cancers. Materials and Methods: Data were obtained from the Western Australia Cancer Registries and from major hospitals in the west of Iran. Age at diagnosis, sex, and site code were included in the data sheet. Descriptive analysis was used to describe the basic features, means (±standard deviation) were reported, and tests of significance were used as appropriate. Results: In Iran, cancer of the lip, followed by cancer of the major salivary gland, and cancer of the tongue were the three most frequent types of cancers, whereas in Australia, the most frequent types of cancer were cancer of the lip followed by cancers of the tongue and the tonsil. Distribution of malignancy by site among the patients belonging to different ages indicated that cancer of the lip was the most frequent cancer in both Iran and Australia, except among the patients belonging to the age group of 60–74 years in Iran, where cancer of the major salivary gland had the highest frequency. Both men and women were susceptible for cancers of the head and the neck in the age range of 60–74 years in Iran, whereas in Australia, it was more frequent among men belonging to the age range of 45–59 years and in women above the age of 75 years. Conclusion: This preliminary study defined differences in orofacial malignancy between Iran and Australia. Further studies in countries with different socioeconomic status are recommended.

Keywords: Epidemiology, head and neck, incidence, malignancy, retrospective study

Introduction

Cancer is a noncommunicable disease with a high rate of disability and death, resulting as one of the diseases with the greatest disease burden in the world.1 Recent global studies estimated an incidence of more than 14 million new cases of cancer in 2012. It is expected that by 2025, more than 20 million cancer patients will be diagnosed annually.2,3 Despite progress in prevention methods and treatment options, more than 8 million cancer deaths were reported in 2012.4 The World Health Organization (WHO) reported that deaths from cancer have been overtaking all deaths from coronary heart disease or stroke.5 This increase in the burden of cancer is not only because of lifestyle risk factors, but also because of aging of the global population.4,6 The increasing cancer incidence would have a significant effect on the healthcare status and the individuals’ quality of life.6

Cancers of the head and the neck are a related group of cancers involving the lip and the oral cavity, the pharynx, and the larynx.7 From an anatomic aspect, the oral cavity and the oropharynx are distinct areas; however, there are some differences between these definitions in different databases. Therefore, complete distinction between the oral cavity and the oropharynx may not be possible.8

The fifth version of Global Cancer Incidence, Mortality and Prevalence (GLOBACAN) estimated more than 550,000 new cases of cancer of the head and the neck in 2012 that

accounted for more than 4% of all the cancers. In addition, it was estimated that more than 300,000 people died worldwide from these types of cancers in that year.\textsuperscript{2,7}

WHO categorized the five continents into six regions including the African region, region of the Americas, Southeast Asia, the European region, the East Mediterranean region, and the West Pacific region. The incidence and mortality of each type of cancer varied widely in each region, including cancer of the head and the neck.\textsuperscript{8} Recently, an evaluation by GLOBACAN found the highest age-standardized rate (ASR) for cancer of the lip/oral cavity and other pharyngeal cancers in the Southeast Asia region (6.4 and 3.6 per 100,000 people, respectively) and 4.6 and 1.1 ASR World (W), respectively, for the Eastern Mediterranean region; however, this rate was the lowest for the Western Pacific region (2.0 and 0.8, respectively).\textsuperscript{6}

According to the International Agency of Research on Cancer, the burden of cancer is greater in the low- and middle-income countries. In addition, there was a difference in incidence and mortality of cancer of the head and the neck in less developed versus more developed regions.\textsuperscript{1,2} This difference might be because of the acquisition of cancer-related risk factors such as tobacco smoking, alcohol consumption, and diet, environmental and occupational risk factors, acquisition of human papillomavirus (HPV) infection, or generally different socioeconomic status.\textsuperscript{4,9}

Epidemiological studies on cancer are limited, and some of them are not of high-quality (especially in developing countries). For example, Iran as a developing country has high-quality data for incidence, but the coverage is less than 10%, and there is no availability of mortality data. Conversely, Australia (a more developed region) has high-quality data with more than 50% coverage for incidence and high-quality vital registration for mortality data.\textsuperscript{2,9}

Although many studies have shown wide variations in cancer rates across different parts of the world, to the best of our knowledge, no study has compared in detail the incidence, age, sex of patients, and site of head and neck cancer between patients in a developing country (Iran) versus a developed country (Australia), considering that these regions differ geographically, and in terms of climate, behavioral factors and healthcare systems.\textsuperscript{10-12}

The comparisons of cancer incidence/types across time and geographical areas could provide important insights into the relative burden and cause of disease as a first step toward finding or elucidating cancer pattern variation. This study compared the distribution of all types of cancers of the head and the neck according to the international cancer classification between two similar-sized populations of Western Iran and Western Australia.

