Association between Life course Socioeconomic position and Oral cancer among a sample of Indian subjects

Thekke Purakkal Akhil Soman

Faculty of Dentistry

McGill University

Montreal, Quebec, Canada

August 2011

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science.

DEDICATION

This work is dedicated to my grandparents Mrs. TP Gowri, Mrs. P Bhargavi, Mr. TP KuttyKrishnan (late) and Mr. P Appukuttan for their never ending love, inspiration and all those bedtime stories.

ACKNOWLEDGMENTS

All my failures would be my own but all my successes would be shared with people who influenced me and from whom I learned over my life course

First of all I would like to thank my master's supervisor Dr. Belinda Nicolau for being more than a mentor and guide to me during the past years. She always took great interest in me and my ideas and imparted great support and encouragement at both professional and personal levels to get the best out of me. I am greatly obliged to this absolutely fantastic person for her sound advice, guidance, teaching and learning opportunities and environment provided and immense amount of time she spent for me, during my data collection at the Indian study site, master's and especially during every step of my thesis writing.

I extend my gratitude to my co-supervisor Dr. Paul Allison for being a constant source of encouragement at various levels of my master's and this project. His advices and guidance were invaluable to me.

I am greatly indebted to Dr. V Ipe Varghese, my professor, mentor and principal investigator of this study at the Indian site, and Dr. PM Shameena, my beloved professor and head of the Department of Oral Pathology, Government Dental college, and professors at Medical college, Calicut, Kerala, India, for their indispensable support, encouragement and facilities provided for the data collection of HeNCe Life study and my thesis work. I extend my thanks to my dearest friends and fellow research assistants at the Indian study site Drs. KP Shahul Hameed and AM Sreenath, for being the two concrete pillars of support during the whole course of this study until now. I am also obliged to the staff and non teaching faculty at departments of both dental and medical colleges, Calicut, Kerala, India.

I would also like to thank Mrs. Marie Desy at the INRS-Institut Armand-Frappier for her timely help with the statistical analysis of this work and Dr. Goplalakrishanan Netuveli at Imperial College, London for his encouragement, inputs and advice.

Great lot of appreciation goes to research associate Dr. Genevieve Castonguay whom I rightly call my 'life saver' at professional levels. A great friend and colleague whom I always count on for solid practical advice, this charismatic person has rendered me lots of help and support during my tenure as research assistant at the Indian site and for data entry, data export, data analysis and thesis writing. I also thank research assistants Ms. Christine Gurekian and Ms. Hilina Hitimana for their help with the study.

I am grateful to the funding agencies of this project: Canadian Institutes of Health Research (CIHR), McGill India Strategic Research Initiative (MISRI), Fonds de la Recherche en Santé du Québec (FRSQ), Ministère du Développement économique, de l'Innovation et de l'Exportation du Québec (MDEIE), Canada

Foundation for Innovation (CFI) and also to the CIHR Strategic Training Program in Applied Oral Health Research for providing me with full fellowship during my masters.

This thesis would not have been possible without the patients and cooperation of the study participants in our project. I appreciate and gratefully acknowledge their contribution to this thesis work.

I extend my gratitude to professors, colleagues and friends at the Oral Health and Society Research Unit, Faculty of Dentistry, McGill and INRS-Institut Armand-Frappier for providing a cordial learning environment at the units. Their enthusiasm and passion for the field of research has been really contagious and highly motivational for the young researcher in me. Special thanks to Maria Palumbo, student's affairs coordinator, Faculty of Dentistry, McGill University for helping me out, from my admission into this program until this date and also to the library facilities at McGill University.

I also wish to acknowledge my relatives, teachers, friends and well wishers back home in India and in Montreal for being with me at various stages of my personal and professional career over the past years. Special thanks to my high school teachers Mrs. MN Nisha and Mrs. UB Manjula for their love, great support and encouragement and for solidifying my interest towards science.

This humble achievement is a cumulation of smaller successes I had in the past years in both my personal and professional life which would never have been possible without the people who influenced me the most during this time. My heartfelt gratitude to my sister, Ms. TP Arsha Soman, my best friends Dr. Anu Joseph, Ms. Inna Smirnova and my doggy Bruno and my dearest friends Ms. T Mirunalini, Mr. Mohammad S Mahani and Mr. R Rajaprakash, for the 'regular doses' of encouragement, infusions of fun and laughter, camaraderie and for being the greatest sources of my moral and emotional support. I declare them as equal partners in this success.

My mom Mrs. P Prabhadevi, a constant source of love and my dad Dr. TP Somasundaran, my hero; they bore me, raised me, taught me and supported me through all these years, giving utmost importance to my needs, education, career and life. Words are not sufficient to express my gratitude towards them. And I am sure they would join me in thanking each and every person who has stood with me over the years.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

SEP - Socioeconomic position
ICD - International Classification of Diseases
ASR – Age Standardised Rate
OR - Odds Ratio
CI – Confidence interval
AIC - Akaike's Information Criterion

ABSTRACT

Background: Oral cancer has high incidence and mortality rates in both the developed and developing world. Its main risk factors are tobacco and alcohol consumption and, in India, paan chewing habits. Although socioeconomic position (SEP) has been associated with oral cancer, no studies have assessed this association using life course SEP in an Indian population. **Objective**: To estimate the extent to which life course SEP is an independent risk factor for oral cancer and how much of this association is explained by behavioural habits and oral health related factors in a sample of Indian subjects. **Methods:** Data from 200 oral cancer cases and 150 controls were drawn from an ongoing hospital-based case-control study: HeNCe Life (Head and Neck Cancer Life course) study. Detailed information regarding SEP, behavioural and oral health factors over the life course was collected using a questionnaire and a life grid technique. Data analysis involved descriptive and logistic regression analysis. **Results:** Subjects who were in low SEP throughout their lives were at significant risk for oral cancer (OR=5.81, 95% CI: 2.90-11.64) when compared to those who spent their lives in high SEP. The addition of behavioural and oral health factors into the models attenuated this association (OR= 2.08, 95% CI: 0.89-4.89 for low SEP compared to high SEP). However, low lifetime SEP was still related to an increased risk of oral cancer. **Conclusion**: Low life course SEP is a significant risk factor for oral cancer in this population.

RÉSUMÉ

Introduction: Le cancer oral présente des taux d'incidence et de mortalité élevés, à la fois dans les pays développés et ceux en voie de développement. Ses facteurs de risque principaux sont la consommation de tabac et d'alcool et, en Inde, les habitudes de mâchage. Bien que la position socioéconomique (PSE) ait été associée avec le cancer oral, aucune étude n'a encore évalué cette association en utilisant la PSE tout au long de la vie chez une population indienne. **Objectif**: Estimer le degré auquel la PSE tout au long de la vie est un facteur de risque indépendant pour le cancer oral et à quel point cette association est expliquée par des habitudes comportementales et des facteurs reliés à la santé buccodentaire dans un échantillon de sujets indiens. **Méthode**: Des données portant sur 200 cas de cancer oral et 150 témoins ont été tirées d'une étude cas-témoins en cours dans les hôpitaux: l'étude HeNCe Life (*Head and Neck Cancer Life course*). De l'information détaillée concernant la PSE, des facteurs comportementaux et de santé buccodentaire tout au long de la vie a été recueillie à l'aide d'un questionnaire et de la technique de la grille de vie. L'analyse des données impliquait des analyses descriptives et de régression logistique. **Résultats**: Les sujets qui étaient dans une PSE faible tout au long de leur vie avaient un risque significativement plus élevé d'être diagnostiqué d'un cancer oral (RC=5.81, IC 95%: 2.90-11.64) comparativement à ceux qui ont vécu leur vie dans une PSE élevée. L'ajout de facteurs comportementaux et de santé buccodentaire aux modèles a atténué cette association (RC= 2.08, IC 95%: 0.89-4.89 pour une SEP faible comparativement à une PSE élevée). Cependant, la PSE au cours de la vie est demeurée reliée à un risque accru de cancer oral. **Conclusion**: Une PSE faible tout au long de la vie est un facteur de risque significatif de cancer oral dans cette population.

1. Introduction

Oral cancer is a devastating chronic disease that strikes high incidence and mortality rates across the globe. This cancer has an annual incidence of around 263,861 cases and a mortality of 127,654(1). It is the 10th most common cancer among men and the 15th most common cancer in women worldwide(1). India has the highest incidence of oral cancer in the world. It accounts for 30% of all cancers in that country, whereas it represents only about 3% of malignancies in North America(2). Despite advancements in diagnosis and treatment, the five-year survival rate (50-55%) has not changed over the past few decades (3).

Behavioural habits like tobacco smoking, alcohol consumption and diet have been identified as the main risk factors for this cancer. In the Indian population specifically, the habit of betel quid chewing has been reported to account for almost 50% of cases in men and 90% in women(4). Cancer research has recently shifted its attention from the proximal cause of the disease (tobacco, alcohol among others) to the 'cause of the cause' (or distal) factors of various health outcomes, most importantly socioeconomic position (SEP)(5). A wealth of literature highlights the impact of socioeconomic position on chronic disease outcomes, including oral cancer (6-8). However, most of these studies have considered SEP as a confounding factor in the risk assessment of cancers rather than as the main exposure variable. In addition, these were cross sectional studies that assessed this factor at only one point in time. But SEP can change over a person's life (9). Thus, assessing this factor at one point in time may not capture

the true effect of this variable on chronic diseases (e.g., oral cancer) which have long latency periods.

This evidence underpins the need for a study considering SEP as the main exposure for risk assessment of oral cancer. However, the challenge for such a study is the precise estimation of this time dependent variable, which calls for the employment of a novel methodology with a strong theoretical framework like the life course approach(10). The life course hypothetical model takes into account both proximal factors (e.g., recent changes - in SEP and behavioural habits) and distal factors (e.g., changes in SEP earlier in life and across the life). This framework allows a more comprehensive understanding of the associations between SEP, behavioural factors and oral cancer risk than those obtained from analysis looking at risk factors in one point in time(10). Undertaking such a study in a population with a high burden of oral cancer and a wide variation in socioeconomic disparities and behavioural habits may contribute to fill the existing gaps on this topic.

Based on the life course approach, the theoretical framework of this case-control study considers SEP as the fundamental risk factor for oral cancer in a sample of Indian subjects.

2. Literature review

2.1. Oral cancer - Definition

Due to dilemmas in clearly delineating the oral cavity and surrounding structures mentioned in the international classification of diseases (ICD), defining oral cancer has been a challenge(11). Based on the revised ICD classification (ICD 10), oral cancer (C00 – 06) can be defined as cancer affecting the lips, tongue, gums, floor of the mouth, palate, cheek mucosa, vestibule of mouth, and retro-molar area(12).

The following sections will present current knowledge regarding the epidemiology of oral cancer, the role of specific risk factors such as socioeconomic position, bidi smoking, betel quid chewing and a broad overview of other risk factors followed by a brief account of these factors pertaining to the Indian population and study site Kerala.

2.2 Epidemiology

Oral cancer constitutes a heterogeneous group of cancers arising from different parts of the oral cavity, with different predisposing factors, prevalence, and treatment outcomes. Two thirds of the cases occur in men and the incidence of this cancer increases with age, peaking in the 6^{th} and 7^{th} decades of life, although recent studies have shown an increased incidence among young people(13-16). Histologically, 95% of these cancers are squamous cell carcinomas(17). Approximately a 20 fold variation in the geographical distribution of incidence of oral cancer across the globe has been reported(18). According to 2002 statistics,

the prevalence of oral cancer worldwide was 741,000. The latest reports from 2010(1) show that it is the 15th most common cancer reported globally with an annual incidence of around 263,861 cases and a mortality of 127,654. Worldwide age standardised incidence and mortality rates are 3.9 and 1.9, respectively, per 100,000 population. Of these cases, 65% arise in developing countries and almost 55% in Asia alone. Indeed, some areas characterized by the highest incidence rates of oral cancer in the world are found in Asia. The age standardised incidence rates vary from 24.0 per 100,000 population in Papua New Guinea to less than 2 in the middle east. A comparison of the first ten countries with the highest age standardised incidence rates of oral cancer and their total incidence according to 2010 statistics(1) is shown in Table 1.

India has often been cited as the country with the highest incidence of oral cancer in the world. Almost 70,000 new cases of oral cancer arise in India alone every year which is the highest in any country. This figure rises above 100,000 when oropharyngeal cancers are also taken into account. The age standardised incidence and mortality rates are 7.5 and 5.2 per 100,000 population respectively. Oral cancer is the 3rd most common cancer in India after lung and breast cancer, the 2nd most common cancer in men (excluding cancers of other pharynx) and the 4th most common among women(1). Kerala is a state in the south-western coast of India which has a relatively high incidence of oral cancer. The age standardized incidence rate in males and females in Kerala is estimated to be around 10 and 7 per 100,000 population respectively (19).

Table 1: Top ten countries with highest incidence rates of oral cancer – All ages

Countries	ASR*	Numbers
Papua New Guinea	24	795
Maldives	16.5	30
Chinese Taipei	16.1	4,861
Brunei	12.5	34
Sri Lanka	10.3	2,290
Pakistan	9.8	11,698
Bangladesh	9.7	10,402
Hungary	9.4	1,489
Namibia	7.7	94
India	7.5	69,820

*Age standardised rates/ 100,000 population

2.3 Risk factors for oral cancer – A look beyond the two dimensional approach

Although the statistics and documented reports show that overall incidence of oral cancer is decreasing globally and in India specifically(20), this disease still poses a major problem in the developed and even more so in developing countries. Despite advances in the surgery, radiation and chemotherapy, the five-year survival rate for oral cancer has not improved over the past several decades and it remains at around 50-55% (3). A number of risk factors for oral cancer have been studied. Most existing studies have supported the role of tobacco and alcohol habits as the strongest aetiological factors in the development of this disease(21).

But the present global disparities in the incidence and geographical distribution of oral cancer cannot be explained by these two strong risk factors which forces researchers to think beyond this 'two dimensional' aetiological explanation. According to Rose (1992), for the prevention of diseases, one should focus not only on the immediate or proximal causes of diseases (e.g., diet, smoking, alcohol, toxic exposure) but also on the 'cause of the cause' which determines the exposure to the proximal factors. He hypothesized social, economic and political factors as the 'cause of the cause'(5). Indeed, the strong evidence showing an association of social and economic factors (e.g., poverty) and health (8, 22, 23) and global inequality in the distribution of several chronic diseases including oral cancer have diverted the attention of researchers into this field. Although indicators of SEP have been taken into consideration in studies investigating the aetiology of chronic diseases including cancer, mostly they are used as a confounder factor rather than the main exposure of interest (24). However, recent research focusing on SEP and oral cancer risk has established it as an important risk factor for this disease(25). In this thesis work, we will be focusing on SEP as the potential fundamental risk factor of oral cancer.

2.4 Socioeconomic position

Socioeconomic position is strongly associated with the morbidity and mortality of various diseases, especially chronic diseases. Research conducted since the 1900's has consistently shown that being in the lower SEP increases the risk of chronic diseases(6) including oral cancer. Indeed, a large number of studies have looked into various indicators of SEP and their relationship with chronic diseases.

The main objective of this thesis work is to test whether adverse SEP, measured along the life course, increases the risk of oral cancer. Therefore, in the following section we present in greater details the concept and measurements of SEP.

2.4.1 Definition

The term 'socioeconomic position' has been used to understand the economic and social well being of a person through the assessment of components like occupation, income, wealth, education and social status. SEP is an aggregate concept that includes both resource based (income, wealth, education) and prestige based (individuals' rank or status in the social hierarchy, evaluated with reference to people's access to and consumption of goods, services and knowledge) measures that are linked with both childhood and adult social class position(26). Even though the term socioeconomic status has been used by many researchers(27, 28), we will be using the term SEP in this thesis to refer to socially determined economic factors that influence what position individuals hold within the multiple stratified structure of a society(29).

2.4.2 Indicators of SEP

Various indicators of SEP have been used by economists, sociologists and public health researchers and the standards of these measures differ according to distinct areas of the world. There is a wide range of difference in SEP within a country, between continents and also between the developed and developing world. Most of the indicators are correlated with each other because they all measure aspects of the underlying SEP either cumulatively or at different periods of an individual's life(30). The most common indicators of SEP are addressed here.

2.4.2.1 Education

Education is one of the most widely used individual measures of SEP. Many studies suggest that education is easy to measure, allows the assessment of people who are not a part of active labour, and is associated with many health outcomes(31); attributes which make education an important SEP indicator. Equal availability to both sexes, exclusion of only few members of the population and less subjectivity to negative adult health selection are factors considered underscoring the usefulness of education as a SEP indicator(32).

An individual's educational attainment would influence various aspects of his life like his ability to look for opportunities, decision making powers, general awareness and interaction with people, access to information and health care, life style behaviours, job and income levels, housing conditions, status in the society and stress levels. It would impact various health outcomes including oral cancer(29).

When assessing the education of individuals for epidemiological studies, we need to consider whether they have received formal education or not, number of years of study, whether they can read and write and also the milestones/level of education they have attained in their lives(29). Level of education is an important marker of SEP, which, from a life course point of view, marks the transition from childhood to adolescence or would indicate an individual`s independence from parental care(29). Studies have also underlined the importance of considering parents' education level as an indicator of childhood health status as well as the

importance of neighbourhood education in assessing health outcomes in a population(26, 32).

Even though studies have reported strong connections between education and the mortality and morbidity associated with various diseases including oral cancer, analysis of this indicator can be complicated because the level of education and number of years of education are not the same everywhere, and they are related to age and birth cohort, social class position, race/ethnicity and gender(26). Educational achievement has had different social meanings and consequences at different time periods and in different cultures. Number of years of education does not convey any message regarding the quality of the education and its social and economic value. These aspects can pose an important challenge during the analysis of education based indicators of SEP

2.4.2.2 Occupation, income and wealth

Occupational status is one of the more commonly used SEP indicators in social class literature. It represents the estimated public perception of the relative power associated with specific occupations(33). It is the major structural link between education and income(34). Income and wealth are more direct indicators of SEP used to measure material circumstances in relation to health outcomes (30). Income is a result of an individual's occupation where as wealth would be a collection of anything of economic value (e.g., money, material assets like house, land and personal property). An individual's occupation puts him in a specific working environment. The link between different working environments and health outcomes has been explored in various studies. For example, following a

low educational attainment, one can get a job which exposes him/her to chemicals and physical hazards including carcinogens, physical and psychological stress, noise, heat, cold, unsafe conditions, and dust, among others. These exposures lead to increased risks of diseases. Higher income levels have a positive impact on health outcomes by influencing the material circumstances of an individual such as quality, type and location of housing, food, clothing, medical care, transportation opportunities for cultural, recreational and physical activities, child care and exposure to various toxins(34).

Unemployment has been shown to increase the risk of depression, anxiety and disability, which may lead to unhealthy coping practices (e.g., cigarette smoking and alcohol consumption)(35). Occupation and health outcomes such as oral cancer could also be related through the reverse pathway: behaviours that increase the risk of oropharyngeal cancer, such as heavy alcohol consumption, can interfere with productive employment, leading to a cycle of events mentioned above (33).

2.4.2.3 Housing

Another category of indicators linked to material circumstances is comprised of housing variables. Considered to be proxy indicators of people's general socioeconomic circumstances, the main components that are directly linked to SEP are housing tenure, housing conditions and household amenities(36). Housing tenure considers the status of house ownership, land or farm ownerships. Housing conditions would refer to the type of material used for floor, roof, wall and windows, their cost or presence or absence, toilet facilities, water supply

among others. Household amenities like car or bike ownership in the developed countries and number of livestock, owning a bicycle, refrigerator, radio, sewing machine, TV and clock in the more agrarian societies like India have been used as indicators of SEP (37, 38). It has been documented that health and mortality are sensitive to fine gradations of neo-material conditions like access to cars, home ownership, presence of a home garden and healthier food(39, 40). These indicators can help us understand childhood as well as adulthood SEP in various social contexts. Overcrowding in houses, which has been linked to sanitation and spread of infections, is also considered an indicator of SEP.

2.4.2.4 Other indicators

Some of the variables that could be possible indicators of SEP are the quality of diet and marital status as an indicator of social stability, and others(38). In societies like India, religion and caste (structure of Hindu religion) can also be strong indicators of SEP as people from higher castes enjoyed greater privileges and prestige in society than people from lower castes(41, 42) until the late 1900's.

2.4.3 Different SEP indicators and their association with oral cancer

New research suggests that lower than average SEP is a significant risk factor for oral cancer independent of lifestyle behaviours. A recent meta-analysis of SEP and oral cancer which considered the various important indicators of SEP from studies conducted around the world suggests that lower educational attainment increased the risk of oral cancer by 1.8-2 times as compared to higher educational attainment. The findings were comparable across studies from developed and

developing countries. A similar relation was seen between low occupational class and oral cancer. The relation between housing conditions and the development of oral cancer was also considered in this study but was shown to reflect household income indirectly rather than being an independent risk factor (43).

The above sections have underlined the significance of SEP and the importance of studying its effect on chronic disease outcomes like oral cancer. However, there are various other factors, established by traditional risk-factor epidemiology, which we need to consider when conducting a risk factor assessment for oral cancer.

2.5 Known risk factors for oral cancers

Established risk factors for oral cancer include tobacco use, alcohol consumption, betel quid chewing and the combination of these life style risk factors. Dietary micronutrients have been shown to exert a protective effect in the development of oral cancer while the role of human papillomavirus as a risk factor is gaining importance. Other risk factors and risk indicators linked to oral cancer include general oral health, dental conditions, occupational exposure, sexual behaviour, genetic factors, medical and hormonal factors, age, sex and race/ethnicity. A brief overview of risk factors of oral cancer is given below.

2.5.1 Tobacco

Tobacco use is one of the most important risk factors for oral cancer. More than 60 carcinogens have been identified in cigarette smoke and 16 in unburnt tobacco. The most important of these carcinogens, which have also been causally linked to

oral cancer are tobacco specific nitrosamines such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN), polycyclic aromatic hydrocarbons (PAH) such as benzo[a]pyrene, and aromatic amines(44).

Tobacco is used in various forms and patterns. Because different forms of tobacco consumption can impact health in different ways, the main forms in which tobacco is used, especially in India, are presented below.

2.5.1.1 Smoked tobacco

Cigarette smoking

More than one fourth of oral cancer cases worldwide are attributed to cigarette smoking alone (45). Literature pertaining to smoking status has shown an approximately 3-10 fold increase in risk in current smokers over never smokers and a 1-5 fold increase in ex-smokers(46). Studies indicate that there is a marked increase in the risk of oral cancer when smoking duration is greater than 20 years, and when the daily frequency of smoked cigarettes is higher than 20(45). An increased risk with inhalation of the smoke, use of non filtered cigarettes and handmade cigarettes over their counterparts have also been documented(46).

Bidi smoking

Bidi, another form in which tobacco is smoked, is highly prevalent among the low socioeconomic strata in the South Asian countries, including India, as it is particularly cheap. Its use has been reported in the western world as well. Bidi consists of 0.2-0.5g of raw, dried and crushed tobacco flakes (naturally cured) rolled by hand in tendu leaves (Diospyrus mebunoxylon or Diospyrus ebenum). It

has been documented that bidis produce more carbon dioxide, nicotine, tar and alkaloids than regular cigarettes(47, 48).

The practice of bidi smoking dates back to early 1700's in India and has been documented to account for the largest proportion (40%) of tobacco consumption in this country(49). The bidi industry was promoted as a cottage industry (meaning that production is home-based rather than factory-based) in many states by the Indian government because of its potential to provide employment to many people. Unlike cigarette packets, bidi packs do not carry the statutory warning on the health hazards of tobacco smoking. They have a filter-less design. A comparative study of chemicals found in a popular brand of American filter-less cigarette with bidi showed that a single bidi delivered about one and a half times the carcinogenic hydrocarbons delivered by a cigarette(50).

Various studies show that 20-30% of oral cancer cases are attributable to cigarette or bidi smoking (51, 52). A study conducted in India in 1990 indicated that, compared to non smokers, those who smoked bidi for 20 years and over had 7 times the risk of developing oral cancer and those who smoked cigarettes for the same duration had a five time higher risk (53).

Cigar, pipe, marijuana and passive smoking

Some studies conducted in the western world have shown a 2-9 fold increase in the risk of oral cancer with exclusive cigar smoking and a 2 fold increase in risk with exclusive pipe smoking. In combination, they pose a greater risk of buccal mucosa, soft palate and floor of the mouth cancers (46). The reports on marijuana as a risk factor for oral cancer are controversial and inconclusive due to the fact

that marijuana is smoked in conjunction with other tobacco products which are more important risk factors.

2.5.1.2 Smokeless tobacco

Studies conducted in the US and Sweden show a 3-4 fold increase in the risk of oral cancer associated with smokeless tobacco use(54). In Asia, particularly in India, various forms of smokeless tobacco (betel quid/paan, paan masala, naswar, nas, gutka) are used which accounts for the high incidence rates of oral cancer in this region(55). Contributing factors include the fact that tobacco processing for these forms of consumption is mostly done in households and small scale sectors with less control over fermentation and curing, leading to increased concentration of several carcinogens, the non homogeneity in the use and composition of smokeless tobacco in India, and different additives which increase their psychotropic and genotoxic effects (56). Studies report betel quid chewing as the most common form of smokeless tobacco used by men and women in India, which has the largest betel quid consuming population in the world(57, 58). It has been documented that the ratios between male and female incidence rates of oral cancer in central and Eastern Europe, South America range between 3 and 10 where as in India it is approximately 1 or lower than 0.5(59). This high incidence rates in Indian women is attributed to the persistence of betel quid chewing habit as smoking and alcohol habits are not so common among them(4). Recent research has established links between betel quid chewing and oral cancer that cannot be explained by the presence of tobacco alone(60). In light of its relevance

to the Indian population, an account of the betel quid chewing habit, its components and its reported association with oral cancer are given below.

Paan/Betel quid chewing

The habit of betel quid chewing is widespread and its use has been documented from the east African coast to eastern Melanesia (a sub-region of Oceania), South East Asia and throughout India. A study conducted in Kerala, India, indicates that individuals who chewed more than 10 times a day were at 15 times more risk of developing oral cancer than non chewers(61).

The most common components of the quid are: betel leaves, taken from a perennial plant also called piper betel, commonly seen in South and South East Asia; Arecanut, which is the nut from a palm tree called Areca catechu, originating from the Philippines and Malaysia; lime (calcium oxide or calcium hydroxide); and dried or raw tobacco. Apart from these basic ingredients, many other flavouring agents, spices, catechu (an extract of Acacia catechu with tannins and catechols), and others can be incorporated into the betel quid. Pindborg et al. have described 38 different combinations of betel quid components in India(62). All the ingredients are wrapped in the heart shaped betel leaf, put in the mouth and chewed. The juice is spit or swallowed. Betel quid chewing is a well established aetiologic factor in oral cancer as well as oral premalignant lesions like oral sub mucous fibrosis and oral leukoplakia(63-65).

Components and carcinogenicity

Betel leaf

Betel leaf has been an intricate part of different cultures from time immemorial and is considered to occupy an important positive role in the social setup of countries such as India. Its uses range from welcoming guests as a sign of respect on important occasions like marriages, to being employed as mouth fresheners, or antiseptic and antibacterial agents. Various studies have been conducted to determine the carcinogenicity of betel leaf. Most of these studies have failed to find evidence of genetic disturbance despite using high concentrations of betel leaf extracts(66). Ranadive et al. reported a reduction of 53 - 22% in the incidence of carcinoma when betel quid containing betel leaf was used(67). Taken together, these studies suggest that the effect of betel leaf is anti-carcinogenic rather than mutagenic. The euphoric effect that one gets after chewing betel leaf is attributed to a mixture of phenols and terpene-like constituents(68).

Areca nut

Studies indicate that the Areca nut is carcinogenic, and this effect is mainly attributed to its alkaloids and poly-phenolic constituents. Arecoline, a natural cholinergic agonist similar to nicotine is the dominant alkaloid (7.5mg/g of the nut), along with arecaidine, guvacoline and guvacine. Betel chewers have been found to express nitrites and thiocyanates in their saliva. They combine with the alkaloids in the nut to produce nitrosamines, which are known carcinogens(69). Furthermore, these alkaloids are biological thiol reagents analogues to other alkylating agents, which is a common feature among many chemical carcinogens

leading to cell proliferation and cancer. These alkaloids are also responsible for the stimulant effect of betel quid, inducing dependence among heavy chewers(70).

Slaked lime

The slaked lime used in betel quid is produced from sea shells or lime stones, the former being more potent due to the presence of pure calcium hydroxide(69). Oral epithelia undergoes atypical changes following exposure to calcium hydroxide(51). This exposure causes severe caustic damage to both the epithelium and the underlying tissues. The increased alkalinity results in the leaching of intercellular mucus leading to inflammatory and proliferatory changes in the tissue. In this altered environment, exposures (e.g., oral microorganisms, chemicals) can act as cancer-promoting factors leading to neoplastic changes(71). The alkaline environment created by the slaked lime facilitates the generation of reactive oxygen species following auto-oxidation of polyphenols in the areca nut (44).These oxygen species initiate cellular free radical reaction causing damage to proteins, lipids, carbohydrates and DNA(72).

Association with oral cancer

With the exception of the betel leaf, all the components of betel quid, including tobacco discussed earlier have strong carcinogenic effects. These combined effects substantially increase the likelihood of developing oral cancer. A study on oral cancers in southern India showed that 50% of men's and 90% of women's oral cancer cases can be attributed to frequent betel quid usage without tobacco chewing in areas where chewing prevalence is high(51). The chance of disease

development is high in frequent and long-term chewers(73). Some recent studies have failed to establish an increased risk of oral cancer in association with betel quid chewing among low to moderate chewers in the absence of concomitant exposures such as smoking and alcohol drinking(71, 73).

2.5.2 Alcohol consumption

The World Health Organization estimates that there are approximately two billion alcohol consumers worldwide(74). There is wide variation in the type, quality and quantity of alcohol consumed across the globe. Drinking patterns vary from occasional to habitual drinking, to alcohol abuse. Genetic, environmental and psychosocial factors have been recognized to contribute to heavy alcohol use and abuse, which may lead to health problems including oral cancer.

The association between alcohol consumption and oral cancer is dose dependent. Over all 7-19% of oral cancer cases are attributed to heavy alcohol consumption (45). Compared to non drinkers, there is a 2-3 fold increase in the risk of oral cancer in people who consume 4-5 drinks daily(75). Heavy drinkers have approximately 2 to 9 times the risk of developing oral cancer compared to light drinkers(76). However, no increase in risk has been observed in people who drink but have never used tobacco, irrespective of drinking duration and frequency (45).

The role of alcohol as a promoter in cancer causation has been established, but its effects as an initiator is still under investigation. The main component of alcoholic beverages investigated for its relation to cancer is ethanol. Alcohol dehydrogenase, the main alcohol metabolizing enzyme in our body, oxidises ethanol to acetaldehyde. Acetaldehyde exerts multiple mutagenic effects on DNA

hence leading to the carcinogenic effect of ethanol. Nitrosamines, acrylamide and oxidized polyphenols in alcohol are other minor components classified as probable carcinogens for oral epithelial cells. Although this carcinogenic mechanism of ethanol metabolites has been proved in animal studies, it has not been proved for oral cancer in human beings(77).

2.5.3 Combination of tobacco and alcohol

The combination of tobacco products in any form with alcohol can lead to lethal consequences. A study from India reported an 11 fold greater risk of oral cancer with joint tobacco/betel quid chewing, bidi/cigarette smoking and heavy alcohol consumption(78). About three fourths of oral cancer cases are attributed to tobacco and alcohol consumption combined in Western countries(76). The great challenge in understanding the individual contribution of these factors is that these habits are strongly associated with each other(79).