### Materials and Methods

#### Ethics

Ethical approval for this study was not required, because only completely de-identified data from cancer registries were used in the analysis. In this retrospective study, de-identified data on cancer of the head and the neck for a 10-year period (2002–2012) were obtained from the Western Australia Cancer Registries and from the major hospitals in the west of Iran.

#### Exclusion criteria

Only patients from metropolitan areas were included to eliminate the issue of remoteness from services. Recurrent, metastatic, and premalignant lesions were not included.

#### Definitions

Tumors were classified into the following subsites according to the International Classification of Diseases in Oncology: the tongue; the tonsils; the oropharynx; the gum and the cheek; the floor of the mouth; the palate and other parts of the mouth; and the internal mucosa of the lip. Age at diagnosis, sex, and site code were included in the data sheet. Descriptive analysis was used to describe the basic features, means (±standard deviation) were reported, and tests of significance were used as appropriate.

#### Results

Totally, 2400 oral cancers evaluated in this study were from the registries in Western Australia and Iran [Figure 1]. In Iran, cancer of the lip followed by cancers...
of the major salivary gland and the tongue were the three most frequent cancers, whereas in Australia, cancer of the lip followed by cancers of the tongue and the tonsil were the three most frequent cancer sites [Figure 2]. Distribution of malignancy by site among the patients belonging to different ages indicated that cancer of the lip was the most frequent cancer in both Iran and Australia [Figure 3], except among the patients belonging to the age group of 60–74 years in Iran, where cancer of the major salivary gland had the highest frequency [Figure 4]. Results also showed that both men and women were susceptible for cancer of the head and the neck in the age range of 60–74 years in Iran, whereas in Australia, cancer of the head and the neck was more frequent in men aged 45–59 years and in women above the age of 75 years [Figure 5].

**Discussion**

This study showed the difference in the distribution of cancer of the head and the neck among patients in west of Iran and Western Australia over a 10-year period. We estimated the same trends for cancer of the head and the neck in these 10 years.

The results showed that there was a large difference in the distribution of orofacial malignancy by site among the patients in Iran and Australia. The most frequent cancer was cancer of the lip in both Iran and Australia; however, cancer of the lip had a much higher incidence in Australia than Iran (39 and 26% of the total cancers of the head and the neck, respectively). In addition, this difference was higher in women (42 and 29% from total cancer incidence, respectively). It is speculated that the higher Ultra Violet (UV) index in Australia may cause this difference. In a systematic review on the epidemiology of oral cancer in Iran, cancer of the lip was reported as the second most frequent cancer, just after cancer of the tongue.

Moreover, results revealed that cancers of the major salivary gland and the gum were much more frequent in Iran. The difference in the incidence of the salivary gland malignancies might be because of differences in etiological factors. Although the contributing factors of the salivary gland neoplasms are not well recognized, it seems that smoking and drinking are not the major risk factors; low intake of some nutrients such as vitamin A and C and ionizing radiation might be affecting the development of the tumor.
This study found cancer of the tonsils to be reported much more frequently in Australia. Some studies reported an increase in incidence of head and neck squamous cell carcinoma (HNSCC) in Australia, especially of the oropharynx, despite a fall in the number of patients diagnosed with other smoking-related cancers. They concluded that the recent increase in HSNCC among younger patients has been attributed to the rising prevalence of HPV infection, and was hypothesized to reflect the changing sexual behaviors during the recent decades.

According to a WHO report on the global tobacco epidemic 2015, Australia and Iran were among the countries with the highest level of achievement for effective tobacco use surveillance, strong smoke-free legislation, appropriate cessation support, health warning labels about the danger of tobacco, and anti-tobacco mass media campaigns. In addition, both had an adult daily smoking prevalence (2013) of less than 15%. However, there was a difference in smoking rates across the states.
and provinces in a vast country such as Australia or a populated country such as Iran. Moreover, other risk indicators such as socioeconomic disparities might contribute to the differences seen between Iran and Australia in terms of cancer of the head and the neck.

This study had some of the following limitations: data was not collected from all cancer patients in Iran but from only three major hospitals in the metropolitan area of Kermanshah province in the west of Iran because of the lack of availability of data.

Considering the fact that cancer of the lip and the oral cavity ranked globally from 16 to 14 between 1990 and 2013 and cancer of the other pharynx from 21 to 18 in terms of absolute years of life lost is an indication that these conditions should be investigated.

We conclude that differences exist in orofacial malignancy among the patients of Iran and Australia in terms of incidence, site of cancer, and age and gender. Further studies to identify the patterns of cancer of the head and the neck and ways for prevention are recommended.

Acknowledgements

Dr. Azimi acknowledges the support of postgraduate award from the University of Western Australia.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References


Appendix C
Population Survey of Knowledge about Oral Cancer and Related Factors in the Capital of Iran.

Azimi S, Ghorbani Z, Tennant M, Kruger E, Safiaghdam H, Rafieian N.

Abstract

Knowledge about oral cancer risk factors and signs is thought to improve prevention and early diagnosis, and in turn, increases survival. In this population-based survey, knowledge about oral cancer was assessed in Iran. A total of 1800 self-administered questionnaires (collecting sociodemographic data and questions regarding oral cancer risk factors and signs) were distributed through random sampling. Final scores ranged between 0 and 15 for the risk factors and 0-11 for the signs. Scores below the median indicated a low level of knowledge, scores representing the third quartile of correct answers indicated a moderate level of knowledge, and scores representing the upper quartile indicated a high level of knowledge. Statistical tests were used for analysis of knowledge level in different sociodemographic categories. A total of 1312 participants completed the questionnaires. The average of knowledge scores for risk factors was 5.3 ± 3.0 and for signs was 4.5 ± 2.9. Overall, 75 and 56% respectively were able to identify major risk factors (smoking and alcohol); 23.5% could not define any related signs and symptoms. Dividing scores into quartiles indicated that three out of four people had "low" knowledge about risk factors and 58% had "low" knowledge about signs and symptoms. Females and highly educated people had more knowledge of oral cancer. Significant difference was found between job and level of knowledge (P = 0.001). This survey revealed that public knowledge of oral cancer was not satisfactory in Iran. Efforts should be done to inform and educate people with risk factors, initial clinical presentation, and symptoms, in order to improve prevention and promote early diagnosis.

KEYWORDS: Knowledge; Oral cancer; Public

PMID: 28840479 DOI: 10.1007/s13187-017-1275-7
Appendix D

Azimi S¹, Ghorbani Z², Ghasemi E³, Tennant M¹, Kruger E¹.

Abstract

Oral cancer is a life-threatening disease with low survival rates, especially when diagnosed in an advanced stage. Lack of awareness about this cancer among the population is proposed as a possible reason for this diagnostic delay. The aim of this study was to evaluate oral cancer awareness, as well as the association of this with sociodemographic status in Tehran. In this cross-sectional population-based survey, 1800 self-administered questionnaires (collecting sociodemographic data, questions regarding oral cancer awareness and the source of information) were distributed through multistage stratified random sampling. Scores for questions ranged from 0 to 4, and totals were summed. The outcome of question responses was also analyzed separately. In total, 1312 questionnaires were available for analysis, from 788 females and 489 males (37.8 ± 9.02 years). Only 30% of the respondents were aware of oral cancer. The average score for awareness was 1.09 ± 1.6 with no significant differences between age groups and genders. Almost 6.5% of participants had complete awareness about oral cancer. A significant difference was found between mean scores in different levels of education and occupation (p = 0.0001). From 585 responses to the "source of information" question, "public media" was the most important source (almost 50%). Only 2% mentioned "dentists" as a source of information. This study indicated an alarming lack of oral cancer awareness and literacy in Tehran, Iran. Dentists should be obliged to practice their pivotal role in informing the public about oral cancer.

KEYWORDS: Awareness; Oral cancer; Public; Social status

PMID: 29526020 DOI: 10.1007/s13187-018-1337-5
Appendix E
Socioeconomic determinants as risk factors for squamous cell carcinoma of the head and neck: a case-control study in Iran.

Azimi S¹, Rafieian N², Manifar S³, Ghorbani Z⁴, Tennant M⁵, Kruger E⁵.