2.5.4 Dietary factors

Oral cancer is associated with diet, more specifically with food deficient in fruits, non-starchy vegetables, and carotenoids. Approximately 10-15 percent of cases are attributed to low vegetable and fruit intake (73). Although not conclusive, there is evidence indicating that plant food with antioxidant and anti-carcinogenic properties containing nutrients such as vitamins A, C, E, carotenoids, flavonoids, phytosterols, folates and fibers could counter balance the risk posed by tobacco smoking, alcohol consumption and betel quid chewing. These agents, especially antioxidants, act by reducing the free radical reaction that can cause DNA mutations and changes in the lipid peroxidation of cellular membranes and in

enzymatic activities. The micronutrients also play a role in the modulation of carcinogen metabolism, inhibition of cell proliferation and oncogenic expression, immune function and inhibition of endogenous formation of carcinogens (72, 73).

2.5.5 Human papillomavirus

Human papillomavirus (HPV) and its association with oral cancer as a risk factor have gained prominence in the recent past. HPV is transmitted in humans through sexual contact, including oral sex. Approximately 3% of oral cancer cases have been attributed to this viral infection(80). There are more than 100 HPV types, among which HPV-16 has been shown to have a strong association with oral cancer pathogenesis at the molecular level. A systematic review by Kreimer et al reports that HPV infection was present in 25% of oral cancer cases and 36% of oropharyngeal cases studied. HPV-16 and HPV-18 were associated with 68% and 34% of oral cancer cases, respectively. Larger case-control studies have also reported a 3 fold increase in the risk of oral cancer in the presence of HPV infections(81).

2.5.6 Other oral cancer risk factors

Various studies have investigated the association between dental conditions (e.g., missing teeth, denture wearing, poor oral hygiene and use of mouthwash) and oral cancer. Results are contradictory. For example, some studies have reported an increased risk of oral cancer with increasing number of tooth loss while some have failed to establish any association(82-85). Recent studies have suggested an association between chronic periodontitis and increased risk of tongue cancer(86).

Studies on family history of oral cancer indicate that the risk of this disease increases a 2-3 fold in patients having a first order family relation with oral cancer(46). Other risk factors that have been explored with relatively weak or inconsistent results are occupational exposures, race/ethnicity, hormonal factors, the role of high-penetrance and low-penetrance genetic mutations, and alteration of expression of intra-nuclear enzyme telomerase(87, 88).

The above sections looked into the wide range of risk factors for oral cancer. Now the question would be, what methodology can be used efficiently to study the association of these dynamic factors, spread over the life course of an individual, and chronic diseases like oral cancer?

2.6 Risk factor assessment for chronic diseases – Need for life course framework

Lynch(1997) suggested that "if social class position in childhood and educational experience were important in the adoption and maintenance of adult health behaviours or influential in the development of psychosocial orientations, then it would be inappropriate to "adjust" for these variables, because the socioeconomic status exposures would be temporally prior to the behaviours and so the behavioural and psychosocial characteristics would be in the causal pathway"(89). Chronic diseases develop over a long period of time. A risk factor like SEP is a time dependent variable which changes over the life course of a person. People indulge in behavioural habits like tobacco smoking, paan chewing, alcohol drinking and food consumption in various patterns at different stages of life. To understand when and how exposures lead to various health outcomes in later life

and to investigate the causal pathways in the development of diseases, it is important to implement a more comprehensive methodology than the traditional risk factor epidemiology, which mostly assesses risk factors at one point in time. There is a need for a methodology addressing the issues of temporal sequencing, tracing the development of health behaviours, socioeconomic and psychosocial orientations in order to understand the aetiology of chronic diseases. A conceptual framework particularly well suited for this purpose, encompassing all the above mentioned dimensions, would be the life course approach.

2.7 Life course epidemiology in oral cancer risk assessment

The life course approach studies the long term effects of physical, social and psychosocial exposures during gestation, childhood, adolescence, young adulthood and later adult life. Importance is given to time and timing in understanding causal links between exposures and outcomes during an individual's life course and across generations(90). In the development of chronic diseases such as cancer, the involvement of phases like exposure, initiation of disease and longer latency periods explains the importance of time, and the fact that exposures at particular stages of the life course exert effects later on, underlines the importance of timing(91).

Different models derived from the life course framework, such as the critical period and cumulative effects models, have been used to understand the various impacts of exposures on health outcomes in later stages of life. The critical period model argues that an exposure during a particular time window has lasting effects that result in higher disease risk. In addition to critical periods, there could be

sensitive periods when an exposure has a particularly marked but not unique effect. This is called the critical period with effect modifier. The accumulation of risk model hypothesizes that effects are accumulated incrementally through the life course, with adverse environmental conditions and behaviours increasing the risk of eventually developing chronic diseases(30, 92). The cumulative effects model suggests that additive effects of exposures like SEP variables throughout childhood and adulthood increases the risk of adult diseases like chronic heart disease(40).

Because oral cancer is a chronic disease, the life course approach is particularly relevant in understanding its risk factors, including lifestyle risk factors. Due to the time dependent nature of these risk factors, it is advantageous to examine them using this framework. Childhood circumstances related to lower SEP like opportunities for education and lower social support have effects on deprivation and choices in later life, such as exposure to behavioural risk factors including tobacco and alcohol use and even initiation of sexual activity at a younger age and the development of HPV infection. Relevant SEP indicators, such as education, occupation, and housing conditions can vary at different ages. Measuring these indicators at different stages of the life course can be useful in examining how socioeconomic conditions operating at different stages of life influence the development of oral cancer in later adult life (30). For example parental occupation can be used to characterize childhood SEP and the first and longest and last occupations may be used as indicators of adult SEP. Housing and living conditions can be used to assess the SEP of an individual from childhood through

early adulthood to late adulthood. The life course approach can help us understand the combined effect of these indicators over the whole time period.

2.8. Indian context

Oral cancer was the most common cancer in India until the recent past, accounting for 50-70% of total cancer mortality in the country(93). The following section focuses on the factors mentioned in the previous sections in this chapter, from an Indian context.

2.8.1 Socioeconomic indicators

The Indian society is commonly referred to as an agrarian society, which has implications for its socio-cultural background and life style of individuals. Quality of education and educational status, occupations and housing conditions vary in different parts of India and also along the life course of each individual. Since oral cancer is a disease with a long latency period and most cases are in the age group of 50 to 70 years of age, a thorough understanding of the SEP indicators and their status in the Indian society since the early 1900's is important. Considering their relevance for this thesis work, a broad overview of education and housing conditions is presented in the following sections.

2.8.1.1 Education

In the case of education, India has been one of the pioneering societies in the history of humankind with Nalanda University in north India being considered the oldest university in the world. From 'Charaka samhita sutra' and 'Sushruta Samhita', ancient texts on medicine, considered to be the oldest sources of

medical understanding and practice, the invention of 'zero' and decimals in mathematics to the 'Raman scattering effect' in physics, India's contribution to the world of education has been considerable. In fact, the first description of oral cancer appears in, 'Sushruta Samhita'(around 600BC) and some of the first hypotheses on oral cancer were also recorded in India(94). Education always had prime importance in the Indian society, but was not provided equally to all. The complex social makeup of this society characterized by various religions, and the structure of the Hindu religion (castes, sub castes and sub-sub-castes) further made access to education by certain social classes difficult. The potential for disparities in education, an important source of human capital, has therefore been substantial in the Indian society.

Since the 'Vedic age' in Indian history, schools of education called 'Gurukul' existed but were accessible only to people from the higher caste. Restrictions were made for the education of people from the "backward"[1] (or lower) castes.

Kerala is one of the Indian states were tremendous educational reforms have taken place during the past century. Until around the 1960's, higher caste Hindus and Syrian Christians enjoyed privileges and had a higher education status and SEP than the other social groups in Kerala(41). At present, although educational disparities have been brought down to a low level by government policies, the remaining socioeconomic disparities still exert a strong impact on the health of the Indian population.

[1] This includes the castes in the Hindu religion and sections of other religions that has been classified as backward by the state governments of India (here; Kerala) due to discrimination faced by them historically.

2.8.1.2 Housing conditions

Variation in the quality of housing conditions is another factor to focus on when considering the SEP of this population. The use of concrete, good flooring and roofing materials and proper sanitation methods has gained importance only in the recent past. Crowded houses, lack of bathrooms and other sanitation facilities especially in the rural population, roofs of houses thatched with coconut and palm leaves, floors polished with mud, cow-dung or wood charcoal irrespective of SEP were almost indigenous to this part of the world. The use of household materials like refrigerators, televisions, and electricity were almost nonexistent until the late 1960's and 70's.

Even though the standards of living conditions and education have increased in India, many disparities still exist and an obvious gradation can be seen from the low to the high SEP in this society. These important background factors have to be taken into consideration when assessing the SEP of the Indian society.

2.8.2 Behavioural factors

Oral cancer started receiving increased empirical attention in the mid 1950's. Risk factors like tobacco smoking, betel quid chewing, and alcohol consumption are common in the male population of India, while smoking and alcohol consumption are infrequent in females(95). However the habit of betel quid chewing is widespread in both sexes.

Literary references to the habit of chewing betel quid (betel leaf, areca nut and lime) in India are at least 2,000 years old (94). For centuries, areca nut chewing

was considered to be a completely innocuous practice in India with widespread socio-cultural acceptance. This habit began to get recognized as a public health issue around 400 years ago with the introduction of tobacco into the Indian society by European traders. In addition to its use for smoking, as the Europeans demonstrated, tobacco began to be mixed with betel quid and chewed. The combination of tobacco with a culturally accepted substance gave it a similar status. The association of these practices with oral cancer was noted over 100 years back and in the second half of the 20th century, the causal association between chewing of betel quid with tobacco and oral cancer got well established. From this time forward, the chewing habit was no longer considered to be an innocuous practice(96).

There is much variation in the type and pattern of use of these products in different parts of India. For example, in the state of Kerala, the betel quid used for chewing consists of a fresh betel leaf smeared with aqueous calcium hydroxide, combined with sliced fresh or dried areca nut and locally cured dried tobacco leaves and/or stem. This preparation is much simpler than the betel quid in northern India, which contains many spices and other condiments. (97).

Besides the common alcoholic beverages, other frequently used preparations are a beverage called “toddy”, produced locally from fermented and distilled sap palm trees (approximately 8-10% ethanol) and a locally brewed liquor; “arrack”, traditionally produced from fermented palm sap and also fruit, grain, or sugarcane (approximately 40-60% ethanol)(53).

2.8.3 SEP, behavioural habits and oral cancer in India

The common risk factors for oral cancer in India (e.g., smoking, betel quid chewing; alcohol consumption and diet) have been extensively studied and established as independent risk factors for this disease. A recent case-control study conducted in the western part of India, which considered the role of education, occupation, smoking and alcohol habits, suggests that the risk of oral cancer is inversely proportional to level of education and economic status. Low levels of education, occupation in agriculture and blue collar jobs, as well as low household income are independent risk factors for oral cancer(98).

As previously discussed, low SEP has been strongly associated with an increased risk of oral cancer in developed and developing countries. But no significant work has been done focusing on the individual indicators of SEP as independent risk factors for oral cancer(98), the existence of any dose response relationship with SEP, and the association of the different SEP measures with the common behavioural risk factors for oral cancer, in southern India. The importance of using a life course approach in the assessment of risk factors for chronic diseases like oral cancer has been discussed earlier. However, to our knowledge, none of the studies conducted in India reported using this epidemiological approach as their conceptual framework. SEP indicators like education and housing, and other oral health related behavioural habits have considerably evolved in the Indian population over the past century. To thoroughly understand the association of these risk factors with oral cancer in a population of Indian subjects, a study using the life course framework appears to be the most advantageous approach.

2.9 Kerala study site

Situated on the south western coast of India, the state of Kerala has a population of 31.8 million with a population density of 819 per sq. Km (99). (Canadian population: 34.2 million, population density: - 3.3 per sq. Km (100)). The main ethnic group is that of 'Malayalies', and the official language of this state is 'Malayalam' spoken by 96% of the population. The majority of people are from the middle class. Main religions followed by people of Kerala are Hinduism (56.2%, predominantly Thiyya/Ezhava caste) with many castes and sub caste divisions, Islam (24.7%) and Christianity (19%) (99).

Until the mid 1900's, a feudalistic system existed in Kerala in the case of land ownership, wealth, access to education and privileges. This was based mainly on the caste system, the forward caste and Syrian Christians enjoying most of the privileges. The lower castes/backward castes were seen as untouchables. The right to get educated was considered as a monopoly of the elite class. Four years of education was considered to be a high education level. Teachers were not paid well by management run institutions which led to less people taking up teaching as profession. Political movements and revolutions since Indian independence in 1947 brought the whole of India together(41, 101). Subsequently, based on language spoken, the state of Kerala, like other states, got unified and thus the present day Kerala state was born in 1956. The first ministry under communist leadership took form in 1957. The minister of education, Prof. Joseph Mundassery, who was a famous teacher, educationalist, literary critic and revolutionary, gave attention to the existing state of education in Kerala and made

way for passing an education bill in the assembly in 1958 which made quiet a revolution in the history of Kerala. According to the bill, education until 14yrs (8yrs of education) was made free and compulsory, books and other materials for students and lunch were provided for free and wages for teachers were increased. Teachers were paid directly by the state government and a good amount of dignity was added to the profession(101). Overcoming the stiff resistance from the forward caste and Syrian Christians, the bill succeeded in imparting quality education to people from all castes and walks of life in Kerala. Along with this, reforms in land resources and ownership, health and social welfare also contributed to revolutionary changes in the SEP of Kerala in the 1950's(101).

Today, Kerala ranks highest in India with respect to social development indices such as elimination of poverty, primary education and healthcare. In less developed countries, the education level of women has consistently been demonstrated to be an important determinant of population health and SEP(34). Kerala has the highest overall and female literacy rates among all the states in India. The health status of a population is generally measured in terms of mortality indicators like death rate, infant mortality rate and life expectancy at birth among others. Mortality indicators show that the health status of Kerala is far higher than the overall average for India and is even comparable to that of developed countries. This Indian state has the greatest number of hospitals and health facilities (5,095 government, private and co-operative medical institutions) and low child death rates (102-104). With only 3% of India's population, the tiny state provides two-thirds of India's palliative care. Female life expectancy

exceeds that of males, as seen in developed countries. Incidence of absolute poverty in rural Kerala (17.52%) is about half of that in rural India overall (32.82%)(102). Table 2 shows comparison of important health indicators between Kerala and India according to 2008-09 statistics(105). Figures 1 and 2 present a comparison of India, Kerala, and the United States with relevance to some of these indicators based on data collected in 2009(106). In spite of the advancements in education, social and health sectors, there is high variability in SEP, and in the use of tobacco products, alcohol and betel quid, and others. Kerala is one of few Indian states that maintain good cancer registries, and these indicate that there is a high incidence of oral cancer in its population. A recent study from Calicut, Kerala, suggested that there is an increase in oral cancer incidence among young adults in this region but was unable to establish any significant risk factor association(107). Under these circumstances, Kerala, India, appears particularly well suited as the site for a hospital-based case-control study on oral cancer risk factors incorporating the life course approach.

Table 2: Basic health indicators, Kerala and India (2008-09)

Indicators	**Kerala**	**India**
Birth rate (per 1000 population)	14.7	23.1
Death rate (per 1000 population)	6.8	7.4
Infant mortality rate (per 1000 population)	13	55
Child mortality rate (per 1000 population)	3	17
Maternal mortality rate (per 100000 live birth)	110	301
Total fertility rate (children per woman)	1.7	2.9
Life expectancy at birth		
Males (years)	71.3	62.3
Females (years)	76.3	63.9

Figure 1: Life expectancy and literacy rates 2009

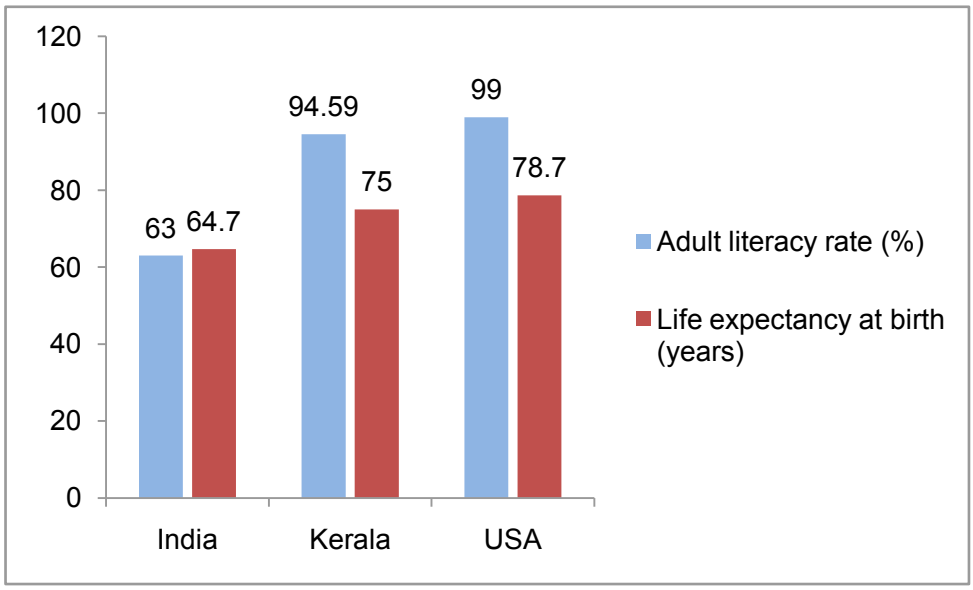
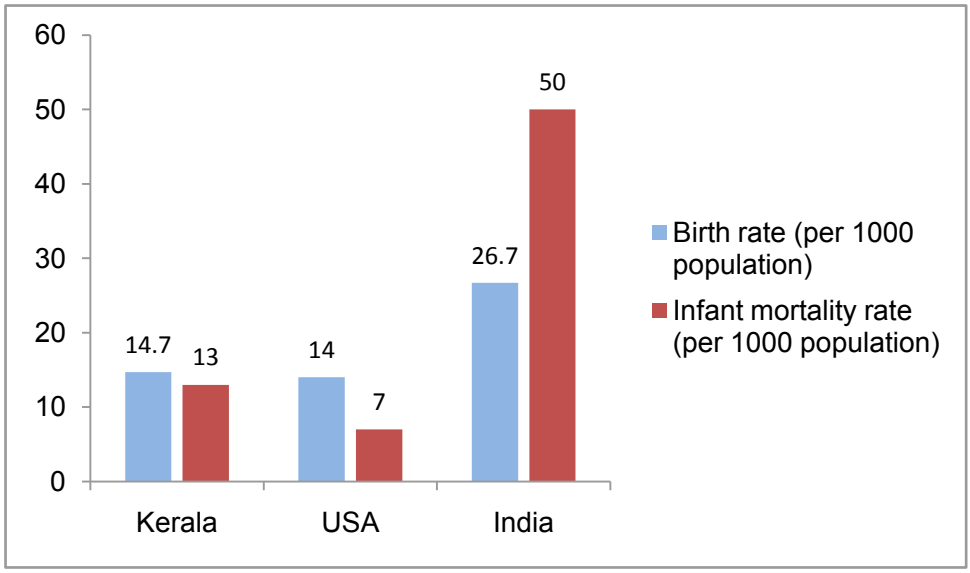


Figure 2: Birth rate and Infant mortality rates 2009



3. Rationale

Oral cancer is a devastating chronic disease with high incidence and mortality rates in both the developed world and developing countries like India. The fact that this disease is still a challenge with serious physical, psychological and social consequences even after decades of research in this area and advancements in the fields of diagnostics and treatment, points to the poor understanding of its aetio-pathogenesis. The importance of SEP as a potential risk factor for oral cancer has been examined in the previous sections. A thorough understanding of this complex construct, which changes over the life course of an individual, and a methodology conceptually solid to measure it as provided by the life course approach are needed to understand the role of SEP as a potential risk factor for this disease. As explained earlier, the life course approach allows the ordering of exposures in time and the examination of relationships among them. Thus, this approach could be of tremendous benefit to gain a more comprehensive understanding of the associations between SEP, behavioural factors and oral cancer risk than those obtained from basic cross-sectional analysis. By identifying these associations, links between the biology of oral cancer development and exposures including SEP can be uncovered. There is a consensus that with respect to cancer that earlier the diagnosis, better the prognosis of treatment. Thus, the understanding of biology and the various bio markers expressed as a result of these exposures is crucial in powering new and efficient diagnostic techniques for this disease. This would be of particular importance in developing countries like India with a high incidence of oral cancer and a wide variation in the known risk

factors (e.g., tobacco/ paan chewing, alcohol consumption). Although behavioural habits have been established as the strongest aetiologic factors of oral cancer in India (like elsewhere), there is very limited literature investigating the association between SEP and oral cancer in this population. In addition, to the best of our knowledge, no one has examined the effect of SEP across the life course and its association with oral cancer. This study attempts to fill these gaps in the literature by examining an array of life course exposures and SEP indicators and the risk of oral cancer among a sample of Indian subjects.

4. Aim and Hypothesis

4.1 Aim

The aim of this study is:

To estimate the extent to which life course socioeconomic position is an independent risk factor for oral cancer and how much of this association is explained by behavioural habits and oral health related factors in a sample of Indian subjects.

4.2 Hypothesis

We hypothesis that being in a low SEP throughout the life course will increase the risk of oral cancer irrespective of effects of other risk factors.

5. Methods

5.1. Overview of study design

The case-control study design is very effective for epidemiological studies. In this design, subjects with a particular disease, (e.g., oral cancer) are compared with a control group of people who do not have the disease under study. All cases or a random sample of those in the population base who develop the disease during the study period are recruited. Controls should be representative of the population from which the cases come from so that the two groups can be comparable in all respects except the presence of the disease studied, that is, controls are selected from the same population base independent of exposure (e.g., smoking, chewing habits, alcohol consumption, socioeconomic position) so that the distribution of the exposures among them is the same as in the base(108).

The data for this study was drawn from the Indian site of a large hospital based case-control study – The Head and Neck Cancer Life course study (HeNCe Life study), that uses a multidisciplinary approach to investigate the role of genetic, viral, behavioural, psychosocial and socioeconomic factors in the aetiology of upper aero digestive tract cancers incorporating the novel life course framework. The higher incidence and mortality rates of oral cancer, existence of large socioeconomic disparities in health and wide distribution of behavioural habits and other risk factors associated with oral cancer justifies the selection of India as a study site. Oral cancer cases and controls were recruited from the Government Dental and Medical College and Hospital, Calicut, Kerala, India. Questionnaire

based interviews were performed and biological samples collected for HPV and genetic analysis by trained dentists.

5.2. Study setting and study population

The sample of this ongoing hospital based case-control study was recruited from the outpatients of Government Dental and Medical College and Hospital in the state of Kerala, India. These two hospitals cater their service to the populations of mainly four districts (Calicut, Malappuram, Kannur, and Wayanad) and serve approximately a 150-Km radius referral base in northern Kerala. The study sample is comprised of 350 subjects recruited between September 2008 and January 2011, including 200 oral cancer cases and 150 non cancer controls.

5.3. General inclusion and exclusion criteria

The eligibility criteria for study entry are: (i) subjects who were Indian born, (ii) living within a 150Km radius from the hospitals to ensure a good representation of the risk base and social and cultural patterns, (iii) speaking English or the local language Malayalam, (iv) with no previous history of cancer and without any cognitive debilitating diseases, HIV, AIDS, disease of the central nervous system or mental disorders. In addition, those who were unable to respond due to severe illness were not recruited into the study. Since oral cancer is a disease only diagnosed in adults, all subjects were above 18 years of age.

5.4. Case definition and selection

Cases are newly diagnosed histologically confirmed stage I to IV squamous cell carcinomas of the oral cavity which according to the WHO ICD-10

classification(12), includes the upper and lower lip inner aspect (C00.3,C00.4, C00.5), base of tongue and tongue(C01-C02), gums(C03), floor of the mouth(C04), palate(C05), cheek mucosa, vestibule of mouth, and the retro-molar area(C06) and tonsil(C09). Cancers of the external lips(C00.0-C00.3), parotid glands, other major salivary glands(C07-C08), and naso-pharynx were excluded due to their different aetiology and histologic features(109). All cases were recruited into the study without any delay, immediately after their histologic diagnosis. They were recruited from the oral pathology clinic at the Government Dental College and from the cancer outpatient unit of the Government Medical College, Calicut, Kerala, India. Prevalent cases were not included in this study because of various reasons; a) recall of exposure would be better in incident cases as prevalent cases are much distant in time from their exposure history than incident cases; b) inferior recall in prevalent cases since exposure history may have changed as a result of and subsequent to disease incidence; c) it can be made sure in incident cases that recalled exposures preceded the diagnosis and not followed it; d) It has also been stated that since diagnostic methods change periodically, recent diagnosis will be more uniform than the one diagnosed in earlier or different time periods; e) relation of exposure to survival; since prevalence data are length biased with regard to survival, exposure frequencies will differ between incident and prevalent cases, leading to bias(110-112). Cases previously treated or undergoing treatments were not recruited as local or systemic treatment interferes with the biomarkers under study.

5.5. Control definition and selection

Controls were frequency matched to cases (age period of 5 years and sex) and recruited from several outpatient clinics at the same hospitals as the cases. Hospital controls have the advantage of being more cooperative and the collected information is less affected by recall bias compared to population controls. Their recruitment is more convenient and involves less cost when compared to population controls(111). All controls were randomly selected from outpatients clinics [dental, dermatology, ENT (ear, nose, and throat), gastroenterology, gynecology, ophthalmology, orthopaedics, and nephrology clinics] at the Government Dental and Medical College and Hospital. In order to maintain good balance in the distribution of disease among controls, care was taken to ensure that no single diagnostic group contributed to more than 20% of the total. These procedures ensure a good representation of the risk base.

5.6. Data collection

5.6.1 Recruitment procedure

At the study site, trained dentists, including the author of this thesis, were appointed as research assistants (RA) for the recruitment of subjects and data collection. They were trained in the procedures used in this project by the principal investigators of the study. Also, an interviewer guide and a DVD with information describing the study procedures step by step was provided to the research personnel at the site. The RA would verify the list of patients to attend the clinics each day. Oral cancer cases, who meet the eligibility criteria, were explained the study and invited to participate soon after they were histologically

diagnosed. The selection of controls was based on the sex/ age distribution of cases. For this purpose, a monthly frequency matching list was generated by international coordinating office of the study located at the Canadian site and sent to the Indian site. To assure that a good balance among the control clinics was maintained over the study period, the list also included the distribution of controls according to the clinics they should be recruited from. The control clinics were visited by the RA and the details of subjects attending them were obtained. Subsequently, random selections of subjects were made to participate in the study from the pool of eligible subjects. Next, the RA approached the eligible subjects, explained the study, confirmed their eligibility for entry into the study and invited them to participate in the study.

All participants who agreed to take part in the study were asked to read and sign the consent forms, which were available in both English and Malayalam (please refer to appendix III). The RA explained the consent form to the subjects who were unable to read. These procedures were done in presence of a witness. One of the copies of the consent form was kept at the study site and one was given to the subject.

5.6.2 Participation rate

This is an ongoing study thus the participation rates refer to those subjects who were approached to be recruited from September 2008 to January 2011. Out of 260 eligible cases, 60 refused to participate, leaving a total of 200 subjects in the study. This represents a participation rate of 76.9%. The main reason for refusing to participate in the study was the advanced disease state and reluctance shown by

acquaintances/spouses accompanying the patients to cooperate with study procedures and timings. Regarding the controls, out of 178 eligible controls, 28 declined the invitation to participate whereas 150 agreed to take part in the study, representing a participation rate of 85.3%. Their refusal was mainly due to the lengthy study procedure.

5.6.3 Study instruments

5.6.3.1 Questionnaire

General information on the subjects was collected using a 'rout sheet'. Subsequently a face to face interactive interview (approximately 1.5hrs long) was conducted using a questionnaire and a life grid (please refer to appendix I and II). The questionnaire collects information on several domains of exposures such as socioeconomic (e.g., education, occupation, housing conditions), health related behavioural habits (e.g., tobacco smoking, tobacco chewing, alcohol, diet, sexual behavior), oral health status, family and work environments at 3 stages of a person's life [childhood (1-16 years), early adulthood (17-30 years), late adulthood (31years and above)]. The questionnaire was developed based on previous studies including British cohort studies - British Civil Servants, Whitehall II (113), British Birth Cohort (BBC) 1946 (114), BBC 1958 (115) and International Agency for Research on Cancer (IARC). The instrument was first developed in English, then translated in Malayalam by a native Indian and back-translated in English to verify the quality of translation. The instrument was used in two pilot studies with the target population and refined before being used in the main study reported here.

5.6.3.2 Life grid

The life grid is an interview tool that has been used successfully to improve the reliability of retrospective data in epidemiology since the 1980's. This tool was originally developed in social science and adapted by Blane(1996) and Berney and Blane(1997) for health research(116). The instrument basically helps the subject to recollect information more precisely by relating them to important events in their past life. The life grid is introduced at the beginning of the interview and consists of four columns (housing, education/job, habits and subjects' memorable life events (e.g., time of marriage, birth of children, death of an important person or any other) and one central line which indicates the subject's age. Important events in the subject's life like, change of housing, years and levels of education, start or end of behavioural habits (e.g., smoking, drinking alcohol, paan chewing) are noted down. Information collected in the 4 separate columns is then cross referenced with each other to check that the timeline given by the subject is accurate. Overlaps between the events are discussed and corrected when relevant. Subsequently, the information collected in the life grid is used to guide the subjects to recollect information during the core interview session using the questionnaire. Reminders throughout the questionnaire help the interviewer to use the life grid while collecting information. In summary, throughout the interview process the questionnaire and life grid are used in tandem helping to retrieve a clear outline of the person's life events and major changes in their lives therefore allowing the collection of a more precise information. The use of life grid has also been found helpful in establishing

interviewer-participant rapport (116). This aspect is of particular importance when involving long interview sessions like ours. Indeed, our fieldwork experience showed that building up a good rapport with the subjects was essential to keep the subjects connected to the interviewer allowing for the collection of quality and reliable data until the end of each session.

5.7. Quality assurance of study proceedings and data collected at the Indian site

All interviews and study procedures are conducted by trained dentists. In order to ensure the quality of data collected, a strict protocol and interviewers guide describing all the study procedures is followed. Individual identification numbers are given to each subject to ensure the confidentiality of the data collected After each interview session, the research assistant who conducted the interview goes through each section of the questionnaire to check for missing data or discrepancies and if present, they are clarified immediately with the subject. On the next day, the questionnaires are cross checked by a second research assistant. Log sheets are maintained separately for participant and non participant cases and controls. Matching lists are used to help in the selection of appropriate controls after the cases are selected. To check for reliability 10% of the samples are re-interviewed and these interviews are conducted 6-12 weeks after the original interview sessions. Each questionnaire is filed individually and all supporting documents are filed separately to ensure confidentiality, as well as for ease of re-access to them while performing data entry. Well documented registries are maintained at the site. The performance of the research assistants is monitored by

the head of the faculty and the study collaborator at the site. Updates of the study procedures are done with the main PI's of the study in Canada through regular correspondence.

5.8. Data management

The data collected is entered into an online database using the 'file maker' software. A common server for the database is maintained at the Canadian site. The data is then exported for processing and analysis with the Predictive Analytics Software (PASW) Statistics version 18 software. Prior to data analysis, value labels were assigned for each variable in the database based on the questionnaire. Then initial frequencies were run for performing data cleaning. Data was checked for missing values, discrepancies, mismatches and inconsistencies. Log sheets were maintained for entering these errors and they were sent to the Indian site for clarifications. Multiple data cleaning cycles were performed subsequently to ensure accuracy of data before the analysis.