Abstract
Our aim was to assess the association between different components of sociodemographic status and the risk of developing squamous cell carcinoma (SCC) of the head and neck after we had adjusted for the influence of the known behavioural risk factors of smoking and drinking alcohol. We selected 146 patients with histopathologically-confirmed SCC of the head and neck, and matched them for age and sex with 266 healthy controls for this case-control study. Personal details, occupation, socioeconomic status, smoking, and alcohol consumption were recorded. The association of sociodemographic variables with oral cancer was evaluated both separately and with a composite socioeconomic index. Chi squared tests, adjusted odds ratios (OR), and 95% CI were computed using logistic regression to estimate the effect. There was a significant difference between the two groups in the composite socioeconomic index (p<0.001). The group with "low" socioeconomic status had the highest risk of oral cancer (OR=3.89, 95% CI 1.28 to 11.82). Better-educated people with higher incomes had a lower risk of SCC of the head and neck after we had controlled for behavioural risk factors. However, marital and employment status and place of residence were not significantly associated with risk. Our findings confirm that some socioeconomic determinants were associated with the development of oral cancer in this study group.
OBJECTIVE: Considering the higher rate of oral cancer, and reduction in salivary antioxidants in smokers as indicated in previous studies, antioxidant-containing nutrients such as green tea, seem to be beneficial in counteracting against oxidative stress in this group. This study assessed the salivary total antioxidant alteration in smokers compared to nonsmokers, after short-term (7 days) and long-term (3 weeks), green tea drinking.

DESIGN: In this experimental study, 20 volunteer moderate-to-heavy male smokers, and 20 matched healthy non-smokers were selected to participate, according to the inclusion criteria. Participants were instructed to drink two cups of green tea per day, by dissolving 2g of green tea in 150ml of hot water for each cup. After saliva collection, antioxidant capacity of saliva was measured at baseline, after 7 days, and after 21 days. Statistical evaluation was done by SPSS 21, using paired sample t tests, one-way ANOVA and Bonferroni tests.

RESULTS: At day zero nonsmokers had a higher antioxidant capacity than smokers (686.6±62.22 vs. 338.8±59.9 mM/50µl, P<0.001. There was also a significant difference between two groups in salivary total antioxidant capacity after one week and three weeks of green tea consumption (P<0.001). However, there was an upward trend in both smokers and non-smokers over the study period (after tea drinking). In addition, a significant difference was found in total antioxidant capacity alteration in smokers compared to non-smokers from baseline to day 21.

CONCLUSIONS: Results support the effectiveness of green tea consumption in salivary antioxidants enhancement in smokers, in both the short- and long term.

Copyright © 2017 Elsevier Ltd. All rights reserved.

KEYWORDS: Antioxidant capacity; Green tea; Saliva; Smokers
Appendix G
See 1 citation found by title matching your search:


Is there any association between green tea consumption and the risk of head and neck squamous cell carcinoma: Finding from a case-control study.

Rafieian N1, Azimi S2, Manifar S3, Julideh H4, ShirKhoda M5.

Author information

Abstract

OBJECTIVE: Green tea consumption has been shown to reduce the incidence of head and neck squamous cell carcinoma (HNSCC) in experimental animal models, however the results from human studies are inconclusive. The aim of this study was to evaluate the relationship between green tea consumption and the risk of HNSCC.

DESIGN: The study utilised a standardised questionnaire to investigate the relationship between green tea consumption and HNSCC experience. Data about amount of green tea consumption was recorded from 147 patients with HNSCC and 263 age and gender matched controls. The results were analyzed with SPSS statistical software Version 21 using Chi-square test, and Logistic Regression (with a 95% confidence interval). Significance levels were set at 95% and p-values less than 0.05 were considered significant.

RESULTS: Statistical analysis indicated significant differences between different groups of tea consumers in terms of HNSCC risk (P < 0.001). The risk of developing oral cancer those who consume <1 cup of green tea daily was (OR = 0.29 (0.16-0.52) and for the group of > = 1 cup green tea consumers was 0.38(0.17-0.86) of those who never consume green tea (Reference point) after adjustment for other risk factors.

CONCLUSIONS: The findings support that green tea consumption may reduce the risk of HNSCC. To confirm the efficacy of green tea intake in preventing the development of HNSCC in humans further investigation is needed.

Copyright © 2018 Elsevier Ltd. All rights reserved.

KEYWORDS: Case-control; Green tea; Head and neck; Squamous cell cancer
Appendix H
Questionnaire:
This questionnaire is designed to determine your awareness of mouth and lip cancer. Participation in this study is entirely voluntary and unconditional, and your answers to the questions will remain completely confidential with the researchers. Please ask for help, if you find any difficulty in answering questions. After completing the questionnaire, you will find a brochure containing useful information about this cancer.

1- General Information:
Date of birth: Gender:
Educational attainment: .........year last degree:

2- Employment Status:
Unemployed ☐ Employed ☐ Others (students, housewives, and retired)☐
If you are employed please define the category accordingly:
Labor and related ☐ Clerical in private sector ☐ Clerical in public sector ☐
Self-employed ☐ Managerial/ professionals (engineer, doctor, lawyer) ☐
Others …..
* If you are not a head of household, please also mention the head of household job: .........

Have you ever had an unemployment history? (Head of household) Yes ☐ No ☐
If the answer is yes, specify the time: ....... year

3- Medical Status:
Do you have any particular disease: Yes ☐ No ☐
Have you ever had a history of cancer? Yes ☐ No ☐
Do you take any special medications regularly? Yes ☐ No ☐
Write down if you are taking it: ............
Do you have a history of taking vitamin supplement? Yes ☐ No ☐

4-Knowledge of mouth and lip cancer:
Have you ever heard of mouth and lip cancer? Yes ☐ No ☐
Is mouth and lip cancer a contagious disease? Yes ☐ No ☐
Are you aware that a small lesion in your mouth can develop into mouth and lip cancer? Yes ☐ No ☐
Are you aware that early treatment of oral lesions can prevent them from developing mouth and lip cancer? Yes ☐ No ☐
In your opinion, which of the following factors definite risk of developing cancer of the mouth and lips:

1. Tobacco (Smoking cigarettes, pipe, hookah or chewing tobacco): Yes ☐ No ☐ Do not know ☐
2. Being over 60 years of age: Yes ☐ No ☐ Do not know ☐
3. Drinking alcohol almost every day: Yes ☐ No ☐ Do not know ☐
4. Spending time in the sever sunlight: Yes ☐ No ☐ Do not know ☐
5. Sexually transmitted virus (Human papilloma virus): Yes ☐ No ☐ Do not know ☐
6. Having a family member with mouth or throat cancer: Yes ☐ No ☐ Do not know ☐
7. Eating spicy foods: Yes ☐ No ☐ Do not know ☐
8. Eating and drinking hot foods: Yes ☐ No ☐ Do not know ☐
9. Lip and cheek biting habit: Yes ☐ No ☐ Do not know ☐
10. Long term using false teeth: Yes ☐ No ☐ Do not know ☐
11. Being overweight: Yes ☐ No ☐ Do not know ☐
12. Pollution in the air: Yes ☐ No ☐ Do not know ☐
13. Allergy to foods and medicine: Yes ☐ No ☐ Do not know ☐
14. Not eating enough fruits and vegetables: Yes ☐ No ☐ Do not know ☐
15. Untreated tooth caries: Yes ☐ No ☐ Do not know ☐

In your opinion, which of the following can be signs of cancer of the mouth and lips:

1. White or red patches in mouth that do not go away: Yes ☐ No ☐ Do not know ☐
2. Non-healing ulcer in the mouth lasting more than a month: Yes ☐ No ☐ Do not know ☐
3. Long-lasting swelling or growth in mouth: Yes ☐ No ☐ Do not know ☐
4. Small ulcer that healing in two week: Yes ☐ No ☐ Do not know ☐
5. Having difficulty or pain in swallowing: Yes ☐ No ☐ Do not know ☐
6. Mouth blisters that healing and recurring: Yes ☐ No ☐ Do not know ☐
7. Hoarseness or change in voice that does not go away: Yes ☐ No ☐ Do not know ☐
8. Immediate weight loss: Yes ☐ No ☐ Do not know ☐
9. Discomfort and soreness in mouth that does not go away: Yes ☐ No ☐ Do not know ☐
10. Tooth sensitivity to hot or cold: Yes ☐ No ☐ Do not know ☐
11. Long-lasting swelling in neck or sore throat that does not go away Yes ☐ No ☐ Do not know ☐

Does your family have a history of oral cancer? Yes ☐ No ☐

Where did you get information about oral cancer? .............