5.9. Measures

5.9.1 Outcome variable

5.9.1.1 Oral cancer

Although several studies have investigated oral cancer risk factors, its aetiology is still not clearly understood. Therefore, there is a need for exploring new realms of risk factors for this disease. Based on the revised ICD classification (ICD 10), oral cancer (C00 – 06) can be defined as cancer affecting lips, tongue, gums, floor of the mouth, palate, cheek mucosa, vestibule of mouth, and the retro-molar area. As

detailed in section 5.4**,** only histologically confirmed squamous cell carcinomas are included in the study. Histological confirmation is the most reliable method as it is the gold standard for diagnosis of malignant lesions (117). In addition, trained dentists employed as research assistants collected the data thus contributing to the quality of the data. This variable was treated as categorical variable based on the presence or absence (Yes/No) of the disease.

5.9.2 Explanatory variables

5.9.2.1 Socioeconomic position

As previously discussed, SEP is considered to be the most distal causes of chronic diseases(118). Its measurement allows the understanding of social distribution of diseases, helping policy makers to design and evaluate public health strategies. In addition, studying SEP over the life course could help in explaining the causal mechanisms through which SEP generates health differences(30). The various ways to measure SEP reflect the complexity of the construct. There is no single measure that is suitable for all research questions, applicable to all time points and to all regions of the world. For example, education may reflect individuals' SEP at young adulthood and also influences their SEP in later life. On the contrary, indicators of material deprivation (e.g., housing conditions, tenure and amenities) over the life course gives a good idea about SEP throughout a person's life(37). Then again, these indicators may vary in different societies. For example, car ownership is an important marker of SEP in Britain but not in India. Education and material deprivation indicators have been used as a measure of SEP in non

industrialised or more agrarian societies (e.g. India), therefore we examined these measures in this thesis work (37, 119).

Education

Detailed information regarding education was collected from each subject. Details on whether the subject attended school or not, whether they could read and/or write, number of years of formal education attained, degree obtained and whether they failed any year of school were recorded. In our data analysis, we used education first as a continuous variable expressed by number of years of completed education. However, bias could have occurred due to the inclusion of subjects from different birth cohorts (i.e., from a range of age groups) in this study (37, 120). For example, the meaning of levels of education (e.g., 4 years of formal education) is different for subjects born in the 1930's compared to those born in the 1960's. This effect, also known as a cohort effect, should be taken into consideration when analyzing life course data. Otherwise subjects from the older cohort will mostly fall into the low education category(121). To address this issue, we converted the continuous variable (number of years of education) into a dichotomy variable (low and high levels of education) taking into consideration the age of the participants. First, we divided our sample into two groups according to the participants' age: those born before 1950 (older) and since1950 (younger). This categorization was based on the evidence that significant changes in the educational system occurred around the 1950's in many parts of India(41). The social and political changes that took place in Kerala since the 1950's leading to major changes in factors effecting SEP, has been looked into in section 2.9. As

mentioned previously (please refer to section 5.2), the last person included in this analysis was recruited in January 2011, which limits the maximum age of a subject in the second category (born since 1950) to approximately 60 years of age. Therefore we had two groups: Group 1) Subjects who were 60 years old or older and Group 2) Subjects below the age of 60 years. In group 1, participants who attained 4 or more years of formal education were classified as having a high level of education while those who had less than 4 years of education were included in the category of low level education. In group 2, participants who attained 8 years of formal education were categorized as having a high level of education and those who had less than 8 years of formal education were categorized as having a low level of education. This high and low education level categorization was done by considering the meaning of education attainment, with specific relevance to the respective birth cohorts(120).

Housing tenure, housing conditions and amenities

We constructed an indicator of material deprivation based on a series of questions which collected information on housing conditions, tenure and amenities. This information was collected on the longest residence of the subject in each of three periods of life: childhood, early and late adulthood. We computed an index of material deprivation for each of these periods using 11 questions addressing housing tenure, house conditions (e.g., material used to build the floor, roof and wall, type of windows, main source of drinking water, presence or absence of toilet, electricity) and house amenities(e.g., clock, radio, motorbike). The answer to each of these questions were coded as zero (low SEP) and one (high SEP)

according to the presence or absence of the items or the cost (e.g., floors, ceilings, widows). Subsequently, we created three continuous variables, which represented material deprivation for each period of life (childhood, early and late adulthood), by adding the scores for each question. The possible scores of these new summary variables ranged from 0 to 11. We then categorized this variable into low and high levels of material deprivation using the mean as the cut off point. Finally, a life course SEP indicator was constructed by combining the participant's social position in each period of life. This combination generated 4 categories: 1) Subjects who were in low SEP in all three stages of life(3L); 2) Subjects who were in low SEP in 2 stages and high SEP in 1 stage of life(2L 1H); 3) Subjects who were in high SEP in 2 stages and low SEP in 1 stage of life(2H 1L); and 4) Subjects who were in high SEP in all 3 stages of life(3H).

5.9.2.2 Behavioural habits

Tobacco Smoking

Smoking tobacco in various forms is an important risk factor for oral cancer. The two most common forms of tobacco smoking in the general population of India are bidi and cigarette smoking. The multidimensional nature of tobacco smoking warrants its investigation to be done in a very precise and extensive manner. Our study collected detailed information regarding the subjects' smoking history. The data collected included duration (age of initiation and cessation), and consumption (how many cigarettes and /or bidis per day or per week or per month) of these tobacco products. In addition, for cigarette smoking the brand used and the type of cigarette (filtered or non- filtered) were also recorded.

The next step was to create a variable to represent life-time intensity of tobacco smoking by taking the subject's complete smoking history into account. This cumulative exposure variable called 'pack years' is calculated by multiplying smoking duration with daily (per day) tobacco consumption (45, 122). For example, 1 pack year is equivalent to smoking 1 pack per day for 1 year, or 2 packs per day for half a year.

Now as an example, suppose a subject smoked cigarette from 18 to 50 years of age, both years included. So the 'total duration' of smoking cigarette over the life course for this individual would be 33 years (50-18=33). If this subject reports that he smoked 10 cigarettes per day (or per week or per month) from age 18 to 30 and 15 cigarettes per day (or per week or per month) from 31 to 50 years, he has two 'smoking periods' in his life course; 1)18 to 30 (13 years) and 2) 31 to 50 (20 years). From this data collected, first we converted the consumption (per day / week / month) of cigarettes and bidis to per day consumption. Now we have per day consumption for each separate smoking period. Subsequently, we calculated the number of packs consumed in each smoking period from the number of cigarettes or bidis smoked per day in each period. For cigarettes, the number of individual filtered and non-filtered cigarettes in each time period was divided by 10 (there are 10 cigarettes in a pack in India). We used a similar procedure to calculate the numbers of bidi packs. However, the number of individual bidis in each time period was divided by 20 as it corresponds to number of bidis in a pack in India.

Then, the number of packs per day consumed in each smoking period (1 pack per day and 1.5 packs per day in the two smoking periods respectively as in the example) of life was multiplied by the number of years of consumption in each period (13 years and 20 years in the two periods respectively as given in the example). Then we added up the pack years in each smoking period to get the cumulative pack year variable for cigarette smoking over the life course (total duration).

The distribution of cigarette and bidi usage among the controls was used to categorize each of these variables into 3 groups. Subjects who never used these products formed the never smokers group. The remaining distribution which consisted of subjects who used these products was divided into two by using the median of the distributions as the cut-off points. The final three categories obtained for each variable (cigarette and bidi) were non smokers, moderate smokers and heavy smokers. These three categories were maintained for bidi smoking in the final analysis due to wider distribution and heavier usage of bidi in the Indian population when compared to cigarettes. Cigarette smoking variable was divided into smokers and non smokers. Limited number of subjects also contributed to this categorisation.

The variables for cigarette and bidi smoking were used as both continuous and categorical for the analysis. These variables were computed as two independent variables due to their difference in processing, pattern of usage among people from various socioeconomic strata and tobacco content(47, 50, 53).

Paan/ betel quid chewing habit

Paan chewing is one of the strongest etiologic factors for oral cancers. It essentially refers to the consumption of betel quid which is a combination of betel leaf, areca-nut, slaked lime and tobacco in varying combinations. It was important to understand in detail the usage patterns and types of paan chewing habit among the subjects. Thus, we collected comprehensive data on this habit. Information regarding the time frame of each chewing period (age of initiation and cessation), and consumption (how many chews per day / week / month) were collected. Literature suggests that various oral lesions seen in paan chewers are highly associated with the duration of each chew and total duration of chewing(69, 123). So the time taken for each chew in minutes was also recorded. We also collected details on the type of chew based on the ingredients. For example, we defined betel quid as a combination of areca nut, betel leaf and slaked lime. Tobacco was considered as a separate entity. Based on this, the types of chewed substances were categorized into: only tobacco, betel quid with tobacco, betel quid without tobacco, areca nut and tobacco, areca nut without tobacco, paan masala (basically a mixture of tobacco and other flavouring items sold in packets), and betel leaf alone. Information on any other substance or combination of substances used other than the above options (e.g., betel leaf with arecanut) were also recorded. From the details collected, we formed a cumulative variable representing the total minutes of chewing per year over a person's life course (a method similar to the one used for pack year calculation for smoking variable was followed). The magnitude of this variable (in minutes) was very large. In order to reduce the size

of these numbers, we converted the minutes into days. We did this by dividing the total minutes of chewing per year over the life course by number of minutes in a day (i.e., 60 min X 24 hrs = 1400 minutes a day).Thus we created the final continuous variable which expressed the number of days of chewing per year over the subject's life course. This variable was then categorized into never chewers, moderate chewers and heavy chewers, similar to cigarette and bidi smoking, based on the distribution of the consumption patterns of the controls. For the final analysis, we used the two categories of ever and never chewers.

Alcohol consumption

Even though the role of alcohol as an initiator (an agent that produce changes at the DNA level, starting the process of mutation in cells) has not been proved in oral cancers, it's a very strong promoter (an agent whose repeated action over a period of time stimulates the growth of mutated cells) of cancer(124, 125). By alcohol intake, we are basically referring to the total amount of ethanol consumed(126). Detailed information on type of beverage (toddy; a wine from coconut trees, wine, beer/cider, hard liquor, or other), the age at the start of drinking and age at the end of drinking, the unit of drinking (small glass (50ml) (1-2oz), medium glass (100ml) (2-3oz), big glass (250ml) (7oz), ½ small bottle (330ml) (1beer), bottle (700-750 ml) (21oz)), as well as consumption rate (number per day, per week, per month) were collected. Next, a calculation was made to obtain the total amount of lifetime ethanol consumption. Ethanol concentration was estimated in this study to be 5% for beer, 10% for toddy and wine, and 50% for hard liquor(127). The next step was to divide the total ethanol

consumption by the amount of ethanol in a standardised drink. Studies report that in India, a standard drink of various alcohols (foreign liquor or locally made) available would vary from 13 to 28 g of pure ethanol(128). In order to make it equivalent and comparable to what is being used widely in north America as a standard drink (18ml alcohol containing 14g of pure ethanol), we divided the total ethanol consumption by 18(128, 129). This resulted in the number of standardised drinks consumed over the life course. The number was again divided by the total duration period (total sum of number of years of all drinking periods) giving the number of standardised drinks per year. Since there are 52 weeks in a year, we again divided the above value by 52 which ultimately gave the number of standard drinks per week. Now based on the distribution of the consumption patterns of alcohol among controls, we divided the sample into 3 groups. The first group was never consumers. The remaining sample was divided into two by using the median of the remaining distribution as the cut-off point. The resulting groups were moderate drinkers (<=5 drinks/week) and heavy drinkers (> 5 drinks per week). This categorical variable was used for the final analysis.

Diet

The two variables that were used as indicators of dietary habits were fruits and vegetables. Since the dietary habits of the subjects would have changed according to their health status, the information was collected regarding the subjects' dietary habits from 2 years prior to their disease diagnosis. They were asked how often they consumed fruits and vegetables per week. Questions were asked regarding consumption patterns of fruits like bananas, citrus fruits (oranges, lemons,

grapefruits), apples/pears and other tropical fruits like mangos, jackfruit, papaya and pine apple readily available in Kerala. Vegetables considered were cruciferous vegetables (cabbage, cauliflower), yellow-orange vegetables (tomatoes, carrots, pumpkin), green leafy vegetables like spinach, others like cucumbers and onions. Summary variables (continuous) were created separately by adding the various frequencies for the fruit and vegetables mentioned above. Next, we categorized the variables for fruits and vegetables into two groups each based on the distribution of the consumption patterns of the controls (50^{th} percentile as cut off point). For fruits, the resulting categorization was:0-2 servings per week and more than 2 servings per week and for vegetables; less than 13 servings per week and 13 or more servings per week.

5.9.2.3 Oral health indicators

The importance of oral health indicators, like the number of missing teeth as risk factors for oral cancer has been explained in Chapter 2, section 2.5.6. The number of missing teeth was used as an indicator of oral health. Each subject's mouth was clinically examined to identify the missing teeth. Each missing tooth was then added up to get the total number of missing teeth over the life course of the participant. This continuous variable was then dichotomized based on the frequency distribution of the controls (the 50^{th} percentile was used as the cut-off point). The two categories were: 6 missing teeth or less and more than 6 missing teeth.

5.9.2.4 Other confounding variables

Based on the study design the controls were frequency matched based on age and sex with the cases. For a few subjects who were willing to participate in the study but couldn't respond to questions asked because of their disease condition or stress (either full interview or part of the interview), the help of a proxy was sort. This proxy or respondent was usually the subject's spouse or close relative. The response from the proxy was recorded in the presence of the subject. Since a difference was expected between the quality of information collected between the subject and proxy, we considered it as a potential confounding factor. Age was taken as a continuous variable and sex (male, female) and proxy (yes/no) as categorical. These variables were adjusted in the statistical analysis to account for their confounding effects.

5.10 Data analysis

5.10.1 Descriptive statistics

In order to describe the basic features of the data collected, descriptive statistics was performed first. For continuous variables, we use T-Tests to estimate the differences in mean between cases and controls and their corresponding standard deviations. For categorical variables we use cross tabulations to compare the distribution of cases and controls. Age, was considered as continuous variable whereas gender, proxy, caste, education, SEP variables (SEP in 3 stages of life and life course SEP), cigarette smoking, bidi smoking, paan chewing, alcohol consumption, fruit and vegetable consumption and oral health status were taken as

categorical variables. For describing the association between exposures and outcome, we proceeded with performing logistic regression analysis.

5.10.2 Logistic regression

Logistic regression analysis is a statistical method where a binary or dichotomous outcome variable is related to the explanatory variable by means of the logistic function. It is used for predicting the probability of occurrence of an event by fitting data to a logistic curve. For example, if P is the probability of disease and (1-P) the probability of the disease not occurring , then P/(1-P) represents the 'odds' of developing the outcome and the log odds of disease is expressed as ln[P/1-P)] (130, 131).Thus, the log odds of the disease (dependent variable) can be expressed as a linear function of the independent variables as shown in equation below.

$$\ln[P\backslash 1-P)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots\ldots + \beta_k X_k$$

Where β_0 is the y-intercept and X_1 to X_k represents k independent variables included in the model. β_1 to β_k are coefficients indicating the degree of association between each independent variable and the outcome (change in outcome variable per unite change in the independent variable).

The coefficients obtained from the logistic regression can be converted directly to an odds ratio (OR) that provides an estimate of the relative risk that is adjusted for confounding factors. Its precision is marked by confidence intervals (CI; usually at 95%) which is obtained using the regression coefficient and its standard error(132, 133).

The method therefore is appropriated for analyzing the data of this study since the outcome variable oral cancer is a dichotomous variable (Yes/No) and we can simultaneously adjust for potential confounder variables. Controls were frequency matched to cases based on age and sex. This was done to improve statistical efficiency by equally distributing these confounding factors between cases and controls Since the number of matching variables or parameters are small compared to the total sample size, we used unconditional logistic regression and included the matching variables in the models(134).

5.10.2.1 Building the logistic regression models

The main objective of this study was to evaluate to what extent life course SEP is associated with oral cancer. In addition, we aimed to evaluate how much of this association was explained by behavioural and oral health factors (e.g., chewing habits, smoking, alcohol consumption, diet and missing teeth).

To evaluate which set of variables best explained the association between life course SEP indicators and oral cancer risk, we conducted simple and multiple logistic regression analyses.

First, we conducted logistic regression analyses to evaluate the associations between (i) life course SEP in each stage of life (ii) behavioural variables and (iii) oral health indicator and oral cancer risk, adjusting for age, sex and proxy/respondent type. Then, we included life course SEP in each stage and all the other independent variables in a single model to evaluate whether the effect of life course SEP on oral cancer remains after adjusting for behavioural and oral health related factors.

The presence of an interaction between the variables representing life course SEP at different stages of life was verified by including the product terms of these variables. A statistically significant interaction was observed and to estimate the effect of this interaction a new variable representing overall life course SEP was created. Therefore, our final model is presented using this new variable.

The next step was to build the models following the procedures described below.

We built several models. Model 1 included a set of socio-demographic characteristics, i.e., age (continuous), sex, respondent type (self / proxy) and life course SEP. Model 2 included all variables from Model 1 plus alcohol, smoking and chewing habits (all categorical). Model 3 included all variables from Model 2 plus missing teeth (categorical), a measure of oral health status. Model 4 included all variables from Model 3 plus diet (categorical) i.e., the weekly frequency of use of fruit and vegetables. In addition, we tested whether other measures of SEP (education and caste) would further contribute to the fitness of the models.

We calculated the P value for linear trends across the life course SEP indicator categories and oral cancer risk. This calculation was performed by including an ordinal variable as a continuous covariate in the regression models.

We used the Akaike's Information Criterion (AIC) to assess the goodness-of-fit of the various models. The AIC is computed as [-2 log likelihood + 2*k] (k=number of parameters estimated in the model). We compared the AIC of different models to identify which set of variables was a better predictor of oral cancer risk. As a rough rule of thumb, smaller values of the AIC for a given dataset indicate better fit, but an absolute difference of less than 4 is considered as minor, and an

absolute difference more than 10 is seen as important. Any difference under 0 indicates better fit while any difference above 0 indicates a worse fit (135).

5.10.3 Missing values

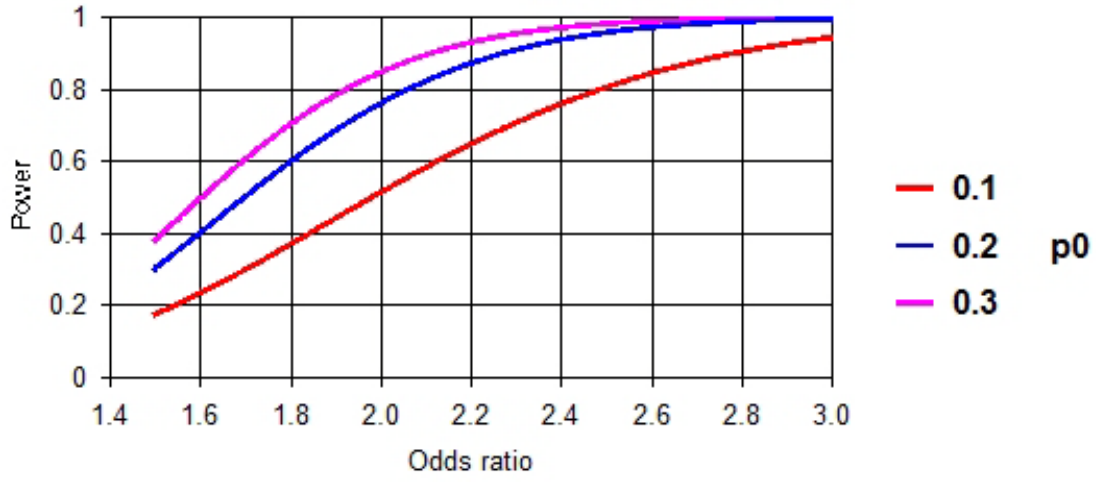
In-spite of taking every possible measure available to make sure that missing values are avoided during data collection and its entry into the database, missing values were still present. This missing data was mainly related to the information collected in relation to housing conditions and the corresponding categorical SEP variables. This was mostly because a few subjects who were at the old age category found it difficult to remember some details from their past life even after using the life grid. We also had to use the help of a proxy for certain subjects because of an advanced disease stage. Proxies were usually spouses or relatives accompanying the participants to the hospitals and obviously they couldn't provide complete account of the subject's younger stages of life. The proportion of missing values ranged from 1.4% to 6.6%. Since the missing values were related to our main exposure but was very low in percentage, we excluded them from the analysis.

5.10.4 Statistical power

We performed post-hoc power calculation using the prevalence of our main exposure variable (life course SEP) that was obtained from our results (Table 5). For a sample of 200 cases and 150 controls, different power calculation scenarios using different exposure levels and different ORs were performed, as shown in Figure 3. For example, the proportion of controls in our sample who were in low SEP in all three stages of their life was 12.6% (Table 5). Assuming a type I error

of 0.05, we will have a power of 80% to detect an OR of 2.35. The power to detect an OR 2.08 (Table 7, Model 4) is around 66%.

Figure 3: Statistical power analyses based on the whole sample (n=350), for a range of ORs and according to different prevalence of exposure among controls (type-1 error=0.05).



5.11 Ethical considerations

Prior to the start of the study, approval was obtained from the Institutional Review Board (IRB) and ethics committee of Government Dental College and Medical College and Hospital, Calicut, Kerala. As mentioned previously, the study procedure was explained to each subject before the start of each interview session. Signatures were requested and obtained from the participants (who accepted to participate) and a witness, on two copies of the study consent forms. Thumb impressions were obtained from illiterate subjects. It was made sure that the research assistant who explained the study procedures also signed these forms in the presence of the subject and the witness. One copy of the consent form was given to the participant and the other was kept at the study site for records.

6 Results

6.1. Descriptive statistics

For this thesis work, 200 incident oral cancer cases and 150 age and sex frequency matched controls were considered for analysis. The data on socio-demographic characteristics are presented in Table 3. The age of the subjects ranged from 29 to 85 yrs and 54% were men. Cases were slightly older on average than controls [cases mean= 60.9 (SD=10.69), controls mean=57.6 SD=10.89)]. The differences in age and gender between cases and controls even after employing frequency matching in the selection of controls could be due to the fact that we had more cases than controls. Majority of subjects belonged to the middle class ("Other Backward Caste"). Almost 35% of this group was from the caste named "Thiyya" of which 56% were cases. During the interviews, the help of a proxy was sought for a higher percentage of cases than controls [17% for cases vs. 3.3% for controls]. Most participants had a low education level [66%] and three-fourths of the cases belonged to this category.

An overview of the behavioural factors is presented in Table 4. Overall, 61% of paan chewers, 47% of alcohol drinkers and 39% of bidi smokers were cases who consumed these products heavily over their life course. The majority of subjects who smoked cigarettes were cases but they used this product at moderate levels. A high proportion of subjects had more than 6 missing teeth and 63.5% of cases fell in this category. Consumption of fruits and vegetables were seen to be

generally low. Among cases, 86% consumed less than 2 servings per week of fruits and 73% consumed less than 13 servings per week of vegetables.

Table 5 presents the data on SEP with respect to material deprivation in childhood, early and late adulthood stages over participants' life course. The proportion of subjects who occupied low and high SEP was similar in childhood and early adulthood stages. More than one fourth of the participants, who formed the majority, were cases who were in low SEP in these stages of life. In late adulthood, 58% of subjects lived in high SEP households. However, the majority of cases were in low SEP at all three stages of their lives when compared to controls.

Data on the cumulative life course SEP variable (Table 5) show that almost 60% of cases were in low SEP in two or more stages of their lives. Half of the control participants occupied high SEP in all 3 stages of their lives. A greater proportion of cases than controls were in low SEP in at least one stage of their lives.

6.2 Associations between life course SEP variables, behavioural factors, oral health indicators and the risk of oral cancer

Multivariate logistic regression analyses were performed to estimate the extent to which SEP variables in each stage of life, and various behavioural habits and oral health status were risk factors for oral cancer in this population. The results of these analyses are presented in Table 6.

The first column represents results from the logistic regression analysis adjusted for age, sex and proxy/respondent type. Results suggested a strong, significant

association between life course SEP variables in each stage of life and oral cancer risk. In childhood, subjects with low SEP were 2.6 times (OR=2.60, 95% CI: 1.63-4.14) at risk of getting the disease when compared to those with high SEP. The risk association increased for participants with low SEP in early adulthood (OR=3.35, 95% CI: 2.04-5.51) and late adulthood (OR=2.93, 95% CI: 1.82-4.74) when compared to the high SEP group in the respective stages. Low level of education was statistically significant associated with oral cancer. Subjects who attained low level of education were 2.78 times (OR=2.78, 95% CI: 1.69-4.57) more at risk when compared to those who had higher levels of education.

Examining oral health, dietary habits and other behavioural factors, we did not find evidence for an association between cigarette smoking and oral cancer. However, heavy bidi smokers were at significant risk for the disease (OR=2.70, 95% CI: 1.32-5.52). In this analysis, the strongest risk association with oral cancer was seen in paan chewers. Subjects who reported indulging in this habit over their life course were almost 10 times more at risk of developing oral cancer (OR=10.44, 95%CI: 6.08-17.92) compared to those subjects who never used paan. With regards to alcohol consumption, while moderate drinking did not show any significant association with oral cancer, heavy drinking increased the risk of the disease by almost 4 folds compared to never drinkers. Subjects who lost more than 6 teeth were at a significantly higher risk of the disease (OR=1.62, 95% CI: 1.01-2.60) than people who lost 6 teeth or less. No significant relationship was evident between consumption of fruits (OR=0.92, 95% CI: 0.50-1.68) and oral

cancer risk. However, vegetables intake showed a protective effect on oral cancer risk (OR=0.35, 95% CI: 0.22-0.55).

The second column in Table 6 presents the results of the logistic regression analysis in which all the variables in the column were mutually adjusted for each other (age, respondent, gender, education, life course SEP in all 3 stages of life, cigarette smoking, bidi smoking, paan chewing, alcohol consumption, fruit and vegetable consumption). While paan chewing and missing teeth were still related to an increased risk for oral cancer, the effect of education, childhood, early adulthood and late adulthood SEP, bidi smoking and alcohol consumption were attenuated and lost their statistical significance. For vegetable consumption, the analysis showed a significant reduction in the overall risk of oral cancer of 51% (OR: 0.49, 95% CI: 0.27-0.88).

Next, we tested for interaction among SEP variables at different stages of life. We observed a statistically significant interaction between these variables. Following this finding, we conducted sequential logistic regression analysis by creating and including a cumulative life course variable in the models. The aim of this step by step procedure was to estimate the association of this life course SEP variable with oral cancer and to estimate how much of this association is explained by behavioura and oral health status variables. The fit of the models were tested by the AIC values. The results are presented in Table 7.

Model 1 represents the logistic regression analysis result for the life course SEP variable adjusted for age, sex and respondent. We observed that subjects who were in low SEP in all three stages of their lives (3L) were almost 6 times at risk

(OR=5.81, 95% CI: 2.90-11.64) of oral cancer when compared to those who were in high SEP in all 3 stages of their lives (3H). A descending linear trend was observed in this association from the poorest to the richest (P value for trend <0.0001). Subjects who were in low SEP in any two stages and high SEP in any one stage of their lives (2L 1H) (OR=4.11, 95% CI: 2.19-7.72) and those who were in high SEP in any two stages and low SEP in any one stage (2H 1L) (OR=2.5, 95% CI: 1.24-5.03) were at increased risk of oral cancer when compared to the subjects who were in high SEP in all three stages of life. The AIC for this model was 401.39.

The next step was to observe the variation in this association when tobacco and alcohol habits were taken into consideration. As shown in Model 2, adding smoking, paan chewing and alcohol consumption in the model considerably attenuated the associations between life course SEP and risk of oral cancer. However, this variable was still related to an increased risk of the disease; (P value for trend=0.016). In addition, the AIC values were consistent with an important improvement in the fit of the model when the different smoking, chewing and alcohol consumption habits were considered.

Subsequently, we included the missing teeth variable as the indicator for oral health status in the regression analysis. The results are depicted in Model 3. Similar to Model 2, on adding oral health as a covariate in the model, odds ratios for life course SEP generally tended to move further toward the null. The linear trend in the life course SEP variable maintained its statistical significance at the 5% level (P value for trend=0.028). This suggests that, in addition to smoking and

alcohol habits, oral health contributed independently to the life course SEP and oral cancer association. AIC values were reduced by approximately 7 units.

Next, we added the dietary habits into the regression model (Model 4). The inclusion of these variables further decreased the magnitude of the association between life course SEP and oral cancer and statistical significance was lost (P value for trend=0.055). The inclusion of these variables did not have an effect on the fit of the model. The use of continuous variables, representing behavioural habits, in the models did not show any change in the results.

Finally, we tested whether including other SEP variables [e.g., education (as shown in Model 5) or caste (data not shown)] would improve the fitness of our model. The inclusion of either variable in the model did not make any notable difference in the association between the life course SEP variable and oral cancer risk. Indeed, the addition of these variables decreased the fit of the model. Model 4 had the lowest AIC value and hence provided the best fit to the data among all the models considered.

To test the effect of education we also did a second sequence of analysis reversing the sequential modeling (results not presented), i.e. adding education first and then, progressively in the next models, adding tobacco and alcohol habits, missing teeth, diet and then life course SEP in the final model. Not only did education lose its statistical significance considerably, but this sequential modeling had a decreased fit over all (based on the AIC values of the models) when compared to the first sequence.

Table 3: Socio-demographic characteristics of controls and oral cancer cases

Variable	**Control (n=150) N (%)**	**Case (n=200) N (%)**
Age in years– Mean (SD)	57.56 (10.89)	60.87 (10.69)
Gender		
Female	75 (50.0)	86 (43.0)
Male	75 (50.0)	114(57.0)
Respondent type		
Use of proxy	5 (3.3)	34 (17.0)
No use of proxy	145(96.7)	166(83.0)
Caste		
Lower	7 (4.7)	38 (19.0)
Middle	114(76.0)	137(68.5)
High	29 (19.3)	25 (12.5)
Education		
Low	81(54.0)	151(75.5)
High	69 (46.0)	49 (24.5)

Table 4: Behavioural habits and oral health characteristics among controls and oral cancer cases

Variable	Control (n=150) N (%)	Case (n=200) N (%)
Tobacco related and drinking habits		
Cigarette smoking		
Never smoked	102(68.0)	130(65.0)
Moderate smokers	26 (17.3)	46 (23.0)
Heavy smokers	22 (14.7)	24 (12.0)
Bidi smoking		
Never smoked	111(74.0)	115(57.5)
Moderate smokers	20 (13.3)	36 (18.0)
Heavy smokers	19 (12.7)	49 (24.5)
Paan chewing		
No chewing	120(80.0)	52 (26.0)
Moderate chewers	14 (9.30)	40 (20.0)
Heavy chewers	16 (10.7)	108(54.0)
Alcohol consumption		
Never drinkers	131(87.3)	145(72.5)
<=5 drinks/week	10(6.7)	20 (10.0)
>5 drinks/week	9(6.0)	35 (17.5)
Oral health and dietary habits		
Missing teeth		
<= 6 teeth missing	77(51.3)	73 (36.5)
> 6 teeth missing	73(48.7)	127 (63.5)
Fruit consumption		
0-2 servings per week	126 (84.0)	172 (86.0)
>2 servings per week	24 (16.0)	28 (14.0)
Vegetable consumption		
<13 servings per week	69 (46.0)	146 (73.0)
>=13 servings per week	81 (54.0)	54 (27.0)

Table 5: Life course SEP among controls and oral cancer cases

Variable	Control (n=150) N (%)	Case (n=200) N (%)
Childhood SEP		
Low	52 (34.7)	120 (60.0)
High	98 (65.3)	75 (37.5)
Early adulthood SEP		
Low	47(31.3)	126 (63.0)
High	96 (64.0)	70 (35.0)
Late adulthood SEP		
Low	39 (26.0)	101 (50.5)
High	108 (72.0)	95 (47.5)
Life course SEP[1]		
3 Low (3L)	19 (12.6)	62 (31.0)
2 Low 1 High (2L 1H)	28 (18.7)	61 (30.5)
2 High 1 Low (2H 1 L)	23 (15.3)	29 (14.5)
3 High (3H)	70 (46.7)	35 (17.5)

[1]3L – Low SEP in all the three stages of life, 2L 1H- Low SEP in any 2 stages and High SEP in any one stage of life, 2H 1L- High SEP in any 2 stages and Low SEP in any one stage of life, 3H- High SEP in all three stages of life

Table 6: Odds ratios (OR) and 95% confidence intervals (CI) for the associations between life course SEP, education, behavioural and oral health indicators and oral cancer risk

Variables in each model	Controls	Cases	Age, sex, respondent type adjusted OR(95%CI)	Fully adjusted Model [1] OR(95%CI)
Education				
High	69	49	Reference	Reference
Low	81	151	2.78 (1.69-4.57)	0.91 (0.45-1.84)
Childhood SEP				
High	98	75	Reference	Reference
Low	52	120	2.60 (1.63-4.14)	1.00 (0.50-2.00)
Early adulthood SEP				
High	96	70	Reference	Reference
Low	47	126	3.35 (2.04-5.51)	1.81 (0.88-3.70)
Late adulthood SEP				
High	108	95	Reference	Reference
Low	39	101	2.93 (1.82-4.74)	1.25 (0.66-2.37)
Cigarette smoking				
No smoking	102	130	Reference	Reference
Smokers	48	70	0.98 (0.54-1.77)	0.81 (0.33-1.99)
Bidi smoking				
Never smoked	111	115	Reference	Reference
Moderate smokers	20	36	1.93 (0.95-3.90)	1.18 (0.45-3.12)
Heavy smokers	19	49	2.70 (1.32-5.52)	1.45 (0.51-4.10)
Chewing Habits				
No chewing	120	52	Reference	Reference
Chewers	30	148	10.44 (6.08-17.92)	8.45 (4.43-16.11)
Alcohol consumption				
Never drinkers	131	145	Reference	Reference
<=5 drinks/week	10	20	2.00 (0.85-4.73)	1.57 (0.51-4.79)
>5 drinks/week	9	35	3.82 (1.67-8.75)	2.82 (0.93-8.54)
Missing teeth				
<=6 teeth missing	77	73	Reference	Reference
>6 teeth missing	73	127	1.62 (1.01-2.60)	2.41 (1.29-4.49)
Fruit consumption				
0-2 servings per week	126	172	Reference	Reference
>2 servings per week	24	28	0.92 (0.50-1.68)	1.05 (0.47-2.35)
Vegetable consumption				
< 13 servings per week	69	146	Reference	Reference
>= 13 servings per week	81	54	0.35 (0.22-0.55)	0.49 (0.27-0.88)

[1] Adjusted for age, sex, respondent type/proxy and all the variables considered in the first column.

Table 7: Odds ratios (OR) and 95% confidence intervals (CI) for the associations between life course SEP indicators and oral cancer risk

	Controls	Cases	**Model 1 OR(95%CI) AIC = 401.39**	**Model 2 OR(95%CI) AIC=350.30**	**Model 3 OR(95%CI) AIC=343.86**	**Model 4 OR(95%CI) AIC=341.64**	**Model 5 OR(95%CI) AIC= 343.59**
Variables in each model			Age, sex, respondent type	Variables Model1+smoking/ /chewing/alcohol	Variables Model2+oral health	Variables Model3+diet	Variables Model4+education
Life course SEP							
3 High(3H)	70	35	Reference	Reference	Reference	Reference	Reference
2 High 1 Low (2H 1L)	23	29	2.50 (1.24-5.03)	1.42 (0.63-3.20)	1.15 (0.50-2.64)	1.10 (0.47-2.55)	1.12 (0.48-2.62)
2 Low 1 High (2L 1H)	28	61	4.11 (2.19-7.72)	2.13 (1.02-4.46)	1.82 (0.85-3.87)	1.78 (0.83-3.82)	1.82 (0.83-3.99)
3 Low (3L)	19	62	5.81 (2.90-11.64)	2.48 (1.10-5.63)	2.36 (1.02-5.46)	2.08 (0.89-4.89)	2.14 (0.88-5.17)
P for trend			0.0001	0.016	0.028	0.055	0.056
Cigarette smoking							
No smoking	102	130		Reference	Reference	Reference	Reference
Smokers	48	70		0.87 (0.38-2.00)	0.87 (0.37-2.06)	0.79 (0.32-1.93)	0.80 (0.33-1.96)
Bidi smoking							
Never smoked	111	115		Reference	Reference	Reference	Reference
Moderate smokers	20	36		1.54 (0.61-3.86)	1.37 (0.53-3.50)	1.26 (0.48-3.29)	1.25 (0.48-3.27)
Heavy smokers	19	49		1.78 (0.68-4.69)	1.40 (0.51-3.81)	1.45 (0.52-4.05)	1.46 (0.52-4.11)
Chewing Habits							
No chewing	120	52		Reference	Reference	Reference	Reference
Chewers	30	148		7.98 (4.40-14.46)	9.34 (5.01-17.42)	8.16 (4.34-15.36)	8.27 (4.34-15.74)
Alcohol consumption							
Never drinkers	131	145		Reference	Reference	Reference	Reference
<=5 drinks/week	10	20		1.42 (0.49-4.09)	1.52 (0.51-4.49)	1.67 (0.56-5.01)	1.65 (0.55-4.97)
>5 drinks/week	9	35		2.19 (0.76-6.33)	2.59 (0.88-7.65)	2.79 (0.92-8.47)	2.79 (0.92-8.50)
Missing teeth							
<=6 teeth missing	77	73			Reference	Reference	Reference
> 6 teeth missing	73	127			2.49 (1.34-4.65)	2.46 (1.31-4.63)	2.47 (1.31-4.64)

	Controls	Cases	Model 1 OR(95%CI) AIC = 401.39	Model 2 OR(95%CI) AIC=350.30	Model 3 OR(95%CI) AIC=343.86	Model 4 OR(95%CI) AIC=341.64	Model 5 OR(95%CI) AIC= 343.59
Variables in each model			Age, sex, respondent type	Variables Model1+smoking/ /chewing/alcohol	Variables Model2+oral health	Variables Model3+diet	Variables Model4+education
Fruit consumption							
0-2 servings per week	126	172				Reference	Reference
>2 servings per week	24	28				1.03 (0.47-2.28)	1.03 (0.47-2.28)
Vegetable consumption							
< 13 servings per week	69	146				Reference	Reference
>=13 servings per week	81	54				0.48 (0.27-0.86)	0.48 (0.26-0.85)
Education							
High	69	49					Reference
Low	81	151					0.92 (0.46-1.85)

7 Discussions

7.1 Introduction

Guided by the study's objectives, this chapter will provide a brief overview of results and their comparison with previous literature, and plausible explanations for our findings. We also make an attempt to propose a hypothetical model combining the life course and biological cancer models which depicts the intricate pathways connecting life course SEP to oral cancer development. The strengths and limitations of this thesis work are also discussed.

This thesis work (a part of the HeNCe Life study) takes advantage of the unique life course framework to study the associations between life course SEP and oral cancer. It addresses the question: is life course SEP associated with oral cancer risk in a sample of Indian subjects? If yes, how much of this association is explained by behavioural and oral health related factors.

7.2 Life course SEP and oral cancer risk

Our study confirms the association between life course SEP and oral cancer incidence, with relative risks and gradients going in the well-known direction. We observed that an increase in levels of deprivation across the life course was significantly related to an increase in oral cancer risk when adjusting for age, sex, and type of respondent. Entering each set of variables progressively in the logistic regression model, i.e., group 1 (cigarette and bidi smoking, paan chewing, alcohol consumption) group 2 (number of missing teeth) and group 3 (dietary habits) gradually decreased the effect of life course SEP on the risk of oral cancer and

tended to bring the odds ratios for these associations progressively toward the null (Table 7).

Smoking, alcohol drinking and chewing habits have the strongest effect on the associations between life course SEP and oral cancer risk. Oral health and diet appeared to be additional important factors. Once these factors were taken into account, the addition of education did not improve the fitness of the model. Although the estimates for the life course SEP-oral cancer risk associations became statistically insignificant after the successive adjustments with the three groups of variables (Table 7), we still observed a positive trend between the exposure and the outcome (P value for trend= 0.055 Model 4, Table 7).

Our results are similar to those of a recent European study which suggest that a downward life course social trajectory is an independent risk factor for head and neck cancer among men (25). Studies in the field of breast, prostate and testicular cancers have obtained similar results (10). Others have reported loss of effect of social factors when adjusted for smoking and alcohol (27, 33).

Indeed, habits like paan chewing have been reported to be more common among the low SEP population in Kerala (136) and this case-control study confirmed the known association of paan chewing with oral cancer risk(4, 97, 127, 137). This relationship was very strong (OR=8.16, 95% CI: 4.34-15.36, best fit model, Table 7) to probably over-ride the effect of SEP variables. These results are consistent with those of another study on head and neck cancer that reported the masking effect of tobacco usage (27).

With regards to education, our results showed that subjects who had a low education level were 2.78 times more at risk of the disease. Studies from low and high income countries worldwide have reported that low education level is an independent risk factor of oral cancer(43). Estimates from studies conducted in Asia (OR=2.38, 95% CI: 1.76-3.21) were not very different from those of a study in European countries (OR=1.63, 95% CI: 1.00-2.66) or from North America (OR 1.61, 95% CI: 1.33-1.95)(43). However, there was apparent loss of statistical significance for this variable in the final model and it did not improve the fitness of the model (Table 7). The reason for this result could be that childhood education is a variable that determines SEP in later stages of life. It is very closely associated with life course SEP and the effects of education could directly reflect on SEP indicators like housing conditions, which are associated with oral cancer risk in our study, as discussed above.

7.3 Other relevant findings

Cigarette smoking, bidi smoking, paan chewing, alcohol consumption, diet and oral health factors were also tested for their association with risk of oral cancer. We observed that heavy bidi smoking and alcohol consumption were significantly associated with an increased oral cancer risk. This association of smoking, paan chewing, alcohol product usage with increased oral cancer risk is well established in the literature (51, 138). In our study, we found that subjects smoked bidi more heavily than cigarettes. In addition to being a traditional method of tobacco consumption in India, bidis are considerably less expensive than cigarettes, which could explain their greater use in our sample. Also the mean consumption of

cigarettes did not differ between cases and controls. This could be the reason why we did not observe an association between cigarette smoking and oral cancer risk in this work. Literature also shows evidence that drinking among non-smokers does not increase the risk of oral cancer but the combination of both drinking and smoking among non-alcoholics increases the risk association(139). However estimation of these associations was beyond the scope of this thesis work. Finally, similar to other studies(78), we observed an increase of almost 10 times in oral cancer risk among people who used paan/betel quid.

The biological pathways through which smoking, alcohol and paan chewing habits cause oral cancer are well established (please refer to chapter 2). It is also well understood that tobacco is an initiator of cancer whereas alcohol acts as a promoter. A decreased detoxification capacity of the liver due to diseases like hepatic cirrhosis related to alcohol consumption may be another pathway through which alcohol increases the risk of cancer development(140).

With respect to dietary habits, we did observe a protective effect of vegetable consumption on the risk of oral cancer, but did not find an association with fruit consumption. Although increased fruit and vegetable consumption has been documented to have a protective effect on cancer development by various studies (72, 73, 141), there exists several potential explanations for our findings. A study from south India reported a decreased oral cancer risk with consumption of vegetables and fruits like apples, pears and citrus fruits (142). The protective effect of these fruits has been documented by other studies (143) whereas no association has been found with tropical fruits like bananas (142). In our study,

the consumption of vegetables among the subjects was greater than that of fruits and the consumption of apples, pears and citrus fruits were very low. The participants usually consumed tropical fruits such as bananas and mangoes which are much less expensive and readily available in this part of the world. Another factor that has to be considered in case-control studies is recall bias. It is possible that healthy controls could have overestimated and cases could have underestimated their fruit and vegetable consumption(144). Moreover, high chance of measurement error is associated with this variable as dietary habits are very difficult to measure precisely. Also the small sample size of our study might limit our ability to draw conclusions regarding the effect of diet on oral cancer.

This epidemiologic study supports the existence of an association between number of missing teeth and oral cancer. Loss of more than 6 teeth was associated with an increased risk of oral cancer. This variable and paan chewing were the only factors that remained associated with oral cancer risk in a statistically significant way when all the variables in the study were adjusted for each other.

Multiple studies have shown the increased risk association of missing teeth with oral cancer (51, 82, 83, 85) while some have not(145). Researchers have tried to explain this association through two pathways which consider tooth loss as an indicator of periodontal disease(86). First, microorganisms in the periodontal tissue produce endotoxins and metabolic by-products which in turn induce mutation in tumour suppressor genes and proto-oncogenes, or alter signalling pathways that effect cell proliferation and /or survival of epithelial cells. A second pathway suggests an indirect effect whereby the chronic infection or inflammation

activates host cell response generating oxygen species, other reactive nitrogen species, reactive lipids, metabolites and matrix metalloproteases which in turn induces DNA damage to epithelial cells. They can also produce cytokinins, chemokinins and growth factors which help epithelial cells to accumulate mutation and increase proliferative growth of the cells. These two pathways might of course operate simultaneously.

Some studies investigating the relation ship between oral health , chronic diseases and SEP have produced results suggestive of the fact that tooth loss could be a proxy measure for SEP(146, 147).

7.4 Plausible explanations and hypothesis relating life course SEP and oral cancer.

As discussed before, life course epidemiology is the study of long-term effects on later health and disease risk of physical or social exposures during gestation, childhood, adolescence, early and late adulthood life(10, 91). It has also been proposed that the risk factors for chronic diseases cluster together as they are related to SEP and also could be linked in a temporal sequence to form a chain of risk leading to the outcome(10). Building on the life course model's aim of elucidating the underlying biological, behavioural, psychosocial and socioeconomic processes operating across an individual's life course leading to chronic disease outcomes, this unique study relating SEP to oral cancer through a life course approach tries to dissect and explore the 'cause of the cause' hypothesis. In this section, we make an attempt not to assess the distal (SEP

variables) and proximal factors (such as behavioural factors) as separate but as intricately intertwined entities leading to the development of oral cancer.

The society in which a person is born and lives has a tremendous impact in shaping his/her personality and life style. The association between oral cancer and SEP is complex. Childhood SEP, as a direct translation of parents' SEP, influence the behavioural habits in the early and late adulthood life of a person and can lead to disease outcome in later life but may also have a more direct role in the biological pathway of cancer development. In terms of the association with oral cancer risk, the potential explanations we looked into are as follows.

7.4.1 Pathways to later life choices and behavioural habits through education

Parental SEP and educational status can directly affect the environment and experiences of children including their education. This effect would be through the choices and decisions that are made by the parent for the child depending on the degree of social, economic and cultural conditions / adversities they lived in. The educational status of a person is generally fixed earlier in his/her life (39, 148). It provides foundation for an individual's preferences(39); cognitive skills development, critical thinking and decision making powers; determines social networks (39, 149); shapes values for the future and healthier choices (150-152). In turn, these personal attributes provide foundation for the individual's occupational choices, indulgence in 'risky' behaviours, housing and living conditions and choice of diet, among others(152). It has been documented that low parental SEP as well as a person's own low SEP significantly increased the

risk of first cigarette use and the likelihood of progression to regular use, and decreased likelihood to quit(153).

7.4.2 Culture, SEP and behavioural habits

An individual's behaviour has been recognized to be culturally influenced and culture is unique to various societies and associated with different values (154). For example, paan chewing was and still is an intricate part of India's ancient and rich cultural history. Although the association of paan chewing with oral cancer is well established, a major proportion of the population, especially those from low SEP, tends not to refrain from this cultural habit as it is a common practice and socially accepted. In fact, according to the changing norms and pace of the society, paan has been replaced by more convenient to use products containing all the ingredients of paan (e.g., paan masala)(155). Choice of diet, cooking and eating patterns (which could determine the amount of nutrients taken up by the body) are associated with culture. In Indian Hindu culture, the individuals belonging to the higher caste (higher SEP) known as Brahmins are vegetarians and eat more vegetables and fruits than the middle and lower caste people(154). Another food-related cultural practice seen in societies like India is overcooking, which could lead to loss of important anti-oxidants and vitamins which have protective effects on oral cancer(156).

7.4.3 Socioeconomic deprivation induced stress and coping through behavioural habits

Education in childhood and early adulthood is a key factor influencing an individual's position in society, opportunities and occupational choices (157); It

has also been documented to reflect income and access to health care and health information(39). Individuals from low SEP and low educational background usually getting into blue collar jobs with short term employment (158) or periods of unemployment (154) are among other common findings. Occupational status directly translates to household income and this may have a direct determining factor on housing and living environment. It is also well documented that diet is related to access and affordability (cost) of healthy foods and not just a life style choice(159). In Kerala, higher prevalence of tobacco and alcohol habits and lower fruit and vegetable intake is seen in individuals with low income(136). Housing, living conditions and neighbourhood can determine access to health services, social facilities, and affordable quality food(159). These factors are known to be linked to several health outcomes (157) including oral cancer. More precisely, the disease outcome can be related to harmful physical agents in the working and living environment(160) or related to constant stress(161). This stress could accumulate from interplay between general anxiety of an individual towards day to day challenges, work environment, social and living conditions, It has been suggested that low SEP, by all measures, potentially infers some form of 'stress' (161); a result of job insecurities, unemployment, fear of crime, debt, lack of social support, low social capital and community cohesion(162-164).

The stress and the various mechanisms used to cope with it play an important role in determining quality of life and chronic disease outcomes(165). The choice of coping mechanisms may depend on factors like education. Healthier choices would be physical exercise and involvement in recreational activities, but risky

behaviours like smoking and alcohol consumption have also been reported as mechanisms used to cope with stress, including the stress associated with deprivation(35). According to the "tension reduction theory", people consume alcohol heavily to overcome stress and this behaviour is strongly reinforced in stressful environments related to determinants of SEP(166). Our results show that the majority of participants who reported engaging in tobacco and alcohol related habits, with the exception of those who smoked cigarettes, fell into the heavy usage category. A greater number of cases engaged in these habits than controls. For alcohol consumption, it has been documented that members of higher class tend to drink more frequently, while those from the lower class tend to drink more heavily (167, 168). From this evidence, we could hypothesize that subjects in lower SEP, especially cases, were exposed to more stressful environments over their life course, thus increasing their risk for oral cancer.

The above discussion helps us to appreciate the impact of determinants of SEP from childhood through adulthood, as well as their influence on various behavioural patterns at different stages of life and other mechanisms which affect chronic disease outcomes, including oral cancer. Now, how are the determinants of SEP involved with the probable pathogenesis of oral cancer?

7.5 The biological plausibility – SEP and Oral cancer

The biological pathway leading to tumour formation is influenced by multiple genetic alterations, which can act at three different stages of tumour development. The three stages of the cancer model are a) Initiation: changes at the DNA level starting the process of mutation in cells b) Promotion: repeated action of the agent

over a period of time confers the growth of mutated cells. C) Expression: this involves the development of the disease(125). For example, tobacco is known to cause changes at the DNA level and so it is classified as an initiator while alcohol is considered a promoter because it cannot produce such changes. From the above hypothetical explanations, we could summarize the influence of SEP through common behavioural habits linked to oral cancer. However, the other pathways by which socioeconomic factors lead to biological changes resulting in oral cancer development is not entirely clear. Most research relating to SEP and cancer is now focussing on the role of stress, the effect of ageing and the inactivation of tumour suppresser genes by hypermethylation of DNA. In the next subsections, we provide an explanation for each of these factors.

7.5.1 SEP, stress and oral cancer

The possible influence of SEP and stress development has been discussed earlier. One of the important links between stress and cancer development could be related to a shortening of telomeres in cell DNA and an increase in telomerase activity (169, 170). Telomeres are DNA protein complexes that cap chromosomal ends, promoting chromosomal stability and integrity. Telomere shortens with each cell cycle and so shortening of telomere has been considered as a biomarker for ageing of cells. The shortening of telomeres increases telomerase enzyme activity and allows for increased cell division(169). Various studies have shown that shortening of telomeres and increased telomerase activity are associated with an increased risk of cancer, including oral cancers (170-172).

Studies have also reported that the features of telomere shortening and increased telomerase activity are seen in psychological stress and oxidative stress; the latter is produced by the gluco-corticoid hormones due to psychological stress. (169, 173). Habits like cigarette smoking also produce oxidative stress, which results in the oxidation of cells(174). The anti-oxidants and vitamins in diet protect against this oxidative stress. Considering the above, it could be hypothesize that 1) low SEP produces psychological and oxidative stress; 2) stress causes the shortening of telomeres, a change at the DNA level causing mutation; and 3) once initiated, the pathway can lead to the expression of oral cancer with or without the action of promoters like alcohol.

7.5.2 SEP, biological ageing and oral cancer

Another pathway through which SEP could be related to cancer is through the phenomenon of biological ageing. It refers to the progressive loss of function accompanied by decreasing fertility and increasing mortality that occur with advancing age(174). At the cellular level, it is a result of oxidative stress, mitochondrial changes and somatic mutation(174). Factors like ultraviolet and ionizing radiations, heavy metals (occupational exposures), and cigarette smoke all increase oxidative stress. Diets containing anti-oxidants, vitamins C and E, in fruits and vegetables among others, exert a protective effect against stress-induced oxidation of cells. Cancer is the uncontrolled clonal proliferation of cells due to acquired or inherited somatic mutations, which cause cellular damage, and this basically translates to the biological ageing process(174, 175). The effect of stress on the shortening of telomeres has been discussed before and telomere shortening

is an important feature of cell death and biological ageing. It has been documented that the rate of biological aging leading to cancer is socioeconomically patterned(175). Combining all: 1) SEP mediated factors through environmental, occupational and behavioural exposures can cause oxidative stress; 2) oxidative stress enhances the rate of biological ageing and associated somatic mutation; and 3) these processes result in initiation, promotion and expression of oral cancer.

7.5.3 Hypermethylation of DNA and epigenetic changes

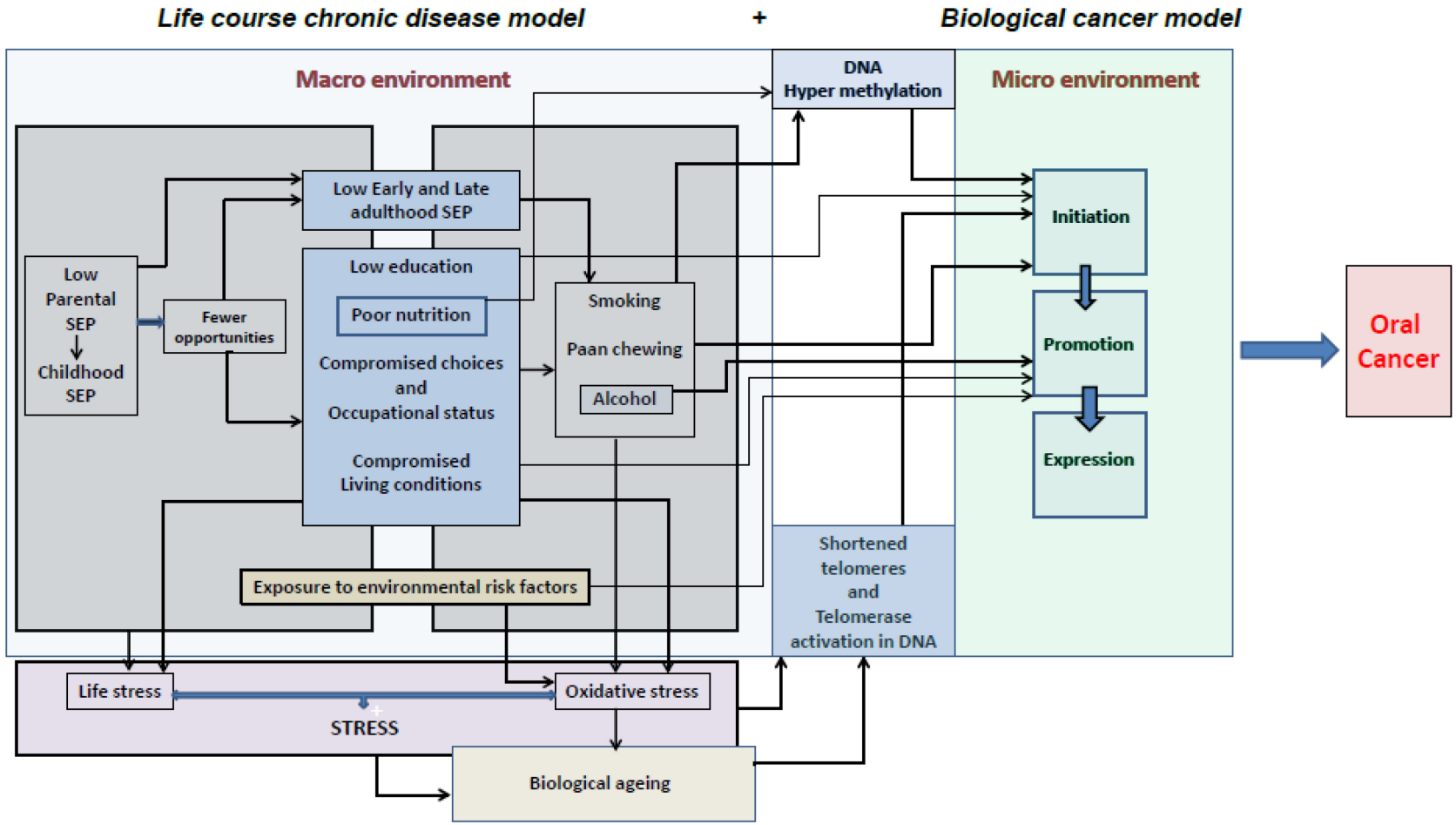
Cells in our body have tumour suppressor genes that protect them against mutation. DNA methylation is an important process which helps to maintain the integrity of DNA through regulation of gene transcription (176, 177). Studies have found that factors like diet, smoking, alcohol consumption and other environmental factors induce hypermethylation of DNA, which suppresses these protective genes(178). Epigenetic changes in the form of hypermethylation of tumour suppressor genes is one of the proven biological pathways leading to head and neck cancers, including oral cancer(177). The effect of SEP on the factors known to cause hypermethylation of DNA has already been discussed in the previous sections. Hence, low SEP increases the probability that a person's diet will be of poor nutritional value, increases vulnerability to risky behaviours and harmful working and living environments, potentially inducing hypermethylation of DNA and associated inactivation of tumour suppressor genes. This makes the cell susceptible to various cancer initiators and promoters, leading to expression of oral cancer.

7.6 Hypothetical model for pathways connecting life course SEP to oral cancer development

The above explanations provide plausible support for the existence of a pathway through which SEP associated behavioural habits (developed in early or late adulthood) and life-stress (starting from childhood and accumulating through other stages of life) causes a shortening of telomeres and telomerase activation, enhance biological ageing and induce DNA hypermethylation leading to initiation of cancer development. A diet poor in anti-oxidants and vitamins enhances this effect. Alcohol and other adverse environmental factors can act as strong promoters, ultimately leading to oral cancer expression. A hypothetical model depicting the possible pathways through which the macro environment associated with adverse life course SEP may lead to changes in the micro environment at cellular levels and oral cancer development, based on the life course model for chronic disease and the biological cancer model is represented in Figure 3.

These proposed pathways encourages us to look into the results of this thesis work from a more comprehensive perspective, underpinning the increased risk association of oral cancer with adverse SEP over the life course in this sample of subjects from India.

Figure 4: Hypothetical model depicting pathways thorough which adverse SEP may lead to oral cancer



7.7 Strengths of the study

This study has several strengths. First and foremost, the application of the life course approach in this case-control study investigating the SEP and oral cancer risk association allowed a broader perspective on the subject, encompassing important distal factors, in addition to the more commonly studied risk factors. The study had strict inclusion and exclusion criteria and only histologically confirmed incident cases were selected. Two pilot studies were conducted before the main study, which helped to understand study logistics/feasibility and adapt study instruments (e.g., questionnaire), to the Indian site. Interview procedures were carried out by trained dentists who were blinded to the hypothesis of the study which could avoid interviewer bias. The data was collected through a face-to-face interview with the subjects and explored extensively the details of exposures like socioeconomic indicators (education, housing conditions), behavioural habits (cigarette, bidi smoking, paan chewing, and alcohol consumption dietary, sexual) over the life course as well as a clinical oral health examination. The use of the life grid memory tool in tandem with the extensive questionnaire throughout the whole interview procedure likely improved the subjects' capacity to recall their life events and details on the exposures measured. This would have improved the precision of retrospective data collected. A study testing the effectiveness of the life grid technique documented an agreement of 80% between recalled information and that stored in archives when details of occupation and housing conditions were collected retrospectively after 50

years(179). Methodological rigor was employed throughout, including training and calibration of the interview process, data management, entry and analysis.

7.8 Limitations of the study and measures adopted to minimise bias and errors

7.8.1 Selection bias

Possibility of selection bias occurs if controls are not representative of the general population from which the cases are selected, subjects are not recruited through a valid diagnostic criteria, differential referral patterns and improper training of staff(111). Our study was a hospital based case-control study and, although bias is inherent in this design when compared to population based studies, ease of recruitment of subjects, low expense, and better response rate among others underpinned our choice. The Government Dental and Medical College serves a large population in the north of Kerala and most patients irrespective of their SEP approach these hospitals for treatment because of the quality and economical health service provided by these public sector institutions. Cases and controls were recruited from these two hospitals. This is a very important aspect because it decreases the possibility that the referral was biased based on SEP, the main exposure variable of this study, or on other variables. An indication that the recruited subjects represented the general population comes from the fact that most of them were Hindus from the middle class (other backward caste) and a major proportion of these subjects belonged to the Thiyya sub caste. This is in accordance with the religion and caste distribution of the general population of northern Kerala(99). Even though maximum efforts were made to recruit all

eligible cases and controls, the possibility that certain eligible cases and controls were missed can never be ruled out.

Differences in the exposure profile are a problem in selecting hospital controls. To minimize this bias, control subjects attending clinics that primarily treat diseases related to the exposure of interest (tobacco usage, alcohol consumption among others) were not recruited in the study. Efforts were made to ensure a fair distribution of diseases among controls and a representation of no more than 20% of the diseases by any disease group among the controls. Maximum efforts were made to limit non response from subjects. The help of proxy was sought in certain situations of non-response from subjects. Since it was found that proxies were used more frequently for cases than controls, this variable was adjusted for in the analysis. Only incident or newly admitted cases and controls were recruited into the study, which also contributed to minimize admission bias.

7.8.2 Sample size

A higher sample size would have increased the overall power of the study both in analytical terms and also in terms of ability to draw strong conclusions about the association of the main exposures (SEP) under study and the outcome. For example, although we observed a positive trend between life course SEP and the risk of cancer, this association was not statistically significant at 5% level. A higher sample size would have allowed us to test for other interactions in the model (e.g., chewing habits and smoking and alcohol) and also to stratify our analysis by sex.

7.8.3 Exposure misclassification and measurement error

The possibility of exposure misclassification and measurement errors cannot be ruled out in our study in spite of the fact that we used the life grid tool and the interview procedures were carried out in a similar fashion with cases and controls, which would have minimized information bias. In the following subsections, we look at the possible exposure misclassifications and measurement errors.

7.8.3.1 Socioeconomic position variables

As described in earlier sections, we measured SEP by collecting a detailed history of the education and housing conditions of each subject. Since SEP is a time varying exposure (9), it changes along the life course of an individual and is subject to recall bias. Moreover, the impact of a cohort effect would be large when measuring life course SEP. In this study, we did not consider parental education as this has been reported to be subject to more recall bias than subjects' own educational status(180). It is possible that the education and housing classification in this study was imprecise because of various secular, socioeconomic, and political changes over the life course of these subjects. Even though we attempted to deal with this cohort effect for the variable representing education (please refer to chapter 5), it is a crude attempt to adjust for the significant changes mentioned above in a state like Kerala in India. Some were not able to recollect information about their housing conditions, especially in childhood. This missing data could be another source of imprecision. It has been documented that there is no single best measure for accessing SEP and its measurement is very complex. The fact that we did not consider SEP indicators

like occupation and income, proxy indicators like number of siblings, and area based measures among others could be a possible source of error in our SEP estimation.

7.8.3.2 Behavioural habits and oral health status

Smoking and alcohol habits are not accepted well in Indian and Kerala society, unlike the habit of paan chewing. Our results show that most of the subjects did not indulge in smoking and alcohol drinking. The outlook towards these habits among cases and controls might be different and even though we measured all aspects of these habits, the possibility of underreporting is high considering their low social acceptance. This could have led to exposure misclassification. But due to the one on one interview technique where subject's privacy was assured, subjects were comfortable in answering the questions. So if there was any under reporting, we would expect it to be similar for both cases and controls, leading to non-differential misclassification and shifting the results towards the null. However, our results regarding smoking, alcohol consumption and paan chewing habits were similar to those of many other studies.

Dietary factors, as exposure, are difficult to measure. Our results show that fruit and vegetable consumption was generally low among subjects and more so among cases. Possible measurement errors and chance of misclassification in our study could have occurred, considering that current diet influences the recollection of what subjects think they ate in the past(181). Therefore, although we asked the subjects about their dietary habits 2 years prior to their diagnosis, it is still possible that our data was biased by the different diseases affecting the

cases and the controls. However these errors could be similar in cases and controls and would lead to non-differential misclassification, bias being towards the null. Missing teeth was recorded through clinical examination by trained dentists and error in this simple measurement is unlikely.

7.8.4 Outcome misclassification

The outcome under study was oral cancer. Outcome status was represented by presence or absence of the disease. With regards to the validity of case diagnosis, only histologically confirmed squamous cell carcinomas were recruited and it is the gold standard procedure to identify and diagnose malignant oral lesions(117). Specimens are usually checked by multiple pathologists before recruitment, which could contribute to increased validity and reliability of the procedure. Therefore, we consider that the possibility of misdiagnosis and misclassification of cases is extremely low in our study.

7.9 Validity and reliability of reported indicators of life course SEP and health related behaviours

The validity and reliability of the information collected are crucial in case-control studies related to chronic diseases. Despite the patients approaching the hospital only at advanced disease stages, tough study logistics and limitations imposed by the ethics committee, the participation rates for our study was high for both cases and controls. This would contribute to increased validity of our study results. The percentage of females was slightly lower among participants when compared to non participants. The non participants were on an average 8 years older than participants.

The use of education and housing conditions as measures of SEP has been validated in previous quantitative studies(182). Early life socioeconomic circumstances have been shown to be recalled with high accuracy and among most respondents. Housing conditions have been found to be recalled more accurately than categories such as parent's education and occupation. Even though these measures are subjected to recall bias, the use of the life grid technique has been shown to improve recall and the reliability of recalled information (182, 183). Regarding health related behaviour habits, the validity of pack years calculated from retrospective data has been questioned in the literature(122). However, this study uses the life grid technique which has been shown to increase the accuracy of recall (179). Thus, we expect less measurement error in this variable. Recall after 20 years of past smoking status has been shown to be valid (kappa=0.80), while amount smoked (kappa=0.63) wasn't recalled as well as smoking status(184). The accuracy of recall of alcohol status and consumption was similar to that of smoking(184). We were unable to find any studies that assessed the reliability of recall for chewing status. But we would expect it to be similar to that for smoking and alcohol habits. The use of the life grid in this study along with the extensive questionnaire used to collect the information, would contribute to an improved reliability of the data collected. Various measures have been followed in this study to check for the validity and reliability of the data collected as mentioned in chapter 5. But no analysis has yet been done with the data collected towards these procedures.

8. Conclusion and recommendations

8.1 Conclusion

Within the limitations of the study, this thesis work provides supportive evidence to the fact that lower levels of life course SEP, translated by increased levels of deprivation, constitute a significant risk factor for oral cancer. These associations attenuated when behavioural habits and oral health status were taken into consideration. But the various pathways through which SEP can influence these lifestyle risk factors underline the importance of SEP as a 'cause of the cause' for oral cancer in particular and chronic disease more generally . The 'macro-micro' model proposed in this work makes an attempt to look at the hypothetical pathways under one hood through which the macro environment of distal (e.g., low SEP) factors conglomerate and influences the proximal (e.g., behavioural) factors. This constant interplay between socioeconomic, psychosocial and behavioural factors could affect the micro environment associated with the biology of individuals, leading to oral cancer.

8.2 Public health implications

To this date, interventions to tackle oral cancer has been downstream or upstream approaches. The former includes strategies focusing on behavioural risk factors as life style choices (e.g., policies and public health strategies against smoking). The relative failure of this approach gave way to the later, highlighting the importance of society, culture and condition in which individuals are born, grow and live. The results from this life course study support the need for both these approaches to

work in tandem to efficiently decrease the burden of oral cancer. For example, education must be imparted with a holistic approach. It could emphasise not only on the main risk factors of oral cancer (e.g., tobacco, alcohol and non nutritious diet) being avoidable, but also be successful in spreading awareness on their social patterning and these factors being more prevalent among the low-income and disadvantaged groups. Effective techniques like mixed methodology research (e.g., narratives in focus groups) could be carried out in specific populations from the low SEP to understand the hurdles between them and effective education. Participatory approaches like this can help us understand the perception of these groups about the existing health education system and services. The deficiencies in the existing system could be teased out from the themes captured. Henceforth, effective measures of education and awareness programmes in specific groups (what would work and what wouldn't) tailored to their needs could be implemented. The knowledge empowers people and this would reflect on demands for better conditions of life. (e.g., implementing usage of protective gears in small scale industries, stress free working environments, housing conditions with proper sanitation and basic facilities, positive coping strategies to psychosocial stress) to protect and improve their own health and that of others.

8.3 Future research directions

A better understanding of pathways leading to disease (e.g., SEP to oral cancer) could lead to improvements in the study of biomarkers expressed in the initial stages of the disease. Subsequently, research could develop diagnostic tools based on these biomarkers. Such efforts may help to achieve an early diagnosis of oral

cancer and precancerous lesions, potentially leading to a better prognosis for patients. This underlines the need and importance of further research, incorporating methodologies like the life course approach, considering proximal, distal and biological factors to tease out the hypotheses and components of low SEP associated with an increased oral cancer risk. This study, which is a part of an ongoing international multi center case control study (HeNCe Life), incorporates all these dimensions. Future work using the full sample size, incorporating other indicators of SEP (e.g., occupation, parental education other known risk factors), data from other sites and the study of associated biologic and genetic changes could help to gain a better understanding of the aetio-pathogenesis of oral cancer.

9. List of References

1. GLOBOCAN [database on the Internet]2008. Available from: http://globocan.iarc.fr/.
2. Kekatpure Vikram, Abraham KM. Oral Cancer in India: Learning from Different Populations. Cancer Prevention [serial on the Internet]. 2010; (14): Available from: http://www.nypcancerprevention.com/issue/14/cancer_prevention/feature/india.shtml.
3. Silverman SOL. Demographics and occurrence of oral and pharyngeal cancers: The outcomes, the trends, the challenge. The Journal of the American Dental Association. 2001;132(1):7-11.
4. Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. Int J Cancer. 2002 Mar 20;98(3):440-5.
5. Rose GA, Khaw K-T, Marmot MG. Rose's strategy of preventive medicine : the complete original text. Oxford; New York: Oxford University Press; 2008.
6. Adler NE, Ostrove JM. Socioeconomic Status and Health: What We Know and What We Don't. Annals of the New York Academy of Sciences.. 1999;896(1):3-15.
7. Socioeconomic factors in head and neck cancer. J Otolaryngol Head Neck Surg. 2008 Aug;37(4):597-601.
8. Great Britain. Working Group on Inequalities in H, Black D, Townsend P, Davidson N. Inequalities in health : the Black report. Harmondsworth, Middlesex, England ; New York, N.Y.: Penguin Books; 1982.
9. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). Journal of Epidemiology and Community Health. 2006 February 1, 2006;60(2):95-101.
10. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. International journal of epidemiology. 2002;31(2):285-93.
11. Moore SR, Pierce AM, Wilson DF. ‘Oral cancer’—The terminology dilemma. Oral Diseases. 2000;6(3):191-3.
12. ICD [database on the Internet]2007. Available from: http://apps.who.int/classifications/apps/icd/icd10online/.

13. Stimson P, Schantz M, Guo-Pei Y. Head and neck cancer incidence trends in young Americans, 1973-1997, with a special analysis for tongue cancer. Arch Otolaryngol Head Neck Surg. 2002;128:268-74.
14. Franceschi S, et al. Trends in cancer mortality in young adults in Europe, 1955-1989. European Journal of Cancer 1994;30(14):2096-118.
15. Iype E, et.al. Oral cancer among patients under the age of 35 years. J Postgrad Med. 2001;47(3):171-6.
16. Gaitan-Cepeda L, Peniche-Becerra A, Quezada-Rivera D. Trends in frequency and prevalence of oral cancer and oral squamous cell carcinoma in Mexicans. A 20 years retrospective study. Med Oral Patol Oral Cir Bucal. 2011;16(1):1-5.
17. Moore S, et.al The epidemiology of mouth cancer: a review of global incidence. Oral Dis. 2000;6(2):65-74.
18. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. [Review]. 2009 Apr-May;45(4-5):309-16. Epub 2008 Sep 18.
19. National cancer registry programme, ICMR, INDIA [database on the Internet]2010. Available from: http://www.ncrpindia.org/Cancer_Atlas_India/map.htm.
20. Trends of head and neck cancers in urban and rural India. Asian Pac J Cancer Prev. [Comparative Study]. 2006 Jan-Mar;7(1):108-12.
21. Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya S. An analysis of risk factors for oral cancer in young people: a case-control study. Oral Oncology. 2004;40(3):304-13.
22. Adler N, Ostrove J. Socioeconomic status and health: what we know and what we don't. Ann N Y Acad Sci. 1999;896:3-15.
23. Sauvaget C. Socioeconomic factors and longevity in a cohort of Kerala State, India. Indian J Med Res. 2011 May 2011;133:479-86.
24. Schottenfeld D, Fraumeni JF. Cancer epidemiology and prevention. Oxford; New York: Oxford University Press; 2006.
25. Schmeisser N. Life course social mobility and risk of upper aerodigestive tract cancer in men. European Journal of Epidemiology. 2010;25(3):173-82.
26. Kreiger N, Williams D, Moss N. Measuring social class in US public health research:concepts, methodologies, and guidelines. Annu Rev Public Health. 1997;18:341-78.

27. Conway D, et.al. Components of socioeconomic risk associated with head and neck cancer: a population-based case-control study in Scotland. Br J Oral Maxillofacial Surg. 2010;48(1):11-7.
28. Conway D. Socioeconomic factors influence selection and participation in a population-based case-control study of head and neck cancer in Scotland. Journal of Clinical Epidemiology. 2008;61(11):1187-93.
29. Lynch J, Kaplan G. Socioeconomic position: Oxford University Press; 2000.
30. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. British Medical Bulletin. 2007;81-82(1):21-37.
31. Liberatos P, Link B, Kelsey J. The measurement of social class in epidemiology. Epidemiol Rev. 1988;10:87-121.
32. Hauser R. Measuring Socioeconomic status in childhood development: Blackwell Publishing; 1994.
33. The relation of socioeconomic status to oral and pharyngeal cancer. Epidemiology. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 1991 May;2(3):194-200.
34. Lynch Jw KGA. Socioeconomic Position. Socio economic factors. In:Berkman LF and Kawachi I. (eds.) Social Epidemiology: New York: Oxford University Press; 2000.
35. Wills TA. Stress and coping in early adolescence: Relationships to substance use in urban school samples. Health Psychology. 1986;5(6):503-29.
36. Shaw M. Housing and public health. Annu Rev Public Health. 2004;25:397-418.
37. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). Journal of Epidemiology and Community Health. 2006 January 1, 2006;60(1):7-12.
38. Filmer D, Pritchett L. Estimating Wealth Effects without Expenditure Data-or Tears: An Application to Educational Enrollments in States of India. Demography. 2001;38(1):115-32.
39. Berkman LF, Macintyre S. The measurement of social class in health studies: old measures and new formulations. IARC scientific publications. 1997(138):51-64.
40. Smith G, et.al. Lifetime socioeconomic position and mortality: prospective observational study. British medical Journal. 1996;314(7080):547-52.
41. Nair PRG. Education and Socio-Economic Change in Kerala, 1793-1947. Social Scientist. 1976;4(8):28-43.

42. Tharakan PKM. Socio-Economic Factors in Educational Development: Case of Nineteenth Century Travancore. Economic and Political Weekly. 1984;19(46):1959-67.
43. Conway DI, Petticrew M, Marlborough H, Berthiller J, Hashibe M, Macpherson LMD. Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies. International Journal of Cancer.. 2008;122(12):2811-9.
44. Iarc LF. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans1985.
45. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, et al. Alcohol Drinking in Never Users of Tobacco, Cigarette Smoking in Never Drinkers, and the Risk of Head and Neck Cancer: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium. Journal of the National Cancer Institute. 2007;99(10):777-89.
46. Mayne St MDEWDM. Cancers of the Oral Cavity and Pharynx. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer Epidemiology and Prevention. 3rd Ed Oxford University Press; New York: . 2006. p. 674-96.
47. Bidi smoking and oral cancer: a meta-analysis. Int J Cancer. [Meta-Analysis]. 2003 Sep 10;106(4):600-4.
48. Pakhale-et.al. Chemical analysis of smoke of Indian cigarettes, bidis and other indigenous forms of smoking-levels of steam-volatile phenol, hydrogen cyanide and benzo(a)pyrene. The Indian journal of chest diseases and allied sciences. 1990;32(2).
49. Reddy Ks GPC. Report on tobacco control in India. New Delhi: Ministry of health and family welfare, Govt. of India, Centers for disease control and prevention, USA, WHO. 2004.
50. D. Hoffmann LDS, Wynder EL. Comparative chemical analysis of indian bidi and American cigarette smoke. International Journal of Cancer. 1974;14:49-55.
51. Balaram P, Sridhar H, Rajkumar T, Vaccarella S, Herrero R, Nandakumar A, et al. Oral cancer in southern India: The influence of smoking, drinking, paan-chewing and oral hygiene. International Journal of Cancer. 2002;98(3):440-5.
52. Calculation of population attributable risk for bidi smoking and oral cancer in south Asia. Prev Med. [Comparative Study Meta-Analysis]. 2005 May;40(5):510-4.

53. Tobacco and alcohol as risk factors in cancer of the larynx in Kerala, India. Int J Cancer. [Research Support, Non-U.S. Gov't]. 1990 May 15;45(5):879-82.
54. Smokeless tobacco use and cancer of the upper respiratory tract. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. [Meta-Analysis Research Support, Non-U.S. Gov't]. 2002 May;93(5):511-5.
55. Epidemiology of cancer by tobacco products and the significance of TSNA. Crit Rev Toxicol. [Research Support, Non-U.S. Gov't Review]. 1996;26(2):183-98.
56. Allen CM, Vigneswaran N, Tilashalski K, Rodu B, Cole P. Tobacco use and cancer: A reappraisal. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 1995;80(2):178-82.
57. Sinha. Tobacco use among School Personnel in Eight North-Eastern States of India. Indian journal of Cancer. 2003;40(1):14.
58. Sudha. Mixture of betel leaf, areca nut and tobacco chewing is a risk factor for cytogenetic damage in construction workers from south India. Braz J oral Sci. 2009;8:148.
59. Franceschi S, Bidoli E, Herrero R, Muñoz N. Comparison of cancers of the oral cavity and pharynx worldwide: etiological clues. Oral Oncology. 2000;36(1):106-15.
60. Merchant A, et.al. Paan without tobacco: An independent risk factor for oral cancer. International Journal of Cancer. 2000;86(1):128-31.
61. Tobacco chewing, alcohol and nasal snuff in cancer of the gingiva in Kerala, India. Br J Cancer. [Research Support, Non-U.S. Gov't]. 1989 Oct;60(4):638-43.
62. Pindborg Jj KJGPC, Chawla TN. Studies in oral leukoplakias. Prevalence of leukoplakia among 10 000 persons in Lucknow, India, with special reference to use of tobacco and betel nut. Bull World Health Organ. 1967;37(1):109-16.
63. Lee C-H, et.al. The precancer risk of betel quid chewing, tobacco use and alcohol consumption in oral leukoplakia and oral submucous fibrosis in southern Taiwan. Br J Cancer. 2003;88(3):366-72.
64. Yang Y, et.al. The effects of chewing areca/betel quid with and without cigarette smoking on oral submucous fibrosis and oral mucosal lesions. Oral Dis. 2005;11(2):88-94.

65. Amarasinghe HK, Usgodaarachchi US, Johnson NW, Lalloo R, Warnakulasuriya S. Betel-quid chewing with or without tobacco is a major risk factor for oral potentially malignant disorders in Sri Lanka: A case-control study. Oral Oncology. 2010;46(4):297-301.
66. A preliminary assessment of possible mutagenicity of betel nut and ingredients of the betel quid when administered alone or in combinations to larvae of Drosophila melanogaster. Mutat Res. [Comparative Study]. 1979 Mar;66(3):261-6.
67. Ranadive KJ, Gothoskar SV, Rao AR, Tezabwalla BU, Ambaye RY. Experimental studies on betel nut and tobacco carcinogenicity. International Journal of Cancer.. 1976;17(4):469-76.
68. Pickwell S, Schimelpfening S, Palinkas L. 'Betelmania'. Betel quid chewing by Cambodian women in the United States and its potential health effects. WJM. 1994;160(4):326-30.
69. Awang MN. Betel quid and oral carcinogenesis. Singapore Med J. 1988;29:589-93.
70. Chandra P, et.al. Prevalence and correlates of areca nut use among psychiatric patients in India. Drug and Alcohol Dependence. 2003;69(3):311-16.
71. Shiu M, Chen T. Impact of betel quid, tobacco and alcohol on three-stage disease natural history of oral leukoplakia and cancer: implication for prevention of oral cancer. Eur J Cancer Prev. 2004;13(1).
72. Zain RB. Cultural and dietary risk factors of oral cancer and precancer--a brief overview. Oral Oncology. 2001;37(3):205-10.
73. Petti S. Lifestyle risk factors for oral cancer. Oral Oncology.45(4-5):340-50.
74. WHO. Global status report on alcohol 2004 - Woeld health organisation-department of mental health and substance abuse, Geneva. 2004. p. 1-2.
75. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer. 2007;7(8):599-612.
76. Blot W. Oral and Pharyngeal cancers. Cancer Surv. 1994;19-20:23-42.
77. Brennan P, Broffetta P. Mechanistic considerations in the molecular epidemiology of head and neck cancer. IARC scientific publications. 2004;157:393-414.
78. Assessment of risk factors for oral squamous cell carcinoma in Chidambaram, Southern India: a case-control study. Eur J Cancer Prev. 2007 Jun;16(3):251-6.

79. Waddell WJ, Levy PS. RE: "interaction between tobacco and alcohol consumption and the risk of cancers of the upper aero-digestive tract in brazil". American Journal of Epidemiology. 2000;152(2):193-.

80. Parkin D, Bray F. Chapter 2: The burden of HPV-related cancers. Vaccine. [Review]. 2006 Aug 31;24(Suppl 3):S3/11-25.

81. Kreimer AR, Bhatia RK, Messeguer AL, González P, Herrero R, Giuliano AR. Oral Human Papillomavirus in Healthy Individuals: A Systematic Review of the Literature. Sexually Transmitted Diseases. 2010;37(6).

82. Zheng T, Boyle P, Hu H, Duan J, Jiang P, Ma D, et al. Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. Cancer Causes and Control. 1990;1(3):235-41-41.

83. Lissowska J, et.Al. Smoking, alcohol, diet, dentition and sexual practices in the epidemiology of oral cancer in Poland. Eur J Cancer Prev. 2003;12(1):25-33.

84. Marshall JR, Graham S, Haughey BP, Shedd D, O'Shea R, Brasure J, et al. Smoking, alcohol, dentition and diet in the epidemiology of oral cancer. European Journal of Cancer Part B: Oral Oncology. 1992;28(1):9-15.

85. Kabat GC, Hebert JR, Wynder EL. Risk Factors for Oral Cancer in Women. Cancer Research. 1989;49(10):2803-6.

86. Tezal M, et.al. Chronic Periodontitis and the Risk of Tongue Cancer. Arch Otolaryngol Head Neck Surg. 2007 May 1, 2007;133(5):450-4.

87. Sebastian S, Grammatica L, A P. Telomeres, telomerase and oral cancer (Review). Int J Oncol. 2005;27(6):1583 -96.

88. Prime SS, Thakker NS, Pring M, Guest PG, Paterson IC. A review of inherited cancer syndromes and their relevance to oral squamous cell carcinoma. Oral Oncology. 2001;37(1):1-16.

89. Lynch JW, Kaplan GA, Salonen JT. Why do poor people behave poorly? Variation in adult health behaviours and psychosocial characteristics by stages of the socioeconomic lifecourse. Social Science & Medicine. 1997;44(6):809-19.

90. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. International Journal of Epidemiology. 2002;31(2):285-93.

91. Lynch- J, Smith. A life course approach to chronic disease epidemiology. Annals review of public health. 2005;26:1-35.

92. Kuh D B-S. A Life Course Approach to Chronic Diseases Epidemiology (Oxford Medical Publications). Shlomo DK, Yoav B, editors: 2nd edition, Oxford University Press, USA; 2004.
93. Khandekar Sp bPSTRR. Oral cancer and some epidemiological factors: A hospita based study. Indian Journal of community medicine. 2006;31(3).
94. G. Gandhi RK. Chewing Pan Masala and/or Betel Quid–Fashionable Attributes and/or Cancer Menaces? J Hum Ecol. 2005;17(3):161-6.
95. Iype M, et.al. Squamous cell carcinoma of the tongue among young Indian adults. Neoplasia. 2001 Jul-Aug;3(4):273-7.
96. Areca nut use in India. Indian J Med Sci. [Comment Editorial]. 2007 Jun;61(6):317-9.
97. Risk factors for cancer of the buccal and labial mucosa in Kerala, southern India. J Epidemiol Community Health. [Research Support, Non-U.S. Gov't]. 1990 Dec;44(4):286-92.
98. Madani AH, Dikshit M, Bhaduri D, Jahromi AS, Aghamolaei T. Relationship between Selected Socio-Demographic Factors and Cancer of Oral Cavity - A Case Control Study. Cancer Informatics. 2010;9:163-8.
99. Census of India Website [database on the Internet]2011. Available from: http://www.censusindia.gov.in/.
100. Statistics Canada: Canada's national statistical agency [database on the Internet]2011. Available from: http://www.statcan.gc.ca/start-debut-eng.html.
101. http://www.cpimkerala.org/eng/education-23.php?n=1 [database on the Internet]2009.
102. Suryanarayana. Morbidity profile of kerala and All India: An Economic Perspective. Fifth All India Conference of the Indian Association for Social Sciences and Health at the Centre for Healthcare Management, Xavier Institute of Management; Bhubaneswar, India2008.
103. Health - Vital Statistics for Kerala http://www.kerenvis.nic.in/isbeid/health.htm [database on the Internet]2009. Available from: http://www.kerenvis.nic.in/isbeid/health.htm.
104. What is true Development? The Kerala Model [database on the Internet]1998. Available from: http://www.ashanet.org/library/articles/kerala.199803.html.
105. Kerala.gov. Chapter-12 , Medical and public health. In: review Gok-E, editor.2009. p. 288-310.

106. UNICEF [database on the Internet]2009. Available from: http://www.unicef.org/index.php.
107. Changing trends in oral cancer. Indian J Cancer. 2008 Jul-Sep;45(3):93-6.
108. Robert H. Fletcher SWF. Clinical epidemiology: the essentials. Fourth edition ed: Lippincott Williams and Wilkins; 2005.
109. Moore S, Johnson N, Pierce A, Wilson D. The epidemiology of lip cancer: a review of global incidence and aetiology. Oral Dis. 1999 Jul;5(3):185-95.
110. MacMahon B, Pugh TF. Epidemiology; principles and methods. second ed. Boston: Little, Brown; 1970.
111. Schlesselman JJ. Case-control studies: design, conduct and analysis: Oxford university press; 1982.
112. Begg CB, Gray RJ. Methodology for Case-Control Studies with Prevalent Cases. Biometrika. 1987;74(1):191-5.
113. Marmot MG, Stansfeld S, Patel C, North F, Head J, White I, et al. Health inequalities among British civil servants: the Whitehall II study. The Lancet. 1991;337(8754):1387-93.
114. M W. The imprint of time: childhood, history and adult life: Oxford: Clarendon Press.; 1991.
115. Power C MO, Fox J. Health and Class: The Early Years:London: Chapman Hall; 1991.
116. Bell AJ. "oh yes, i remember it well!" reflections on using the life-grid in qualitative interviews with couples. Qualitative Sociology Review. 2005;1(1):67.
117. Mehrotra-et.al. Application of cytology and molecular biology in diagnosing premalignant or malignant oral lesions. Molecular Cancer 2006. 2006;5:1-9.
118. Rogers R, Hummer R, Krueger P. Adult Mortality. In: Poston D, Micklin M, editors. Handbook of Population: Springer US; 2005. p. 283-309-.
119. Mohindra K, et.al Women's health in a rural community in Kerala, India: do caste and socioeconomic position matter? J Epidemiol Community Health. 2006;60(12):1020-6.
120. Beebe-Dimmer J, Lynch JW, Turrell G, Lustgarten S, Raghunathan T, Kaplan GA. Childhood and Adult Socioeconomic Conditions and 31-Year Mortality Risk in Women. American Journal of Epidemiology. 2004;159(5):481-90.
121. Hadden WC. Annotation: the use of educational attainment as an indicator of socioeconomic position. Am J Public Health. 1996 Nov;86(11):1525-6.

122. Bernaards CM, Twisk JWR, Snel J, Van Mechelen W, Kemper HCG. Is calculating pack-years retrospectively a valid method to estimate life-time tobacco smoking? A comparison between prospectively calculated pack-years and retrospectively calculated pack-years. Addiction.. 2001;96(11):1653-61.
123. Trivedy. The_Oral_Health_Consequences_of_Chewing_Areca_Nut. Addiction Biology-Arecanut Symposium. 2002;7:115-25.
124. Nachiappan V, Mufti SI, Chakravarti A, Eskelson CD, Rajasekharan ram. lipid peroxidation and ethanol-related tumor promotion in fischer-344 rats treated with tobacco-specific nitrosamines. Alcohol and Alcoholism. 1994;29(5):565-74.
125. Kerr DJ. W.B. Coleman & G.J. Tsongalis (eds). The Molecular Basis of Human Cancer. Annals of Oncology. 2002 April 1, 2002;13(4):639--a.
126. Castellsague X, et.al. The role of type of tobacco and type of alcoholic beverage in oral carcinogenesis. Int J Cancer. 2004;108(714-749).
127. Gajalakshmi V, Hung RJ, Mathew A, Varghese C, Brennan P, Boffetta P. Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in southern India. International Journal of Cancer.. 2003;107(3):441-7.
128. Nayak MB, Kerr W, Greenfield TK, Pillai A. Not All Drinks Are Created Equal: Implications for Alcohol Assessment in India. Alcohol and Alcoholism. 2008;43(6):713-8.
129. Kerr.W. Alcohol policy research & Alcoholic beverage control systems: An annotated bibliography & review 2008. Available from: http://www.nabca.org/Resources/Files/200917104238.pdf.
130. Neupane RP, Sharma KR, Thapa GB. Adoption of agroforestry in the hills of Nepal: a logistic regression analysis. Agricultural Systems. 2002;72(3):177-96.
131. Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley; 1989.
132. David W.Hosmer SL. Applied logistic regression. 2nd ed. New York: John Wiley & Sons, Inc; 2000.
133. Chao-Ying Joanne peng KLlGMI. An Introduction to Logistic regression, Analysis and reporting. Journal of Educational Research. 2002;96(1):11.
134. Jungheim ES, Allsworth JE, Jimenez PT, Schon SB, Doblado MA. Early menstrual characteristics and endometriosis: Treloar et al. American Journal of Obstetrics and Gynecology. 2010;202(6):660-1.

135. Kenneth P. Brunham DRA. Model Selection and Multimodel Inference - A Practical Information-Theoretic Approach. Second Edition ed. Springer-Verlag H, editor: Elsevier; 2002.
136. Socioeconomic status, lifestyle factors and oral premalignant lesions. Oral Oncol. [Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2003 Oct;39(7):664-71.
137. Tobacco use & social status in Kerala. Indian J Med Res. [Review]. 2007 Oct;126(4):300-8.
138. Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: a nested case-control design using incident cancer cases. Oral Oncol. [Evaluation Studies Research Support, Non-U.S. Gov't]. 2008 May;44(5):446-54. Epub 2007 Oct 22.
139. Schlecht NF, Franco EL, Pintos J, Negassa A, Kowalski LP, Oliveira BV, et al. Interaction between Tobacco and Alcohol Consumption and the Risk of Cancers of the Upper Aero-Digestive Tract in Brazil. American Journal of Epidemiology. 1999;150(11):1129-37.
140. Guyton K, Kensler T. Prevention of liver cancer. Current Oncology Reports. 2002;4(6):464-70-70.
141. Pavia M, Pileggi C, Nobile CGA, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. The American Journal of Clinical Nutrition. 2006;83(5):1126-34.
142. Rajkumar, al e. Oral cancer in Southern India: the influence of body size, diet, infections and sexual practices. Eur J Cancer Prev. 2003;12(2):135-43.
143. De Stefani E, Boffetta P, Oreggia F, Brennan P, Ronco A, Deneo-Pellegrini H, et al. Plant foods and risk of laryngeal cancer: A case-control study in Uruguay. International Journal of Cancer. 2000;87(1):129-32.
144. Peters ES, Luckett BG, Applebaum KM, Marsit CJ, McClean MD, Kelsey KT. Dairy products, leanness, and head and neck squamous cell carcinoma. Head & Neck. 2008;30(9):1193-205.
145. Talamini R, Vaccarella S, Barbone F, Tavani A, Vecchia CL, Herrero R, et al. Oral hygiene, dentition, sexual habits and risk of oral cancer. British Journal of Cancer. [Article]. 2000;83(9):1238.
146. Nguyen.et.al. Oral health status of adults in Southern Vietnam - a cross-sectional epidemiological study. BMC Oral Health. 2010;10(2):1-11.

147. Sogi.GM;Bhaskar.DJ. Dental caries and Oral Hygiene Status of school children in Davangere related to their Socio - Economic levels : An Epidemiological study. J Indian Soc Pedo Prev Dent. 2002;20(4):152-7.
148. Neumark YD, Rahav G, Jaffe DH. Socio-economic status and binge drinking in Israel. Drug and Alcohol Dependence. 2003;69(1):15-21.
149. Turrell G, Lynch JW, Kaplan GA, Everson SA, Helkala E-L, Kauhanen J, et al. Socioeconomic Position Across the Lifecourse and Cognitive Function in Late Middle Age. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences. 2002;57(1):S43-S51.
150. Evans R SG. Producing health, consuming healthcare. Med, Sci S, editors1990.
151. Parmenter K, Waller J, Wardle J. Demographic variation in nutrition knowledge in England. Health Education Research. 2000;15(2):163-74.
152. Nutbeam D. Health literacy as a public health goal: a challenge for contemporary health education and communication strategies into the 21st century. Health Promotion International. 2000;15(3):259-67.
153. Gilman SE, Abrams DB, Buka SL. Socioeconomic Status over the Life Course and Stages of Cigarette Use: Initiation, Regular Use, and Cessation. Journal of Epidemiology and Community Health (1979-). 2003;57(10):802-8.
154. Bartley M. Health inequality : an introduction to theories, concepts and methods. Cambridge: Polity Press; 2004.
155. Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms. Mutagenesis. [Review]. 2004 Jul;19(4):251-62.
156. Turkmen N, Sari F, Velioglu YS. The effect of cooking methods on total phenolics and antioxidant activity of selected green vegetables. Food Chemistry. 2005;93(4):713-8.
157. Marmot M. The influence of income on health: views of an epidemiologist. 2002.
158. Stewart Pa Fau - Schairer C. Comparison of jobs, exposures, and mortality risks for short-term and long-term workers. 1990;32(8):703-8.
159. Wrigley N. 'Food Deserts' in British Cities: Policy Context and Research Priorities. Urban Studies. 2002;39:2029-40.
160. Maier H Fau - Tisch M. Occupational hazardous substance exposure and nutrition. Risk factors for mouth, pharyngeal and laryngeal carcinomas? HNO. 2002;50(8):743-52.

161. Marmot M. Social determinants of health inequalities. The Lancet. 2005;365(9464):1099-104.
162. Kawachi I, Kennedy BP. Health and social cohesion: why care about income inequality? BMJ. 1997 Apr 5;314(7086):1037-40.
163. Berton HK, Cassel JC, Gore S. Social Support and Health. Medical Care. 1977;15(5):47-58.
164. Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. Social Science & Medicine. 2000;51(6):843-57.
165. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-Based Stress Reduction in Relation to Quality of Life, Mood, Symptoms of Stress, and Immune Parameters in Breast and Prostate Cancer Outpatients. Psychosomatic Medicine. 2003;65(4):571-81.
166. Droomers M, Schrijvers CTM, Stronks K, van de Mheen D, Mackenbach JP. Educational Differences in Excessive Alcohol Consumption: The Role of Psychosocial and Material Stressors. Preventive Medicine. 1999;29(1):1-10.
167. Hemmingsson T, et.al. The roles of social class of origin, achieved social class and intergenerational social mobility in explaining social-class inequalities in alcoholism among young men. Social Science & Medicine. 1999;49(8):1051-9.
168. Hemmingsson T, et.al. Explanations of social class differences in alcoholism among young men. Social Science & Medicine. 1998;47(10):1399-405.
169. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, et al. Accelerated telomere shortening in response to life stress. Proceedings of the National Academy of Sciences of the United States of America. 2004;101(49):17312-5.
170. Willeit P, Willeit J, Mayr A, Weger S, Oberhollenzer F, Brandstätter A, et al. Telomere Length and Risk of Incident Cancer and Cancer Mortality. JAMA: The Journal of the American Medical Association. 2010;304(1):69-75.
171. Patel M, et.al, . Clinical usefulness of telomerase activation and telomere length in head and neck cancer. Head & Neck. 2002;24(12):1060-7.
172. Sainger. Clinical significance of telomere length and associated proteins in oral cancer. Biomark In. 2007;14(2):9-19.
173. von Zglinicki T. Oxidative stress shortens telomeres. Trends in Biochemical Sciences. 2002;27(7):339-44.

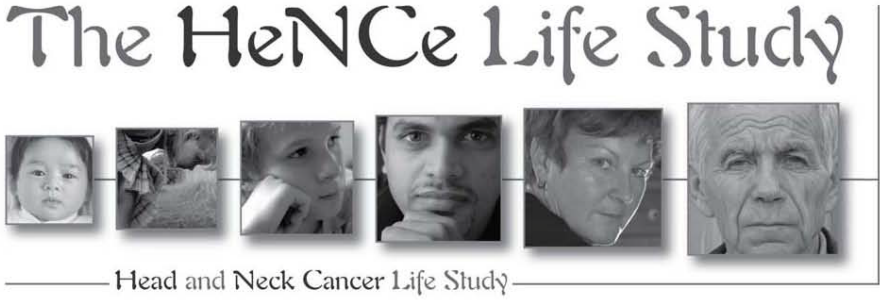
174. Adams JM, White M. Biological ageing. The European Journal of Public Health. 2004;14(3):331-4.
175. Adams J Fau - White M. Is the rate of biological aging, as measured by age at diagnosis of cancer, socioeconomically patterned? J Epidemiol Community Health. 2005;59(2):146-51.
176. Das PM, Singal R. DNA Methylation and Cancer. Journal of Clinical Oncology. 2004;22(22):4632-42.
177. de Freitas Cordeiro ea. Methylation analysis of cancer-related genes in non-neoplastic cells from patients with oral squamous cell carcinoma. Molecular Biology Reports. 2011:1-7-.
178. Ross SA. Diet and DNA Methylation Interactions in Cancer Prevention. Annals of the New York Academy of Sciences. 2003;983(1):197-207.
179. Blane B-. Collecting retrospective data: accuracy of recall after 50 years judged against historical records. Social Science & Medicine. 1997;45(10):1519-25.
180. Harper-et.al S. Life course socioeconomic conditions and adult psychosocial functioning. International Journal of Epidemiology. 2002;31:395-403.
181. Margetts-Nelson. Measuring dietary exposure in nutritional epidemiological studies. Nutrition Research Reviews. 1995;8:165-78.
182. Chittleborough CR, Baum FE, Taylor AW, Hiller JE. A life-course approach to measuring socioeconomic position in population health surveillance systems. Journal of Epidemiology and Community Health. 2006;60(11):981-92.
183. Berney L, Blane DB. Collecting retrospective data: accuracy of recall after 50 years judged against historical records. Social Science & Medicine. 1997;45(10):1519-25.
184. Krall EA, Valadian I, Dwyer JT, Gardner J. Accuracy of recalled smoking data. Am J Public Health. 1989 Feb;79(2):200-2.

10. Appendix I

Questionnaire

CONFIDENTIAL

MULTI CENTER STUDY OF HEAD AND NECK CANCER:
HeNCe Life Study



UNIT OF EPIDEMIOLOGY & BIOSTATISTICS
INRS-INSTITUT ARMAND FRAPPIER – LAVAL – CANADA

FACULTY OF DENTISTRY & DEPARTMENT OF EPIDEMIOLOGY
MCGILL UNIVERSITY – MONTREAL - CANADA

HOSPITAL DO CÂNCER-DEPARTAMENTO DE CIRURGIA DE CABEÇA E PESCOÇO - SÃO PAULO-BRASIL

SCHOOL OF DENTISTRY - FACULTY OF HEALTH SCIENCES
UNIVERSITY OF LIMPOPO - MEDUNSA - SOUTH AFRICA

GOVERNMENT DENTAL COLLEGE –MEDICAL COLLEGE CAMPUS
KOZHIKODE – SOUTH INDIA

2008

Medical information | 0 5 Country | ID N°

TABLE OF CONTENTS

Medical information 0 5 (Country) ___ (ID N°)

A. MEDICAL INFORMATION

Interviewer Reminder: Prior to interview, obtain information below from research file or medical records.

Identification Number..... 0 5 - ___
Country: (01) Brazil (03) South Africa **Country** **Participant**
(02) Canada (04) United Kingdom
(05) India

A1 Status: .....
(01) Case (02) Control

A2 Subject's Initials (Surname, Name) .....

A3 Hospital / Recruitment site.....
(01) Governmental Dental College (02) Governmental Medical College

FOR CONTROLS :

A4 Control Department: *(Code 88 for cases)*.....
(01) Dermatology (05) Gynecology
(02) Dental Clinic (06) Opthalmology
(03) Ear, Nose and Throat (07) Orthopedics
(04) Gastroenterology (08) Nephrology

A5 Main Diagnosis of CONTROL in this department (LC)..... -
Condition description: _____

FOR CASES:

A6 Cancer site: .....
(01) Tongue (02) Floor of mouth (05) Others specify……
(03) Gum (04) Buccal mucosa

A7 Global TNM stage T_____ N_____ M____ → Global Staging **(LC)** _____

A8 Date of Diagnosis..... - -
(99-99-9999) Don't know Day Month Year

A9 Time since Diagnosis (months).....

A10 Interviewer's Initials (Surname, Name).....

A11 *Interviewer:* **Was a proxy used?**
(01) Yes (02) No

Section B – General Information | **0 5** Country | ID N°

B. GENERAL INFORMATION

B1 Date of Interview..... ☐☐ - ☐☐ - ☐☐☐☐ (Day - Month - Year)

B2 Time of beginning of Interview..... ☐☐ - ☐☐ (Hour - Minute)

B3 Interview .....☐☐
(01) Original (02) Duplicate *(6-12 weeks later)* (3) Duplicate *(+12 weeks later)*

B4 Sex.....☐☐
(01) Female (02) Male

Interviewer Reminder: Present life grid here. See instructions in guidebook.

B5 What is your date of birth?..... ☐☐ - ☐☐ - ☐☐☐☐
(99-99-9999) Don't know (Day - Month - Year)

B6 How old are you?.....☐☐☐

B7 Do you live in a rural (farm) or urban (in a city) area? .....☐☐
(01) Urban (02) Rural (GO TO B9)

B8 If you live in an urban area, what city do you live in? (LC).....☐☐
Name of City: _____

Interviewer Reminder: Confirm name of city from list of codes.Rural area is in the farm

B9 How many years have you been living there? (Last consecutive years).....☐☐
(00) Less than one year (GO TO B10)

B10 Were you born in a rural (farm) or an urban (in a city) area?.....☐☐
(01) Urban (02) Rural (GO TO B12)

B11 If you were born in an urban area, what city were you born in? (LC) .....☐☐
Name of city: _____
(00) Other country

B12 How many years did you live there?.....☐☐
(00) Less than one year

Section B – General Information | 0 5 Country | ID N°

B13 What is your religion? (Show Answer Sheet).....

(00) None (GO TO B16)
(01) Hindu
(02) Muslim
(03) Christian
(04) Sikh
(05) Buddhist/Neo-Buddhist
(06) Jain
(07) Jewish
(08) Parsi/ Zoroastrian
(09) Other, specify_____.....

B14 Do you practice this religion?.....

(00) No (GO TO B18)
(01) Yes

B15 How old were you when you started practicing this religion?.....

(00) My whole life

B16 What is the cast or tribe of you belong to?

Caste:_____ Tribe: _____

(00) No Cast/Tribe
(99) Don`t know / Prefer not to say

B17 What type of caste / tribe is this?.....

(01) Forward caste
(02) Backward caste
(03) Other backward caste (OBC)
(04) Scheduled caste
(05) Scheduled tribe
(06) None of them
(99) NA/ Christian

5

Section C – Education | 0 5 Country | ID N°

C. EDUCATION

This section is about your education. Firstly,

C1 Did you ever attend school?.....
(01) Yes (GO TO C3)
(02) No, school was too far away
(03) No, transport was not available
(04) No, education was not considered necessary
(05) No, I was required for household work/ farm work/ family business
(06) No, I was required for outside work for payment in cash or kind
(07) No, school costed too much
(08) No, there were no proper school facilities for girls
(09) No, other reason for not attending, specify:_____

C2 Can you read and write?.....
(00) No (GO TO SECTION D)
(01) Yes (GO TO SECTION D)
(02) Yes, I learned with Saksharatha

Interviewer Reminder: Collect general information using the **life grid**
- Situate years of **formal** education i.e. that were successfully completed at school.

C3 How many years of formal education do you have? .....

C4 What was the highest standard that you obtained?.....

(01) Lower Primary (1-4 yrs)
(03) Upper Primary (5-7 yrs)
(04) High School (8-10 yrs)
(05) PDC (11-12)
(06) University
(07) Post-graduate
(07) Technical certificate

C5 Have you ever failed a school year?.....

(00) No
(01) Yes, once
(02) Yes, twice
(03) Yes, 3 or more times

Section D – Occupations & Employment | 0 5 Country | ID N°

D. OCCUPATIONS & EMPLOYMENT

In this section I would like to ask you a few questions about jobs you may have had.

Interviewer Reminder:. A job is a **continuous period of time of ONE YEAR OR MORE working and paid by the same employer** even though the participant may have had different positions during that period. If the participant was self-employed, a job is considered to be a period of time doing the same type of self-employed work.

D1 Have you ever had a paid job in your life (> 1 year)?..... ☐☐
(00) No (GO TO SECTION E) (01) Yes
(02) No, I was a housewife (ANSWER D13-D27)

D2 Which of the options below best describes your work situation in the past 7 days?..... ☐☐
(01) Full time work (30+ hours/ week) (05) Permanently sick or disabled
(02) Part time work (< 30 hours/ week) (06) On sick leave
(03) Unemployed (07) Other (Specify:_____)….. ☐☐
(04) Fully retired from work

Let's look at the different jobs you've had, the different positions you may have held. Again, we will use this grid to help us out and refer to it for the specific questions I will have afterwards.

D3 Since you started working how many jobs have you had?..... ☐☐
(01) (02) (03) (04) (05) (06) (07) (08) (09 or more)

Section D – Occupations & Employment | 0 5 Country | ID N°

FIRST JOB

Interviewer Reminder: Confirm which job is 1st job with life grid.

I would like to ask you a few questions about your **first job**. So,

D4 You were doing that job...

From age?	To age?	# Years	# Months
			8 8

D5 Did you occupy different positions at that job?.....
(00) No (Fill in FIRST column only) (01) Yes

	FIRST	LAST
D6 Please describe your job / different positions (LC).....		

FIRST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

LAST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

D7 What did the company you worked for specialise in?(LC).....
_____
_____

D8 Were you an employee or self-employed?.....
(01) Employee (02) Self-employed (GO TO D10)

8

Section D – Occupations & Employment | 0 5 Country | ID N°

D9 As an EMPLOYEE, which of the following best suited your position?.....

(00) I did not supervise anyone
(01) Foreman, supervisor, team leader
(02) Manager: Firm of <25 employees
(03) Manager: Firm of >25 employees

D10 If SELF-EMPLOYED, which of the following best suited your position?.....

(00) Without business
(02) With business but without employees other than family members
(03) With <25 employees
(04) With >25 employees
(05) Professional

D11 How many hours a week?.....

D12 How much were you paid PER YEAR at that time?

Describe: _____

- Calculate average amount in thousands of Indian Rupees
- Average: hourly rate x 35 hours x 50 weeks OR Min + Max / # yrs, prorated
- Self-employed: average earnings per year as per income tax declarations if submitted

Now I would like to ask you a few questions about work environmental hazards. Consider your job in general, regardless of the different positions you may have occupied.

Did your work often expose you to...?

D13 Dust.....
For example: Coal dust, metal dust, insulation material dust, wood dust, grain dust, textile fibers, plastic fibers, silica dust, saw dust, sanding dust, epoxy-resins, welding...)
(00) No (01) Yes

D14 Oils (Mineral oils, lubricating oils, cutting oils).....
(00) No (01)Yes

D15 Solvents (ex. Degreasing agents, cleaning agents, paint or lacquer removers or thinners).....
(00) No (01)Yes

D16 Acids or alkalis.....

(00) No (01) Yes

D17 Smoke (e.g., Engine emissions from diesel, gas or propane engines, or gases from coal, wood, rubber...).....
(00) No (01) Yes

Section D – Occupations & Employment | 0 5 Country | ID N°

D18 Gas (e.g. Combustion gases from industrial ovens, oxygen, ammonia...) or Fumes (ex. Metal fumes.....
(00) No (01) Yes

D19 Fumes (e.g., Metal fumes).....
(00) No (01) Yes

D20 Pesticides (e.g., insecticides, herbicides, fungicides or wood preservatives)
(00) No (01) Yes

D21 Did your work involve working with substances such as: Bethune, asphalt, alcohol, gasoline, glue, mercury, kerosene, dyes, inks etc? .....
(00) No (01) Yes

D22 Cigarette smoke.....
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

D23 Did your work <u>often</u> involve exposure to other chemicals?.....
(00) No (01) Yes, specify: _____.....

D24 Electromagnetic radiations (x-rays, microwaves, radioactive substances)?
(00) No (01) Yes

D25 Did you use any kind of protection for chemical / physical hazards (ex. masks, gloves)?.....
(00) No (02) Yes, sometimes
(01) Yes, most of the time (03) Yes, rarely

D26 Was your first job the same one as your longest job?....
(00) No (01) Yes, the same one as my longest job (GO TO D50)
(02) Yes, the same one my whole life (GO TO SECTION E)
(03) Yes, I was a housewife my whole life (GO TO SECTION E)

Section D – Occupations & Employment | 0 5 Country | ID N°

LONGEST JOB

Now I would like to ask you some questions about your **longest job**. I will be using the same set of questions I used in the previous section. So,

Interviewer Reminder: Confirm which job is longest job with life grid.

D27 You were doing that job...

From age?	To age?	# Years	# Months
			8 8

D28 Did you occupy different positions at that job?.....
(00) No (Fill in FIRST column only) (01) Yes

	FIRST	LAST
D29 Please describe your job / different positions (LC).....		

FIRST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

LAST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

D30 What did the company you worked for specialise in?(LC).....
_____
_____

D31 Were you an employee or self-employed?.....
(01) Employee (02) Self-employed (GO TO D33)

Section D – Occupations & Employment | 0 5 Country | ID N°

D32 As an EMPLOYEE, which of the following best suited your position?.....
(00) I did not supervise anyone
(01) Foreman, supervisor, team leader
(02) Manager: Firm of <25 employees
(03) Manager: Firm of >25 employees

D33 If SELF-EMPLOYED, which of the following best suited your position?.....
(00) Without business
(02) With business but without employees other than family members
(03) With <25 employees
(04) With >25 employees
(05) Professional

D34 How many hours a week?.....

D35 How much were you paid PER YEAR at that time?
Describe: _____

- Calculate average amount in thousands of Indian Rupees
- Average: hourly rate x 35 hours x 50 weeks OR Min + Max / # yrs, prorated
- Self-employed: average earnings per year as per income tax declarations if submitted

Now I would like to ask you a few questions about work environmental hazards. Consider your job in general, regardless of the different positions you may have occupied.

Did your work expose you to...?

D36 Dust .....
For example: Coal dust, metal dust, insulation material dust, wood dust, grain dust, textile fibers, plastic fibers, silica dust, saw dust, sanding dust, epoxy-resins, welding...)
(00) No (01) Yes

D37 Oils (Mineral oils, lubricating oils, cutting oils).....
(00) No (01)Yes

D38 Solvents (ex. Degreasing agents, cleaning agents, paint or lacquer removers or thinners).....
(00) No (01)Yes

D39 Acids or alkalis.....
(00) No (01) Yes

D40 Smoke (ex. Engine emissions from diesel, gas or propane engines, or gases from coal, wood, rubber...).....
(00) No (01) Yes

Section D – Occupations & Employment | 0 5 Country | ID N°

D41 Gas (ex. Combustion gases from industrial ovens, oxygen, ammonia...) or Fumes (ex. Metal fumes.....
(00) No (01) Yes

D42 Fumes (ex. Metal fumes).....
(00) No (01) Yes

D43 Pesticides (ex. insecticides, herbicides, fungicides or wood preservatives)
(00) No (01) Yes

D44 Did your work involve working with substances such as: Bethune, asphalt, alcohol, gasoline, glue, mercury, kerosene, dyes, inks etc? .....
(00) No (01) Yes

D45 Cigarette smoke…….
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

D46 Did your work <u>often</u> involve exposure to other chemicals?.....
(00) No (01) Yes, specify: _____.....

D47 Electromagnetic radiations (x-rays, microwaves, radioactive substances)?
(00) No (01) Yes

D48 Did you use any kind of protection for chemical / physical hazards (ex. masks, gloves)?.....
(00) No (02) Yes, sometimes
(01) Yes, most of the time (03) Yes, rarely

D49 Was your longest job the same one as your latest/ or current job?.....
(00) No
(01) Yes, the same one as my latest/current job (GO TO SECTION E)

13

Section D – Occupations & Employment | 0 5 Country | ID N°

LAST/LATEST JOB

Finally about your last/latest job...

Interviewer Reminder: Confirm which job is last/latest job with life grid.

D50 You were doing that job...

From age?	To age?	# Years	# Months
			8 8

D51 Did you occupy different positions at that job?.....
(00) No (Fill in FIRST column only) (01) Yes

	FIRST	LAST
D52 Please describe your job / different positions (LC).....		

FIRST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

LAST POSITION

Job Title: _____
Work environment: _____
Most frequent tasks: _____
_____
_____

D53 What did the company you worked for specialise in?(LC).....
_____
_____

D54 Were you an employee or self-employed?.....
(01) Employee (02) Self-employed (GO TO D56)

D55 As an EMPLOYEE, which of the following best suited your position?.....
(00) I did not supervise anyone (02) Manager: Firm of <25 employees
(01) Foreman, supervisor, team leader (03) Manager: Firm of >25 employees

Section D – Occupations & Employment | 0 5 Country | ID N°

D56 If self-employed, which of the following best suited your position?.....

(00) Without business
(02) With business but without employees other than family members
(03) With <25 employees
(04) With >25 employees
(05) Professional

D57 How many hours a week?.....

D58 How much were you paid PER YEAR at that time?

Describe: _____

- Calculate average amount in thousands of Indian Rupees
- Average: hourly rate x 35 hours x 50 weeks OR Min + Max / # yrs, prorated
- Self-employed: average earnings per year as per income tax declarations if submitted

Now I would like to ask you a few questions about work environmental hazards. Consider your job in general, regardless of the different positions you may have occupied.

Did your work often expose you to...?

D59 Dust.....
For example: Coal dust, metal dust, insulation material dust, wood dust, grain dust, textile fibers, plastic fibers, silica dust, saw dust, sanding dust, epoxy-resins, welding...)
(00) No (01) Yes

D60 Oils (Mineral oils, lubricating oils, cutting oils).....
(00) No (01)Yes

D61 Solvents (ex. Degreasing agents, cleaning agents, paint or lacquer removers or thinners).....
(00) No (01)Yes

D62 Acids or alkalis.....
(00) No (01) Yes

D63 Smoke (ex. Engine emissions from diesel, gas or propane engines, or gases from coal, wood, rubber...).....
(00) No (01) Yes

D64 Gas (ex. Combustion gases from industrial ovens, oxygen, ammonia...) or Fumes (ex. Metal fumes.....
(00) No (01) Yes

Section D – Occupations & Employment | 0 5 Country | ID N°

D65 Fumes (ex. Metal fumes).....
(00) No (01) Yes

D66 Pesticides (ex. insecticides, herbicides, fungicides or wood preservatives)
(00) No (01) Yes

D67 Did your work involve working with substances such as: Bethune, asphalt, alcohol, gasoline, glue, mercury, kerosene, dyes, inks etc? .....
(00) No (01) Yes

D68 Cigarette smoke.....
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

D69 Did your work <u>often</u> involve exposure to other chemicals?.....
(00) No (01) Yes, specify: _____.....

D70 Electromagnetic radiations (x-rays, microwaves, radioactive substances)?.....
(00) No (01) Yes

D71 Did you use any kind of protection for chemical / physical hazards (ex. masks, gloves)?.....
(00) No (02) Yes, sometimes
(01) Yes, most of the time (03) Yes, rarely

Section E – Housing conditions & Residential environment | 0 | 5 | | | | ID Nº

E. HOUSING CONDITIONS & RESIDENTIAL ENVIRONMENT

In this section I would like to ask you a few questions about your housing conditions and residential environment at different times in your life. We will use the life grid first to look at the different addresses you lived at, noting the times you moved from one place to another.

Interviewer Reminder: Collect general information using the **life grid**, referring to it later when asking questions in Section E.

- **An address is a place where the participant lived for at least 1 YEAR.**

E1 Up until you were 16 years old (incl.) at how many *different* addresses did you live?
(01) Same place (02) (03) (04) (05) (06) (07) (08) (09 or more).. ☐☐

E2 Between the ages of 17 and 30 (incl.) at how many *different* addresses did you live?
(01) Same place (02) (03) (04) (05) (06) (07) (08) (09 or more)... ☐☐

E3 From the age of 30 (excl.) until today at how many *different* addresses did you live?
(01) Same place (02) (03) (04) (05) (06) (07) (08) (09 or more)... ☐☐
If the respondent is less than 30 years old, mark (88) and GO TO E4

Section E – Housing conditions & Residential environment | 0 5 | ID N° | | | |

CHILDHOOD RESIDENCE

I would like to ask you a few questions about the residence/home in which you lived **for the longest time during your childhood**. By childhood I mean up to age 16 (incl.).

Interviewer Reminder: Identify and confirm longest residence in childhood using the life grid.

E4 You lived at that place...?

From age? ☐☐ **To age?** ☐☐ **i.e. # Years** ☐☐

For all the following questions, refer to the situation that was present "MOST OF THE TIME" while living in that residence.

E5 What type of setting were you living in at that place?..... ☐☐
(01) With family (03) Other, specify: _____
(02) Hostel/Orphanage (GO TO E35)
(99) Don't know

E6 Was your home owned or rented?..... ☐☐
(01) Owned (99) Don't know
(02) Rented (03) Other, specify: _____... ☐☐

E7 How many people lived in the household?..... ☐☐
(99) Don't know

Count the number of people at once, for the longest period of time. Include permanent residents including borders, live-in maids, roommates…

E8 How many rooms did your place have?
(99) Don't know ☐☐

-Include: kitchen, living room, dining room, bedroom, furnished basement
-Do not include: toilet, bathrooms, laundry room, hallway, garage, patio
-If renovated, count # rooms during longest period living there

E9 How many rooms did your household use for sleeping?..... ☐☐
(99) Don't know

Section E – Housing conditions & Residential environment | 0 | 5 | | | | ID N°

Interviewer Reminder:
- To save time, do not read out all the options for questions E10 to E15.
- Allow the subject to respond and then check the appropriate box.

E10 What was the main material of the floor?.....

(01) Mud/Clay/Earth
(02) Sand
(03) Dung
(04) Raw wood planks
(05) Palm/Bamboo
(06) Brick
(07) Stone
(08) Parquet or polished wood
(09) Vinyl or Asphalt
(10) Ceramic Tiles
(11) Cement
(12) Carpet
(13) Polished stone/Marble/Granite
(14) Other, specify:_____
(99) Don`t know

E11 What was the main material of the roof?.....

(01) No roof
(02) Thatch/Palm leaf/Reed/Grass
(03) Sod/Mud and Grass Mixture
(04) Plastic/Polythene sheeting
(05) Palm/Bamboo
(06) Raw wood planks/Timber
(07) Loosely packed stone
(08) Metal/GI
(09) Wood
(10) Calamine/Cement Fiber
(11) Asbestos Sheets
(12) RCC/RBC/Cement/Concrete
(13) Slate
(14) Other, specify:_____
(99) Don`t know

E12 What was the main material of the exterior walls?.....

(01) No walls
(02) Cane/Palm/Trunks/Bamboo
(03) Mud
(04) Grass/Reeds/Thatch
(05) Bamboo with mud
(06) Stone with mud
(07) Plywood
(08) Cardboard
(09) Unburnt brick
(10) Raw wood/Reused wood
(11) Cement/Concrete
(12) Stone with lime/Cement
(13) Burnt bricks
(14) Cement blocks
(15) Wood planks/Shingles
(16) GI/Metal Asbestos sheets
(17) Other, specify:_____
(99) Don`t know

E13 What type of windows were there?.....

(01) No windows
(02) Windows with glass
(03) Windows with screen
(04) Windows with curtains or shutters
(05) Windows with no glass, screen or cover
(06) Other, specify:_____
(99) Don`t know

Section E – Housing conditions & Residential environment | 0 | 5 | | | | ID N°

Now, I will read a list of facilities you may have had in the place where you lived. We would like to know **which of these facilities were present inside your childhood residence and some details about them.**

E14 What was the main source of drinking water for members of your household? ☐☐

(01) Piped water into dwelling
(02) Piped water to yard/ plot
(03) Piped water (public tap/standpipe)
(04) Tube well or borehole
(05) Dug well (protected)
(06) Dug well (unprotected)
(07) Water from protected spring
(08) Water from unprotected spring
(09) Rainwater
(10) Tanker truck
(11) Cart with small tank
(12) Surface water (river, dam, lake, pond, stream, canal
(13) Bottled water
(99) Don`t know

E15 How many toilet facilities did you have? ..... ☐☐

(99) Don`t know (00) None (GO TO E18)

E16 What kind of toilet facility did members of your household usually use? ..... ☐☐

(01) Flush to piped sewer system
(02) Flush to septic tank
(03) Flush to pit latrine
(04) Flush to somewhere else
(05) Ventilated improved pit/ biogas latrine
(06) Pit latrine with slab
(07) Pit latrine without slab/ open pit
(08) Twin pit/ composting toilet
(09) Dry toilet
(10) Other, specify _____
(99) Don`t know

E17 Did you share this toilet facility with other households?..... ☐☐

(00) No (99) Don't know
(01) Yes

E18 Did your home have electricity?..... ☐☐

(00) No (02) Yes, by a generator/ battery only
(01) Yes, by a central system (99) Don`t know

E19 What type of fuel did your household mainly use for cooking?..... ☐☐

(01) Electricity (GO TO E22) (05) Coal/lignite (09) Agricultural crop waste
(02) LPG/ Natural gas (GO TO E22) (06) Charcoal (10) Dung cakes
(03) Biogas (GO TO E22) (07) Wood (11) Other, specify:_____
(04) Kerosene (GO TO E22) (08) Straw/Shrubs/Grass (99) Don't know

E20 Did the stove have a chimney? ..... ☐☐

(00) No (01) Yes (99) Don't know

E21 Was the stove located in an area with any ventilation/windows?... ..... ☐☐

(00)No (01)Yes (99) Don't know

Section E – Housing conditions & Residential environment 0 5 ☐☐☐
ID Nº

E22 Where was the cooking usually done?.....☐☐
(01) Inside the house (02) Separate building (03) Outdoors
(99) Don`t know

E23 Did your home have a separate room which was used as a kitchen?.....☐☐
(00) No (01) Yes (99) Don't know

E24 Were you exposed to cigarette smoke in this house?.....☐☐
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

I will now read a **list of household goods** you may have had in your childhood residence or not. You may find that some of these appliances were not applicable to the epoch you were a child. Choose the answer that best represents your situation, regardless.

E25 Did your place have a watch or clock?.....☐☐
(00) No (01) Yes (99) Don't know

E26 Did your place have a radio or transistor?.....☐☐
(00) No (01) Yes (99) Don't know

E27 Did your place have a TV? .....☐☐
(00) No (02) Yes, color
(01) Yes, black and white (99) Don't know

E28 Did your place have a refrigerator?.....☐☐
(00) No, it had no appliance to cool food (01) Yes
(99) Don't know

Also, I would like to ask you...

E29 Did your household have a bicycle?.....☐☐
(00) No (01) Yes (99) Don't know

E30 Did your household have a motorcycle or scooter?.....☐☐
(00) No (01) Yes (99) Don't know (GO TO E32)

E31 How many?.....☐☐

E32 Did your household have a car?.....☐☐
(00) No (01) Yes (99) Don't know (GO TO E34)

E33 How many?.....☐☐

21

Section E – Housing conditions & Residential environment | 0 | 5 | | | | ID N°

E34 Is this childhood residence the same one as the longest residence between ages of 17-30…….. | |

(00) No

(01) Yes, same as the longest residence between ages of 17-30 (Please still fill out the section entitled 'Longest Residence in Early Adult Life')

(02) Yes, the same residence in my whole life (Please still fill out the sections entitled 'Longest Residence in Early Adult Life' and 'Longest Residence in Late Adult Life')

Section E – Housing conditions & Residential environment | 0 5 | ID N°

LONGEST RESIDENCE IN EARLY ADULT LIFE (17-30 yrs)

Now I would like to ask you a few questions about the residence/home in which you lived **for the longest time during your early adult life, that is between the ages of 17 (incl.) and 30 (incl.)**. I will use the same set of question I used in the previous sections.

Interviewer Reminder: Identify / confirm longest residence in early adulthood using life grid.

E35 You lived at that place...?

From age? **To age?** **i.e. # Years**

For all the following questions, refer to the situation that was present "MOST OF THE TIME" while living in that residence.

E36 What type of setting were you living in at that place?.....
(01) With family (02) Other, specify: _____
(99) Don't know

E37 Was your home owned or rented?.....
(01) Owned (99) Don't know
(02) Rented (03) Other, specify: _____...

E38 How many people lived in the household?.....
(99) Don't know

Count the number of people at once, for the longest period of time. Include permanent residents including borders, live-in maids, roommates…

E39 How many rooms did your place have?.....
(99) Don't know

-Include: kitchen, living room, dining room, bedroom, furnished basement
-Do not include: toilet, bathrooms, laundry room, hallway, garage, patio
-If renovated, count # rooms during longest period living there

E40 How many rooms did your household use for sleeping?.....
(99) Don't know

Section E – Housing conditions & Residential environment | 0 | 5 | | | | ID N°

Interviewer Reminder:
- To save time, do not read out all the options for questions E41 to E47.
- Allow the subject to respond and then check the appropriate box.

E41 What was the main material of the floor?.....

(01) Mud/Clay/Earth
(02) Sand
(03) Dung
(04) Raw wood planks
(05) Palm/Bamboo
(06) Brick
(07) Stone
(08) Parquet or polished wood
(09) Vinyl or Asphalt
(10) Ceramic Tiles
(11) Cement
(12) Carpet
(13) Polished stone/Marble/Granite
(14) Other, specify:_____
(99) Don`t know

E42 What was the main material of the roof?.....

(01) No roof
(02) Thatch/Palm leaf/Reed/Grass
(03) Sod/Mud and Grass Mixture
(04) Plastic/Polythene sheeting
(05) Palm/Bamboo
(06) Raw wood planks/Timber
(07) Loosely packed stone
(08) Metal/GI
(09) Wood
(10) Calamine/Cement Fiber
(11) Asbestos Sheets
(12) RCC/RBC/Cement/Concrete
(13) Slate
(14) Other, specify:_____
(99) Don`t know

E43 What was the main material of the exterior walls?.....

(01) No walls
(02) Cane/Palm/Trunks/Bamboo
(03) Mud
(04) Grass/Reeds/Thatch
(05) Bamboo with mud
(06) Stone with mud
(07) Plywood
(08) Cardboard
(09) Unburnt brick
(10) Raw wood/Reused wood
(11) Cement/Concrete
(12) Stone with lime/Cement
(13) Burnt bricks
(14) Cement blocks
(15) Wood planks/Shingles
(16) GI/Metal Asbestos sheets
(17) Other, specify:_____
(99) Don`t know

E44 What type of windows were there?.....

(01) No windows
(02) Windows with glass
(03) Windows with screen
(04) Windows with curtains or shutters
(05) Windows with no glass, screen or cover
(06) Other, specify:_____
(99) Don`t know

Section E – Housing conditions & Residential environment | 0 | 5 | | | | ID N°

Now, I will read a list of facilities you may have had in the place where you lived. We would like to know **which of these facilities were present inside your early adulthood (17-30 yrs) residence and some details about them.**

E45 What was the main source of drinking water for members of your household? ☐☐

(01) Piped water into dwelling
(02) Piped water to yard/ plot
(03) Piped water (public tap/standpipe)
(04) Tube well or borehole
(05) Dug well (protected)
(06) Dug well (unprotected)
(07) Water from protected spring
(08) Water from unprotected spring
(09) Rainwater
(10) Tanker truck
(11) Cart with small tank
(12) Surface water (river, dam, lake, pond, stream, canal
(13) Bottled water
(99) Don`t know

E46 How many toilet facilities did you have? ..... ☐☐

(99) Don`t know (00) None (GO TO E49)

E47 What kind of toilet facility did members of your household usually use? ..... ☐☐

(01) Flush to piped sewer system
(02) Flush to septic tank
(03) Flush to pit latrine
(04) Flush to somewhere else
(05) Ventilated improved pit/ biogas latrine
(06) Pit latrine with slab
(07) Pit latrine without slab/ open pit
(08) Twin pit/ composting toilet
(09) Dry toilet
(10) No facilities
(11) Other, specify _____
(99) Don`t know

E48 Did you share this toilet facility with other households?..... ☐☐

(01) No (99) Don't know
(01) Yes

E49 Did your home have electricity?..... ☐☐

(00) No (02) Yes, by a generator/ battery only
(01) Yes, by a central system (99) Don`t know

E50 What type of fuel did your household mainly use for cooking?..... ☐☐

(01) Electricity (GO TO E53) (05) Coal/lignite (09) Agricultural crop waste
(02) LPG/ Natural gas (GO TO E53) (06) Charcoal (10) Dung cakes
(03) Biogas (GO TO E53) (07) Wood (11) Other, specify:_____
(04) Kerosene (GO TO E53) (08) Straw/Shrubs/Grass (99) Don't know

E51 Did the stove have a chimney? ..... ☐☐

(00) No (01) Yes (99) Don't know

E52 Was the stove located in an area with any ventilation/windows?... ..... ☐☐

(00)No (01)Yes (99) Don't know

E53 Where was the cooking usually done?..... ☐☐

(01) Inside the house (02) Separate building (03) Outdoors
(99) Don`t know

25

Section E – Housing conditions & Residential environment 0 5 ☐☐☐
ID Nº

E54 Did your home have a separate room which was used as a kitchen?..... ☐☐
(00) No (01) Yes (99) Don't know

E55 Were you exposed to cigarette smoke in this house?..... ☐☐
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

I will now read a **list of household goods** you may have had in your early adulthood (17-30 yrs) residence or not. You may find that some of these appliances were not applicable to the epoch you were a child. Choose the answer that best represents your situation, regardless.

E56 Did your place have a watch or clock?..... ☐☐
(00) No (01) Yes (99) Don't know

E57 Did your place have a radio or transistor?..... ☐☐
(00) No (01) Yes (99) Don't know

E58 Did your place have a TV? ..... ☐☐
(00) No (02) Yes, color
(01) Yes, black and white (99) Don't know

E59 Did your place have a refrigerator?..... ☐☐
(00) No, it had no appliance to cool food (02) Yes
(01) No, it had an ice box (99) Don't know

Also, I would like to ask you...

E60 Did your household have a bicycle?..... ☐☐
(00) No (01) Yes (99) Don't know

E61 Did your household have a motorcycle or scooter?..... ☐☐
(00) No (01) Yes (99) Don't know (GO TO E62)

E62 How many?..... ☐☐

E63 Did your household have a car?..... ☐☐
(00) No (01) Yes (99) Don't know (GO TO E64)

E64 How many?..... ☐☐

Section E – Housing conditions & Residential environment 0 5 ☐☐☐
ID N°

LONGEST RESIDENCE IN LATER ADULTHOOD (30 yrs+)

Now lets talk about your **longest residence in later adulthood**, that is after age 30 (excl.).

Interviewer Reminder: Identify / confirm longest residence in later adulthood using life grid.

E65 Is this residence the same one as the residence you lived in for the longest time between the ages of 17 and 30 or your childhood residence?..... ☐☐

(00) No (01) Yes, same as longest residence between ages of 17-30 (Please still fill out the section entitled 'Longest Residence in Late Adult Life')
(02) Yes, same as childhood residence 30 (Please still fill out the section entitled 'Longest Residence in Late Adult Life')
(88) None of the above : ex: Subject is less than 30 yrs old (GO TO SECTION F)

E66 You lived at that place...?

From age? ☐☐ **To age?** ☐☐ **i.e. # Years** ☐☐

For all the following questions, refer to the situation that was present "MOST OF THE TIME" while living in that residence.

E67 What type of setting were you living in at that place?..... ☐☐
(01) With family (02) Other, specify: _____
(99) Don't know

E68 Was your home owned or rented?..... ☐☐
(01) Owned (99) Don't know
(02) Rented (03) Other, specify: _____... _____

E69 How many people lived in the household? (At once, for the longest period of time)… ☐☐
(Include borders, live-in maids, roommates...) (99) Don't know

Count the number of people at once, for the longest period of time. Include permanent residents including borders, live-in maids, roommates…

E70 How many rooms did your place have? (If renovated, count # rooms during longest period living there)……
(99) Don't know ☐☐

-Include: kitchen, living room, dining room, bedroom, furnished basement
-Do not include: toilet, bathrooms, laundry room, hallway, garage, patio
-If renovated, count # rooms during longest period living there

E71 How many rooms did your household use for sleeping?..... ☐☐
(99) Don't know

Section E – Housing conditions & Residential environment | 0 | 5 | | | | ID N°

Interviewer Reminder:
- To save time, do not read out all the options for questions E72 to E78.
- Allow the subject to respond and then check the appropriate box.

E72 What was the main material of the floor?.....
(01) Mud/Clay/Earth
(02) Sand
(03) Dung
(04) Raw wood planks
(05) Palm/Bamboo
(06) Brick
(07) Stone
(08) Parquet or polished wood
(09) Vinyl or Asphalt
(10) Ceramic Tiles
(11) Cement
(12) Carpet
(13) Polished stone/Marble/Granite
(14) Other, specify:_____
(99) Don`t know

E73 What was the main material of the roof?.....
(01) No roof
(02) Thatch/Palm leaf/Reed/Grass
(03) Sod/Mud and Grass Mixture
(04) Plastic/Polythene sheeting
(05) Palm/Bamboo
(06) Raw wood planks/Timber
(07) Loosely packed stone
(08) Metal/GI
(09) Wood
(10) Calamine/Cement Fiber
(11) Asbestos Sheets
(12) RCC/RBC/Cement/Concrete
(13) Slate
(14) Other, specify:_____
(99) Don`t know

E74 What was the main material of the exterior walls?.....
(01) No walls
(02) Cane/Palm/Trunks/Bamboo
(03) Mud
(04) Grass/Reeds/Thatch
(05) Bamboo with mud
(06) Stone with mud
(07) Plywood
(08) Cardboard
(09) Unburnt brick
(10) Raw wood/Reused wood
(11) Cement/Concrete
(12) Stone with lime/Cement
(13) Burnt bricks
(14) Cement blocks
(15) Wood planks/Shingles
(16) GI/Metal Asbestos sheets
(17) Other, specify:_____
(99) Don`t know

E75 What type of windows were there?.....
(01) No windows
(02) Windows with glass
(03) Windows with screen
(04) Windows with curtains or shutters
(05) Windows with no glass, screen or cover
(06) Other, specify:_____
(99) Don`t know

Section E – Housing conditions & Residential environment | 0 | 5 | | | | ID N°

Now, I will read a list of facilities you may have had in the place where you lived. We would like to know **which of these facilities were present inside your late adulthood (30+ yrs) residence and some details about them.**

E76 What was the main source of <u>drinking</u> water for members of your household? ☐☐

(01) Piped water into dwelling
(02) Piped water to yard/ plot
(03) Piped water (public tap/standpipe)
(04) Tube well or borehole
(05) Dug well (protected)
(06) Dug well (unprotected)
(07) Water from protected spring
(08) Water from unprotected spring
(09) Rainwater
(10) Tanker truck
(11) Cart with small tank
(12) Surface water (river, dam, lake, pond, stream, canal
(13) Bottled water
(99) Don`t know

E77 How many toilet facilities did you have? ..... ☐☐

(99) Don`t know (00) None (GO TO E80)

E78 What kind of toilet facility did members of your household usually use? ..... ☐☐

(01) Flush to piped sewer system
(02) Flush to septic tank
(03) Flush to pit latrine
(04) Flush to somewhere else
(05) Ventilated improved pit/ biogas latrine
(06) Pit latrine with slab
(07) Pit latrine without slab/ open pit
(08) Twin pit/ composting toilet
(09) Dry toilet
(10) No facilities
(11) Other, specify _____
(99) Don`t know

E79 Did you share this toilet facility with other households?..... ☐☐

(00) No (99) Don't know
(01) Yes

E80 Did your home have electricity?..... ☐☐

(00) No (02) Yes, by a generator/ battery only
(01) Yes, by a central system (99) Don`t know

E81 What type of fuel did your household mainly use for cooking?..... ☐☐

(01) Electricity (GO TO E84) (05) Coal/lignite (09) Agricultural crop waste
(02) LPG/ Natural gas (GO TO E84) (06) Charcoal (10) Dung cakes
(03) Biogas (GO TO E84) (07) Wood (11) Other, specify:_____
(04) Kerosene (GO TO E84) (08) Straw/Shrubs/Grass (99) Don't know

E82 Did the stove have a chimney? ..... ☐☐

(00) No (01) Yes (99) Don't know

E83 Was the stove located in an area with any ventilation/windows?... ..... ☐☐

(00)No (01)Yes (99) Don't know

Section E – Housing conditions & Residential environment 0 5 | ID Nº

E84 Did your home have a separate room which was used as a kitchen?.....
(00) No (01) Yes (99) Don't know

E85 Were you exposed to cigarette smoke in this house?.....
(00) No (01) Yes, very smoky
(02) Yes, moderately smoky
(03) Yes, a little smoky

I will now read a **list of household goods** you may have had in your late adulthood (30+ yrs) residence or not. You may find that some of these appliances were not applicable to the epoch you were a child. Choose the answer that best represents your situation, regardless.

E86 Did your place have a watch or clock?.....
(00) No (01) Yes (99) Don't know

E87 Did your place have a radio or transistor?.....
(00) No (01) Yes (99) Don't know

E88 Did your place have a TV? .....
(00) No (02) Yes, color
(01) Yes, black and white (99) Don't know

E89 Did your place have a telephone?.....
(00) No (01) Yes (99) Don't know

E90 Did your place have a refrigerator?.....
(00) No, it had no appliance to cool food (02) Yes
(01) No, it had an ice box (99) Don't know

Also, I would like to ask you...

E91 Did your household have a bicycle?.....
(00) No (01) Yes (99) Don't know

E92 Did your household have a motorcycle or scooter?.....
(00) No (01) Yes (99) Don't know (GO TO E94)

E93 How many?.....

E94 Did your household have a car?.....
(00) No (01) Yes (99) Don't know (GO TO SECTION F)

E95 How many?.....

Section F – Smoking and Chewing habits | 0 5 Country | ID N°

F. SMOKING AND CHEWING HABITS

Now I would like to ask you some questions about your smoking and/or chewing habits.

F1 Have you ever smoked in your life? (or chewed, any product, any amount)…….. ☐☐
(00) Never (GO TO F6) (01) Yes (I still do) (02) Yes, but only in the past

Think of the periods in your life during which you smoked cigarettes, cigars, pipe, chewed tobacco products and/or took drugs, the amount you smoked/chewed/took and other details about the products. Please try to summarise the most important changes in the amount and type of product.

Interviewer Reminder: Use **life grid** if necessary to help answer Q F2 to F8.
- Avoid overlapping years for the same product, type of cigarette or amount smoked, i.e. record 30-40, 41-45 rather than 30-40, 40-45.
- Only note changes occurring for **one year or more**.
- Exclude quitting during pregnancy(ies) if for less than one year.

F2 Do/did you smoke cigarettes?..... ☐☐
(00) No (GO TO F3) (01) Yes (02) Yes, only in the past

From age	To age (A)	Type (B)	Brand	Consumption (how many)	Per (C)
☐☐	☐☐	☐☐		☐☐	☐☐
☐☐	☐☐	☐☐		☐☐	☐☐
☐☐	☐☐	☐☐		☐☐	☐☐
☐☐	☐☐	☐☐		☐☐	☐☐
☐☐	☐☐	☐☐		☐☐	☐☐
☐☐	☐☐	☐☐		☐☐	☐☐

To Age (A)	**Type (B)**	**Per (C)**
If still smoking, write age at time of interview	(01) Filter (02) Non-filter (03) Hand rolled	(01) Day (02) Week (03) Month

Section F – Smoking and Chewing habits | 0 5 Country | ID N°

F3 Do/did you smoke bidis?..... (00) No (GO TO F8) (01) Yes (02) Yes, only in the past

From age	To age (A)	Consumption (how many)	Per (C)

To Age (A)	Per (C)
If still using, write age at time of interview	(01) Day (02) Week (03) Month

F4 Do/did you smoke or inhale drugs (marijuana, grass, dope, joints...) at least once a week for at least 6 months in your lifetime?..... (00) No (GO TO F6) (01) Yes (02) Yes, only in the past

From age	To age (A)	Type (B)	Unit	Consumption (how many)	Per (C)

To Age (A)	Type (B)	Unit (C)	Per (C)
If still smoking, write age at time of interview If less than one year, write same age From and To	(01) Marijuana (02) Grass (03) Crack (04) Hashish	(01) Grams (02) Joints	(01) Day (02) Week (03) Month

Section F – Smoking and Chewing habits | 0 5 Country | ID N°

F5 Do/did you use any other drugs (cocaine, heroin, lsd...) at least once a week for at least 6 months in your lifetime?.....

(00) No (GO TO Section G) (01) Yes (02) Yes, only in the past

From age	To age (A)	Type (B)	Unit	Consumption (how many)	Per (C)

To Age (A)	Type (B)	Unit (C)	Per (C)
If still using, write age at time of interview If less than one year, write same age From and To	(01) Cocaine (02) Acid / LSD (03) Heroin (04) Opium (05) Brown sugar powder (06) Churut (07) Ghutka	(01) Grams (02)Joints (03)Injections (04) Pills	(01) Day (02) Week (03) Month

Section F – Smoking and Chewing habits | 0 5 Country | ID N°

F6 Do/did you use chewing tobacco, betel quid (nut), areca nut and/or pan masaala?
(00) No (GO TO SECTION G) (01) Yes (02) Yes, only in the past

From age	To age (A)	Type (B)	Duration	Consumption (how many)	Per (C)

Interviewer Reminder: Betel Quid = areca nut + betel leaf + slaked lime

To Age (A)	Type (B)	Per (C)
If still smoking, write age at time of interview	(01) Tobacco (02) Betel quid (nut) with tobacco (03) Betel quid (nut) without tobacco (04) Areca nut with tobacco (05) Areca nut without tobacco (06) Pan masalla (07) Betel leaf (08) Other, specify_____	(01) Day (02) Week (03) Month y

F7 What is the reason that you began chewing tobacco, betel quid (nut), areca nut and/or pan masaala?.....
(01) Toothaches (02) Enjoyment
(03) Mouth freshener (88) Not applicable

Section G – Drinking habits

0 5	
Country	ID Nº

G. DRINKING HABITS

Now I would like to ask you some questions about your drinking habits.

G1 Did/do you drink alcoholic beverages at least once a month?..........................

(00) No (GO TO SECTION H) (01) Yes, I do (02) Yes, only in the past

We can use the grid to help us describe the periods in your life during which you consumed alcoholic beverages. Please try to summarise the most important changes in your life regarding the amount and type of beverage.

Interviewer Reminder: Use **life grid** if necessary to help answer Q G3.
- Avoid overlapping years for the same beverage i.e. record 30-40, 41-45 rather that 30-40, 40-45. Ask about each beverage separately.
- Note only changes occurring for **one year or more.**
- Exclude quitting during pregnancy(ies) if for less than one year.

G2 When do/did you usually drink alcoholic beverages?..

(01) With meals (03) Both

(02) Between meals (04) Only at social events

G3 Beverage (A)	If (A) = (05), Then specify other beverage	From age	To age	Unit (B)	Consumption (how many)	Per (C)

Beverage (A)
(01) Toddy
(02) Wine
(03) Beer
(04) Hard liquor (>35) (arak, whisky, cognac, vodka, brandy, grappa, marc, gin, rum)
(05) Other (specify): ___________________

Unit (B)
(01) Small glass (50ml) (1-2oz)
(02) Medium glass (100ml) (2-3oz)
(03) Big glass (250ml) (7oz) (1/2 pint)
(04) ½ small bottle (330ml) (1beer)
(05) Bottle (700-750 ml) (21oz)

Per (C)
(01) Day
(02) Week
(03) Month

35

Section H – Dietary habits | 0 5 Country | ID N°

H. DIETARY HABITS

Now, I have some questions about your dietary habits during your childhood (up to 16 years old).

H1 How many large meals did you normally eat per day in your childhood (up to 16 years old)?

(01) 1 (03) 3
(02) 2 (04) 4 or more (99) I don't know

H2 During your childhood (up to 16 years old), how often did you eat the following foods?

		Never	Occasionally	Weekly	Daily
H2a	**Bananas**				
H2b	**Citrus fruits** (e.g., oranges, grapefruits)				
H2c	**Apples/ Pears**				
H2d	**Other fruits** (e.g., mango, jackfruit, papaya, pineapple)				
H2e	**Raw vegetables**				
H2f	**Cooked vegetables** (e.g., in a curry)				
H2g	**Sweet potato**				
H2h	**Tapioca**				
H2i	**Red meat** (e.g., beef, mutton)				
H2j	**White meat** (e.g., chicken, turkey)				
H2k	**Fish**				
H2l	**Dairy products** (e.g., milk, yogurt, curd, cheese)				
H2m	**Nuts** (e.g., cashews)				
H2n	**Dals**				
H2o	**Rice**				
H2p	**Appam**				
H2q	**Flat breads** (e.g., chapati , porotta)				
H2r	**Dosa & Idly**				
H2s	**Gruel & cereal**				
H2t	**Palm products** (e.g. palm rice)				
H2u	**Fried foods** (e.g., chips, fried fish, fried chicken)				
H2v	**Desserts** (e.g., chocolate)				
H2w	**Sugary drinks** (e.g. soda, juice)				

Section H – Dietary habits

0	5			
Country		ID N°		

As your dietary habits may have recently changed somewhat according to your health status, **please tell me about your usual habits approximately 2 years prior to your diagnosis of the disease / being seen at this clinic**.

H3 How many large meals did you normally eat per day in your adult life? ☐☐

(01) 1 (03) 3
(02) 2 (04) 4 or more (99) I don't know

H4 During your adulthood (approx. 2 years prior to your diagnosis), please tell me how often you ate the following foods per week.

		Never	<Once per week	# times per week
H4a	**Bananas**			
H4b	**Citrus fruit** (e.g., oranges, lemons, grapefruit)			
H4c	**Apples/pears**			
H4d	**Other fruits** (e.g., mango, jackfruit, papaya, pineapple)			
For the following vegetables, please specify the amount eaten raw and/or cooked				
H4e	**Cruciferous vegetables** (e.g., cabbage, cauliflower)			
H4f	**Yellow-orange vegetables** (e.g., tomatoes, carrots, pumpkin)			
H4g	**Spinach**			
H4h	**Other vegetables** (e.g., cucumber, onions)			
H4i	**Sweet potato**			
H4j	**Tapioca**			
H4k	**Red meat** (e.g., beef, mutton)			
H4l	**White meat** (e.g., chicken, turkey)			
H4m	**Fish**			
H4n	**Milk**			
H4o	**Other Dairy products** (e.g., yogurt, curd, cheese)			
H4p	**Nuts** (e.g., cashews)			
H4q	**Dals**			
H4r	**Rice**			
H4s	**Appam**			
H4t	**Flat breads** (e.g., chapati , porotta)			
H4u	**Dosa & Idly**			
H4v	**Gruel & Cereal**			
H4w	**Palm products** (e.g., palm rice)			
H4x	**Fried foods** (e.g., banana chips, chips, fried fish, fried chicken)			
H4y	**Desserts** (e.g., chocolate)			
H4z	**Sugary drinks** (e.g. soda, juice)			

Section H – Dietary habits | 0 5 Country | ID N°

Please answer the following questions based on your usual habits approximately 2 years prior to your diagnosis of the disease / being seen at this clinic.

H5 Did you eat foods which are?
(01) Not spicy at all
(02) A little spicy
(03) Moderately spicy
(04) Very spicy
(99) I don't know

H6 Did you eat foods which have ?
(01) No chile
(02) A little chile
(03) Moderate amount of chile
(04) A lot of chile
(99) I don't know

H7 Please tell me how often did you eat the following spices?

		Never	<once per week	# per week
H7a	**Chile**			
H7b	**Red chile**			
H7c	**Coriander**			
H7d	**Garam Masala**			
H7e	**Pepper**			
H7f	**Turmeric**			
H7g	**Ginger**			

H8 Did you reuse your oil?.....
(00) No (01) Yes

H9 If yes, how many times?.....
(00) Once (01) Twice (03) More than 2 times

H10 How many cups of coffee did you drink per day?.....
(00) I didn't drink coffee (98) Less than one a day

H11 How many cups of tea did you drink per day?.....
(00) I didn't drink tea (98) Less than one a day

H12 How did you usually drink your tea/coffee?.....
(00) I didn't drink tea/coffee (01) Hot (02) Warm (03) Cold

Section H – Dietary habits | 0 5 Country | ID N°

BODY IMAGE

CHILDHOOD

Think about your appearance when you were a CHILD (5-6 years old, when you had just started school) and compare it to other children your age.

APPEARANCE:

H13 When you were a child (5-6 years old); were you?.....
(01) much slimmer than other children your age
(02) slimmer
(03) similar
(04) heavier
(05) much heavier than other children your age
(99) I don't know

HEIGHT

H14 When you were a child (5-6 years old); were you?.....
(01) much shorter than other children your age
(02) shorter
(03) similar
(04) taller
(05) much taller than other children your age
(99) I don't know

H15 Which of the following silhouettes (1 to 9) resembles your appearance when you were 5-6 years of age?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

ADOLESCENCE

Think about your appearance when you were an ADOLESCENT (12-15 years old) and compare it to other adolescents your age.

APPEARANCE:

H16 When you were an adolescent (12-15 years old); were you?.....
(01) much slimmer than other adolescents your age
(02) slimmer
(03) similar
(04) heavier
(05) much heavier than other adolescents your age
(99) I don't know

Section H – Dietary habits | 0 5 Country | ID N°

HEIGHT

H17 When you were an adolescent (12-15 years old); were you?.....
(01) much shorter than other adolescents your age
(02) shorter
(03) similar
(04) taller
(05) much taller than other adolescents your age
(99) I don't know

H18 Which of the following silhouettes (1 to 9) resembles your appearance when you were 12-15 years of age?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

EARLY ADULTHOOD

Think about your appearance when you were an EARLY ADULT (17-30 years old).

H19 Which of the following silhouettes (1 to 9) resembles your appearance when you were 17-30 years of age?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

LATE ADULTHOOD

Think about your appearance when you were an LATER ADULT (30+ years old).

H20 Which of the following silhouettes (1 to 9) resembles your appearance when you were 30+ years of age?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

2 YEARS AGO

Think about your appearance 2 YEARS AGO.

H21 Which of the following silhouettes (1 to 9) resembles your appearance 2 years ago?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

PRESENT

Think about your appearance PRESENTLY.

H22 Which of the following silhouettes (1 to 9) resembles your appearance presently?.....
(01) (02) (03) (04) (05) (06) (07) (08) (09) (99) Don't know

Section H – Dietary habits | 0 5 Country | ID N°

INTERVIEWER REMINDER: Weight measurement
Weigh the participant using the HeNCe Life study scale provided. Measurement should be done in **kgs**, but if it is done in **lbs**, convert the measurement to **kgs** as specified below.

H23 Weight measurement?
(_____ lbs) ÷ 2.2042 = _____**kgs**

INTERVIEWER REMINDER: Height measurement
Measure the participant using the measuring tape provided in the HeNCe Life study package. The participant must be positioned with their
- -feet together and flat on the ground
- -heels touching the wall
- -legs straight
- -buttocks against the wall
- -arms loosely at their side
- -ensure that their feet and heels do not raise up off the ground

Measurement should be done in **cms**, but if it is done in **inches**, convert the measurement to **cms** as specified below. You may find it easier to ask someone to help you take the measurement.

H24 Height measurement? .....
(___feet ___ inches) = _____inches x 2.54 = _____**cm**

INTERVIEWER REMINDER: Finger measurements
Please ask the participant to lay their **right hand** on the table palm-up, with the fingers fully extended. Measure the lengths of both the index finger (2nd finger) and the ring finger (4th finger). ***Note: the thumb is considered the 1st finger.*** The measurement should be taken from the tip of the finger to the lowest (most proximal) crease using the ruler provided in the HeNCe Life package. The index finger usually has only one proximal crease, whereas the ring finger sometimes has two.

H25 Finger measurements (right hand)? .....
Index (2nd finger):_____ cm (1 decimal)
Ring finger (4th finger): _____ cm (1 decimal)

H26 Wrist measurement? .....
Around the small of the right wrist:_____ inches (1 decimal)

Section H – Dietary habits | 0 5 Country | ID N°

H27 What sized body frame does the subject have?

Please refer to the Interviewer's Guide for coding

(01) small body frame
(02) medium body frame
(03) large body frame
(04) man under 165 cm height

H28 When you're AT WORK (include work as a housewife), which of the following best describes your level of activity?

(01) Very active (e.g., farmer, labourer, athlete)
(02) Moderately active
(03) Sedentary (e.g., desk job)
(04) I don't work
(99) I don't know

H29 When you're AT HOME, which of the following best describes your level of activity?

(01) Very active
(02) Moderately active
(03) Sedentary
(99) I don't know

H30 DURING LEISURE TIME, which of the following best describes your level of activity?

(01) Very active
(02) Moderately active
(03) Sedentary
(99) I don't know

Section I – Oral health | 0 5 Country | ID N°

I. ORAL HEALTH

I am going to ask you some questions about your oral health **before your diagnosis / being seen at this clinic** and at different time in your lifetime.

I1 Did you wear complete dentures? .....
(00) No (GO TO I4) (02) Yes, top only
(01) Yes, bottom only (GO TO I3) (03) Yes, top AND bottom

I2 At what age did you start wearing complete top dentures? (Years).....

I3 At what age did you start wearing complete bottom dentures? (Years).....
Code (888) if QI1 = (02)

I4 Did you wear partial dentures?.....
(00) No (02) Yes, bottom only
(01) Yes, top only (03) Yes , top AND bottom

I5 How often did you clean your teeth?.....
(00) Never (03) Every other day
(01) Less than once a week (04) Once a day
(02) 1-2 time a week (05) Twice or more a day

I6 Did you use toothpicks / sticks?.....
(00) No (02) Yes, once a week
(01) Yes, daily (03) Rarely

I7 Did you use any kind of substance to clean your teeth?.....
(00) No (02) Charcoal
(01) Toothpaste (03) Other (specify)_____.....

I8 Did your gums bleed when you cleaned your teeth?.....
(00) No (01) Sometimes (02) Always or almost always

Now, let's look at your oral health habits and oral health at different periods of your life.

I9 In the <u>last 20 years</u>, how often did you see a dentist?.....
(00) Never (03) Every 2 –5 years
(01) Every 6 months (04) Once every 5 years
(02) Every year (05) Only when I had pain

I10 Have you ever had an ulcer or a cut in your cheek because of a tooth or dentures?
(00) No (01) Yes

Section J – Family history of cancer | 0 5 Country | ID N°

J. FAMILY HISTORY OF CANCER

Interviewer Reminder:
- Family includes these **biological** relatives: father, mother, brother, sister, son, daughter, aunt, uncle, grand-mother, grand-father.
- Input one person per line in chart below.

J1 Has any member of your biological family ever had cancer? .....
(00) No (GO TO SECTION K) (01) Yes (99) Don't know

J2 Relationship (A)	Status (B)	Current/Last Age (C)	Type of cancer	Age at Diagnosis (D)

Relationship (A)	Status (B)	Current / Last Age (C)	Age at diagnosis (D)
(01) Mother (02) Father (03) Sister (04) Brother (05) Daughter (06) Son (07) Grand-mother (08) Grand-father (09) Aunt/uncle	(00) Deceased (01) Alive	(999) Don't know If alive, give present age If deceased, give age at death	(999) Don't know

Section K – Family environment | 0 5 Country | ID N°

K. FAMILY ENVIRONMENT IN CHILDHOOD

I would like to ask you a few questions about your parents (mother and father), or the women or men who cared for you **during your childhood, that is from your birth until you were 16 years (incl.)**. If you were cared for by only one person, please respond only to the questions related to that person. We may refer to the life grid to help us out at times.

This first set of questions is related to their level of education and their occupation.

K1 At your birth, how old was your father?.....
(99) Don't know

K2 How many years of education did your father/the man who cared for you most of your childhood have?.....
(99) Don't know

K3 What was his longest occupation during your childhood?(LC).....
Describe: _____
(999) Don't know

K4 At your birth, how old was your mother?.....
(99) Don't know

K5 How many years of education did your mother/the woman who cared for you most of the time during your childhood have?.....
(99) Don't know

K6 What was her longest occupation during your childhood? (LC).....
Describe: _____
(999) Don't know

Interviewer Reminder: Confirm occupation codes in K3 and K6 with list of codes.

Now I have a few questions on family environment during your childhood.

K7 In total, how many brothers and sisters do you have? (natural only).....

K8 What was your birth order in your family?.....
(00) Only child (02) Second child (04) Fourth child or more
(01) First child (03) Third child

K9 Did your family have continuous financial difficulties during your childhood?
(00) No (01) Yes (99) Don't know

Section K – Family environment | 0 5 Country | ID N°

K10 Did your parents argue or fight during your childhood?.....
(00) Never (02) Often
(01) Sometimes (99) Don't know

K11 How often did your father use to drink alcohol during your childhood?.....
(00) Never (02) Once a week / weekends (04) Everyday
(01) Occasionally (03) 3-4 times a week (99) Don't know

K12 How often did your mother use to drink alcohol during your childhood?.....
(00) Never (02) Once a week / weekends (04) Everyday
(01) Occasionally (03) 3-4 times a week (99) Don't know

K13 Did your father smoke? (any product).....
(00) No (01) Yes (99) Don't know

K14 Did your mother smoke? (any product) .....
(00) No (01) Yes (99) Don't know

K15 Did your father chew tobacco, betel quid (nut), areca nut, pan masaala or betel leaf?.....
(00) No (01) Yes (99) Don't know

K16 Did your mother chew tobacco, betel quid (nut), areca nut, pan masaala or betel leaf?.....
(00) No (01) Yes (99) Don't know

K17 Were your parents divorced?.....
(00) No (01) Yes (99) Don't know

Now I would like to ask you a few questions about your mother / father figure during your childhood.

K18 Who was the woman who cared for you most of your life during your childhood?.
(00) None (GO TO K25) (03) Adoptive mother
(01) Mother (04) Grand-mother
(02) Step mother (05) Other, specify_____.....

Section K – Family environment | 0 | 5 | Country | | | ID N°

Here are some questions about how you remember your **MOTHER** (or the woman who cared for you) during the years you were growing up, that is, until you were age 16 – incl. (Use Answer Sheet)

(01) A great deal (02) Quite a lot (03) Little (04) Not at all

K19 How much did she understand your problems and worries?.....

K20 How much could you confide in her about things that were bothering you?....

K21 How much love and affection did she give you?.....

K22 How much time and attention did she give you when you needed it?.....

K23 How strict was she with the rules for you?.....

K24 How harsh was she when she punished you?.....

K25 How much did she expect you to do your best in everything you did?.....

Now I would like to ask you how you remember your **FATHER** (or the man who cared for you) during the years you were growing up that is, until you were 16 years old. (Use Answer Sheet)

K26 Who was the man who cared for you most of your life during your childhood?.....

(00) None (GO TO K33) (03) Adoptive father
(01) Father (04) Grand-father
(02) Step father (05) Other, specify: _____.....

(01) A great deal (02) Quite a lot (03) Little (04) Not at all

K27 How much did he understand your problems and worries?.....

K28 How much could you confide in him about things that were bothering you?...

K29 How much love and affection did he give you?.....

K30 How much time and attention did he give you when you needed it?.....

K31 How strict was he with the rules for you?.....

K32 How harsh was he when he punished you?.....

K33 How much did he expect you to do your best in everything you did?.....

Section K – Family environment | **0 5** Country | ID N°

K34 Can you remember any life event(s) in your childhood that have either positively or negatively impacted upon you?.....
(00) No (GO TO SECTION L) (01) Yes

K35 Can you tell me what? (Describe)**(LC)**.....
1 _____
2 _____
3 _____
4 _____
5 _____

K36 Could you please tell me how much impact this (se) event (s) had on your life?
(Use Answer Sheet).....

-4 -3 -2 -1 0 1 2 3 4
Very negative no impact Very positive

Event 1 .....score: _____.....
Event 2 .....score: _____.....
Event 3 .....score: _____.....
Event 4 .....score: _____.....
Event 5 .....score: _____.....

Section K – Family environment | 0 5 Country | ID N°

K37 For each of the following diseases, please tell me if you ever had it and, if so, how often?

Presence (A)	Frequency (B)
(00) No	(01) Once
(01) Yes	(02) Sometimes
(99) Don't know	(03) Often

	Presence (A)	Frequency (B)
Measles		
Mumps		
Chicken pox		
Whooping cough		
Infectious hepatitis		
Jaundice		
Tuberculosis		
Asthma attack		
Disease of the ear(s)		
Disease of the nose		
Disease of the throat		
Depression treated with medication		
Repeated or prolonged infections (>6 weeks)		
Diabetes		

Specify other diseases: (ex. Diabetes, thyroid disease, chronic heartburn, bulimia):

_____ _____

K38 What type of medicine do you use for management of common diseases?

(00) None
(01) Allopathy
(05) Homeopathy
(03) Ayurvedic
(04) Other, specify: _____.....

Section L – Marriage, intimacy and life as a couple | 0 5 Country | ID N°

L. MARRIAGE, INTIMACY & LIFE AS A COUPLE

Now, I would like to ask you some questions about marriage and living as a couple.

L1 What is your marital status?.....

(01) Single (GO TO L8)
(02) Living with a husband/wife (married)
(03) Married, gauna not performed
(04) Married to more than one wife
(05) Living with partner common-law
(06) Widowed
(07) Divorced
(08) Separated
(09) Deserted

INTERVIEWER REMINDER: Use **life grid** if necessary to help answer Q L2 to L26.

L2 How many times have you been married or lived in common law?.....

(01) Once (Fill in first column only) (02) More than once

At the time you FIRST/LAST got married or FIRST/LAST lived in common law...

	FIRST	LAST
L3 How old were you?.....		
L4 How many years did your partner go to school for? (until today)		
L5 What was your partner's longest occupation? (until today) **(LC)**		

FIRST: _____

LAST: _____

L6 How did the relationship end?.....

(00) Still ongoing! (GO TO L8) (02) Separation
(01) Divorce (03) Partner deceased

L7 How old were you when the relationship ended?.....

L8 In your whole life, how many (biological) children have you had?.....

(00) None (GO TO L13) *(Do NOT include miscarriage or stillborn)*

L9 With how many <u>different</u> partners?.....

(00) All with the same one

L10 Do you have any sons or daughters that you have fathered/mothered that are now living with you?.....

(00) No (01) Yes

L11 How old is your oldest child?.....

(99) Don`t know

Section L – Marriage, intimacy and life as a couple | 0 5 Country | ID N°

L12 How old is your youngest child?.....
(99) Don't know

I will ask you some questions regarding your sexuality. The reason I am asking these questions is because medical science has found some links between viruses that are sexually transmitted and some types of cancers. You have no obligation to answer these questions if you do not feel comfortable doing so.

L13 Have you ever had sexual intercourse?.....
(00) No (GO TO L14) (01) Yes
(99) Prefer not to say / Don't know

L14 How old were you when you had sexual intercourse for the first time?
(99) Prefer not to say / Don't know

Answer's options L15 and L16		
(00) None	(03) 06-10	(06) 51-100
(01) One	(04) 11-20	(07) More than 100
(02) 2-5	(05) 21-50	(99) Prefer not to say / Don't know

L15 How many sexual partners have you had in total in your life? (regular and casual)...
Up to 16 yrs old .....
Between 17-30 yrs old .....
After 30 yrs old .....

L16 How many of these people did you pay in exchange for sex?
Up to 16 yrs old .....
Between 17-30 yrs old .....
More than 30 yrs old .....

L17 Have you ever had oral sex? (your mouth and a woman/man genitals).....
(00) No (GO TO (GO TO L17) (99) Prefer not to say / Don't know (GO TO L17)
(01) Yes

L18 How old were you when you had oral sex for the first time?.....
(99) Prefer not to say / Don't know

Answer's options Q16	
(00) Occasionally	(02) Most of the time
(01) Frequently	(99) Prefer not to say / Don't know

L19 How often? .....
Up to 16 yrs old .....
Between 17-30 yrs old .....
After 30 years old .....

51

Section L – Marriage, intimacy and life as a couple | 0 5 Country | ID N°

L20 Have you ever had non-consenting sex?..... ☐☐
(00) No (GO TO (GO TO L19) (99) Prefer not to say / Don't know (GO TO L19)
(01) Yes

L21 How old were you or from what age to what age? *(mark same age if one episode or if during less than one year)* (99) Prefer not to say / Don't know

From age?	**To age?**	**i.e. # Years**
☐☐	☐☐	☐☐

L22 Have you ever had skin warts?..... ☐☐
(00) No (GO TO (GO TO L22) (99) Prefer not to say / Don't know (GO TO L22)
(01) Yes

L23 If yes, where? (01) Yes (00) No (99) Prefer not to say / Don't know

Hands……	☐☐
Feet……	☐☐
Head and Neck……	☐☐
Other, specify_____……	☐☐

L24 At which age, were you? (99) Prefer not to say / Don't know

Hands……	☐☐
Feet……	☐☐
Head and Neck……	☐☐
Other, specify_____……	☐☐

L25 Since you started you sexual life have you ever had Candida Albicans (yeast infection)? ☐☐
(00) No (GO TO (GO TO L24) (99) Prefer not to say / Don't know (GO TO L24)
(01) Yes

L26 If yes, where? (01) Yes (00) No (99) Prefer not to say / Don't know

Genital……	☐☐
Mouth……	☐☐
Other, specify_____……	☐☐

L27 Have you ever had a sexually transmitted disease?..... ☐☐
(00) No (GO TO SECTION M) (99) Prefer not to say / Don't know (GO TO SECTION M)
(01) Yes

L28 If yes, which ones? (01) Yes; (00) No; (99) Prefer not to say / Don't know

Gonorrhea ……	☐☐
Syphillis ……..	☐☐
Herpes ……	☐☐
Chlamydia ……	☐☐
AIDS ……..	☐☐

52

Section L – Marriage, intimacy and life as a couple

0	5			
Country		ID N°		

L29 At which age, were you? (99) Prefer not to say / Don't know

Gonorrhea ……	
Syphillis ……	
Herpes ……	
Chlamydia ……	
AIDS ……	

Section M – Social support | 0 5 Country | ID N°

M. SOCIAL SUPPORT

Finally I would like to ask you some questions about your friends, relatives and the people you live with.

M1 Is there <u>someone in particular</u> in your life that you think would listen to you and give you emotional support if you needed it?.....
(01) Yes (00) No

M2 In your life in general, do you think you have enough opportunities to talk openly and share your feelings about things?.....
(00) No (01) Yes

M3 In general, do you prefer to keep your feelings to yourself?.....
(00) No (01) Yes

M4 Can you remember any life event(s) in your adulthood that have either positively or negatively impacted upon you?.....
(00) No (01) Yes

M5 Can you tell me what? (Describe)**(LC)**.....
1_____
2_____
3_____
4_____
5_____

M6 Could you please tell me how much impact did this (se) event (s) have in your life?
(Use Answer Sheet)……..

-4 -3 -2 -1 0 1 2 3 4
Very negative no impact Very positive

Event 1 ……..score: _____……..
Event 2 ……..score: _____……..
Event 3 ……..score: _____……..
Event 4 ……..score: _____……..
Event 5 ……..score: _____……..

M7 10% of participants of this study will be re-interviewed. Do you agree to be re-contacted for you to participate a second time?

M8 Incomplete questionnaire?……..
Reason:_____

_____ _____

Section M – Social support | 0 5 Country | ID N°

M9 Time of end of interview..... Hour - Minute

M10 Data enterer's initials? .....

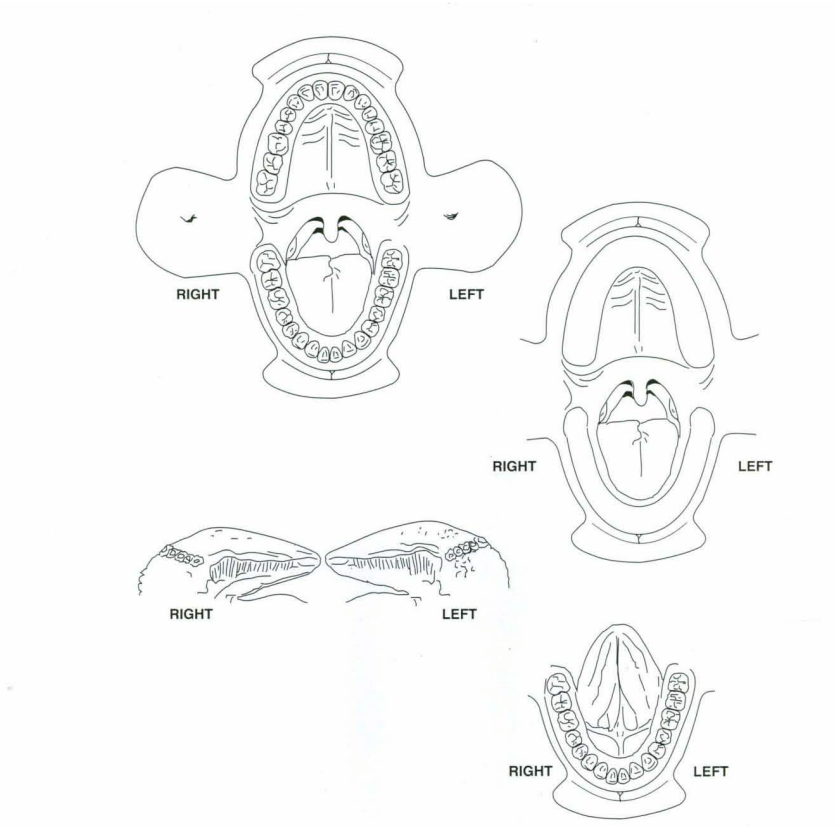
Participant's comments:

Section N – Oral Assessment Form & Biological Sampling | 0 5 Country | ID N°

N. ORAL ASSESSMENT FORM & BIOLOGICAL SAMPLING

N1. VISIBLE LESIONS AND IRRITATIONS

Circle the place in the mouth where you see the lesion.



Section N – Oral Assessment Form & Biological Sampling | 0 5 Country | ID N°

N2 Where is the lesion located?
(01) Oro-pharynx
(02) Tongue (e.g., lateral, posterior, beneath)
(03) Palate
(04) Cheek
(05) Alveol (e.g., buccal, lingual, palatine)
(06) Floor of mouth
(88) NA/ Control

N3 What type of lesion is this?
Please refer to the Interviewer's Guide for thorough definitions
(01) White lesion
(02) Red lesion
(03) Ulcerated lesion
(04) Blistering/ sloughing lesion
(05) Pigmented lesion
(06) Papillary lesion
(07) Soft tissue enlargement
(88) NA/ Control

N4 DECAYING TEETH ASSESSMENT

18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
48	**47**	**46**	**45**	**44**	**43**	**42**	**41**	**31**	**32**	**34**	**34**	**35**	**36**	**37**	**38**

Place the following codes to correspond with each tooth above.

Code 0: Sound Tooth
All surfaces that are present and have no caries experience. A surface is recorded as "sound" if it shows no evidence of treated or untreated dental caries in dentine.

Code 1: Cavities/ Decay
All surfaces that present cavities or decay.

Code 2: Filling
All surfaces that have received any kind of filling.

Code 3: Missing
All the teeth that are missing on the arcade

Section N – Oral Assessment Form & Biological Sampling | 0 5 Country | ID N°

N5 PERIODONTAL STATUS

Please provide a description of the subject's general periodontal status (e.g., gingival colour, alteration of colour in the gingival, loss of attachment, etc.)

Note: this should be done visually without any instrumentation

BIOLOGICAL SAMPLING

N6 Was a mouthwash sample taken?
(01) Yes (00) No

N7 Was a sample for HPV analysis taken?
(this sample is taken from the lesion site for cases, and from healthy buccal cells for controls)
(01) Yes (00) No

N8 Was a sample for genetic analysis taken?
(this sample is taken from healthy buccal cells from both the cases and controls)
(01) Yes (00) No

N9 Were all 3 above samples stored in the HeNCe refrigerator?
(01) Yes (00) No

N10 Please document below if there was any comments from the biological sampling (e.g., occurrence of untoward/adverse events such as patient discomfort, bleeding).

11. Appendix II

Life grid

LIFE GRID

Other	Housing	Yr	Age	Education/Jobs	Habits
			5		
			10		
			15		
			20		
			25		
			30		
			35		
			40		
			45		
			50		
			55		
			60		
			65		
			70		
			75		

12. Appendix III

Consent forms

(English and Malayalam[2])

[2] Malayalam is the local language spoken in the state of Kerala, India.

A LIFE COURSE APPROACH TO THE AETIOLOGY OF HEAD AND NECK CANCER: HeNCe LIFE STUDY

Dr Ipe Varghese

Government Dental College

Purpose of the study

Previous studies have shown that certain adult chronic diseases such as cancer and heart disease may be influenced by social and psychological circumstances during birth, childhood, adolescence and early adult life. It is suggested that the build-up of problematic circumstances throughout life is the cause of disease rather than circumstances that happen at one point in time. Based on this idea, we are conducting a study to clarify if certain conditions and habits that people experience at different periods of their life are related to cancer of the mouth and/or throat. We want to know, for example, if people who experienced physical and/or chemical hazards at work will be more likely to have cancer in their mouth and/or throat; if people who had fewer educational opportunities were more likely to start behaviours such as smoking and alcohol drinking, and how these behaviours in turn, would affect their chances of having cancer in the mouth and throat.

Description of the research

The study will compare people who have mouth and/or throat cancer (Group 1) to people who do not have this disease (Group 2). It will take place in the Government Dental College in Calicut-India. A total of 800 people, 400 with cancer of the mouth or throat and 400 without will be invited to participate in this project. The research will be conducted in two parts and it will follow the same steps for both groups.

1. In the first part we are going to collect information from the medical records. For people in group 1, for example, we want to know medical details about the cancer. For people in group 2, we need to collect information on the reason for being in seen at the hospital, at which clinic they are consulting, etc.
2. The second part of the study will be an interview. In this second phase, we are going to use a questionnaire to ask people more detailed information about different aspects of their life such as work, housing conditions and family life. This part of the interview will take about 2 hours.

If I participate in this study, what will be involved?

Participating in this study means that you will allow us to look at your hospital medical records and that you will attend an appointment to carry out a two hour interview.

Potential harms, injuries, discomforts or inconveniences

There is no risk associated with participating in this study. It involves no treatment or procedures that can cause harm, injuries or discomfort. It involves only collection of data by means of an interview and medical files.

Potential benefits

Participants will not benefit directly from their participation in this study. However, the results from this study may contribute to the understanding of the development of head and neck cancers.

Participation

Participation in this research project is entirely voluntary.

Will participation in this study affect my treatment?

Participating will in no way affect your treatment or your medical follow-up.

What happens if I want to withdraw from this study?

You are perfectly free to withdraw from this research project at any time you want to – even in the middle of the interview. Such withdrawal will in no way affect your medical follow-up or treatment.

Confidentiality

We assure that all information gathered during the course of this research project will be kept completely confidential. Only the researchers involved in this project and the research assistants gathering the data will have access to the information you provide, which will be kept locked in the research office. All the data will be identified through a code number so we will not know to whom the data are related. The results of the research will be published in scientific journals in an anonymous form. All the data will be kept for a period of 5 years after which they will be destroyed.

Further information

If you would like any more information or have any questions related to this study, please do not hesitate to contact the project leader, Shameena ***phone number***.

Consent

I have read the information above, asked questions and received answers concerning areas that were unclear and I willingly agree to participate in this study. My participation is completely voluntary. I may withdraw at any time without it affecting my medical

follow-up or treatment. I will not have waived any of my legal rights by signing this consent form. Upon signing this form, I will receive a copy of the entire consent.

_____
Participants Name

_____Date _____
Participants Signature

_____
Witness/. Name

_____Date_____
Witness/ signature

_____
Name of the person who explained the consent form.

_____ _____
Signature of the person who explained the consent form Date

തലയെയും കഴുത്തിനെയും ബാധിക്കുന്ന അർബുദത്തിന്റെ കാരണങ്ങളെക്കുറിച്ചുള്ള സമഗ്രപഠനം

ഡോ ഐപ്പ് വർഗീസ്
ഗവ. ഡെന്റൽ കോളേജ്

പഠനലക്ഷ്യം

മുൻകാലപഠനങ്ങൾ കാണിക്കുന്നത് ഒരു വ്യക്തിയുടെ ജനനം കുട്ടിക്കാലം, യൗവനം തുടങ്ങിയ കാലഘട്ടങ്ങളിലെ മാനസിക സാമൂഹിക സാഹചര്യങ്ങൾ അർബുദം, ഹൃദയസംബന്ധമായ അസുഖങ്ങൾ എന്നിവയെ സ്വാധീനിക്കുന്നു എന്നാണ്. ജീവിതകാലം മുഴുവൻ നീണ്ടുനിൽക്കുന്ന പ്രശ്നകരമായ സാഹചര്യങ്ങളാണ് പെട്ടെന്ന് ഒരു ദിവസം ഉണ്ടാകുന്ന കാരണങ്ങളേക്കാൾ അസുഖത്തിന് കാരണമാകുന്നത്. ആയതിനാൽ ജനങ്ങൾ ജീവിതത്തിന്റെ ഓരോ ഘട്ടങ്ങളിൽ തുടങ്ങിവെക്കുന്ന ശീലങ്ങൾ വായിലേയും തൊണ്ടയിലേയും അർബുദവുമായി എങ്ങിനെ ബന്ധപ്പെട്ടിരിക്കുന്നു എന്നറിയുവാനാണ് ഈ പഠനം നടത്തുന്നത്. ഉദാഹരണത്തിന് രാസവസ്തുക്കൾ മൂലമോ മോശം ഭൗതികസാഹചര്യം മൂലമോ ആപത്കരമായി ജോലി ചെയ്യേണ്ടി വരുന്ന ആളുകൾക്കാണ് വായിലും തൊണ്ടയിലും അർബുദം വരാനുള്ള സാധ്യത. അല്ലെങ്കിൽ വിദ്യാഭ്യാസപരമായി പിന്നോക്കം നിൽക്കുന്നവരിൽ പുകവലി, മദ്യപാനം മുതലായ ദുഃശീലങ്ങൾ വർദ്ധിക്കുന്നതും അത് വായിലെ അർബുദവുമായി എങ്ങനെ ബന്ധപ്പെട്ടിരിക്കുന്നു എന്നതിനെ സംബന്ധിച്ച്.

ഗവേഷണത്തെക്കുറിച്ചുള്ള വിവരണം

ഈ ഗവേഷണത്തിൽ ആളുകളെ രണ്ടുവിഭാഗമായി തിരിച്ചിരിക്കുന്നു. (ഒന്നാം സംഘം) വായിലും തൊണ്ടയിലും അർബുദം ഉള്ളവർ. (രണ്ടാം സംഘം) അസുഖം ഇല്ലാത്തവർ. ഈ ഗവേഷണം കോഴിക്കോട് ഗവൺമെന്റ് ഡെന്റൽ കോളേജിൽ വച്ച് നടക്കുന്നു. ആകെ 800 ആളുകൾ. അവർ 400 പേർ അസുഖമുള്ളവർ, ബാക്കി നാനൂറ് പേർ അസുഖം ഇല്ലാത്തവർ. ഗവേഷണം രണ്ടുഘട്ടങ്ങളായാണ് നടക്കുക. രണ്ടു വിഭാഗക്കാരിലും ഒരേ പഠന നടപടികളാണ് കൈകൊള്ളുക.

1. ആദ്യഘട്ടത്തിൽ വിവരങ്ങൾ ആശുപത്രിരേഖകളിൽ നിന്നും ശേഖരിക്കുന്നു. ഉദാഹരണത്തിന് ഒന്നാം വിഭാഗക്കാരായ ആളുകളുടെ അസുഖസംബന്ധിയായ വിശദാംശംങ്ങൾ അന്വേഷിക്കും, രണ്ടാംവിഭാഗക്കാരായവർ ആശുപത്രികളിൽ പോകുവാനുണ്ടായ സാഹചര്യങ്ങളെക്കുറിച്ച് തിരക്കും.

2. പഠനത്തിന്റെ രണ്ടാംഘട്ടം അഭിമുഖമാണ്. ചോദ്യാവലിയുടെ സഹായത്തോടെ, തൊഴിൽ, ജീവിതസാഹചര്യങ്ങൾ തുടങ്ങി ജീവിതത്തിന്റെ വിവിധ തുറകളെക്കുറിച്ചുള്ള സൂക്ഷ്മ വിവരം ലഭ്യമാക്കുന്നു. അഭിമുഖത്തിന്റെ ദൈർഘ്യം രണ്ടു മണിക്കൂർ ആണ്.

ഞാൻ ഈ പഠനത്തിൽ പങ്കുചേർന്നാൽ എങ്ങനെ അതുമായി ബന്ധപ്പെട്ടിരിക്കും

ഈ പഠനത്തിൽ പങ്കെടുക്കുക എന്നുവെച്ചാൽ നമ്മുടെ ആശുപത്രി രേഖകൾ പരിശോധിക്കുവാൻ അനുവദിക്കുക എന്നും അഭിമുഖത്തിൽ പങ്കെടുക്കുക എന്നും ആണ്.

പഠനവുമായി ബന്ധപ്പെട്ട് എന്തെങ്കിലും അപകടരമായ സാഹചര്യങ്ങളോ, അസൗകര്യങ്ങളോ നിലനിൽക്കുന്നുണ്ടോ ?

ഈ പഠനവുമായി ബന്ധപ്പെട്ട് യാതൊരു അപകടവും നിലനിൽക്കുന്നില്ല. അപകടമോ, അസ്വസ്ഥതയോ ഉളവാക്കുന്ന ഒരു ചികിത്സാരീതിയും ഇതിൽ ഇല്ല. ആശുപത്രിരേഖകളും അഭിമുഖവും വഴി വിവരങ്ങൾ ശേഖരിക്കുക മാത്രമെ ചെയ്യുന്നുള്ളു.

പഠനവുമായി ബന്ധപ്പെട്ട് എനിക്ക് എന്തെങ്കിലും മെച്ചം ലഭിക്കുമോ ?

പങ്കെടുക്കുന്നവർക്ക് നേരിട്ട് യാതൊരു മെച്ചവും ലഭിക്കുന്നതല്ല. എങ്കിലും ഈ പഠനത്തിന്റെ ഫലം വായിലേയും, തൊണ്ടയിലേയും അർബുദസംബന്ധമായി കൂടുതൽ വിവരങ്ങൾ നമുക്ക് പ്രദാനം ചെയ്യുമെന്ന് പ്രത്യാശിക്കാം.

പഠനത്തിൽ പങ്കെടുക്കുന്നത് സംബന്ധിച്ച്

ഈ പഠനപദ്ധതിയിൽ പങ്കെടുക്കേണ്ടത് സ്വമേധയാ ആണ്

ഈ ഗവേഷണത്തിൽ പങ്കെടുക്കുന്നത് എന്റെ ചികിത്സയെ ബാധിക്കുമോ ?

ചികിത്സയേയോ ചികിത്സാനന്തരനടപടികളെയും പഠനം യാതൊരു കാരണവശാലും ബാധിക്കുന്നതല്ല.

ഈ പഠനത്തിൽ നിന്ന് പിൻവാങ്ങണമെന്ന് കരുതിയാൽ അതിന്റെ അനന്തരഫലങ്ങൾ എന്തായിരിക്കും ?

ഈ ഗവേഷണപദ്ധതിയിൽ നിന്ന് ഏതു സമയത്തും അതായത് അഭിമുഖത്തിന്റെ പകുതിയിൽ വെച്ച് പോലും പിൻമാറാനുള്ള പൂർണ്ണ അവകാശം നിങ്ങൾക്കുണ്ട്. അത് നിങ്ങളുടെ ചികിത്സയെ ഒരു കാരണവശാലും ബാധിക്കുന്നതല്ല.

പഠനത്തിന്റെ വിശ്വസ്തത

ഗവേഷണവേളയിൽ നിങ്ങൾ നൽകുന്ന വിവരങ്ങൾ പൂർണ്ണരഹസ്യസ്വഭാവത്തോടെ സൂക്ഷിക്കുന്നതായിരിക്കും എന്ന് ഉറപ്പ് തരുന്നു. നിങ്ങൾ നൽകിയ വിവരങ്ങളുമ ായി ഗവേഷകർക്കും, വിവരം ശേഖരിക്കുന്ന ഗവേഷകസഹായികൾക്കുമല്ലാതെ മറ്റാർക്കും പ്രാപ്യത ഉണ്ടായിരിക്കുന്നതല്ല. പ്രസ്തുത വിവരങ്ങൾ ഗവേഷണകാര്യാലയത്തിൽ ഭദ്രമായി പൂട്ടി

സൂക്ഷിക്കുന്നതാണ്. കൂടാതെ നിങ്ങൾ നൽകുന്ന വിവരങ്ങൾ ഒരു രഹസ്യ അക്കം ഉപയോഗിച്ച് ഏകോപിപ്പിക്കുന്നതിനാൽ അവയെ വ്യക്തിപരമായി ആരുടേതെന്ന് തിരിച്ചറിയാൻ സാധ്യമല്ല. ഗവേഷണഫലം ശാസ്ത്രമാസികകളിൽ പ്രസിദ്ധീകരണത്തിന് നൽകുമ്പോൾ വ്യക്തിപരമായി തിരിച്ചറിയാത്ത രീതിയിലാണ് നൽകുക. ഗവേഷണസംബന്ധമായ എല്ലാ വിവരങ്ങളും 5 വർഷത്തേക്ക് സൂക്ഷിച്ച് വെക്കുകയും അതിന് ശേഷം നശിപ്പിച്ചു കളയുകയും ചെയ്യുന്നതാണ്.

കൂടുതൽ വിവരങ്ങൾക്ക്

പഠനവുമായി ബന്ധപ്പെട്ടുള്ള നിങ്ങളുടെ സംശയങ്ങൾക്കും ആശങ്കകൾക്കും വിവരങ്ങൾക്കും വേണ്ടി തലവൻ ഡോക്ടർ ഷമീനയുമായി ബന്ധപ്പെടുക.

Ph: .....

സമ്മതം

ഞാൻ മുകളിൽ കൊടുത്തിരിക്കുന്ന വിവരങ്ങൾ വായിക്കുകയും സംശയനിവാരണം നടത്തുകയും സ്വമനസ്സാലെ ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതം രേഖപ്പെടുത്തുകയും
ചെയ്തിരിക്കുന്നു. സ്വമനസ്സാലെയാണ് ഞാൻ ഇതിന് സമ്മതിച്ചിരിക്കുന്നത്. ഞാൻ എന്റെ ചികിത്സയെ ബാധിക്കാത്ത വിധം എപ്പോൾ വേണമെങ്കിലും ഈ പഠനത്തിൽ നിന്ന് പിൻവലിയുന്നതാണ്. ഈ സമ്മതപത്രം ഒപ്പിടുന്നതു വഴി ഞാൻ എന്റെ ഒരു നിയമപരമായ അവകാശവും ബലികഴിച്ചിട്ടില്ല. ഇത് ഒപ്പിടുന്നത് വഴി സമ്മതപത്രത്തിന്റെ ഒരു പകർപ്പ് എനിക്ക് ലഭിക്കുന്നതാണ്.

പങ്കെടുക്കുന്നയാളുടെ പേര് തിയ്യതി

പങ്കെടുക്കുന്നയാളുടെ ഒപ്പ് തിയ്യതി

സാക്ഷി പേര് തിയ്യതി

സാക്ഷി ഒപ്പ് തിയ്യതി

റിസർച്ച് അസിസ്റ്റൻറ് പേര് തിയ്യതി

റിസർച്ച് അസിസ്റ്റൻറ് ഒപ്പ് തിയ്യതി