5- Please answer the following questions about your economic status:
Are you home owner Yes ☐ No ☐
Do you have a car? Yes ☐ No ☐
Which of the following do you have at home:
Personal Computer ☐ Dishwasher ☐ Steam cleaner ☐ Microwave ☐
How satisfied are you with your current household income?
Highly satisfied ☐ satisfied ☐ dissatisfied ☐ highly dissatisfied ☐
Do you have the ability to manage expenditure with the available monthly income?
Can’t make ends meet ☐ manage to get by ☐ have enough money plus some extra ☐
money was not a problem ☐
Do you use health private insurance? Yes ☐ No ☐

6- Please answer following questions about your oral hygiene:
How many times do you brush your teeth: Rarely ☐ One ☐ Two ☐ More than twice ☐
Do you use dental floss daily: Yes ☐ No ☐
Have you had dental visit last year: Yes ☐ No ☐

- Please write down any other opinion:
Appendix I
Information about disease:
Type of disease: ........... Blood type:..........
This questionnaire is designed to evaluate the risk factors for head and neck cancer. Involvement in this survey will be completely confidential to your researchers, completely voluntary and unconditional. Please ask for help, if you find any difficulty in answering questions.

1-General Information:
Date of birth: __________________________ Gender: 
Educational attainment: ...........year last degree:

2-Employment Status:
Unemployed □ Employed□ Others (students, housewives, and retired) □
If you are employed please define the category accordingly:
Labor and related□ Clerical in private sector □ Clerical in public sector □ Self-employed □ Managerial/ professionals (engineer, doctor, lawyer) □ Others …..
* If you are not a head of household, please also mention the head of household job: .........
Have you ever had an unemployment history? (Head of household) Yes □ No □
If the answer is yes, specify the time: ....... year

3-Medical Status:
Do you have any particular disease: Yes □ No □
Have you ever had a history of cancer? Yes □ No □
Do you take any special medications regularly? Yes □ No □
Write down if you are taking it: ............
Do you have a history of taking vitamin supplement? Yes □ No □

Does your family have a history of mouth and lip cancer? Yes □ No □

4-Marital status:
Single□ Married□ Passed away□ Separated□ new marriage□

5-Please answer the following questions about your economic status:
Are you home owner Yes □ No □
Do you have a car? Yes☐ No☐
Which of the following do you have at home:
Personal Computer☐ Dishwasher☐ Steam cleaner☐ Microwave☐
How satisfied are you with your current household income?
Highly satisfied☐ satisfied☐ dissatisfied ☐ highly dissatisfied☐
Do you have the ability to manage expenditure with the available monthly income?
Can’t make ends meet☐ manage to get by☐ have enough money plus some extra☐ money was not a problem☐
Do you use health private insurance? Yes☐ No☐

6- Please answer following questions about habits:

Do you have a history of smoking? Yes☐ No☐
Do you smoke currently? Yes☐ No☐
Do you have a history of other tobacco products consumption: Yes☐ No☐
If the answer is yes:
Type of product: .......... How much....
Have you ever been thinking of quit smoking? Yes☐ No☐
Is there a smoker in your house? Yes☐ No☐
Have you had a smoker at your house in your childhood? Yes☐ No☐
Are you currently drinking alcohol? Yes☐ No☐
If yes: How much....

Do you have a history of oral sex? Never☐ Rarely☐ Occasionally☐ Usually☐
How many fruits do you eat daily? ........ Number
How many times a week do you use raw vegetables? Less than 1 ☐ 1 ☐ more than 1 ☐
How often do you use cooked vegetables several times a week? Less than 1 ☐ 1 ☐ more than 1 ☐
Do you use a lip sunscreen? Never☐ Rarely☐ Occasionally☐ Usually☐
How many cups of green tea you take daily: Never ☐ 1 cup ☐ between 1-2 cups ☐ >2 cups ☐

How many times a week do you exercise? …..

7- Please answer following questions about your oral hygiene:

How many times do you brush your teeth daily?

Never ☐ Rarely ☐ One ☐ Two ☐ More than twice ☐

Do you use dental floss daily?

Never ☐ Rarely ☐ One ☐ Two ☐ More than ☐

How many teeth have you taken out? .......... number

How many teeth did you replace with false teeth (removable or fixed)? ......number

Have you had dental visit last year: Yes ☐ No ☐

- Please write down any other opinion: