Characterization of Temporal Aspects of Tobacco Use and Related Diseases

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in the University of Michigan
2017

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Dedication

To my parents, Te-Sen and Ming-Ling, who sacrificed their lives to immigrate to the United States from Taiwan. They taught me to persevere and constantly encourage me to follow my dreams. Without their love and support, my accomplishments would not have been possible.

I also dedicate this work to my siblings, Ting-Yu and Tom, for their support and inspiration.

Acknowledgments

I would like to express my sincere gratitude to my advisor Dr. Rafael Meza. The completion of this dissertation would have not been possible without his mentorship and support. Throughout my MPH and PhD training, Dr. Meza has not only been my advisor and mentor, but he has also been an esteemed colleague and a wonderful friend. His generosity with his time and extensive knowledge on tobacco and cancer modeling has been most valuable in helping me navigate my career path and reach my goals.

I would like to thank my committee members, Dr. Douglas A. Arenberg, Dr. Mousumi Banerjee, Dr. Jihyoun Jeon, Dr. David Levy and Dr. Leigh Pearce, who have guided my research, each with their unique expertise. Specially, Dr. Jeon, is always willing to meet and talk with me about research projects and ideas. I would like to also thank my Thailand collaborator, Dr. Hutcha Sriplung at Prince of Songkla University. Dr. Hutcha was a kind and knowledgeable host and inspired me to think about global health from a different perspective with his distinctive insights into cancer epidemiology in Thailand. I also would like to thank Dr. Kirsten Herold from the School of Public Health Writing Lab. Dr. Herold has helped me improve my writing and communication skills throughout my PhD career.

For my times living in Ann Arbor, I am fortunate and grateful to have many wonderful friends who are my strong support system. I would like to thank Dr. Sarah Cherng, Dr. Michael Hayashi, Yu-Han Kao, Lisa Lau, Sonia Hegde, Kate Duchowny, Ali Walsh, Velma Lopez, Sofia Gaudioso, and Dr. Sandra Tang. Thank you for making Ann Arbor my second home. I could not have hoped for more. To my best friends in Seattle, Dr. Karen Pang and Hanna Oltean, you have

been always there for me and offered me encouragement whenever I needed it. I appreciate all your friendship, love, and support.

I would like to express my sincere love and appreciation to my parents. Mom and Dad, you are my rock. Thank you for anchoring me in stressful moments. Without you, I could not be who I am today. I am extremely grateful for your unconditional love, support and encouragement. To my sister, Ting-Yu Chang and my brother, Tom Chang, thank you for all your love, patience and support throughout this process.

Finally, I would not be able to complete this dissertation without financial support from the National Institute on Drug Abuse grant R01DA036497 and the Rackham Merit Fellowship. I would also like to thank the Graduate Student Research Fellowship and Thai Studies Grant to allow me to travel to Thailand to complete my dissertation project.

Preface

A version of Chapter 2 (*Trends and Factors Related to Smokeless Tobacco Use in the United States*) is published in Nicotine & Tobacco Research. Chang JT, Levy DT, Meza R. Factor and Trends related to Smokeless Tobacco Use in the United States, 1992-2011. *Nicotine Tob Res.* 2016 Mar 19. pii: ntw090.

A version of Chapter 3 (*Examining the Transitions between Cigarette and Smokeless Tobacco Product Use in the United States Using the 2002-2003 and 2010-2011 Longitudinal Cohorts*) was submitted for publication. The full list of authors is: Joanne T Chang, David T Levy, and Rafael Meza.

A version of Chapter 4 (*COPD Risk Prediction Accounting for Time-varying Smoking Exposures*) will be submitted for publication. The full list of authors is: Joanne T Chang, Rafael Meza, David T Levy, Douglas Arenberg, Jihyoun Jeon.

A version of Chapter 5 (*Temporal Trends and Geographic Patterns of Lung Cancer by Histological Types in Thailand, 1990-2014*) will be submitted for publication. The full list of authors is: Joanne T Chang, Jihyoun Jeon, Seesaiy Yeesoonsang, Laura Rozek, Hutcha Sriplung, Rafael Meza.

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List of Abbreviations

AAPC	Average annual percent change
Add Health	National Longitudinal Study of Adolescent to Adult Health
ALK	Anaplastic lymphoma kinase
APC	Annual percent change
ASEAN	Association of Southeast Asian Nations
AUC	Area under a ROC curve
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Center for Disease Control
CI	Confidence Interval
CI5	Cancer Incidence in Five Continents
COPD	Chronic obstructive pulmonary disease
CTP	Center for Tobacco Products
CVD	Cardiovascular disease
EGFR	Epidermal growth factor receptor
ENDS	Electronic nicotine delivery systems
FCC	Federal Communication Commission
FCTC	Framework Convention on Tobacco Control
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FTC	Federal Trade Commission
FVC	Forced vital capacity
GED	General Education Development
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HDI	Human Development Index
HIC	High income country
HPFS	Health Professional Health Study
HR	Hazard ratio
IARC	International Agency for Research on Cancer
LMIC	Low- and middle- income country
MSA	Metropolitan Statistical Areas
NAS	National Adult Survey
NCD	Non-communicable disease
NHANES	National Health and Nutrition Examination Survey

NHIS	National Health Interview Survey
NHS	Nurses' Health Study
NSCLC	Non-small cell lung cancer
NSDUH	National Survey on Drug Use and Health
OR	Odds ratio
SCLC	Small-cell lung cancer
PATH	Population Assessment of Tobacco and Health
PM	Particulate matter
SDG	Sustainable Development Goals
SLT	Smokeless tobacco
TCA	Tobacco Control Act
TIRC	Tobacco Industry Research Council
TSNA	Tobacco specific nitrosamine
TUS-CPS	Tobacco use supplement of the current population survey
US	United States
WHO	World Health Organization

Abstract

Tobacco use is a causative agent of various diseases including cancer, cardiovascular diseases (CVD), chronic obstructive pulmonary disease (COPD) and other non-communicable diseases (NCDs). However, the way in which complex time-varying tobacco use patterns shape disease risk is less well understood. In the United States (US), smoking prevalence has declined, but the use of alternative tobacco products (chewing tobacco, snus, snuff, e-cigarettes) has remained constant or is increasing. These changes further complicate the relationship between tobacco exposure and health outcomes at the population and individual levels. Globally, there is a drastic shift in global tobacco use from high-income countries to low- and middle- income countries, where the burden of tobacco-related NCDs is predicted to rise 70% by 2030. This dissertation seeks to address the temporal aspects of tobacco use and its related health conditions to further assess the health and financial costs of the tobacco use epidemic globally.

This dissertation addresses the temporal relationship of tobacco use and its related diseases in three parts. First, the Tobacco Use Supplement of the Current Population Survey was used with joinpoint regression analysis to better understand trends and factors related to smokeless tobacco use (SLT) and cigarette smoking in the US. We found that while smoking continues to decrease, SLT has remained constant since the early 2000s. In addition, we found that while smoking cessation rates doubled from 2002 to 2010, SLT cessation rates remained constant. Second, individual smoking history information from the Nurses' Health Study and Health Professionals' Follow-up Study were used to develop and validate a COPD risk prediction model. By including detailed smoking information, we improved the model

calibration and predictability. The resulting model was then used to investigate how time-varying cigarette smoking exposures, characterized by duration, intensity, time since quitting, determine COPD risk. Third, population-based cancer surveillance lung cancer data from four cancer registries were used to characterize and project sex-specific lung cancer incidence trends by histology in Thailand using joinpoint regression, age-period cohort, and Nordpred models. We found that lung cancer trends vary greatly by sex, region and histology, and projected rates of adenocarcinoma will continue to increase compared to those of squamous-cell carcinoma.

This dissertation shows the benefits of, and need for, incorporating for the temporal aspects of tobacco exposure and disease outcomes, and provides examples of methodological approaches that can be used for the analysis of epidemiological time trends. Use of these and other methods is critical to properly assess the current and future burden of tobacco use, and the impact of interventions to reduce its burden.

Chapter 1

Introduction

1.1 Rationale

Tobacco use is a causative agent of non-communicable diseases (NCDs) including cancers, cardiovascular diseases (CVD), and chronic bronchitis and emphysema, and many other chronic conditions such as diabetes.[1–8] According to the International Agency for Research on Cancer (IARC), tobacco smoking is a Group 1 agent "Carcinogenic to humans" to numerous cancer sites, such as lung, oral cavity, pharynx, esophagus, stomach, colon, rectum, liver, and pancreas.[9] Specifically, by 2020, about 71% of lung cancer deaths, 42% of chronic respiratory disease including chronic obstructive pulmonary disease (COPD) and 10% of CVD will be attributable to smoking worldwide.[10] Reducing tobacco use is one of the most effective methods for NCD prevention; however, tobacco epidemics continue globally. Specifically, by 2030, 83% of all tobacco attributable deaths will occur in low- and middle-income countries (LMICs),[11] which projected from about 6 million deaths annually to about 8 million deaths annually by 2030.[12] Tobacco consumption is a barrier to sustainable development. While one of the Sustainable Development Goals (SDG) is to reduce NCD deaths to 25% by 2025,[13] more public health efforts are still needed to address the multiple impacts of tobacco use worldwide.

In recent decades, the United States (US) cigarette smoking prevalence has declined due to tobacco control policies like taxation on tobacco products, clean-air laws and smoke-free workplace and campus policies.[14–21] However, the availability of smokeless tobacco (SLT) products such as snus, snuff, and chewing tobacco, and the emergence of e-cigarettes, have re-

energized the tobacco market and could eventually undo much of the progress over the last decades.[22,23] Based on limited longitudinal tobacco data, dual use (cigarette smoking and SLT use) is hypothesized to potentially lead to additional harmful effects of tobacco by deterring smoking cessation.[24,25] At the same time, replacement of cigarette smoking by SLT and other alternative tobacco products with lower associated health risks is proposed as a potential harm reduction strategy given the lower associated risks.[26,27] The use of multiple tobacco products, polytobacco, is becoming more common in some tobacco users. Thus, more information is needed to understand the trends and transitions between different tobacco products, and the effects that polytobacco use might have on health.

Among many diseases caused by tobacco use, COPD has a prominent place by being the third leading cause of death in the US and worldwide.[28,29] COPD includes conditions such as emphysema and chronic bronchitis.[29] It affects primarily in adult current and former smokers. Although the relationship between cigarette smoking and COPD is well-established, most studies have been limited in examining the relationship between smoking exposures and COPD risk by focusing primarily on summary measures, such as smoking status.[8,30–38] Moreover, cigarette smoking is complex, and other factors, such as intensity, duration, age, and years since quitting (if former smokers), may play an important role in determining the risk of COPD. Thus, it is important to investigate the effect of these multiple factors on COPD risk.

LMICs are undergoing demographic and epidemiologic transitions. The growing population has led to epidemiologic changes and shifted the risk factor profiles, impacting disease patterns with a decrease in communicable diseases related to maternal, perinatal and nutritional diseases and a concomitant increase in NCDs, such as cancer, CVD and diabetes. Particularly, the availability of tobacco products may be a major cause of NCDs in the next two

decades worldwide.[10] For example, worldwide cancer incidence is projected to rise 70% by 2030, with the majority burden to be concentrated in LMICs.[10]

Among LMICs, Thailand provides a positive example with its aggressive tobacco control policies, resulting in decreasing Thai smoking prevalence since 1991.[39] However, the incidence of lung cancer continues to increase in Thailand.[40] This suggests that smoking alone does not fully characterize the risk profile of lung cancer in this country. It is critical to investigate lung cancer incidence trends carefully, which may help to generate hypotheses about the underlying causes for the increase of lung cancer in Thailand and other countries with similar settings.

In sum, although much is known about the harmful impacts of tobacco use,[21,41] there are still considerable research gaps in multiple areas. Particularly important is the temporal relationships between time-varying tobacco exposures and population-level disease risks. And to further characterize how tobacco use patterns differ by multiple temporal perspectives such as age, calendar-year and importantly birth cohort (generations).[21,42] With rapid growth and development of various emerging tobacco products, the potential gain or reduction in harms of these products on public health is uncertain. Tobacco consumption is a barrier to sustainable development,[13] and tobacco use will cost more than one billion lives in this century.[43] The overall goal of this dissertation is to address these research gaps, examine three different aspects of the ongoing public health ramifications of tobacco use, and utilize novel methods to study various temporal aspects of the tobacco epidemic. The findings from studies in this dissertation can be useful to provide more insights and evidence to implement potential policy changes that can succeed the SDG goal of reducing NCD burden.

1.1 Specific aims

Specific Aim 1. Characterize the trends and transition of smokeless tobacco use and smoking in the United States (Chapters 2 and 3)

Although there is a considerable literature on the burden and the determinants of SLT use in the US, [1–3,6] many questions remain in the landscape of changing tobacco use. To understand the implications of SLT use, the Tobacco Use Supplement of the Current Population Survey (TUS-CPS) is used to characterize recent tobacco use trends by SLT products such as snus, snuff and chewing tobacco, smoking status (current, former, and never users), and dual use of SLT and cigarette smoking. More specifically, the patterns of SLT use under different definitions of use and the relationship between SLT use and tobacco consumption are explored using complementary data from the 2011 Federal Trade Commission Smokeless Tobacco Report. In addition to analyzing the time trends of SLT use, the factors associated with SLT use in the US and longitudinal transitions between cigarette smoking and SLT use are also examined. This aim has two objectives: 1) to characterize trends of and factors related to current SLT use and cigarette smoking in the US using the TUS-CPS from 1991 to 2012 (Chapter 2); 2) to examine transition rates between SLT use and cigarette smoking from two longitudinal follow-ups, 2002-2003 and 2010-2011 from TUS-CPS (Chapter 3). Identifying recent trends of SLT and cigarette smoking use can provide more insights into potential patterns of alternative tobacco product use (loose leaf, moist snuff, snus, dissolvable, and e-cigarettes). Moreover, information on transitions between SLT and cigarette smoking is critical to assess the potential long-term impact of smoking, SLT use, and polytobacco use patterns on tobacco-related health outcomes.

Specific Aim 2. Assess the temporal relationship between smoking exposures and COPD risk (Chapter 4)

Previous studies have estimated the effect of smoking on COPD risk by focusing on simple summary measures, such as smoking status.[8,30–38] However, to make more precise predictions for COPD risk, it is necessary to develop risk prediction models accounting for multiple temporal factors related to time-varying smoking exposures and age. In this aim, the time-dependent effect of cumulative smoking pack-years on COPD incidence with adjustment for smoking duration, time-since-quitting (for former smokers), and sex, were examined using data from two prospective cohort studies: The Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The resulting model accounting for multiple time-varying smoking factors will be helpful to establish potential individualized prevention strategies. Moreover, understanding the complex temporal relationship between smoking history and COPD risk is critical to assess the future impact of COPD on public health in the US, as the population tobacco use patterns continue to evolve.

Specific Aim 3. Changing patterns of incidence of lung cancer by histology in Thailand (Chapter 5)

Thailand is undergoing an epidemiologic transition, as NCDs are increasing; importantly, tobacco is a well-established risk factor for many NCDs.[21,41] Unlike many other LMICs, Thailand has universal health care and a very aggressive tobacco control policy program. The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) found that the per capita cigarette consumption in Thailand decreased by 30% from 1990 to 2000.[44] Yet despite the decreasing cigarette consumption, lung cancer rates continue to increase and lung

cancer burden remains high in Thailand; in 2012, lung cancer was ranked as the second and fifth most common cancer for men and women respectively.[40] This aim seeks to better understand trends of incidence of lung cancer by histology in different regions of Thailand using data from four regional cancer registries: Chiang Mai, Khon Kaen, Lampang and Songkhla Cancer Registries. Understanding these trends may provide some insights into the relative contributions of genetic, behavioral, and environmental risk factors on lung cancer incidence rates in Thailand. In addition, projections of the number of lung cancer cases by histologic subtypes in different regions can be useful to suggest effective national and regional cancer control policies. These findings will aid public health professionals and policymakers to gauge the future burden of lung cancer in different regions of Thailand, and help them to determine context-appropriate cancer control policies and strategies.

1.2 The changing landscape of tobacco products

The origin of tobacco can be traced back to before the arrivals of Europeans in Americas in 1492; historians have dated the early usage of tobacco by Native Americans as medicines to reduce swelling and as a cure for cold.[45] Tobacco is a plant of the genus Nicotiana of the Solanaceae (nightshade) family. The primary active ingredient of tobacco is nicotine that is responsible for its soothing qualities.[45] Dr. Nicolas Monardes, a Spanish physician, described tobacco in his book “new world herbal”, which was a description of herbs and medicines from Americans published in 1571.[45] He described this herb, tobacco, “has particular virtue to heal griefs of the head … some there be that do anoint them with the oil of oranges, and it does a very good work.” Many believed that tobacco had curative power for disease, and it was thought to be a preventative against the bubonic plague.[45] Thus, tobacco use began to grow and eventually

became an important product to the worldwide economy. In the 1700s, cigars had become a popular method of tobacco consumption, and these later evolved into cigarettes by the 1830s.

In 1612, an Englishman John Rolfe arrived in Jamestown, Virginia, and he started experimenting growing tobacco. This eventually became the first commercial crop in the US. The main tobacco products at the time were SLT products such as chewing tobacco and snuff, as well as pipe-smoking. By the late 19th century, cigarettes were sold in packs (ten cigarettes in a pack) and marketed throughout the US; however, cigarettes did not become popular in the US until World War I. The cigarette packages were manufactured with logos and designs, which were attractive prints with various types of advertisement.

Cigarette smoking increased substantially throughout the 1950s. In 1900s, US per capita cigarette consumption increased from 54 cigarettes per year to 4,345 cigarettes per year in 1963.[46] Also, lung cancer became "the most common diagnosed disease in American men" by the early 1950s.[47] With the growth in cigarette smoking, many scientists started exploring the health effects of smoking, and in particular, the relationship between cigarette smoking and lung cancer. In a study conducted by Drs. Doll and Hill in 1954,[47] they showed decisively that lung cancer mortality was strongly associated to smoking. Another notable study was that by Drs. Hammond and Horn from the American Cancer Society. In 1952, Hammond and Horn recruited 188,000 healthy American men aged 50 to 69 and collected information about their smoking habits, and followed them till 1955.[48] They found that men with a history of regular smoking had higher death rates than men who had never smoked. These results were part of the evidence that supported the conclusions of the landmark 1964 Surgeon General's Report "Smoking and Health.[49]"

The tobacco industry responded aggressively to these findings. By 1954, the Tobacco Industry Research Council (TIRC) assisted the tobacco companies to begin mass-marketing of filtered cigarettes and low-tar formulation as the "healthier" choice for smokers. On the other hand, the tobacco control community responded with massive anti-tobacco media campaigns. In 1949, the Fairness Doctrine was introduced by the US Federal Communication Commission (FCC) to regulate coverage on controversial issues on a broadcast station. In 1967, the FCC ruled for the Fairness Doctrine to apply to the advertising of tobacco sales, in addition to its marketing and usage.[50,51] In the early 1970s, the US Surgeon General declared the harmful effect of secondhand smoking and air pollution to non-smokers. By mid-1970s, many states implemented the Clean-Air Indoor Act.[52] Since then, smoke-free air laws, media campaigns on smoking cessation, cessation programs, and increasing cigarette tax and other policies have been implemented in the US.

The availability and characteristics of other tobacco products experienced dramatic evolution during the past century. For example, chewing tobacco is the oldest form of SLT, which was historically used by the Native Americans, gold miners and cowboys.[53] In the 1930s, cigarettes became more popular replacing SLT and the most commonly used tobacco product. However, due to new smoking restrictions starting in the 1970s, the promotion of moist snuff, snus and dissolvable tobacco, SLT use began to increase again given their "spit-free" formulations.[54] During the 1980s and 1990s, SLT use decreased together with cigarette smoking; however, SLT use remained roughly constant since the early 2000s in contrast with the further reductions in cigarette smoking that continues today.[16,55] The 2009 Family Smoking Prevention and Tobacco Control Act (TCA) granted the US Food and Drug Administration (FDA) the authority to regulate cigarettes, SLT, and hand-rolled cigarettes.[56] This Act specifies that the

FDA should "consider the impacts of decisions on the population as a whole, including the impacts on the likelihood of initiation of tobacco use among non-users and cessation among users.[56]"

Since the 1964 Surgeon General's Report on smoking and health, adult smoking prevalence has dropped from 42.4% in 1965 to 17.9% in 2013 in the US.[21] Even though great progress has been made in tobacco control, tobacco use remains the single leading cause of preventable deaths in the US.[21] Moreover, the tobacco industry has expanded its product variety. Today, electronic nicotine delivery systems (ENDS), including e-cigarettes and other novel products, are emerging in the US and worldwide. In May 2016, the US FDA issued a rule to deem ENDS, dissolvable, cigar, pipe tobacco and hookah tobacco as tobacco products.[57] Domestically and internationally, although the regulatory bodies are responding to address the significant challenges presented by the dramatic changes in tobacco product form, patterns of use, and the tobacco industry in recent years, continued research addressing old and new tobacco products use and their health consequences is strongly needed.

1.3 Measurement of tobacco use

Measuring tobacco use has become a major challenge due to the rapidly changing landscape of tobacco products. Multiple types of tobacco products can be measured in various ways, depending on the product and its form of use (i.e., smoked, chewed, vaped, or snuffed). Typically, questionnaires studying about tobacco use include age of first use, frequency, and intensity. But as new products emerge, it is becoming increasingly difficult to determine the right exposure metrics. For example, while cigarette use can be easily characterized in number of cigarettes or packs smoked, the e-cigarette market is diverse, both in terms of product

construction and packaging. Many national surveys have attempted to characterize patterns of polytobacco (cigarettes and other tobacco products) consumption by asking multiple questions to capture use of different products. However, many questions remain in order to address how best to reliably measure the use of new tobacco products.[55,58] Since cigarette smoking and SLT use are the most common forms of tobacco products other than cigars in the US,[59] I will first focus on discussing the measurement of the use of these two products.

Measuring prevalence and patterns of tobacco use can provide useful information in designing tobacco control strategies for target populations. Thus, understanding the initiation of tobacco use for non-smokers and the transition of current and former smokers to smoking cessation is important to monitor the changing trends of tobacco use in the population. In the US, several state-wide and federally funded national surveys have been used to assess tobacco use in the population. The six surveys which measure prevalence of smoking and SLT use at national level in the US are the National Health Interview Survey (NHIS), the National Health and Nutrition Examination Survey (NHANES), the Behavioral Risk Factor Surveillance System (BRFSS), the TUS-CPS, the National Survey on Drug Use and Health (NSDUH), and the National Adult Survey (NAS). Survey characteristics and the varying definitions of smoking and SLT between each survey can be found in Chang et al. and Agaku et al.[55,60]

There are a limited number of surveys which provide population level information on transitions between, to, and from tobacco products. These are the National Longitudinal Study of Adolescent to Adult Health (Add Health) and the TUS-CPS (only in 2002/03 and 2010/11). In addition, the FDA Center for Tobacco Products (CTP) administered the first wave of the Population Assessment of Tobacco and Health (PATH) study in 2013. Baseline data have been released, but longitudinal data is still pending.[61]

Smoking is defined as the number of individuals who smoked one day or more in the past 30 days, with smoking prevalence being the proportion of the population that identified as smokers. Smokers are usually defined using questions on ever smoking, smoking status (former or current), duration of smoking, cigarettes smoked per day, pack-years of smoking, and age at smoking initiation. There is a consistency in the literature regarding smoking. However, definition of SLT prevalence has varied greatly across surveys and studies. For example, in the NHIS, SLT use was defined as "every day or some days use of a smokeless tobacco product" whereas the NSDUH defines SLT use as "past 30-day of a smokeless tobacco product". To capture the true number of SLT users in the population, it is important to include detailed information on duration, frequency, and intensity of their SLT consumptions. In Chapter 2, I examine if the trends in sales (equivalent to consumption) of SLT from the US Federal Trade Commission (FTC) reflect the prevalence trends reported in the TUS-CPS using different metrics of SLT use.[55]

In short, the definition of smoking and other tobacco use has varied widely across studies, making it difficult to examine patterns of tobacco use and predict future trends. The importance of accurately measuring prevalence and patterns of tobacco use cannot be overemphasized as such information may be useful in guiding decisions in tobacco control strategies for populations at the international, national, state and local levels. Moreover, when considering the long-term consequences of tobacco use, precise definitions of tobacco use are critical to provide insights into both the population and the individual health burdens of tobacco use.

1.4 Global Burden of Tobacco

The tobacco epidemic is one of the most consequential public health threats that the world has ever faced, with 6.5 million people dying per year prematurely because of it.[62] Globally, about 82% of smokers live in LMICs, with an estimated 250 million female and one billion male smokers.[63] Tobacco consumption has increased substantially in LMICs, with the highest rates in Asia Pacific (56%), Europe (24%), Americas (11%) and Eastern Mediterranean and Africa (9%), respectively. The Association of Southeast Asian Nations (ASEAN) consists of 10 countries: Brunei Darussalam, Cambodia, Indonesia, Lao People's Democratic Republic (PDR), Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam. These nations have a combined population of 625 million people, accounting for 9% of the world's population.[64] Smoking prevalence varies substantially by country. In 2015, male smoking prevalence was the highest in Indonesia (75.9%) and the lowest in Singapore (24.8%), whereas, female smoking prevalence was the highest in Lao PDR (8.8%) and the lowest in Malaysia and Vietnam (1.3%).[64] Cigarette smoking accounts for about one-third of cancer incidence and mortality in the ASEAN countries.[64] The number of cancer deaths attributable to smoking varies by countries, with the highest in Indonesia (34,293) followed by Vietnam (21,571) and Thailand (17,487).[64]

In the US, more than 20 million Americans died prematurely due to smoking from 1964 to 2014.[21] An estimated 480,000 Americans died because of cigarettes smoking each year, and more than 41,000 of these deaths due to secondhand smoking.[65] The costs of smoking-related illness are more than $300 billion per year.[21,66] In 2014, an estimated 40.0 million (16.8%) of U.S. adults were current smokers. Smoking prevalence was the highest in males (18.8%), adults aged 25 to 44 years (20.0%), American Indian/Alaska Native (29.2%), residents of the Midwest

(20.7%), and people with a General Education Development (GED) certificate (43.0%).[65] As cigarette smoking prevalence has decreased in the US, SLT use has increased or remained constant.[55,67] In 2012, 7.1% of US adult males were current SLT users,[21] making SLT use the third most used tobacco products after cigarettes and cigars. SLT users are more likely to be former smokers, young males, white race, living in rural areas or the South, poorly educated, and unemployed.[55] Moreover, while cigarette consumption decreased by 32.8% from 2000 to 2011, consumption of other combustible tobacco products such as cigars increased by 123.1%.[59] Unlike cigar use, SLT use has remained stable in the past decade. The evidence on whether SLT use can aid in smoking cessation is inconclusive. Zhu *et al*. found that switching from cigarettes to SLT was uncommon, but quitting SLT was more common than smoking cessation.[68] Studies outside the US have shown that promoting the use of SLT products such as snus or snuff in replacement of cigarettes aided smoking cessation.[69] Thus, it is important to investigate the transition of use behavior between different tobacco products, and I describe more details in Chapter 3.

COPD burden

COPD is an umbrella term including conditions like chronic bronchitis, emphysema, and bronchiectasis.[29] The disease ranks third on the list of potentially fatal diseases in the US,[70] with nearly 42.1 deaths per 100,000 in 2013, after CVD and stroke. The WHO 2008 report on the burden of lung diseases states that poor respiratory conditions, including COPD, impose an enormous burden on society, with the top 5 respiratory diseases accounting for 13% of all deaths.[71]

Patients with COPD have narrowed airways, which results in breathing difficulties and shortness of breath. In severe cases, lungs are permanently damaged. Symptoms include chronic cough, a rapid breathing rate, wheezing, exertional breathlessness, limitations in exercise tolerance, and chest tightness.[29] Moreover, COPD manifests itself slowly, which can impede early detection and proper treatment of the disease because most people do not identify the first symptom, such as shortness of breath, as a marker of COPD. The diagnostic method for measuring COPD progression is spirometry, which measures the lung volume in two indicators: forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). COPD is defined as airflow obstruction, when fixed ratio of FEV_1/FVC is less than 0.7 and the FEV_1 is less than 0.8. However, in the US, no spirometry screening program is recommended for asymptomatic COPD patients; instead, smoking cessation is strongly recommended for these patients. In Chapter 4 of this dissertation, I examine the relationship of various aspects of time-varying smoking exposures and COPD incidence.

In addition to its independent effects on health, COPD is an independent risk factor for lung cancer.[72–74] For smokers with COPD, the risk of lung cancer increases two- to five- fold compared with smokers with normal spirometry measures.[75] Cigarette smoking is a common risk factor for both COPD and lung cancer, and thus potentially confounds this relationship.[72] COPD tends to occur earlier than lung cancer, suggesting that COPD may act as a mediator of the relationship between smoking and lung cancer.[72–74] Other known COPD risk factors include age, gender, race, occupation, education, asthma, and air pollution (particulate matter micron 2.5).[30,33,37,76–78]

Lung cancer burden

Worldwide, lung cancer has been the most common causes of cancer death for last several decades. In 2012, about 1.8 million new cases of lung cancer were diagnosed, 58% of which occurred in less developed regions.[79] Lung cancer is also the most common causes of cancer death worldwide, responsible for about one in every 5 cancer deaths (1.59 million deaths), with the highest estimated age-standardized incidence rates in Central and Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000), and the lowest in Middle and Western Africa (2.0 and 1.7 per 100,000, respectively).[79]

Lung cancer tumor histology can be classified by two major types: small-cell lung cancer and non-small cell lung cancer (NSCLC). Adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma are the three main NSCLC subtypes. With advancement in subtype classification, the classification of histology became important for choice of targeted therapies.[80,81] Smoking increases risk of all subtypes of lung cancer, with greater impact for squamous-cell and small-cell carcinoma than adenocarcinoma.[82] Adenocarcinoma has been found more in women than men (in both smokers and nonsmokers), with increasing rates observed in high-income countries (HICs).[83] Moreover, lung cancer affects non-smokers, women in particular, at a rate that appears to be increasing.[84–86] Other risk factors such as secondhand smoking,[21] cooking fumes,[84] genetic predisposition,[87] hormones,[88] occupational exposure,[85] household radon,[89] and inflammatory processes can also contribute to the lung cancer risk,[90] but the reasons behind the increase in lung cancer rates in women in several countries, including Thailand, are unclear. In Chapter 5, I analyze trends of lung cancer by region, histology, and sex to provide insights into the underlying causes for the increasing lung cancer rates in Thailand.

1.5 Epidemiologic transition

The epidemiologic transition theory describes the changes in population patterns of factors such as fertility, life expectancy, mortality and leading causes of death resulting from development and the adoption of westernized life styles, and their relationship with other sociodemographic and economic changes in the population.[91] The epidemiologic transition has been characterized in simple terms by decreasing rates of infectious diseases and increasing burden of NCDs such as cancer, CVD, and diabetes. However, as Yach et al suggest that "Chronic diseases have not simply displaced acute infectious ones in developing countries. Rather, such countries are experiencing a polarized and protracted double burden of disease."[92] While LMICs contribute to this double burden, tobacco use has been a major contributor to the increasing NCDs burden. Understanding the change in tobacco use, and the patterns of cancer incidence and mortality in LMICs will be important for the determination of optimal cancer prevention strategies, and more generally for the development of policies and practices that minimize the impact of the epidemiologic transition as LMICs continue to develop.

1.6 Cancer registration and surveillance

As researchers begin to better understand the trends of disease incidence and mortality patterns, policymakers can use this information to set priorities for the public health sector to more effectively reduce disease burden. Utilization of cancer registry data is particularly useful to better understand the patterns of cancer occurrence in different populations. Today, the majority of new cancer cases occurred in LMICs, where the greatest increases in burden of cancer are expected in the next decades.[13] The patterns and causes of cancer in LMICs are not only different from those in HICs, but also are in transition as traditional lifestyles are shifting to

western diet. It is critical to assess the burden of cancer using high quality population-based cancer registries (PBCRs). The WHO notes that PBCRs are a key component to establish cancer control strategies. Parkin et al. has described the role of PBCRs is to estimate the current burden of cancer, examine recent cancer trends and predict the future evolution of cancer.[93] Incidence and survival information are typically used to 1) evaluate primary prevention strategies and interventions against cancer; 2) evaluate and monitor screening programs; and 3) measure and evaluate the effectiveness of cancer care system.

Due to the lack of financial resources and infrastructures, the coverage of the vital statistics and PBCR has been significantly lower than that in HICs. In addition, the coverage of PBCR varies by country, continent, and human development index. IARC has established regional hubs for cancer registration in Africa, Asia, and Latin America to provide more guidance and resources to increase the data quality, coverage, and utility for cancer control progress.[94] Three of four Thai cancer registries that provided data for this dissertation (Chiang Mai, Lampang and Songkhla) were originally developed with the support from IARC as part of this initiative, and contribute now to the IARC Cancer Incidence in Five Continents (CI5) project.[95]

1.7 Summary of background

In summary, the temporal relationship between tobacco exposures and disease risk is becoming increasingly complex. The changing landscape of tobacco products places a major challenge in understanding the patterns of polytobacco use behaviors in different birth cohorts. These changing patterns of tobacco use could influence long-term health outcomes, which is not

yet well-understood. Furthermore, the individual smoking history is complex and cannot be fully described by a simple summary measure, such as smoking status or pack-years. To more accurately assess the smoking effect on NCDs, it is critical to understand the relationship between multiple time-varying smoking parameters and the risk of NCDs. Moreover, the LMICs are facing epidemiologic transitions that make NCDs the most prominent cause of death. While infectious disease and malnutrition are still problematic in the LMICs, we also must pay attention to the growing mortality and morbidity of NCDs. The SDG target 3.4 is "the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries";[13] the WHO FCTC is a treaty that was signed by 168 countries to reduce the tobacco burden.[96] The tobacco control is a critical action to achieve this SDG target and reduce premature mortality due to NCDs.

Although the SDGs have aggressively set goals and priorities to reduce the double burden in LMICs, the progress in HICs cannot be ignored. For example, US smoking prevalence has been reduced by more than 50% since the 1960s, and all-causes mortality has decreased by 60% since 1900.[21] However, while the reduction of cigarette smoking and NCD incidence is cause for celebration, we are also facing the challenges of new tobacco products continuing to be introduced to the market. Longitudinal data for the use of various tobacco products is needed to better understand patterns of switching and adoption between these products. We also do not fully understand how changes in tobacco exposure with time and age translate into disease risk patterns at the population and individual levels. There is thus a need to extend research on understanding the past trends of tobacco use and NCD burden, and develop or adapt novel methods to predict the future burden of NCDs in LMICs and elsewhere. These research efforts can be later used to create better prevention programs and improve limited resource allocations,

including country-specific NCD control planning. This dissertation seeks to contribute to this goal by examining the interaction of smoking and SLT in the US (Aim 1), predicting how COPD risk changes with smoking history (Aim 2), and investigating how lung cancer histology changes in the past 20 years (Aim 3).

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Chapter 2

Trends and Factors related to Smokeless Tobacco Use in the United States

2.1 Abstract

Background: While declines in smoking prevalence in the United States (US) have been well documented, trends in smokeless tobacco (SLT) use are less clear. This study updates previous analyses of US SLT use prevalence to better understand trends and factors related to SLT use.

Methods: We used the Tobacco Use Supplement of the Current Population Survey (TUS-CPS) to examine trends and factors related to SLT use using joinpoint and logistic regression models. SLT consumption from 1985-2011 was obtained from the 2011 Federal Trade Commission Smokeless Tobacco Report. Sensitivity analyses were conducted for assessing the impact of varying frequency definitions of SLT use.

Results: Decreasing trends in smoking and SLT prevalence overall were observed from 1992-2003 independently of use definition. SLT prevalence in the total adult population significantly decreased at an annual percent change (APC) of 4.5% per year from 1992-2003, but has been approximately constant ever since. Similar patterns were also found in adult males (APC=-4.4%) and young males (APC=-9.5%). SLT per capita consumption decreased significantly from 1991-1999 (APC=-2.2%), but has since decreased at only 0.35% per year (1999-2011). SLT use was found to be associated with former smoker status, younger age, white race, living in rural areas, residence in the South, lower education and unemployment, adjusting for other factors.

Conclusions: Declines in SLT use were found in the US, suggesting tobacco control has had positive impacts, but these have slowed since 2003. Targeting tobacco control policies to at-risk demographic groups is needed to further reduce SLT use in the US.

2.2 Introduction

As U.S. smoking prevalence rates have declined, the promotion and consumption of alternative tobacco products, such as smokeless tobacco (SLT) and e-cigarettes, has been increasing.[1,2] While the use of SLT was shown to be declining prior to the year 2002,[3,4] total SLT sales have been increasing in recent years,[2,5,6] likely influenced by the increase in the free nicotine content of SLT[7] and the introduction of new forms and delivery systems.[8] In particular, use of moist snuff, including snus, currently the largest share of the US market (85.6% in 2011)[2], has been increasing since the 1980s. The use of both SLT and cigarettes has been observed in states with weak and strong tobacco control policies. For example, over 10% of smokers also use SLT in states such as Minnesota and Wyoming,[9] with substantial recent increases in dual-use in Minnesota between 2007 and 2010 [10] despite strong anti-tobacco policies. This high level of use could represent a substitution of SLT use for cigarettes in places where smoking is prohibited, which may reduce harm by reducing smoking intensity, but could instead represent an increase in tobacco consumption among smokers.

Smokers generally view SLT as a less harmful alternative to cigarettes;[11] however, SLT may be used alone or with cigarettes. When used alone, SLT has been independently linked to major health risks, although these could vary depending on the product types. For instance, the levels of tobacco specific nitrosamine (TSNAs), which are established carcinogens, vary among different products.[12] Harmful effects include oral and esophageal cancer,[12,13]stomach cancer,[14] pancreatic cancer,[15,16]and cardiovascular diseases.[17–20] Although less is known about the health effects of SLT when used jointly with cigarettes,[21] dual use may lead to additional harmful effects by deterring smoking cessation. For instance, smokers may use these products as an alternative source of nicotine when they are not permitted to smoke, e.g. due to clean air

laws[6,9,10,22–25] or may use these products as nicotine replacements when they are attempting to quit. Both these circumstances have important implications for tobacco control. Thus, continued monitoring to understand trends in SLT product use is critical to inform national efforts to reduce the overall public health harms of tobacco.[26]

In understanding the public health impact of SLT use as well as for other nicotine delivery products, such as e-cigarettes, it will be important to develop measures of use that can inform the transitions to sole and dual use of cigarettes.[27] Unfortunately, the definition of SLT use has been inconsistent across national tobacco use surveys, making the characterization of prevalence trends challenging.[3,28] In particular, the National Health Interview Survey (NHIS), the National Survey on Drug Use & Health (NSDHS), and the Tobacco Use Supplement of the Current Population Survey (TUS-CPS), collect information on SLT use differently.[3,29] The NHIS defines current SLT use as every day or some days use of a SLT product.[30,31] The NSDHS defines current SLT use as past 30-days use of a SLT product.[27] Here, we explore patterns of SLT use under different definitions using the TUS-CPS survey. One of the goals of this study is to assess the sensitivity of SLT use trend estimates to the use definition.

Previously, Mumford *et al*. and Nelson *et al*. have described trends in SLT use under different definitions from the 1980s to 2000.[3,4] In this paper, we update these analyses with three additional waves from the TUS-CPS from 2003 to 2011, focusing on the relationship of SLT use and smoking prevalence. We also consider the relationship of SLT use to tobacco sales using data from the Federal Trade Commission Smokeless Tobacco Report. Currently, there is limited literature on the burden and determinants of SLT use in the US. In addition to investigating the time trends of SLT use, we also examine the factors associated with SLT prevalence in the United States.

2.3 Methods

Smokeless tobacco data

We used data from nine waves of the TUS-CPS, a series of nationally representative cross-sectional surveys: 1992/93, 1995/96, 1998, 1999, 2000, 2001/02, 2003, 2007, and 2010/11. The TUS-CPS collects national and state level representative data on tobacco use in the US household population.[32] The survey includes a civilian, non-institutionalized population of age 15 years or older. Primary data collection was conducted by telephone interviews, but about 30% of interviews were conducted in-person in the household. In this study, we restricted the sample to self-respondents of age 18 or older.

In addition to prevalence analysis, we analyzed trends in SLT consumption from 1985-2011 using data from the 2011 Federal Trade Commission Smokeless Tobacco Report [33] to examine if the trends in sales reflect the prevalence trends. SLT consumption per capita is calculated by dividing all SLT sales in pounds (in a particular year) by the corresponding total US population.

Smokeless tobacco and cigarette use measures

Prevalence of SLT use was calculated using aggregates of monthly samples for each survey wave. The wording of SLT use questions in TUS-CPS varies over time. Table 2.1 summarizes the definitions of current use of SLT in TUS-CPS by survey year. For 1992/93 and 1995/96 surveys, current SLT use was defined as those reporting ever using SLT on a *regular basis* and answering "yes" to the current use question. Because the screening questions changed (removal of "*on regular basis*"), the baseline measure of current use for 1998 to 2010/11 surveys was defined as those reporting having ever used, responding "yes" to every day or some days

current use, and reporting using SLT products at least 10 out of the past 30 days (as a criterion for *"regular use"*). We also explored the sensitivity of our results to varying measures of SLT use based on frequency from 1998 to 2010/11 (1, 20 and 25 days out of the past 30 days), and compared the SLT consumption per capita data with different definitions of SLT use.

Current cigarette smokers were defined as those who reported ever smoking at least 100 cigarettes during their lifetime, and reporting smoking every day or some days at the time of the survey. Current smokers were also distinguished by those reporting smoking every day versus some days, and those reporting quitting attempts within the past year. Former smokers were defined as those who reported ever smoking at least 100 cigarettes during their lifetime, and did not smoke at the time of the survey. Consistently with Mumford *et al*,[3] dual users were defined as those who are simultaneously classified as current smokers and current SLT users according to the definitions above, the later assuming the 10-day metric.

Demographic classifications

We categorized age into seven groups: 18-24 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, 65-74 years and 75 years and older. Due to a low sample size for non-White racial/ethnic groups, race/ethnicity was collapsed into a dichotomous variable, White and Other race. Region was categorized into four categories: Northeast, Midwest, South and West. Education level was grouped into four categories: less than a high school degree, a high school degree or equivalent, some college, and at least a four-year college degree. Household income was grouped into four categories: less than $14,999, $15,000-34,999, $35,000-74,999 and $75,000 or more. Residence was defined by the CPS's use of Metropolitan Statistical Areas (MSAs), which divides major metropolitan and rural areas.

Statistical analyses

Prevalence was estimated using SAS 9.3 (SAS Institute, Cary, NC, USA), applying sample weights and the PROC SURVEY procedures, which allow for adjustment of survey design. Trends in cigarette smoking, SLT use, and dual use prevalence (using both cigarette and SLT products) with 95% confidence intervals (CIs) for different demographic groups were calculated. To characterize trends in SLT prevalence, frequency (number of days used during the last 30 days), and SLT consumption, we performed joinpoint regression analyses using the statistical software Joinpoint, version 4.1.5 (Surveillance Research Program, US National Cancer Institute). Joinpoint regression identifies statistically significant trend change points and the annual percent change (APC) in each significant trend segment.[34] Because SLT prevalence among females is low (less than 0.05% each year), examining the distribution of female SLT use by demographic characteristics yields unstable estimates; therefore, estimations were confined to adult males only.

Binary logistic regression analysis was used to identify potential demographic factors associated with SLT use. Only potential variables with a *p-value* of less than 0.05 in univariate models were retained in the final multivariable logistic regression model. For the multivariate analyses, we categorized age into four groups: 18-24 years, 25-44 years, 45-64 years and 65+ years. The *Cochran-Armitage* trend test was performed to test for trends in age, education and income. For this analysis, odds ratios (ORs) with their corresponding 95% CIs are reported. Regression analyses were performed in SAS 9.3 using the PROC SURVEYLOGISTIC procedure.

2.4 Results

Trends in tobacco use

Tobacco use prevalence for the total population, adult males and females (ages 18 and older), and males ages 18-24 is presented in Table 2.2. Smoking prevalence significantly decreased for adult males with APC rate of 2.7% per year (1998-2011) and for adult females with APC rate of 2.5% per year (1992-2011). For males ages 18-24, smoking prevalence remained approximately constant (non-statistically significant increase of 0.6% per year) from 1992 to 2000 and then decreased at 4.1% per year from 2000 to 2011. Declines in overall SLT prevalence from 1992 to 2003 were observed assuming our baseline SLT use definition (frequency of at least 10 of the past 30 days) from 1998-2011. Total adult SLT use significantly decreased at an APC rate of 4.5% per year from 1992 to 2003. The SLT use prevalence has remained approximately constant since 2003 (non-statistically different from zero). Similar patterns were also found in adult males (APC=-4.4%, 1992-2003) and males age 18-24 (APC=-9.5%, 1992-2003).

The dual use of SLT and smoking also declined. Dual use by adult males declined 5.3% per year, and by adult females decreased at about 8.4% per year throughout the period of analysis.

Smokeless tobacco use by demographic groups

Table 2.3 shows SLT prevalence and trends among adult males by age, race, education, residence, and current smoking frequency. Age-specific SLT prevalence is the highest for males ages 18-24 in early years (1992 and 1995 surveys), but the peak shifted to older ages since 1998 (highest for ages 25-34 from 1998-2003 and for ages 35-44 in 2007 and 2010/11). This shift may

reflect trends in use by birth-cohort, with lower overall consumption of tobacco products in more recent cohorts. The SLT prevalence is highest among whites, those living in rural areas, those with lower education, and non-daily smokers across all survey years. The youngest age group (18-24) had the greatest decline in SLT prevalence from 1992 to 2003 (APC=-9.5%) compared with other age groups; however, the decrease in this and other groups stopped in 2003. Among race/ethnicity, males of other races had a larger decline in prevalence than whites (APCs=-10.6% vs -3.9%, respectively), although their rate decrease stopped earlier. Table 2.4 shows the additional demographic characteristics of SLT use. Among income categories, those earning less than $14,999 per year had the largest significant decline in SLT prevalence compared with other groups (APC=-6.3%), although the decrease stopped in 1993. Among region, SLT prevalence decreased in all regions, with those living in the South having the largest significant declines in SLT prevalence (APC=-5.6%, 1992-2003) compared with other regions. Former and never smokers had also significant declines in SLT use (APCs= -2.4%, 1992-2011 and -5.2%, 1992-2003, respectively).

SLT consumption in the United States

Trends in SLT consumption per capita from 1985-2011 are presented in Figure 2.1a. From 1985 to 1988, there was a significant 3.04% APC decrease per year in SLT consumption per capita. SLT consumption significantly decreased at 2.24% APC from 1991-1999, but has since decreased at 0.35% APC (1999-2011).

Frequency of SLT use

Starting in 1998, respondents were asked about their frequency of SLT use if they reported current use of SLT products every day or some days. Following Mumford *et al*, we defined, as our baseline metric, current regular users of SLT products as those reporting a frequency of at least 10 of the past 30 days. Among those, the average frequency of SLT use (number of days used during the past 30 days) did not vary in total adults, adult males and adult females, throughout the survey years (Table 2.2). Otherwise, the average frequency of SLT use declined in young males by about 1.7% per year from 1998 to 2002.

We also examined different thresholds for defining frequency of SLT use (at least 1 day, 20 days or 25 days of the past 30 days). Figure 2.1b shows the trends of different SLT prevalence assuming different frequency use thresholds (1-day, 10-day, 20-day, and 25-day) in adult males. Prevalence for all demographic groups for all definitions is shown in the appendix (Table 2.5). The 1-day measure leads to 12%-20% (about 17% on average) higher SLT prevalence relative to the baseline (10-day) measure. However, the 1-day definition shows a uniform decline over time, while the 10-day, 20-day and 25-day show that independently of the definition; SLT prevalence decreased until 2003 and has been roughly constant since 2003. While the 10-, the 20-, and 25-day measures show similar patterns, the 10-day definition shows a less pronounced decline. We compared the SLT consumption per capita (Figure 2.1a) with the prevalence of SLT across definitions (Figure 2.1b), and consistent with previous results by Mumford *et al*, the SLT use trends, using the 10-day metric, more closely mirror the SLT consumption per capita compared with other definitions.

Factors associated with SLT use

Due to low SLT prevalence among females, we only included males in the logistic regression analyses. In univariate analyses (Table 2.6), the likelihood of use of smokeless tobacco decreases with increasing age (p_{trend} <0.0001). The likelihood of SLT use decreases with advancing education (p_{trend} <0.0001). People who live in the non-MSA areas (OR=3.2, 95% CI: 3.0-3.4) are more likely to use SLT, residents of the South (OR=2.8, 95% Cl: 2.5-3.1), former smokers are likely to use SLT compared to never smokers, with an unadjusted OR=1.7 (95% CI: 1.6-1.9). In a multivariable logistic regression model, ages 25 to 44 (OR=1.3, 95% CI: 1.1-1.5), white race (OR=3.2, 95% CI: 2.7-3.8), living in a non-MSA area (OR=2.6, 95% CI: 2.4-2.8), unemployment (OR=1.4, 95% CI: 1.1-1.7), lower education, e.g. those with a high school degree or equivalent (OR=1.4, 95% CI: 1.2-1.6), and being a former smoker (OR=2.0, 95% CI: 1.8-2.2) were associated with SLT use after adjusting for other factors.

2.5 Discussion

We examined trends in SLT and cigarette smoking use in the US over a 20-year period using nine cross-sectional, nationally representative surveys. For US adults, significant declines in SLT prevalence for both genders were observed, particularly in males of ages 18 to 24 years old with a decrease of 9.5% per year from 1992 to 2003. However, we found that the decreases in SLT prevalence in most groups stopped since 2003. In contrast, the frequency of SLT use among current users remained approximately constant throughout the period of analysis at an average of 26 out of the past 30 days. Consistent with prevalence trends, SLT per capita consumption declined at a constant rate until 1999, but there was a significant reduction in the rates (APC) since 1999. In contrast, smoking prevalence showed a greater decline since 1998 than prior to that year. The information about SLT use in the TUS-CPS surveys has changed

over time. Importantly, the screening SLT use question was relaxed from "regular use" prior to 1998 to "at least one time" in more recent years (Table 2.1), which may artificially increase the prevalence estimates for recent years relative to earlier years by omitting non-regular users who would have answered yes to ever use. To address this limitation, following the approach by Mumford *et al*[3], we constructed different measures of SLT prevalence based on the reported use frequency, information that has been collected since 1998. Previous analysis of SLT[3] and recent analyses of e-cigarettes by Amato *et al.*[27] demonstrate the importance of accounting for use frequency when estimating tobacco products use prevalence. Here, we found that although the absolute prevalence estimates vary across definitions, with lower prevalence for higher frequency requirements (Figure 2.1b), the estimated male SLT prevalence trends show a consistent pattern of decline until 2003 and stability through 2010 (Figure 2.1b, Table 2.5). The 20- and 25-day measures also show a flattening trend since 2003, but more rapid decline over 1992-2003 compared to the 10-day measure, suggesting that the 20- and 25-day measures are more sensitive metrics of changes in trend.[28] The results also differ somewhat for male ages 18 to 24 compared with adult males, suggesting greater sensitivity to secular trends. Similarly to Amato *et al*, we found that any past 30-day use does not necessarily detect changes in use trends.[27]

Younger age, white race, unemployment, residents of the South, residents of rural areas lower education and former smoker status were found to be associated with SLT use. Those reporting less than 12 years of education were twice as likely to use smokeless tobacco in comparison with those with at least a college degree. White males were nearly 3 times more likely to use smokeless tobacco compared with those who are other races, thus showing the importance of race and SES. These findings are consistent with recent results by Bhattacharyya

et al.,[35] whose analyses found that whites are 2.5 times higher for active snuff use and 2.2 times higher for active chewing tobacco use, as well as with the earlier analyses of TUS-CPS data from 1992-2002 by Mumford *et al.*[3]

The Healthy People 2020 target [36] is to reduce SLT prevalence for U.S adults to 0.3% or below. However, current prevalence is about 1.3% and at current trends, the target will likely not be achieved. The change in the decreasing trend of SLT use since 2003 may be partly attributable to the changing SLT landscape, with the introduction of new alternative nicotine delivery products in recent years, like snus[37,38] and electronic cigarettes, which have reenergized the market, and the increasing influence of products with flavoring and portion pouch packaging.[39,40] Previous studies have found important reductions in chewing tobacco sales, which may explain the decreases observed in SLT prevalence prior to 2003.[39,41] In contrast, the promotion of moist snuff, snus and dissolvable tobacco, with "spit-free" formulations, may be responsible for the trend changes in SLT use.[37] In addition, data from the CDC state system[42] shows that cigarette taxes increased in many states from 2003 to 2010, while SLT taxes changed in fewer states and often by small amounts, which may explain the relative increase in smokeless tobacco use compared to cigarettes (i.e., the flattening in trend in smokeless tobacco use while cigarette use declined more rapidly than in prior years).

Understanding the relative impacts of different products in shaping SLT consumption is needed. It is thus important to conduct studies of SLT use distinguishing by product category and use patterns, although the constant changes in the market and product category distribution, as well as changes in survey questions, make these studies challenging. Preliminary results (data not shown) using TUS-CPS suggest a progressive replacement of chewing tobacco by snus and new forms of SLT.

A strength of our study is having access to detailed tobacco use data from nationally representative surveys, which allows for quantitative joinpoint analyses of SLT use trends for the past two decades in relevant demographic groups. In addition, we examined smokeless tobacco use trends and SLT consumption, allowing for comparisons between self-reported data and market sales. We were able to go beyond recent studies [3,30] to examine trends in SLT use since 2003, and how patterns varied depending on the measure of use (number of days used in the past 30 days) and the socio-demographic group. Nonetheless, our findings should be interpreted with caution due to the following limitations.

First, while the TUS-CPS is a nationally representative survey, all information is self-reported, which may lead to underestimation of the true prevalence. Second, the survey data is cross-sectional, making it difficult to assess trends in initiation and cessation rates of SLT use. Third, the changes across survey years of SLT use definitions may have introduced bias, starting from the regular use to ever use screening question. Nevertheless, as discussed, we use information on frequency to attempt to increase the current use definition across years, and sensitivity analyses show that our general conclusions are consistent across alternative SLT use definitions. Lastly, tobacco companies have continued to introduce new SLT products on the market, making the interpretation of trends difficult given the variability in available products each year.

In sum, we report a significant declining trend in SLT product use from 1992 to 2003, suggesting the impact of tobacco control policies in reducing tobacco consumption. However, the decline ended in 2003 for SLT prevalence and ended in 1999 for per capita, highlighting the need for additional tobacco control efforts focusing on alternative tobacco products. These results are consistent with a recent analysis by Nguyen *et al*. that shows little change in SLT

prevalence between 2011 and 2013 in most states, and increases in prevalence in some states such as Louisiana, Montana, South Carolina and West Virginia.[43] With the Healthy People 2020 goal, extra efforts are necessary in the next 5 years to achieve the 0.3% target. Focusing tobacco control efforts, particularly targeting at-risk demographic groups, is needed to further reduce SLT consumption in the U.S. Little is known about whether the increasing use of e-cigarettes [44,45] and the potential use of snus will impact future SLT trends. E-cigarettes may replace SLT use, especially snus, if it is viewed as a better harm reduction alternative. Continued monitoring of SLT use and its relationship to e-cigarette use is needed.

2.6 References

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Table 2.1 Measures of Smokeless Tobacco Use in TUS-CPS, 1992-2011

	Screening question	Current Use	Frequency of Use Question	SLT DEFINITION	[product]
1992/93	Have you ever used [product] on a **regular basis?**	Do you now use [product]?	n/a	Have ever used on a regular basis; answer "yes" to current use question	Chewing tobacco or snuff
1995/96	Have you ever used [product] on a **regular basis?**	Do you now use [product]?	n/a	Have ever used on a regular basis; answer "yes" to current use question	Chewing tobacco or snuff
1998	Have you ever used [product]?	Do you now smoke/use [product] every day, some days or not at all?	On how many of the past 30 days did you use [product]?	Have ever used; report use on at least 10 of past 30 days	Chewing tobacco or snuff
1999	Have you ever used [product] on a **regular basis?**	Do you now smoke/use [product] every day, some days or not at all?	On how many of the past 30 days did you use [product]?	Have ever used on a regular basis; report use on at least 10 of past 30 days	Chewing tobacco or snuff
2000	Have you ever used [product]?	Do you now smoke/use [product] every day, some days or not at all?	On how many of the past 30 days did you use [product]?	Have ever used; report use on at least 10 of past 30 days	Chewing tobacco or snuff
2001/02	Have you ever used [product], **even one time?**	Do you now smoke/use [product] every day, some days or not at all?	On how many of the past 30 days did you use [product]?	Have ever used on even one time; report use on at least 10 of past 30 days	Chewing tobacco or snuff
2003	Have you ever used [product], **even one time?**	Do you now smoke/use [product] every day, some days or not at all?	On how many of the past 30 days did you use [product]?	Have ever used on even one time; report use on at least 10 of past 30 days	Chewing tobacco or snuff
2007	Have you ever used [product], **even one time?**	Do you now smoke/use [product] every day, some days or not at all?	On how many of the past 30 days did you use [product]?	Have ever used on even one time; report use on at least 10 of past 30 days	Chewing tobacco or snuff
2010/11	Have you ever used any of [products] **even one time**?	Do you now use [product] every day, some days or not at all?	On how many of the past 30 days did you use [product]?	Have ever used on even one time; report use on at least 10 of past 30 days	Smokeless tobacco, such as moist snuff, dip, spit, chewing tobacco or snus

Table 2.2 Prevalence and patterns of tobacco use trends in TUS-CPS, 1992-2011 – Joinpoint Regression

	Prevalence (%)									Trends			
	1992/93	1995/96	1998	1999	2000	2001/02	2003	2007	2010/11	Year 1	APC 1	Year 2	APC 2
Smoking													
Total population 18+	24.5	23.6	22.8	21.7	21.9	21.0	18.9	18.0	16.1	1992-1998	-1.3	1998-2011	-2.8*
	(24.3, 24.7)	(23.3, 23.8)	(22.4, 23.1)	(21.4, 22.0)	(21.6, 22.1)	(20.7, 21.2)	(18.7, 19.1)	(17.6, 18.3)	(15.8, 16.3)		(-3.7, 1.1)		(-3.6, -2.1)
Male 18+	26.8	25.8	25.3	24.1	24.4	23.3	21.2	20.1	18.0	1992-1998	-1.1	1998-2011	-2.7*
	(26.5, 27.1)	(25.5, 26.2)	(24.7, 25.9)	(23.7, 24.6)	(23.9, 24.8)	(23.0, 23.7)	(20.8, 21.5)	(19.5, 20.6)	(17.7, 18.4)		(-3.3, 1.3)		(-3.5, -2.0)
Female 18+	22.6	21.5	20.4	19.5	19.6	18.8	16.8	16.0	14.2	1992-2011	-2.5*		
	(22.3, 22.8)	(21.2, 21.7)	(20.0, 20.9)	(19.1, 19.8)	(19.2, 19.9)	(18.5, 19.1)	(16.5, 17.1)	(15.6, 16.5)	(14.0, 14.5)		(-2.9, -2.1)		
Male 18-24	27.7	28.2	30.0	28.1	29.5	28.1	24.4	21.3	19.5	1992-2000	0.6	2000-2011	-4.1*
	(26.7, 28.7)	(27.0, 29.3)	(28.0, 32.1)	(26.6, 29.6)	(28.1, 30.9)	(26.9, 29.3)	(23.3, 25.6)	(19.3, 23.3)	(18.4, 20.7)		(-1.0, 2.1)		(-5.4, -2.7)
SLT use													
Total population 18+	2.1	2.0	1.8	1.5	1.5	1.4	1.3	1.4	1.3	1992-2003	-4.5*	2003-2011	-0.4
	(2.1, 2.2)	(1.9, 2.1)	(1.7, 1.9)	(1.4, 1.5)	(1.5, 1.6)	(1.4, 1.5)	(1.2, 1.4)	(1.3, 1.5)	(1.2, 1.4)		(6.1, -2.8)		(-10.5, 10.7)
Male 18+	4.2	3.9	3.5	2.9	3.0	2.8	2.6	2.7	2.5	1992-2003	-4.4*	2003-2011	-0.2
	(4.0, 4.3)	(3.7, 4.0)	(3.3, 3.8)	(2.7, 3.0)	(2.9, 3.2)	(2.7, 3.0)	(2.4, 2.7)	(2.5, 2.9)	(2.4, 2.7)		(-6.0, -2.8)		(-9.5, 10.1)
Female 18+	0.42	0.28	0.24	0.18	0.21	0.16	0.14	0.15	0.10	1992-2011	-8.2*		
	(0.38, 0.46)	(0.25, 0.32)	(0.18, 0.30)	(0.14, 0.22)	(0.17, 0.24)	(0.13, 0.19)	(0.11, 0.16)	(0.11, 0.20)	(0.07, 0.12)		(-9.8, -6.5)		
Male 18-24	7.2	5.8	4.4	3.5	3.4	2.9	2.4	2.7	3.0	1992-2003	-9.5*	2003-2011	2.1
	(6.6, 7.7)	(5.2, 6.4)	(3.5, 5.4)	(2.9, 4.1)	(2.9, 4.0)	(2.5, 3.3)	(2.0, 2.8)	(1.9, 3.4)	(2.4, 3.4)		(-11.1, -7.8)		(-7.9, 13.1)
Dual use SLT and smoking													
Total population 18+	0.49	0.45	0.35	0.25	0.32	0.28	0.23	0.23	0.22	1992-2011	-5.2*		
	(0.45, 0.52)	(0.42, 0.49)	(0.30, 0.41)	(0.21, 0.28)	(0.28, 0.36)	(0.25, 0.31)	(0.20, 0.25)	(0.18, 0.27)	(0.19, 0.25)		(-7.1, -3.4)		
Male 18+	1.0	0.91	0.71	0.50	0.65	0.56	0.46	0.45	0.44	1992-2011	-5.3*		
	(0.93, 1.1)	(0.83, 0.98)	(0.60, 0.82)	(0.43, 0.57)	(0.57, 0.73)	(0.50, 0.62)	(0.41, 0.52)	(0.36, 0.54)	(0.38, 0.50)		(-7.1, -3.5)		
Female 18+	0.05	0.04	0.03	0.02	0.01	0.02	0.01	0.02	0.01	1992-2011	-8.4*		
	(0.03, 0.06)	(0.02, 0.05)	(0, 0.05)	(0, 0.03)	(0.00, 0.02)	(0.01, 0.03)	(0.00, 0.01)	(0.005, 0.04)	(0, 0.02)		(-13.2, -3.3)		
Male 18-24	2.3	1.9	1.4	1.0	1.3	1.1	0.83	0.55	1.0	1992-2003	-8.6*	2003-2010	2.3
	(1.9, 2.6)	(1.6, 2.3)	(0.93, 2.0)	(0.66, 1.3)	(1.0, 1.7)	(0.83, 1.4)	(0.60, 1.1)	(0.22, 0.88)	(0.7, 1.2)		(-11.8, -5.3)		(-10.9, 17.5)
Frequency of SLT use (days)													
Total population 18+		-	26.5	26.8	26.3	26.4	26.3	26.6	26.5	1992-2011	0		
			(26.0, 27.0)	(26.5, 27.2)	(26.0, 26.6)	(26.1, 26.7)	(26.0, 26.6)	(26.1, 27.1)	(26.2, 26.9)		(-0.1, 0.2)		
Male 18+		-	26.5	26.8	26.2	26.3	26.2	26.6	26.5	1992-2011	0.1		
			(26.0, 27.0)	(26.4, 27.1)	(25.8, 26.6)	(26.0, 26.6)	(25.8, 26.6)	(26.1, 27.2)	(26.2, 26.9)		(-0.1, 0.2)		
Female 18+		-	27.0	27.5	27.8	27.6	28.1	26.1	25.3	1998-2003	0.6	2003-2011	-1.4
			(25.3, 28.6)	(26.3, 28.8)	(26.8, 28.8)	(26.6, 28.6)	(27.1, 29.1)	(24.0, 28.2)	(23.4, 27.2)		(-7.7, 9.6)		(-14.1, 13.1)
Male 18-24		-	25.9	25.8	24.6	24.5	24.5	24.7	24.9	1998-2002	-1.7*	2002-2011	0.3*
			(24.3, 27.4)	(24.7, 27.0)	(23.4, 25.9)	(23.3, 25.7)	(23.1, 25.8)	(22.4, 27.0)	(23.7, 26.1)		(-1.9, -1.5)		(0.2, 0.3)

95% confidence intervals presented in parentheses; *significant at p<0.05

Table 2.3 Prevalence of current smokeless tobacco use among males ages 18+ – Joinpoint Regression

	Prevalence (%)									Trends			
	1992/93	1995/96	1998	1999	2000	2001/02	2003	2007	2010/11	Year 1	APC 1	Year 2	APC 2
Age Groups													
18-24	7.2	5.8	4.4	3.5	3.4	2.9	2.4	2.7	2.9	1992-2003	-9.5*	2003-2011	2.1
	(6.6, 7.8)	(5.2, 6.4)	(3.5, 5.4)	(2.9, 4.1)	(2.9, 4.0)	(2.5, 3.3)	(2.0, 2.8)	(1.9, 3.4)	(2.4, 3.4)		(-11.1, -7.8)		(-7.9, 13.1)
25-34	5.5	5.6	6.1	4.6	5.1	4.5	3.9	3.4	2.9	1992-2011	-3.3*		
	(5.1, 5.8)	(5.2, 6.0)	(5.4, 6.9)	(4.2, 5.1)	(4.7, 5.6)	(4.2, 4.9)	(3.5, 4.3)	(2.8, 4.0)	(2.6, 3.2)		(-4.8, -1.9)		
35-44	3.1	3.1	2.9	2.8	2.8	3.3	3.2	4.0	3.6	1992-2011	0.9		
	(2.8, 3.3)	(2.9, 3.4)	(2.4, 3.3)	(2.5, 3.1)	(2.5, 3.2)	(3.0, 3.6)	(2.9, 3.5)	(3.4, 4.6)	(3.3, 4.0)		(-0.2, 2.1)		
45-54	2.9	2.7	2.3	1.9	2.0	1.9	1.9	2.3	2.4	1992-2001	-4.9*	2001-2011	2.8*
	(2.6, 3.2)	(2.4, 3.0)	(1.8, 2.7)	(1.6, 2.1)	(1.7, 2.3)	(1.7, 2.1)	(1.7, 2.1)	(1.9, 2.7)	(2.2, 2.7)		(-7.1, -2.8)		(0.2, 5.4)
55-64	3.1	2.5	2.5	2.1	1.8	1.9	1.8	1.8	1.8	1992-2000	-5.0*	2000-2011	0.3
	(2.7, 3.4)	(2.2, 2.9)	(1.9, 3.1)	(1.7, 2.5)	(1.5, 2.1)	(1.6, 2.2)	(1.5, 2.0)	(1.4, 2.2)	(1.5, 2.0)		(-7.0, -2.9)		(-7.4, 8.6)
65-74	3.2	2.6	2.0	1.8	2.3	2.2	1.7	1.8	1.7	1992-2011	-3.5*		
	(2.8, 3.6)	(2.2, 3.0)	(1.4, 2.6)	(1.4, 2.1)	(1.9, 2.8)	(1.8, 2.5)	(1.4, 2.1)	(1.2, 2.4)	(1.4, 2.0)		(-5.1, -1.8)		
75+	3.4	2.8	2.4	2.0	2.2	1.6	1.3	1.0	0.95	1992-2011	-7.5*		
	(2.9, 4.0)	(2.3, 3.4)	(1.6, 3.2)	(1.5, 2.5)	(1.7, 2.7)	(1.2, 1.9)	(1.0, 1.7)	(0.53, 1.5)	(0.69, 1.2)		(-9.0, -6.0)		
Race/Ethnicity													
White	4.5	4.3	3.9	3.2	3.4	3.2	2.9	3.0	2.9	1992-2003	-3.9*	2003-2011	-0.2
	(4.3, 4.6)	(4.1, 4.4)	(3.6, 4.2)	(3.1, 3.4)	(3.2, 3.6)	(3.1, 3.4)	(2.7, 3.0)	(2.8, 3.3)	(2.8, 3.1)		(-5.5, -2.3)		(-7.3, 7.6)
Other	2.1	1.7	1.1	0.89	1.0	0.81	1.1	1.0	0.89	1992-1999	-10.6*	1999-2011	-0.5
	(1.8, 2.4)	(1.4, 2.0)	(0.70, 1.5)	(0.66, 1.1)	(0.80, 1.3)	(0.63, 1.0)	(0.85, 1.3)	(0.7, 1.3)	(0.71, 1.1)		(-17.9, -2.7)		(-4.2, 3.4)
Education													
Less than 12 years	5.8	4.8	4.0	3.5	3.5	3.0	2.8	2.8	2.4	1992-2003	-6.6*	2003-2011	-1.3
	(5.4, 6.2)	(4.4, 5.3)	(3.3, 4.6)	(3.1, 4.0)	(3.1, 3.9)	(2.7, 3.3)	(2.4, 3.1)	(2.3, 3.4)	(2.1, 2.8)		(-7.5, -5.6)		(-6.5, 4.1)
H.S. degree	5	4.9	4.6	3.9	3.8	3.8	3.6	3.7	3.6	1992-2003	-3.2*	2003-2011	0
	(4.7, 5.3)	(4.6, 5.2)	(4.1, 5.1)	(3.6, 4.3)	(3.5, 4.2)	(3.5, 4.1)	(3.3, 3.8)	(3.2, 4.1)	(3.3, 3.8)		(-4.8, -1.6)		(-6.8, 7.2)
Some college	4.1	3.9	3.6	2.8	3.1	2.9	2.6	3.1	2.8	1992-2003	-4.0*	2003-2011	0.9
	(3.8, 4.4)	(3.6, 4.2)	(3.1, 4.1)	(2.5, 3.1)	(2.8, 3.5)	(2.6, 3.1)	(2.4, 2.9)	(2.6, 3.6)	(2.5, 3.1)		(-6.2, -1.7)		(-8.5, 11.2)
College degree +	1.9	2.0	1.8	1.4	1.6	1.7	1.3	1.2	1.3	1992-2011	-2.5*		
	(1.7, 2.1)	(1.8, 2.2)	(1.5, 2.1)	(1.2, 1.6)	(1.4, 1.8)	(1.5, 1.9)	(1.1, 1.5)	(0.93, 1.5)	(1.1, 1.5)		(-3.9, -1.1)		
Residence													
MSA	3.3	2.8	2.5	2.0	2.1	2.0	1.8	1.9	1.9	1992-2003	-5.3*	2003-2011	0.8
	(3.2, 3.5)	(2.7, 2.9)	(2.2, 2.7)	(1.8, 2.1)	(1.9, 2.2)	(1.9, 2.2)	(1.7, 2.0)	(1.7, 2.1)	(1.8, 2.0)		(-6.8, -3.9)		(-6.0, 8.0)
Non-MSA	9.8	8.4	7.9	6.6	7.0	6.4	5.8	6.8	5.9	1992-2003	-4.5*	2003-2011	0.5
	(9.3, 10.2)	(7.9, 8.9)	(7.0, 8.6)	(6.1, 7.1)	(6.5, 7.5)	(6.0, 6.8)	(5.4, 6.2)	(5.9, 7.4)	(5.5, 6.4)		(-2.6, 8.9)		
Smoking Status													
Current	3.8	3.5	2.8	2.1	2.7	2.4	2.2	2.3	2.5	1992-2011	-2.1		
	(3.5, 4.0)	(3.2, 3.8)	(2.4, 3.3)	(1.8, 2.4)	(2.4, 3.0)	(2.2, 2.7)	(2.0, 2.5)	(1.8, 2.7)	(2.2, 2.8)		(-4.1, 0)		
Current, Someday	6.9	7.1	5.8	3.9	5.1	4.5	4.4	4.2	5.1	1992-2003	-5.0*	2003-2011	2.2
	(6.2, 7.9)	(6.1, 8.1)	(4.4, 7.1)	(3.0, 4.8)	(4.2, 6.1)	(3.7, 5.2)	(3.5, 5.2)	(2.9, 5.6)	(4.1, 6.0)		(-8.9, -0.9)		(-16.3, 24.9)
Current, Everyday	3.1	2.7	2.1	1.6	2.0	1.9	1.7	1.8	1.8	1992-1999	-9.7*	1999-2011	-0.3
	(2.8, 3.4)	(2.5, 3.0)	(1.6, 2.5)	(1.3, 1.9)	(1.7, 2.3)	(1.6, 2.2)	(1.5, 2.0)	(1.4, 2.3)	(1.5, 2.1)		(-12.1, -7.3)		(-1.9, 1.4)

95% confidence intervals presented in parentheses; *significant at p<0.05

Table 2.4 Prevalence of current smokeless tobacco use among males ages 18+ - Joinpoint regression, additional demographic variables.

	Prevalence (%)									Trends			
	1992/93	1995/96	1998	1999	2000	2001/02	2003	2007	2010/11	Year 1	APC 1	Year 2	APC 2
Household													
Less than	5.6	4.1	4.1	3.2	3.8	2.9	2.5	2.9	2.6	1992-2003	-6.3*	2003-2011	-0.1
	(5.2, 6.0)	(3.8, 4.5)	(3.4, 4.8)	(2.7, 3.6)	(3.3, 4.3)	(2.5, 3.3)	(2.2, 2.9)	(2.2, 3.7)	(2.2, 3.0)		(-9.3, -3.3)		(-16.3, 19.2)
$15,000 to	4.6	4.7	4.1	3.4	3.5	3.2	2.8	2.7	2.5	1992-2011	-3.8*		
	(4.3, 4.8)	(4.4, 5.0)	(3.6, 4.6)	(3.1, 3.7)	(3.2, 3.9)	(3.0, 3.5)	(2.6, 3.1)	(2.2, 3.1)	(2.2, 2.7)		(-4.9, -2.6)		
$35,000 to	3.6	3.8	4.1	3.2	3.4	3.3	3.1	3.7	2.9	1992-2011	-1.2*		
	(3.4, 3.8)	(3.5, 4.0)	(3.7, 4.6)	(2.9, 3.5)	(3.1, 3.6)	(3.0, 3.6)	(2.8, 3.3)	(3.2, 4.2)	(2.6, 3.1)		(-2.3, -0.1)		
$75,000 or more	1.8	2.4	1.6	1.7	1.9	2.1	2.0	2.0	2.3	1992-2011	0.6		
	(1.5, 2.2)	(2.1, 2.7)	(1.2, 1.9)	(1.4, 1.9)	(1.7, 2.2)	(1.9, 2.3)	(1.8, 2.2)	(1.7, 2.3)	(2.1, 2.5)		(-1.2, 2.4)		
Region													
Northeast	1.8	1.6	1.3	1.3	1.3	1.4	1.3	1.5	1.4	1992-1999	-4.5*	1999-2011	0.7
	(1.6, 2.0)	(1.4, 1.8)	(0.98, 1.7)	(1.0, 1.5)	(1.1, 1.6)	(1.1, 1.6)	(1.1, 1.5)	(1.1, 2.0)	(1.2, 1.6)		(-7.3, -1.7)		(-0.7, 2.1)
Midwest	4.0	3.9	3.8	3.2	3.4	3.4	3.0	3.1	3.1	1992.-2011	-1.7*		
	(3.7, 4.3)	(3.6, 4.2)	(3.2, 4.3)	(2.8, 3.5)	(3.0, 3.7)	(3.2, 3.7)	(2.7, 3.2)	(2.6, 3.5)	(2.8, 3.3)		(-2.5, -0.9)		
South	6.3	5.8	5.1	4.0	4.1	3.8	3.5	3.4	3.2	1992-2003	-5.6*	2003-2011	-0.8
	(6.0, 6.6)	(5.5, 6.1)	(4.6, 5.6)	(3.7, 4.3)	(3.8, 4.4)	(3.5, 4.0)	(3.2, 3.7)	(2.9, 3.8)	(3.0, 3.5)		(-7.6, -3.6)		(-10.2, 9.6)
West	3.3	3.0	2.6	2.2	2.3	2.1	1.8	2.2	1.9	1992-2003	-5.1*	2003-2011	0.2
	(3.0, 3.6)	(2.7, 3.2)	(2.1, 3.0)	(1.9, 2.5)	(2.0, 2.6)	(1.8, 2.3)	(1.6, 2.0)	(1.8, 2.6)	(1.6, 2.1)		(-6.5, -3.7)		(-5.6, 6.3)
Smoking Status													
Current with	4.2	3.3	2.5	1.9	NA	3.3	2.8	2.2	2.6				
quit attempts	(4.0, 4.3)	(2.7, 3.8)	(1.7, 3.3)	(1.4, 2.5)	NA	(2.7, 3.8)	(2.3, 3.4)	(1.3, 3.1)	(2.0, 3.1)				
Former	4.5	4.5	4	3.6	3.6	3.7	3.6	4.0	2.5	1992-2011	-2.4*		
	(4.2, 4.7)	(4.2, 4.8)	(3.5, 4.5)	(3.2, 3.9)	(3.3, 3.9)	(3.4, 3.9)	(3.3, 3.9)	(2.5, 4.5)	(2.2, 2.8)		(-3.6, -1.2)		
Never	4.2	3.8	3.5	2.9	2.8	2.6	2.3	2.3	2.1	1992-2003	-5.2*	2003-2011	-1.3
	(4.0, 4.4)	(3.5, 4.0)	(3.2, 3.9)	(2.7, 3.1)	(2.6, 3.1)	(2.5, 2.8)	(2.1, 2.4)	(2.0, 2.6)	(2.0, 2.3)		(-6.7, -3.8)		(-7.5, 5.4)
Current with													
age ≤45	1.5	1.4	1.1	0.81	NA	1.5	1.3	1.0	1.1	1992-2011	-2.4*		
	(1.3, 1.7)	(1.2, 1.7)	(0.65, 1.5)	(0.55, 1.1)		(1.3, 1.8)	(1.0, 1.6)	(0.58, 1.4)	(0.83, 1.4)		(-3.6, -1.1)		
age >45	0.34	0.36	0.27	0.20	NA	0.20	0.15	0.23	0.28	1992-2003	-5.3*	2003-2011	-1.2
	(0.23, 0.45)	(0.23, 0.49)	(0.09, 0.44)	(0.06, 0.34)		(0.12, 0.28)	(0.07, 0.23)	(0.07, 0.39)	(0.16, 0.40)		(-7.3, -3.2)		(-9.4, 7.7)

95% confidence intervals presented in parentheses; *significant at p<0.05

Figure 2.1 Top panel (a): Trend of SLT consumption per capita in the US, 1985-2011 Bottom panel (b): Trends in SLT prevalence for different SLT use definitions (at least N days of the last 30 days), males (18+).

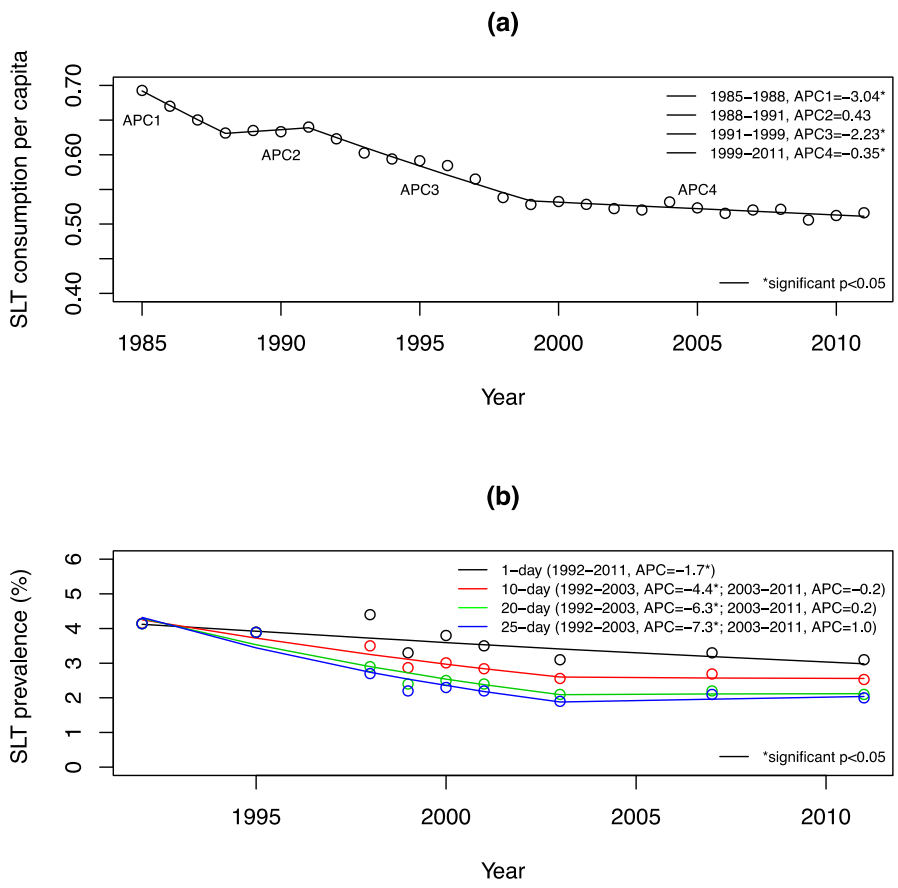

Table 2.5 SLT prevalence for different SLT use definitions (at least N days of the last 30 days)

	1998	1999	2000	2001/02	2003	2007	2010/11
Total population 18+							
At least 1 day	2.2	1.7	1.9	1.8	1.6	1.7	1.6
	(2.1, 2.4)	(1.6, 1.8)	(1.8, 2.0)	(1.7, 1.9)	(1.5, 1.7)	(1.6, 1.8)	(1.5, 1.6)
At least 10 days	1.8	1.5	1.5	1.4	1.3	1.4	1.3
	(1.7, 1.9)	(1.4, 1.5)	(1.5, 1.6)	(1.4, 1.5)	(1.2, 1.4)	(1.3, 1.5)	(1.2, 1.4)
At least 20 days	1.5	1.3	1.3	1.2	1.1	1.2	1.1
	(1.4, 1.6)	(1.2, 1.3)	(1.2, 1.3)	(1.1, 1.3)	(1.0, 1.1)	(1.1, 1.3)	(1.0, 1.1)
At least 25 days	1.4	1.2	1.2	1.1	1	1.1	0.98
	(1.3, 1.5)	(1.1, 1.2)	(1.1, 1.3)	(1.1, 1.2)	(0.9, 1.0)	(0.99, 1.2)	(0.93, 1.0)
Male 18+							
At least 1 day	4.4	3.3	3.8	3.5	3.1	3.3	3.1
	(4.1, 4.7)	(3.1, 3.5)	(3.6, 3.9)	(3.4, 3.7)	(3.0, 3.3)	(3.0, 3.5)	(3.0, 3.2)
At least 10 days	3.5	2.9	3.0	2.8	2.6	2.7	2.5
	(3.3, 3.8)	(2.7, 3.0)	(2.9, 3.2)	(2.7, 3.0)	(2.4, 2.7)	(2.5, 2.9)	(2.4, 2.7)
At least 20 days	2.9	2.4	2.5	2.4	2.1	2.3	2.1
	(2.7, 3.2)	(2.3, 2.6)	(2.3, 2.6)	(2.2, 2.5)	(2.0, 2.2)	(2.1, 2.5)	(2.0, 2.3)
At least 25 days	2.7	2.2	2.3	2.2	1.9	2.1	2
	(2.5, 3.0)	(2.1, 2.4)	(2.1, 2.4)	(2.1, 2.3)	(1.8, 2.1)	(1.9, 2.3)	(1.9, 2.1)
Female 18+							
At least 1 day	0.27	0.2	0.23	0.2	0.17	0.17	0.13
	(0.21, 0.33)	(0.16, 0.24)	(0.19, 0.28)	(0.17, 0.23)	(0.14, 0.20)	(0.12, 0.21)	(0.10, 0.15)
At least 10 days	0.24	0.18	0.21	0.16	0.14	0.15	0.10
	(0.18, 0.30)	(0.14, 0.22)	(0.17, 0.24)	(0.13, 0.19)	(0.11, 0.16)	(0.11, 0.20)	(0.07, 0.12)
At least 20 days	0.21	0.16	0.19	0.14	0.12	0.13	0.07
	(0.16, 0.26)	(0.12, 0.19)	(0.15, 0.22)	(0.11, 0.17)	(0.10, 0.15)	(0.09, 0.17)	(0.05, 0.09)
At least 25 days	0.2	0.15	0.18	0.14	0.12	0.12	0.07
	(0.15, 0.25)	(0.11, 0.18)	(0.14, 0.21)	(0.11, 0.17)	(0.10, 0.14)	(0.08, 0.16)	(0.05, 0.08)
Male 18-24							
At least 1 day	6.3	4.3	4.9	4.1	3.4	3.6	4
	(5.2, 7.4)	(3.7, 4.9)	(4.3, 5.6)	(3.6, 4.6)	(3.0, 3.9)	(2.7, 4.4)	(3.4, 4.6)
At least 10 days	4.4	3.5	3.4	2.9	2.4	2.7	3.0
	(3.5, 5.4)	(2.9, 4.1)	(2.9, 4.0)	(2.5, 3.3)	(2.0, 2.8)	(1.9, 3.4)	(2.4, 3.4)
At least 20 days	3.7	2.8	2.5	2.1	1.7	2	2.2
	(2.9, 4.5)	(2.2, 3.3)	(2.1, 3.0)	(1.8, 2.5)	(1.4, 2.1)	(1.4, 2.7)	(1.8, 2.6)
At least 25 days	3.3	2.6	2.2	1.9	1.6	1.8	2
	(2.5, 4.1)	(2.1, 3.1)	(1.8, 2.7)	(1.6, 2.3)	(1.2, 1.9)	(1.2, 2.4)	(1.6, 2.4)

95% confidence intervals presented in parentheses

Table 2.6 Factors related to smokeless tobacco use among males ages 18+ in the United States, 1992-2011 – Logistic Regression

	Univariate Model		Multivariable Model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (year)*				
18-24	Ref	<0.0001	Ref	<0.0001
25-44	1.2 (1.1, 1.4)		1.3 (1.1, 1.5)	
45-64	0.71 (0.64, 0.79)		0.59 (0.47, 0.73)	
65+	0.56 (0.49, 0.63)		0.39 (0.27, 0.56)	
Birth Year	1.0 (1.0, 1.0)	<0.0001	1.0 (1.0, 1.0)	0.4581
Race				
White	3.1 (2.7, 3.5)	<0.0001	3.2 (2.7, 3.8)	<0.0001
Other	Ref		Ref	
Region				
Northeast	Ref	<0.0001	Ref	<0.0001
Midwest	2.4 (2.2, 2.7)		1.9 (1.6, 2.2)	
South	2.8 (2.5, 3.1)		2.5 (2.2, 2.9)	
West	1.5 (1.4, 1.7)		1.5 (1.3, 1.8)	
Education Level*				
Less than 12 years	Ref	<0.0001	Ref	<0.0001
H.S. degree	1.3 (1.2, 1.4)		1.4 (1.2, 1.6)	
Some college	0.93 (0.84, 1.0)		1.0 (0.90, 1.2)	
College degree+	0.44 (0.49, 0.49)		0.58 (0.50, 0.68)	
Household Income*				
Less than $14,999	Ref	<0.0001	Ref	0.071
$15,000 to 34,999	1.0 (0.93, 1.1)		1.0 (0.88, 1.2)	
$35,000 to 74,999	1.0 (0.94, 1.1)		1.1 (0.98, 1.3)	
$75,000 or more	0.73 (0.66, 0.81)		1.0 (0.87, 1.2)	
Residence				
MSA	Ref		Ref	
Non-MSA	3.2 (3.0, 3.4)	<0.0001	2.6 (2.4, 2.8)	<0.0001
Unemployment				
Yes	1.3 (1.1, 1.6)	0.0016	1.4 (1.1, 1.7)	0.0019
No	Ref		Ref	
Smoking status				
Current smoker	1.1 (1.0, 1.2)	<0.001	0.87 (0.79, 0.97)	<0.001
Former Smoker	1.7 (1.6, 1.9)		2.0 (1.8, 2.2)	
Never Smoker	Ref		Ref	

Ref: Reference; * Cochran-Armitage Trend Test shows $p_{trend}<0.0001$

Chapter 3

Examining the Transitions between Cigarette and Smokeless Tobacco Product Use in the United States Using the 2002-2003 and 2010-2011 Longitudinal Cohorts

3.1 Abstract

Introduction: Smokeless tobacco (SLT) use in the US has remained constant or even increased slightly in recent years, while smoking has continuously decreased. Characterization of transitions between tobacco products is critical to understand the reasons behind the continuing use of smokeless tobacco.

Methods: Two longitudinal cohorts of Tobacco Use Supplement of the Current Population Survey (TUS-CPS), 2002-2003 (n=14,996) and 2010-2011 (n=18,226) were used to examine transitions between cigarette and SLT use over one-year periods. Weighted population percentages of four use categories (exclusive cigarette use, exclusive SLT use, dual use, and neither) were calculated for different demographic groups. Transition between use categories and quit rates by product were calculated for each cohort.

Results: Relative to 2002-2003, smoking quit rates of male exclusive smokers significantly increased in 2010-2011 (11.6% vs. 24.4%, $p<0.0001$), but the corresponding SLT use quit rates remained stable (41.3% vs. 40.0%, $p=0.87$). Similar patterns were found in females with smoking quit rates increasing considerably (12.3% vs 24.2%, $p<0.0001$). Smoking quit rates increased in most sociodemographic groups analyzed. Male SLT use quit rates were significantly lower in SLT exclusive users than in dual users in the 2010-2011 cohort (40.0% vs. 62.2%; $p=0.04$), but smoking

quit rates in exclusive smokers and in dual users were roughly equivalent (24.4% vs. 29.5%, p=0.68).

Conclusions: While smoking quit rates doubled overall and increased in most sociodemographic groups, SLT quit rates remained constant with little transition between products. Longer-term prospective data examining polytobacco use is needed to better understand transitions between tobacco products.

3.2 Introduction

While cigarette smoking prevalence continues to decrease in the United States (US), smokeless tobacco (SLT) use (chewing tobacco, snuff and snus) has remained constant or even increased slightly since the early 2000s.[1,2] Nevertheless, 7.1% of US adult males were current SLT users in 2012,[3] making it the third most used tobacco product after cigarettes and cigars.

SLT has been proposed as a safer alternative to cigarettes.[4,5] However, SLT products are addictive and increase the risk of some cancers[6,7] and cardiovascular diseases.[8,9] Moreover, it has been suggested that SLT products may act as a gateway to cigarette smoking and discourage cessation.[10,11] Consequently, the public health impact of SLT products is unclear.[10]

Information on transitions between smoking and SLT use is needed to assess the potential long-term effects of SLT and potentially other alternative tobacco products on smoking cessation and initiation. Using the 2002-2003 Tobacco Use Supplement of the Current Population Survey (TUS-CPS), Zhu *et al*.[12] found that quit rates were higher for SLT than that for smoking, and that switching between products was infrequent. A systematic review by Tam *et al*.[13] concluded that never users and exclusive cigarette smokers are unlikely to transition to other behaviors, and that exclusive SLT users are more likely to quit than exclusive smokers.

The 2010-2011 TUS-CPS longitudinal design provides an opportunity to examine more recent patterns of switching between tobacco products at the population level. In this paper, we characterize the transitions between cigarette smoking and SLT use in the 2010-2011 TUS-CPS surveys and compare quit rates of tobacco use with those from the 2002-2003 TUS-CPS. In addition to updating the results in Zhu *et al*., we apply an improved metric of SLT use that incorporates frequency.[2]

3.3 Methods

Data Source and Population

The TUS-CPS collects nationally representative data from non-institutionalized individuals ages 15 years or older.[14] We use the TUS-CPS follow-up matched samples from February 2002 to February 2003 (n=14,996)[15] and May 2010 to May 2011 (n=18,226), restricting the analysis to self-respondent adults aged 18 years or older. We excluded those who first self-reported as current smokers and then as never smokers in the corresponding follow-up.

Measures

Current SLT users were defined as those reporting having ever used SLT, responding "yes" to every day or some days use at the time of the survey, and reporting use of SLT products at least 10 of the past 30 days.[2,16] This definition includes the frequency of SLT use, making it comparable to earlier TUS-CPS surveys and more consistent with SLT consumption data.[2]

Current smokers were defined as those who reported ever smoking at least 100 cigarettes during their lifetime, and reporting smoking every day or some days at the time of the survey. Former smokers were defined as those who reported smoking at least 100 cigarettes during their lifetime and not currently smoking. Among former smokers, we differentiated those reporting having quit more than one year before from those having quit one year or less before.

Data analysis

Survey respondents were categorized into four tobacco use groups. "Exclusive cigarette users" (smokers only) are those currently smoking but not using SLT. "Exclusive SLT users" (SLT users only) are those currently using SLT but not cigarettes. "Dual users" are those

currently smoking and using SLT. “Neither” (non-users) are defined as those neither currently smoking nor currently using SLT (i.e., including a combination of never and former users of both products).

To estimate use prevalence and the transition rates to and from SLT and cigarette use, percentages of the population in each use group at baseline and the corresponding follow-up were calculated along with 95% confidence intervals (CIs). Analyses were stratified by gender since SLT use was uncommon among women.[2] Quit rates of cigarette smoking and SLT use, including transitions to exclusive use of the alternative product, were calculated among exclusive and dual users. Smoking quit rates were examined by age, race/ethnicity, income, and education. Percentages, CIs and transition rates were calculated in SAS 9.3 using survey replicate weights developed for the longitudinal designs.[15] Differences in quit rates (cigarette or SLT) between the two cohorts were compared using a two-sample test for equality of proportions with continuity correction in R 3.2.3.

3.4 Results

Table 3.1 shows the transition rates (percentages) between the four tobacco use groups from 2010 to 2011. Among male non-users in 2010 (n=6,013), 3.4% transitioned into smoking and 0.65% into SLT use by 2011. Among female non-users in 2010 (n=9,234), 2.1% became smokers and 0.07% SLT users by 2011. Quitting one form of tobacco and switching to another was infrequent (1.4% SLT to cigarettes vs 1.2% for cigarettes to SLT). Similar results were obtained for 2002-2003 (Table 3.2), except for quitting behaviors. Among male recent former smokers in 2010, 3.5% became SLT users, whereas 24.4% relapsed to cigarettes. Male recent former smokers in the 2010-2011 cohort were three times more likely to turn to SLT than those

in the 2002-03 cohort (3.5% vs 1.0, $p<0.001$). Among male long-term former smokers in 2010, 3.4% turned to SLT, whereas 4.9% relapsed to cigarettes. Never smokers in 2010 were more likely to take up smoking than SLT (2.7% vs 1.7%, $p=0.04$). Similar patterns were observed for women.

Table 3.3 shows comparisons of the transitions between 2002-2003 and 2010-2011. For all male exclusive users, the smoking quit rate increased (11.6% in 2002-2003 vs 24.4% in 2010-2011, $p<0.0001$), while the SLT quit rate remained roughly constant (41.3% vs 40.0%, $p=0.87$). Similar patterns were found in females where the quit rate for smoking increased (12.3% in 2002-2003 vs 24.2% in 2010-2011, $p<0.0001$). Male smoking quit rates were significantly higher in 2010-2011 for age groups 18-29, 30-44, and 45-65 (12.6% vs 29.8%, $p<0.0001$, 11.6% vs 30.9%, $p<0.0001$, 9.9% vs 16.0%, $p<0.0001$, respectively). Insignificant increases were found for those ages 65 and above (18.5% vs 24.3%, $p=0.416$). Large and often significant increases in smoking cessation rates were consistent across most racial, income and education categories (Table 3.4), with exceptions for lowest income males, females with more than college education, Asians, and American Indians and Other races.

3.5 Discussion

Our study provides recent estimates of transitions between cigarettes and SLT products. During 2010-2011, exclusive cigarette use was more stable than exclusive SLT use and dual use. We found that among those who were exclusive SLT users in 2010, the majority became non-users by 2011. Similar patterns were observed in the 2002-2003 TUS-CPS data.[12] In general, use of cigarettes or SLT in the 2010-2011 cohort was lower than that in the 2002-2003 cohort. However, male recent former smokers in the 2010-2011 cohort were more likely to become SLT

users than those in the 2002-2003 cohort. Consistently with Tam *et al*,[13] we found that exclusive smokers were unlikely to switch to other forms of tobacco use compared to exclusive SLT users.[13] Finally, although slightly higher, we found that smoking cessation rates in dual users were not statistically different from exclusive smokers consistent with previous studies.[17–19]

Our main finding is the consistent increase of smoking cessation rates in most sociodemographic groups, in contrast with the stable SLT use cessation rates. These increases may reflect improvements in healthcare coverage of smoking cessation services,[20,21] increases in cigarette price and taxes in 2009,[22,23] the adoption of smoking-free laws,[24,25] changes in social norms[24,26] or the use of alternative nicotine delivery products, such as e-cigarettes or cigars.[27,28]

Strengths of the study include use of nationally representative longitudinal data, which allowed detailed investigation of switching behaviors across tobacco products in recent year. We used an improved metric of SLT use that takes into account frequency, which has been shown to provide comparable estimates of use across TUS-CPS survey years and of use consistent with SLT consumption trends.[2] Sensitivity analyses showed that our conclusions are robust to the SLT use definition (with or without accounting for frequency). Limitations of our study include that the TUS-CPS is self-reported, which could lead to underestimation of true smoking and SLT prevalence. In addition, the follow-up period is one year, which may yield inflated cessation rates. For instance, here we found a 24% relapse rate for former smokers with less than one year quit in 2010. So, our estimated cessation rates are likely an overestimate of permanent smoking and SLT cessation rates. Nonetheless, we were able to perform consistent comparisons of the changes in tobacco cessation rates between the early 2000s and 2010s using longitudinal surveys with a similar follow-up period,[12,29] results which may become updated when the Population

Assessment of Tobacco and Health (PATH) survey[30] becomes available. Finally, we did not consider e-cigarette use, which was only available as first generation devices.[31]

Conclusion

We found that smoking quit rates doubled from 2002-2003 to 2010-2011, while SLT use quit rates remained constant. Dual users were not more likely to quit cigarettes than exclusive smokers. Recent smoking quitters were more likely to relapse smoking than SLT. Longer-term prospective data examining longitudinal transitions among tobacco users is needed to better understand transitions between tobacco products and assess the long-term health impacts of SLT and polytobacco use.

3.6 References

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Table 3.1 Tobacco use transition patterns by gender, 2010-2011, TUS-CPS

		2011					
		% (95% CI)					
2010 Status	**No**	**Smoking only**	**SLT only**	**Dual use**	**Neither smoking nor SLT**	**Transition rate of smoking only to SLT only**	**Transition rate of SLT only to smoking only**
Male							
Smoking only	1229	74.9 (71.7, 78.1)	0.49 (0.0, 1.0)	0.72 (0.0, 1.5)	23.9 (20.7, 27.1)	1.2 (0.31, 2.1)	
SLT only	189	0.08 (0.0, 0.23)	58.7 (50.0, 67.5)	1.3 (0.0, 3.0)	40.0 (31.2, 48.6)		1.4 (0.0, 3.1)
Dual use	29	38.9 (0.0, 100.0)	6.2 (0.0, 26.6)	31.6 (0.0, 100.0)	23.3 (0.0, 63.2)		
Neither smoking nor SLT	6013	3.4 (2.8, 4.9)	0.65 (0.43, 0.87)	0	95.9 (95.3, 96.6)		
Female							
Smoking only	1444	75.8 (73.1, 78.6)	0	0	24.2 (21.4, 26.9)	0	
SLT only	9	0	58.9 (16.5, 100.0)	0	41.1 (0.0, 83.5)		0
Dual use	0	0	0	0	0		
Neither smoking nor SLT	9234	2.1 (1.8, 2.5)	0.07 (0.0, 0.13)	0	97.8 (97.4, 98.2)		
Male							
Former smoker							
Quit ≤ 1 year	147	24.4 (15.4, 33.4)	3.5 (0.0, 7.7)	0	72.1 (62.7, 81.5)		
Quit > 1 year	1915	4.9 (3.6, 4.4)	3.4 (2.4, 4.4)	0	91.8 (90.2, 93.3)		
Never smoker	4287	2.7 (2.1, 3.4)	1.7 (1.3, 2.1)	0.05 (0.0, 0.11)	95.5 (94.7, 96.3)		
Female							
Former smoker							
Quit ≤ 1 year	179	23.6 (16.4, 30.7)	0	0	76.4 (69.3, 83.6)		
Quit > 1 year	1832	2.8 (1.8, 3.7)	0.19 (0.0, 0.42)	0	97.0 (96.1, 98.0)		
Never smoker	7182	1.4 (1.1, 1.8)	0.12 (0.03, 0.21)	0	98.4 (98.1, 98.8)		

Table 3.2 Tobacco use transition patterns by gender, 2002-2003, TUS-CPS

		2003					
		% (95% CI)					
2002 Status	**No**	**Smoking only**	**SLT only**	**Dual use**	**Neither smoking nor SLT**	**Transition rate of smoking only to SLT only**	**Transition rate of SLT only to smoking only**
Male							
Smoking only	1129	87.5 (85.1, 89.9)	0.30 (0.0, 0.59)	0.88 (0.19, 1.6)	11.3 (9.0, 13.7)	1.2 (0.43, 1.9)	-
SLT only	195	4.7 (0.0, 9.6)	57.7 (48.6, 66.8)	1.1 (0.0, 3.0)	36.5 (27.7, 45.3)	-	5.8 (0.66, 11.0)
Dual use	24	33.2 (10.5, 56.0)	9.8 (0.0, 26.6)	45.9 (20.4, 71.3)	11.1 (0.0, 26.0)	-	-
Neither smoking nor SLT	4702	3.5 (2.8, 4.2)	0.74 (0.46, 1.0)	0.04 (0.0, 0.11)	95.7 (95.0, 96.5)	-	-
Female							
Smoking only	1397	87.7 (85.5, 89.9)	0.03 (0.0, 0.09)	-	12.3 (10.0, 14.5)	0.03 (0.0, 0.09)	-
SLT only	21	3.7 (0.0, 11.5)	48.9 (22.4, 75.3)	-	47.5 (21.3, 73.6)	-	3.7 (0.0, 11.5)
Dual use	2	24.5 (0.0, 100.0)	-	-	75.5 (0.0, 100.0)	-	-
Neither smoking nor SLT	7387	2.9 (2.3, 3.4)	0.04 (0.0, 0.09)	-	97.1 (96.6, 97.6)	-	-
Male							
Former smoker							
Quit ≤ 1 year	162	25.3 (17.1, 33.4)	1.0 (0.0, 2.3)	0.92 (0.0, 2.8)	72.8 (64.4, 81.1)		
Quit > 1 year	1672	2.8 (1.9, 3.7)	2.0 (1.3, 2.7)	0.12 (0.0, 0.34)	95.1 (93.9, 96.2)		
Never smoker	3007	2.5 (1.7, 3.3)	2.8 (2.1, 3.5)	-	94.7 (93.6, 95.8)		
Female							
Former smoker							
Quit ≤ 1 year	183	33.5 (24.2, 42.8)	-	-	66.5 (57.2, 75.8)		
Quit > 1 year	1667	3.0 (1.9, 4.0)	0.13 (0.0, 0.31)	-	96.9 (95.9, 98.0)		
Never smoker	5502	1.7 (1.2, 2.1)	0.20 (0.06, 0.33)	-	98.1 (97.7 98.6)		

Table 3.3 Comparisons between 2002-03 and 2010-11 Tobacco Use Transitions (% [95% CI])

Males	2002/03	2010/11	*łp-value*
Quit cigarettes (smokers)	11.6 (9.3, 14.0)	24.4 (21.2, 27.6)	*<0.0001*
Quit SLT (SLT users)	41.3 (32.2, 50.3)	40.0 (31.2, 48.7)	0.878
Quit cigarettes (dual users)	20.9 (0.0, 41.9)	29.5 (8.6, 50.5)	0.688
Quit SLT (dual users)	44.4 (19.6, 69.1)	62.2 (35.5, 88.9)	0.307
Females			*p-value*
Quit cigarettes (smokers)	12.3 (10.1, 14.5)	24.2 (21.4, 26.9)	*<0.0001*
Quit SLT (SLT users)	53.5 (27.6, 79.4)	41.1 (0.0, 83.5)	0.825
Quit cigarettes (dual users)	-	-	-
Quit SLT (dual users)	-	-	-

Males **Quit cigarettes**	2002/03	2010/11	*łp-value*
Age 18-29	12.6 (5.9, 19.3)	29.8 (20.6, 38.9)	*<0.0001*
Age 30-44	11.6 (7.7, 15.5)	30.9 (25.3, 36.5)	*<0.0001*
Age 45-64	9.9 (6.8, 12.9)	16.0 (12.6, 19.3)	0.004
Age 65+	18.5 (8.8, 28.1)	24.3 (15.3, 33.2)	0.416
Quit SLT			
Age 18-29	54.2 (31.6, 76.7)	54.1 (29.9, 78.4)	1
Age 30-44	32.0 (20.1, 44.0)	32.2 (20.5, 43.9)	1
Age 45-64	41.3 (24.6, 57.9)	38.1 (23.5, 52.7)	1
Age 65+	52.5 (22.1, 82.9)	37.6 (9.5, 65.6)	0.9238

Females * **Quit cigarettes**	2002/03	2010/11	*łp-value*
Age 18-29	14.6 (7.7, 21.5)	32.4 (23.9, 40.8)	*<0.0001*
Age 30-44	14.0 (10.3, 17.7)	23.7 (19.0, 28.3)	*<0.0001*
Age 45-64	9.7 (6.8, 12.7)	20.7 (17.4, 24.1)	*<0.0001*
Age 65+	10.4 (5.4, 15.4)	22.3 (15.0, 29.5)	0.005

ł test for differences in proportions

* Quit SLT rates are not available for female due to the low number of female SLT users

Table 3.4 Comparisons between 2002-03 and 2010-11 Quit Smoking Rates by demographic groups (% [95% CI])

Males			
Income	2002/03	2010/11	łp-value
Less than $15,000	10.3 (4.7, 15.9)	17.8 (10.9, 24.7)	0.0615
$15,000 to $34,999	9.3 (6.0, 12.6)	21.3 (16.4, 26.2)	<0.0001
$35,000 to $74,999	15.5 (9.8, 21.1)	28.3 (21.9, 34.7)	<0.0001
$75,000 or more	11.6 (6.9, 16.3)	21.1 (23.3, 38.9)	<0.0001
Race	2002/03	2010/11	łp-value
White	12.1 (9.6, 14.6)	23.2 (19.7, 26.7)	<0.0001
Black	6.0 (1.1, 10.9)	25.3 (16.4, 34.3)	0.002
American Indian/ Alaskan Native	2.3 (0.0, 7.0)	43.3 (7.5, 79.1)	0.019
Asian	36.9 (2.0, 71.9)	39.1 (21.5, 56.6)	1
Other	0.30 (0.0, 0.91)	27.8 (0.94, 54.7)	0.03
Education	2002/03	2010/11	łp-value
Less than 12 years	12.4 (6.9, 17.9)	21.5 (14.3, 28.7)	0.027
HS degree	9.9 (6.7, 13.1)	19.2 (14.9, 23.6)	<0.0001
Some college degree	10.5 (6.4, 15.6)	29.5 (22.5, 36.6)	<0.0001
College degree	18.0 (9.4, 26.6)	32.0 (24.2, 39.8)	0.0038
Females			
Income	2002/03	2010/11	łp-value
Less than $15,000	8.0 (3.3, 12.7)	19.9 (14.6, 25.2)	<0.0001
$15,000 to $34,999	12.1 (8.2, 16.1)	23.9 (19.3, 28.5)	<0.0001
$35,000 to $74,999	15.2 (10.2, 20.2)	22.4 (17.0, 27.7)	0.02
$75,000 or more	13.3 (9.1, 17.5)	33.8 (26.3, 41.2)	0.03
Race	2002/03	2010/11	łp-value
White	12.1 (9.8, 14.3)	22.9 (19.9, 25.9)	<0.0001
Black	11.8 (4.2, 19.4)	29.2 (21.1, 37.4)	0.001
American Indian/ Alaskan Native	4.5 (0.0, 13.3)	19.8 (0.0, 42.7)	0.472
Asian	6.3 (0.0, 18.5)	40.8 (8.3, 73.3)	0.092
Other	24.8 (0.44, 49.1)	38.1 (17.6, 58.5)	0.396
Education	2002/03	2010/11	łp-value
Less than 12 years	12.6 (6.0, 19.1)	23.6 (16.6, 30.6)	0.004
HS degree	10.3 (7.2, 13.3)	20.6 (16.5, 24.7)	<0.0001
Some college degree	12.1 (7.8, 16.3)	27.4 (22.4, 32.4)	<0.0001
College degree	18.3 (11.9, 24.7)	26.9 (19.3, 34.6)	0.06

ł test for differences in proportions

Chapter 4

COPD Risk Prediction Accounting for Time-varying Smoking Exposures

4.1 Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death in the United States. Cigarette smoking is a main risk factor for COPD. Studies have estimated the effect of smoking on COPD risk focusing on summary measures, such as smoking status. Thus, it is unclear how individual time-dependent exposures determine COPD risk.

Methods: The Nurses' Health Study (NHS) (n=89,128) and the Health Professionals Follow-up Study (HPFS) (N=40,088) were used to develop a COPD risk prediction model. The model includes time-dependent smoking covariates, such as duration, smoking pack-years and year since quitting for former smokers. The model also adjusts for age and sex. A Cox regression model with time-varying covariates was used to assess the association of these covariates and the incidence of self-reported COPD diagnosis. We performed a 50-50 random split of the data between model building and validation samples. Using the validation dataset, we evaluated the model calibration and the Area Under the receiver operating characteristic Curve (AUC) as a measure of the discriminatory accuracy of the models. The 6-year absolute risk of developing COPD was computed given selected smoking profiles.

Results: The model was internally calibrated and validated. The AUCs were improved significantly when incorporating time-dependent smoking variables versus using only smoking pack-years. The AUCs of the final model in the validation data were 0.80 (95% CI: 0.74-0.86)

and 0.74 (95% CI: 0.69-0.77) for males and females, respectively. Cumulative smoking duration, years since quitting (if former smokers), sex and interaction of sex and smoking duration, were all associated with the incidence of diagnosed COPD.

Conclusions: A COPD risk model accounting for multiple time-dependent smoking factors would be helpful to establish potential individualized prevention strategies.

4.2 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of death globally and domestically. In 2013, COPD ranked third, after cardiovascular diseases and stroke, on the list of potentially fatal diseases in the United States (US), with nearly 42.1 deaths per 100,000 people.[1] The 2012 World Health Organization (WHO) report on the burden of lung diseases states that respiratory conditions, including COPD, impose an enormous burden on society, with the top five respiratory diseases accounting for 6% of all deaths globally.[2]

Cigarette smoking is the most important risk factor for COPD.[3] In the US, approximately 80% of COPD deaths are linked to cigarette smoking, and about 20% of smokers are expected to be diagnosed with COPD.[4] In 2011, the age-adjusted COPD prevalence was 14.1% among current smokers, 7.1% among former smokers, and 2.9% among never smokers.[5] Other risk factors for COPD include age, sex, race, occupation, education, alpha-1 anti-trypsin deficiency, asthma, and exposures to other chemical fumes and air pollution (particulate matter micron 2.5).[6–11]

Even though many studies have established the association between cigarette smoking and COPD, most studies have been limited to national survey data or clinical case-control studies.[6,10–17] In addition, most of these studies have used only limited smoking information (e.g., smoking status) in their analyses. However, other factors, such as smoking intensity and duration, may play an important role in determining the risk of COPD. More importantly, smokers change their smoking behaviors throughout their lifetime, and these changes might affect and shape how their individual risk of COPD changes with age. Therefore, it is important to investigate how smoking histories shape age-specific COPD risk, and develop models that account for changes in individual smoking behaviors over time, in particular for relevant

exposure measures such as smoking duration, intensity (i.e., cumulative smoking pack-years), and years since quitting for former smokers.[18]

In this study, we developed a COPD risk prediction model accounting for multiple time-varying smoking covariates and estimated the time-dependent effect of smoking pack-years on incidence of diagnosed COPD while adjusting for smoking duration, years since quitting, and sex using two large prospective cohorts: The Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). We evaluated the model performance in terms of calibration and discriminatory accuracy. The final model was used to investigate how COPD risks change as a function of smoking duration, intensity, and age.

4.3 Methods

Nurses' Health Study and Health Professionals Follow-up Study

The NHS was originally established in 1976 with 121,700 female US nurses aged between 30 and 55 years who responded to the initial mailed questionnaires. The participants were asked questions about their medical histories. Follow-up questionnaires have been sent every 2 years to update information about exposure status on various risk factors. The response rate has been at least 90% for each survey. In parallel, the HPFS was established in 1986 with 51,529 male US health professionals aged between 40 and 75 years who also received initial questionnaires about diseases and health-related topics and follow-up questionnaires every 2 years afterwards.

COPD information and smoking data

In the NHS and the HPFS cohort studies, self-reported COPD status was defined by any affirmative response of physician-diagnosis of chronic bronchitis or emphysema or by any diagnostic tests. All participants in the NHS were asked to report any previous diagnoses of COPD on the 1988-2004 and 2008 questionnaires, and the HPFS on the 1998-2008 questionnaires. We excluded prevalent COPD cases in both cohorts that were diagnosed before 1998 from our analysis. We also excluded individuals with missing smoking information. After exclusions, the final dataset consists of 89,128 females in the NHS and 40,088 males in the HPFS. We randomly split the data into 50:50 samples, and used one half of the data (N=64,608) for model building and the other half (N= 64,608) for model validation (Figure 4.1).

Covariates included in the analyses were age, sex, and detailed individual smoking information. At the entry of the study, the NHS participants were asked to report their ages at start and quit smoking (if former smokers), and the average smoking intensity in terms of cigarettes per day (cigs/day) while they smoked. In contrast, in the HPFS cohort, participants reported average smoking intensity (cigs/day) for each age category before age at the entry of study (<15, 15-19, 20-29, 30-39, 40-49, 50-59, and ≥ 60 years). After entering the study, each participant reported smoking status and intensity (if smokers) every two years until the end of follow-up. Intensity is categorized as the number of cigarettes smoked per day using the following categories: 0-4 cigs/day, 5-14 cigs/day, 15-24 cigs/day, 25-34 cigs/day, 35-44 cigs/day, and > 44 cigs/day. An imputation procedure was conducted to complete missing information between follow-up surveys.[19,20] Individual smoking histories from birth to the entry of the study were constructed by applying a similar approach as in the previous literature of lung cancer incidence in these two cohorts.[19]

*Cox Regression Model with Time-varying covariate*s

We used a Cox proportional hazards model to estimate the relative risk of incidence of diagnosed COPD associated with time-varying smoking covariates: cumulative smoking intensity in pack-years, smoking duration in years, years since quit smoking (if former smokers), with adjustment for sex. The values for these smoking covariates change over the course of the smoker's lifetime. The traditional Cox proportional hazards model cannot directly account for variations in lifetime smoking exposure. Therefore, to account for the time-dependent nature of these smoking covariates, we coded these covariates by using annual intervals of time, i.e., recorded the values at every year from birth to the end of follow-up. The end of follow-up was defined as the time whichever comes first among the following four scenarios: death, incident diagnosed COPD, lost to follow-up, and the end of study period. Models were fitted using the 'coxph' function in R (version 3.2.0).[21]

The underlying assumption of the Cox model is that the relative risk of disease associated with a risk factor remains constant over time. This assumption often does not hold for a chronic disease, such as COPD, which tends to develop over a long period of time, and the effect of a risk factor on disease may be modified by age. Therefore, we assumed age as an effect modifier for the association between smoking exposure and COPD,[22] and modeled the non-proportionality in the relative risk by including a time-dependent interaction between cumulative smoking pack-years and age;[23] $h(t) = \lambda_0(t)e^{\beta(t)X(t)}$, where $\lambda_0(t)$ is the baseline hazard at age t , $\beta(t)$ is a vector of regression coefficients, and $X(t)$ represents time-dependent covariates, including duration of smoking in years, cumulative smoking intensity in pack-years, and year-since-quitting. Non-parametric natural splines with 2 degrees of freedom were chosen to model non-

linear age effects for the interaction between cumulative smoking pack-years and age in the model.[24] We also evaluated the interaction effect between each smoking covariate and sex.

As a sensitivity analysis, we also built sex-specific Cox proportional hazards models, i.e., separate analyses by sex. The hazard ratios (HRs) from these sex-specific models were compared with the ones from the joint model.

To develop absolute risk COPD models, we estimated the baseline hazard (age-specific risk), $\lambda_0(t)$, from never smokers in the data. To account for any potential heterogeneity in COPD risk by sex, we estimated separate baseline hazards for males and females. We assumed either Log-Normal or Weibull baseline hazard function, and estimated the parameters in the function using the "survreg" function in R (version 3.2.0).[21]

Model calibration and validation

The model calibration was evaluated using the Nam-D'Agostino goodness-of-fit $\chi 2$ test,[25] and also graphically; we compared expected incidence of diagnosed COPD obtained from our model to the observed data with 95% confidence intervals (CIs) stratified by smoking status. The $\chi 2$ test statistic was calculated by splitting the dataset into 10 equal deciles based on predicted probability of COPD incidence by the model.

We also computed the 6-year incidence of diagnosed COPD at the entry of the study for all individuals in the validation dataset, assuming their smoking behaviors at baseline remained unchanged during the next 6 years. The discriminatory accuracy of the model was also evaluated by examining the Area Under the receiver operating characteristic Curve (AUC). The resulting AUCs from the model were compared to the AUCs obtained using only smoking pack-years as a

risk measure. Bootstrapping with 100 iterations was used to compute 95% CIs of the AUCs. We used the "pROC" package in R (version 3.2.0)[21] to compute the AUCs.

Absolute risk probability of COPD as a function of smoking status, duration, intensity, and age

Using our validated model, we predicted the 6-year incidence of diagnosed COPD for selected individual smoking scenarios. The Bootstrap method with 100 iterations was used to calculate 95% CIs. To account for competing risks, we also estimated 6-year risks of COPD with adjustment for other-causes of deaths by smoking status (see Figure 4.2 for detailed calculation). And the age-specific life-tables stratified by smoking status were obtained from the Cancer Intervention and Surveillance Modeling Network (CISNET).[26,27] Finally, we evaluated COPD relative risks (hazard ratios) by smoking status, where we compared age-specific absolute risks of COPD between current and never or former smokers, respectively.

4.4 Results

Participants' characteristics

Table 4.1 shows the participants' characteristics at the baseline for our study (year 1998). In both model building and validation datasets, males have higher smoking intensity, longer smoking duration and years since quitting compared to females. In the model building dataset, the mean smoking intensity was 10.97 pack-years for males and 9.22 pack-years for females. The average smoking duration was 11.01 years and 9.31 years for males and females, respectively. And the mean years since quitting among former smokers were 6.06 years and 2.84 years for males and females, respectively. Compared to females, males have a lower proportion

of current smokers (8.58% versus 26.43%) but a higher proportion of former smokers (41.11% versus 24.25%). The validation dataset has similar distributions as the model building dataset.

Cox model with time-varying covariates

The parameter estimates for the joint model and the independent sex-specific models are provided in Table 4.2. The results were largely unchanged between the joint model and the sex-specific models. The estimates are similar between males and females, thus, we used the joint model as our main model. Initially we included all interaction terms between smoking parameters and sex, but did not find any significant interaction effects, except sex and smoking duration (results not shown). Our final model includes smoking intensity (pack-year), smoking duration (year), years since quitting (year), sex, interaction between sex and smoking duration, and the interaction between age and smoking intensity. The risk of COPD was higher in females than males (HR=1.78, 95% CI: 1.56- 2.04). Smoking duration was associated with a 1.02-fold increase in COPD risk (95% CI: 1.01- 1.03) for males, and 1.02-fold (95% CI: 1.01-1.02) in females. Although statistically significant, the effect of years since quitting is only marginally different than one. Finally, the increase in the risk of COPD incidence by one additional pack-year exposure behaves non-linearly. It decreases in magnitude with exposures occurring at older ages (Figure 4.3).

Model Validation and Calibration

Overall, the predicted incidence of diagnosed COPD (per 100,000) from our model matched well to the observed incidence in the validation data. Figure 4.4 shows comparisons stratified by smoking status: never, former, former with more than 5 years since quitting, and

current smokers. The observed incidence was within the 95% CIs of predicted incidence in all smoking subgroups. The 95% CIs for old ages in current smokers were wide because of small number of cases in this subgroup. A goodness of fit test shows that there was no significant difference between predicted and observed incidences in all smoking subgroups (*p-value*=1.0).

We estimated the discriminatory accuracy of our joint model (i.e., AUC) and compared it with the AUC from a pack-years only model (Figure 4.5). The AUC estimates by our model in validation dataset were significantly higher (males: 0.80 [95% CI: 0.74-0.86], females: 0.73 [95% CI: 0.70-0.77]) than the AUCs from the pack-years only model (males: 0.73 [95% CI: 0.68-0.80], females: 0.69 [95% CI: 0.64-0.73]).

Age-Specific Incidence and Relative Risk

Figure 4.6 shows age-specific incidence rates and relative risks (RR) of diagnosed COPD for various smoking scenarios and sex. We assumed that smokers smoked 20 or 40 cigs/day starting at age 20 throughout their lifetime (current smokers) or until age 40 (former smokers). The top two panels in Figure 4.6 show the age-specific incidence rates of diagnosed COPD among never and current smokers for both males and females. For never smokers (left panel), the baseline incidence of diagnosed COPD is higher in females than males regardless of age. For current smokers (right panel), the incidence of diagnosed COPD is higher in females than males for those aged 40 to 70; however, the pattern reverses for those over age 70. The middle two panels of Figure 4.6 show the RR of COPD by sex, females vs. males, among never smokers (left panel) and current smokers who smoked 20 cigs/day starting at age 20 (right panel). Although female smokers have higher COPD risk for a given smoking level than male smokers, the difference in COPD incidence between sexes decreases when people get old. Our results

suggest that male smokers even got higher COPD risk than female smokers at old ages. The bottom left panel of Figure 4.6 shows the RR of COPD of current smokers compared to never smokers. As an example, a 60-year-old female current smoker who smoked 40 cigs/day starting at age 20 has 15 times higher COPD risk than a never smoker at the same age. The bottom right panel of Figure 4.6 shows the RR (hazard ratios) of COPD risk of former smokers compared to continuing smokers. The former smokers have lower COPD risk relative to current smokers once they quit smoking. For example, a 60-year-old female former smoker, who smoked 40 cigs/day starting at age 20 until age 40 has only 1/5 of chance of getting COPD compared to a current smoker at the same age.

6-year COPD risk predictions

Using our final model, we computed the probability of getting diagnosis of COPD in next 6 years at a given age for selected smoking scenarios by varying duration, intensity and years since quitting (Table 4.3 and Table 4.4). The probabilities were computed without adjustment for mortality (Table 4.3). For example, for a 70-year-old female current smoker who has smoked 20 pack-years for 30 years, her risk of COPD diagnosis in next 6 years is 3.2% (95% CI: 3.2%-3.3%). Compared to the above scenario, if a 70-year-old female has smoked 40 pack-years for the same duration, the risk of COPD diagnosis in next 6 years increases to 4.8% (95% CI: 4.7%-4.9%). Lastly, if this same female quit smoking at age 70, her risk of COPD diagnosis in the following 6 years is 4.2% (95% CI: 4.1%- 4.3%).

4.5 Discussion

We developed a risk prediction model for the incidence of diagnosed COPD based on 10 years of data for COPD incidence in the NHS and HPFS cohorts. To our knowledge, this is the first COPD risk prediction model incorporating individual time-varying smoking covariates: intensity (pack-years), duration (number of years smoked), and years since quitting (if former smoker). We found that smoking duration, smoking intensity, years since quitting, interaction of sex and smoking duration, and sex were all significantly associated with COPD self-reported incidence. However, the effect of years since quitting is relatively small compared to other factors, suggesting that the COPD risk induced by smoking is somewhat permanent. In addition, we found that the increase in diagnosed COPD incidence risk by one additional pack-year decreases with age. Thus, exposures occurring early in life appear to be particularly harmful. Our model validated well and has high discriminatory power. The model also has the flexibility to predict COPD risk given specific individual smoking histories.

Relative risks of COPD by smoking status

Since smoking is linked to 80% of prevalent COPD cases in the US,[4] smoking cessation may be the most effective intervention to reduce COPD risk.[28] A meta-analysis study showed that COPD prevalence in current smokers was 29% higher than in former smokers.[18] However, this study included only a single smoking measure (smoking status), and was unable to provide age-specific relative risks for COPD prevalence. Our model can predict the probability of being diagnosed with COPD at different ages given a person's smoking history. As expected, our model showed that continuing to smoke leads to significant increases of COPD risk relative to quitting.

Time-since-quitting

Our results showed that years since quitting has a borderline negative effect on the risk of incidence of diagnosed COPD (slight decrease in risk as years since quitting increase). The lack of a stronger association could be due to several factors. First, when lifetime smokers are told they have COPD, they may subsequently quit smoking. This change in smoking behavior shortly after the disease develops can make it seem as if former smokers are more likely to develop COPD than current smokers (reverse causation). Although we are using longitudinal data, smoking information is updated only every two years, so this is certainly a possibility. Second, since our outcome of interest was self-reported COPD diagnosis, it does not indicate the onset of COPD, in which patients might have developed COPD long before the diagnosis. Thus, if quitting occurs between incident COPD and diagnosis, it would have no effect on COPD incidence risk since it already occurred. In contrast, quitting could lead to a false sense of no COPD risk, making it less likely that individuals would be tested for it. This highlights the relevance of having COPD risk prediction models that consider the complete history of smoking to identify individuals at high risk. Moreover, it is plausible that the effects of smoking on the lungs that lead to COPD are non-reversible, so quitting might not decrease the risk other than stopping the exposure to cigarette smoke.

Relative risks of COPD by sex

Overall, our analyses suggest that female never smokers have higher age-specific incidence of diagnosed COPD than male never smokers, although this finding is based on a relatively low number of COPD cases among never smokers and should be taken with caution. In our example for current smokers who have smoked 20 cigs/day, the higher risk for female

smokers is also seen until age 70 years, but the risk then becomes higher in male smokers afterwards. These sex differences could be due to multiple factors. First, health-care seeking behaviors might differ by sex, which affects COPD diagnosis.[29–31] Our study used self-reported COPD diagnosis from participants, and some studies have shown that females are more likely to seek medical attention,[32] and thus have higher rates of detection/diagnosis. In contrast, Chapman et al. have suggested that there is a potential bias towards identification of male COPD cases,[33] given that physicians are more likely to refer males to get spirometry due to their higher smoking prevalence in males than females. Although plausible, our results are not inconsistent with this finding, since we are comparing risks for specific smoking exposures, and once we account for observed smoking patterns by sex, our model predictions do match population rates (Figure 4.1). Second, sex-differences in risk could also be due to biological differences. For instance, females have smaller lungs than males, potentially causing more concentrated cigarette exposure in lungs, resulting in increased production of airway-toxic particles in lungs, and higher effective exposures per cell.[34] In addition, some studies suggested that females might be more likely to be exposed to non-smoking risk factors linked to COPD, such as hormones, environmental or occupational exposures,[35] and that there might be differences in cigarette smoking metabolism by sex.[36] Unfortunately, we were unable to adjust for these covariates due to lack of information in our data. Moreover, our findings come from separate cohorts, which although were designed consistently and conducted by the same institution, might have underlying differences in the study populations that go beyond sex.

6-year COPD risk predictions

We estimated 6-year probability of COPD incidence given various smoking scenarios using our model. The results show noticeable increases in COPD risk for longer smoking durations, higher smoking intensities, and older age. Our model can be used to quantify the impact of differences in exposures between otherwise similar individuals. For example, if a 70-year-old female smoked 40 pack-years for 30 years, the probability of being diagnosed with COPD in next 6 years is a 4.8%, which is 1.6% higher (percentage difference) than a female who smoked 20 pack-years for the same duration. In comparison for comparable females, but who smoked 20 rather than 30 years, the percentage difference would be reduced to 0.4%. These estimates from the model might be useful to identify high-risk individuals for COPD, which may also aid for clinicians to discuss with patients about the harmful effect of smoking for conditions like COPD.

Comparison to previous COPD risk prediction models

Although no previous COPD risk prediction model has used time-varying smoking information, several studies have examined the incidence of COPD by smoking status in various populations.[6,16,37] By using data for COPD diagnosis recorded by general practitioners, Kotz et al developed a COPD risk prediction model in Scotland, which includes history of asthma, smoking status, age, and sex.[16] They found that the incidence of COPD is 9.61 and 6.72 times higher in ever-smokers compared to never-smokers in females and males, respectively, adjusting for deprivation index and prior asthma history. Gershon et al conducted a study in Canada, which examined the lifetime risk of COPD among males and females[38] using smoking exposure as a cross-sectional variable (smoking status). They found the lifetime risk of COPD is 3.89 times higher in ever smokers compared to never smokers adjusting for age, gender and underlying

comorbidities. However, both models did not account for changes in smoking exposure over an individual's life course, such as years since quitting, pack-years, and smoking duration, and did not separate current and former smokers. Our model complements these earlier models by incorporating time-varying smoking variables and attempts to estimate the age-dependent relative risk of COPD associated with increases in smoking intensity.

Strengths and limitations

Strengths of our study include the availability of detailed high quality longitudinal data on two large populations, which enabled us to examine the association between changes in smoking patterns over time and incidence of diagnosed COPD. Our study used lifetime smoking histories prior to incident COPD; therefore, avoiding the temporal ambiguity that is usually present in cross-sectional studies. The resulting model has high discriminatory power, supporting its potential for clinical applications. Our model accounted for time-dependent effects of smoking, which reflects that the association of smoking intensity and COPD incidence is not constant over time. Finally, when calculating a probability of COPD incidence given an individual's smoking history, we were able to adjust for competing cause of death by applying US lifetables stratified by smoking status (Table 4.4).[26,27] This approach provides more realistic predictions for the incidence of diagnosed COPD incidence at the population level.

Our study has some important limitations. First, COPD incidence was defined by a self-report of physician-diagnosis on COPD and lung function results were not available. The absence of spirometry information might lead to underestimation of the true COPD incidence. Nevertheless, Barr *et al* previously validated the self-reported COPD data in the NHS cohort with diagnostic tests (spirometry, chest radiograph, computed tomography or physician

diagnosis) results. They found a 78% concordance between self-reported and diagnostic results in the NHS.[39] Second, our analysis relied on a predominantly white study population. Studies have shown African Americans are more susceptible to COPD than whites.[40] It is unclear whether this is due to other competing causes, difference in genetic susceptibility, or smoking behaviors,[40,41] and we were unable to account for race in our analyses. Our model also did not include any socioeconomic factors, which may be associated with COPD risk.[9] The HPFS and the NHS cohorts consist of health professionals and nurses, so their income levels might be similar across individuals, especially in the NHS cohort. Therefore, our results may not be generalizable to other races or socioeconomic groups. Nonetheless, by accounting detailed individual smoking histories, our model might be more generalizable than models based only on smoking status or pack-years. Moreover, our risk prediction model only includes age and smoking-related information. Although, it would be important to incorporate other relevant predictors such as asthma, exposure to air pollution, secondhand smoking, occupational carcinogens, and lung function markers (Forced Expiration Volume per 1 second [FEV_1] and Forced Vital Capacity [FVC]), the effect of these factors on COPD incidence is likely to be relatively minor compared to smoking. For instance, the AUCs estimated by using smoking pack-years only models were 0.73 for males and 0.69 for females, which indicates that smoking itself may provide sufficient discriminatory power. Finally, we calibrated the model in the same cohort using a split-sample approach, and additional external validation of the model is required and will be the focus of future work.

Conclusion and implications

In conclusion, we developed a COPD risk prediction model that incorporates time-varying smoking information, which shows high discrimination for incidence of diagnosed COPD. The model can be used to provide insights into how COPD risks change as a function of age and individual smoking histories. The model is useful for clinicians to assess the risk of COPD given individual smoking histories; in particular, the model could be used as the basis of clinical tools to identify patients with high risk of COPD and to communicate the benefits of smoking cessation, lifestyle changes and treatment options.[42] Moreover, this model can be integrated into simulation models of smoking and health[43–45] to project the incidence and prevalence of diagnosed COPD during the next decades as smoking patterns continue to evolve in the US. This is also the focus of ongoing work.

4.6 References

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Figure 4.1 Flow chart for model-building and validation datasets

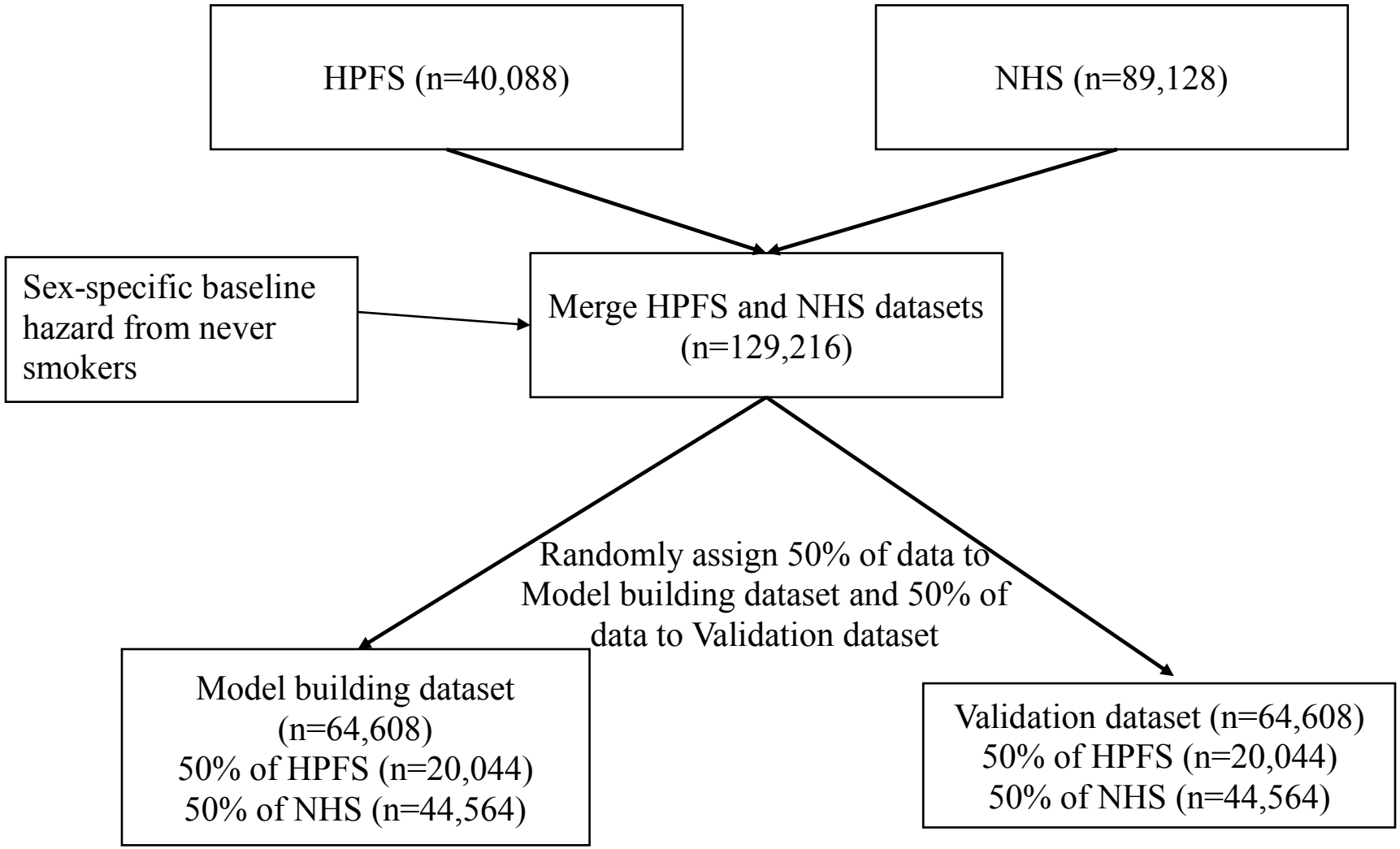

Figure 4.2 Formula to calculate the 6-year risk of COPD with adjustment for other-causes of mortality

T1: age of COPD diagnosis
T2: age of dying from other causes
Te: age of entry

$$P(Te < T1 \leq Te + 6, T1 < T2) = \int_{te}^{te+6} h_1(u) S_1(u) S_2(u) du \ ,$$

where $h_1(u)$ is the hazard function for the COPD diagnosis and $S_1(u)$ the survival function which can be obtained by the following equation: $S_1(u) = \ e^{-\int_0^u h_1(s)ds}$. $S_2(u)$ is the survival function for the other-causes of death, which was obtained from the US life-table stratified by smoking status.

Table 4.1 Baseline (in 1998) Characteristics of NHS and HPFS Cohorts in Model Building and Validation datasets

	Model Building Data (n=64608)		Validation Data (n=64608)	
	HPFS (n=20044)	**NHS (n=44564)**	**HPFS (n=20044)**	**NHS (n=44564)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age at entry (Year)	53.34 (9.27)	42.42 (7.13)	53.36 (9.28)	42.45 (7.11)
Follow-up time (Year)	20.25 (9.47)	31.66 (7.57)	20.24 (9.60)	31.64 (7.43)
Smoking intensity (Pack-year)	10.97 (17.11)	9.22 (13.96)	10.69 (16.71)	9.07 (13.75)
Smoking duration (Year)	11.01 (13.98)	9.31 (11.36)	10.79 (13.84)	9.18 (11.28)
Years since quitting	6.06 (10.03)	2.84 (6.08)	6.11 (10.13)	2.89 (6.17)
Smoking status	No (%)	No (%)	No (%)	No (%)
Never	10093 (50.35)	21976 (49.31)	10205 (50.91)	22124 (49.64)
Former	8241 (41.11)	10808 (24.25)	8126 (40.54)	10751 (24.12)
Current	1719 (8.58)	11780 (26.43)	1713 (8.55)	11689 (26.22)
COPD cases during the follow-up	830	2,955	899	2,998

HPFS: Health Professionals Follow-up Study; NHS: Nurses' Health Study

Table 4.2 Parameter estimates for the Models [HR[3] (95% CI)]

	Males-only	Females-only	Joint model
N	20,044	44,564	64,608
Smoking intensity (pack-year)	0.91 (0.73- 1.15)	1.07 (0.99- 1.15)	1.05 (0.98- 1.12)
Smoking duration (year)	1.02 (1.01- 1.03)	1.02 (1.01- 1.02)	1.02 (1.00- 1.03)
Years since quitting (year)	0.99 (0.99- 1.00)	0.99 (0.99- 1.00)	0.99 (0.99- 1.00)
ns(Age,2)1[1]*smoking intensity	1.22 (0.82- 1.83)	0.93 (0.81- 1.06)	0.96 (0.86- 1.08)
ns(Age,2)2[2]*smoking intensity	1.02 (0.91- 1.15)	0.96 (0.93- 1.00)	0.97 (0.94- 0.99)
Sex*smoking duration			0.99 (0.99- 1.00)
Sex			1.78 (1.56- 2.04)

[1,2] The interaction between age and smoking intensity was modeled as a non-linear relationship using a natural spline with 2 degrees of freedom.; [3] Hazard ratios.

Figure 4.3 Age-dependent effect of smoking pack-years on incidence of diagnosed COPD.

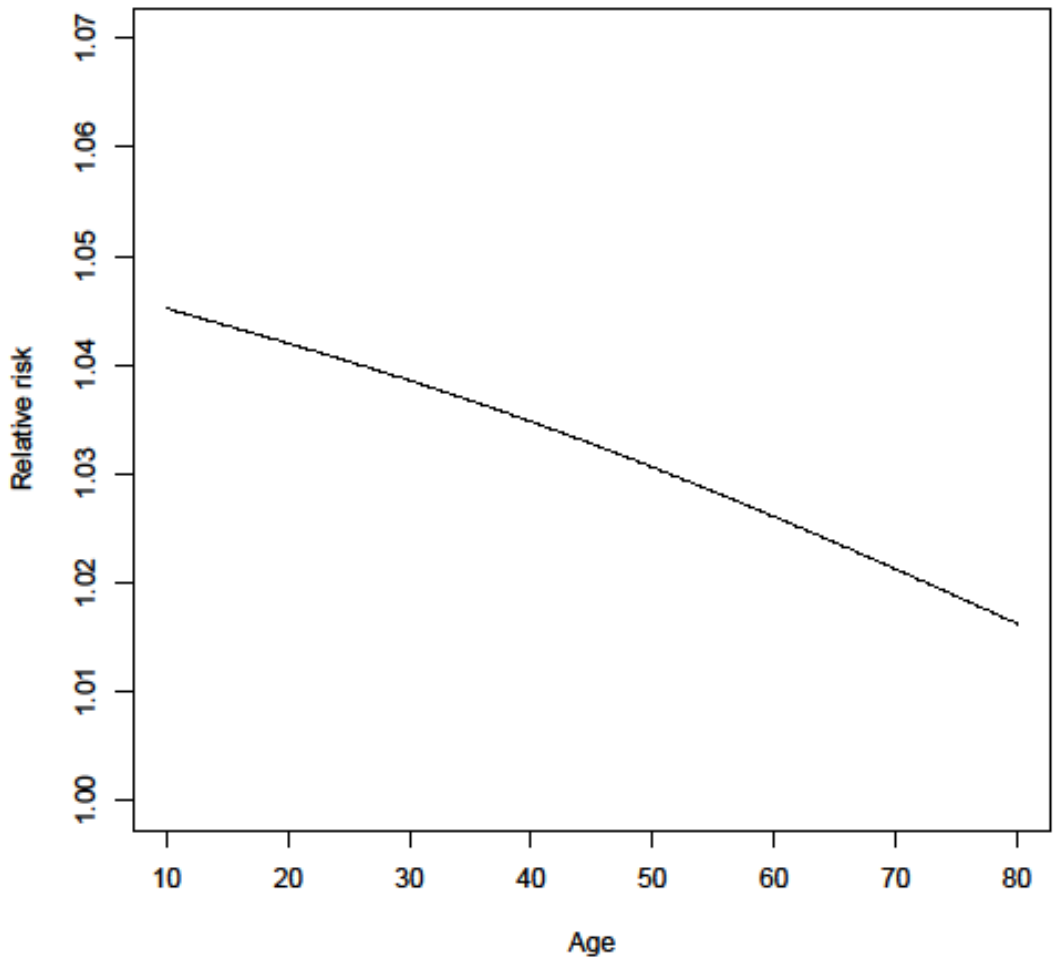

Figure 4.4 Incidence of diagnosed COPD per 100,000 for females and males by smoking status.

The solid line is the expected incidence of diagnosed COPD from the model, and the dashed lines are its 95%CI. The dots represent the observed data in the NHS (females) and the HPFS (males) cohorts.

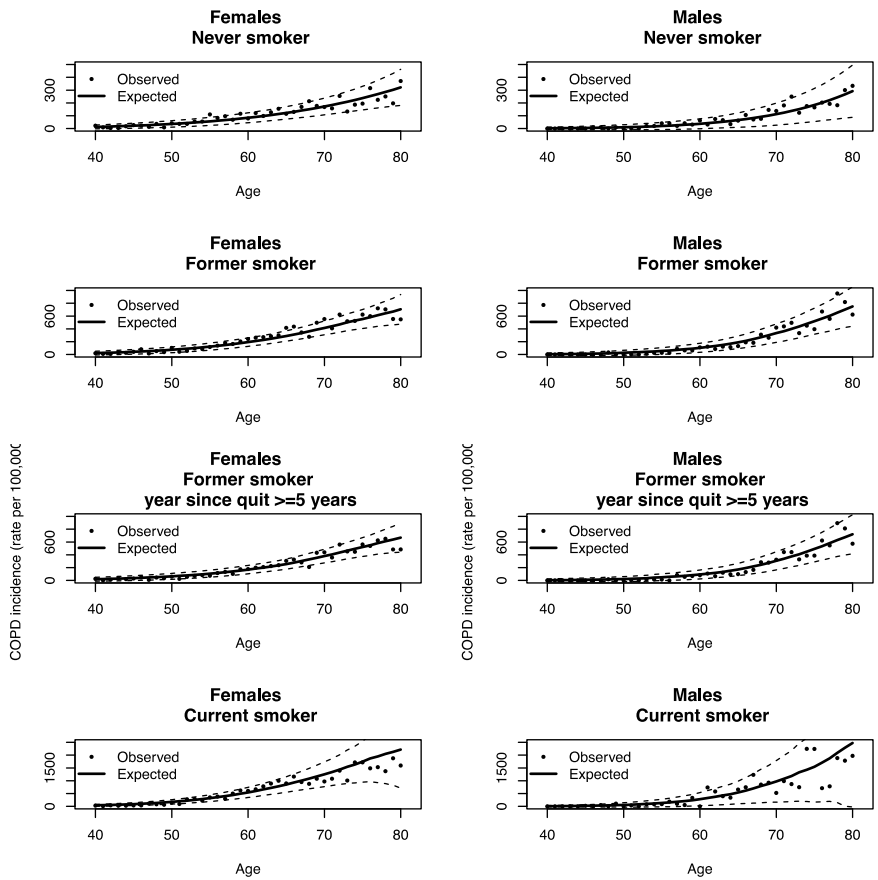

Figure 4.5 AUC comparisons between the joint model and a pack-years only model [AUC (95% CI)]

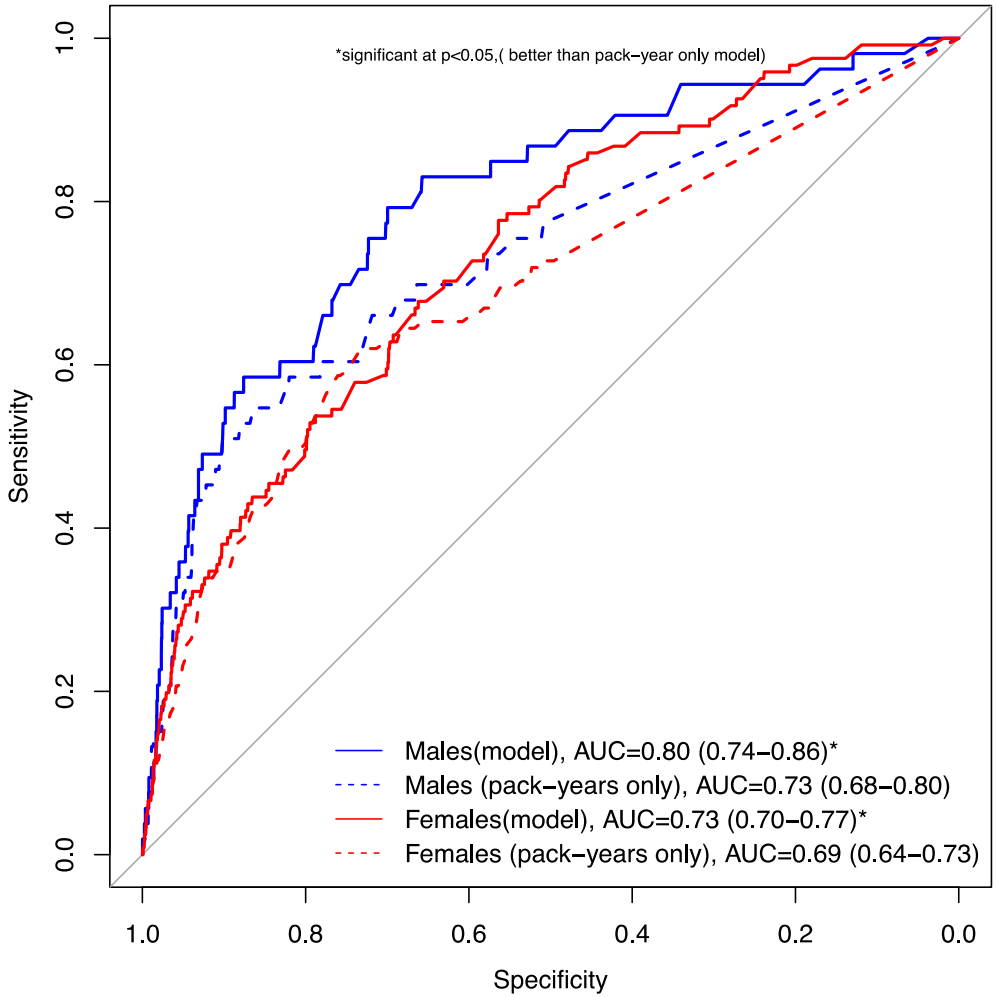

Figure 4.6 Relative Risk examples.

Top 2 panels show the age-specific COPD incidence rates among never smokers and current smokers, middle 2 panels the relative risk of females vs. males among never smokers and current smokers (20 cigs/day), bottom 2 panels the relative risk of COPD of current smokers versus never smokers (left panel) and former smokers versus current smokers (right panel) for females and males. Smokers were assumed smoking either 20 or 40 cigs/day starting at age 20. Former smokers were assumed to quit smoking at age 40

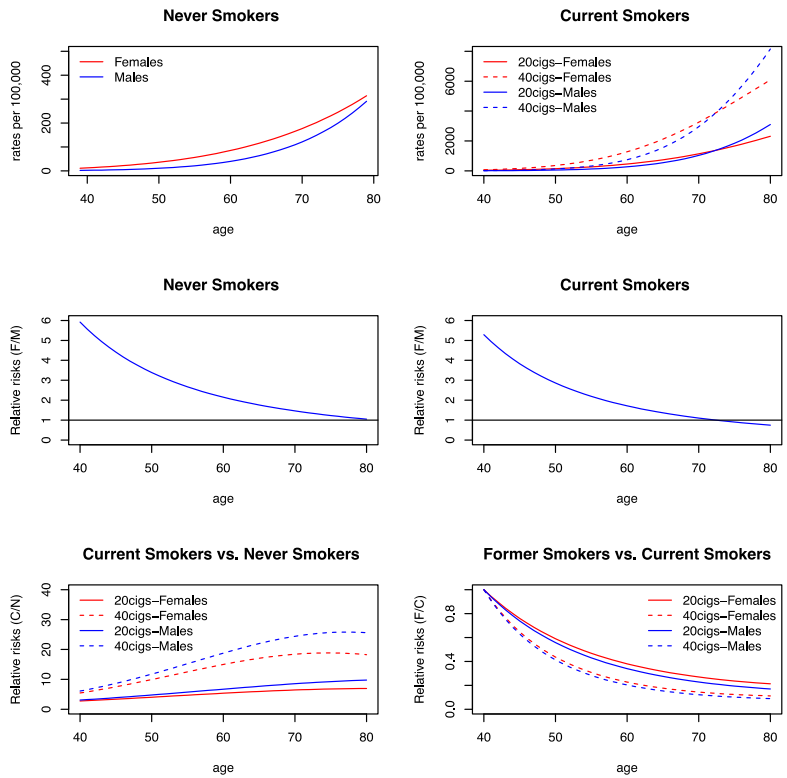

Table 4.3 6-year risk projections for COPD incidence at age 50, 60, 70 or 80 among current and former smokers who have smoked for 20, 30, or 40 years without adjusting for other causes of mortality

	Current smokers	Former smokers*	Current smokers	Former smokers*	Current smokers	Former smokers*
	Smoking Duration (years)					
Age (year)	20 years		30 years		40 years	
Females: 20 pack-years						
50	0.8 (0.8- 0.8)	0.7 (0.7- 0.7)	0.9 (0.9- 0.9)	0.8 (0.8- 0.8)	1.1 (1.0- 1.1)	0.9 (0.9- 1.0)
60	1.6 (1.6- 1.6)	1.4 (1.4- 1.4)	1.8 (1.8- 1.9)	1.6 (1.6- 1.7)	2.1 (2.0- 2.2)	1.9 (1.8- 1.9)
70	2.8 (2.8- 2.9)	2.5 (2.5- 2.5)	3.2 (3.2- 3.3)	2.9 (2.8- 2.9)	3.7 (3.6- 3.8)	3.4 (3.3- 3.4)
80	4.4 (4.4- 4.5)	4.0 (3.9- 4.0)	5.0 (4.9- 5.1)	4.6 (4.5- 4.7)	5.8 (5.6- 5.9)	5.3 (5.1- 5.4)
Females: 40 pack-years						
50	1.6 (1.5- 1.6)	1.2 (1.2- 1.3)	1.7 (1.6- 1.8)	1.4 (1.3- 1.5)	1.9 (1.8- 2.0)	1.7 (1.6- 1.7)
60	2.8 (2.7- 2.9)	2.2 (2.2- 2.3)	3.1 (3.0- 3.2)	2.6 (2.5- 2.7)	3.5 (3.4- 3.6)	3.0 (2.9- 3.1)
70	4.4 (4.3- 4.5)	3.6 (3.5- 3.7)	4.8 (4.7- 4.9)	4.2 (4.1- 4.3)	5.5 (5.3- 5.6)	4.8 (4.7- 4.9)
80	6.0 (5.9- 6.3)	5.2 (5.1- 5.4)	6.7 (6.5- 7.0)	5.9 (5.8- 6.1)	7.5 (7.3- 7.8)	6.7 (6.6- 6.9)
Males: 20 pack-years						
50	0.3 (0.3- 0.3)	0.3 (0.3-0.3)	0.4 (0.4- 0.4)	0.3 (0.3- 0.3)	0.5 (0.4- 0.5)	0.4 (0.4-0.4)
60	1.0 (1.0- 1.0)	0.8 (0.8- 0.9)	1.2 (1.1- 1.2)	1.0 (1.0- 1.1)	1.5 (1.3- 1.5)	1.3 (1.2- 1.3)
70	2.5 (2.4- 2.6)	2.2 (2.1- 2.2)	3.1 (2.9- 3.2)	2.7 (2.5- 2.7)	3.7 (3.4- 3.9)	3.3 (3.0-3.4)
80	5.4 (5.0- 5.8)	4.7 (4.6- 4.9)	6.5 (6.1- 6.7)	5.8 (5.4- 6.0)	7.8 (7.2- 8.2)	7.0 (6.5- 7.3)
Males: 40 pack-years						
50	0.6 (0.6- 0.7)	0.5 (0.5- 0.5)	0.7 (0.7- 0.8)	0.6 (0.5- 0.6)	0.9 (0.8- 0.9)	0.7 (0.7- 0.8)
60	1.7 (1.7- 1.8)	1.4 (1.3- 1.4)	2.0 (1.9- 2.1)	1.7 (1.6- 1.7)	2.5 (2.2- 2.6)	2.1 (1.9- 2.2)
70	3.9 (3.8- 4.1)	3.2 (3.0- 3.3)	4.6 (4.3- 4.8)	3.9 (3.7- 4.0)	5.5 (5.0- 5.8)	4.7 (4.4- 4.9)
80	7.4 (7.0- 7.7)	6.2 (5.9- 6.4)	8.6 (8.1- 9.1)	7.4 (7.0- 7.8)	10.2 (9.5- 10.8)	8.9 (8.4- 9.4)

*Former smokers stop smoking at age 50, 60, 70 or 80.

Table 4.4 6-year risk projections for COPD incidence at age 50, 60, 70 or 80 among current and former smokers who have smoked for 20, 30, or 40 years, adjusting for other causes of mortality

	Current smokers	Former smokers*	Current smokers	Former smokers*	Current smokers	Former smokers*
			Smoking Duration (years)			
Age (year)	20 years		30 years		40 years	
Females: 20 pack-years						
50	0.8 (0.7- 0.8)	0.2 (0.2- 0.2)	0.9 (0.8- 0.9)	0.3 (0.3- 0.3)	1.0 (0.9- 1.0)	0.3 (0.3- 0.3)
60	1.4 (1.3- 1.4)	0.6 (0.6- 0.6)	1.6 (1.5-1.6)	0.7 (0.7- 0.8)	1.8 (1.7-1.8)	0.9 (0.8- 0.9)
70	1.8 (1.8- 1.8)	1.2 (1.2- 1.3)	2.1 (2.0- 2.1)	1.5 (1.4- 1.5)	2.4 (2.3- 2.4)	1.7 (1.6- 1.7)
80	1.5 (1.5- 1.5)	1.4 (1.4- 1.4)	1.7 (1.6- 1.7)	1.6 (1.6- 1.7)	1.9 (1.9- 2.0)	1.9 (1.9- 1.9)
Females: 40 pack-years						
50	1.5 (1.4- 1.5)	0.4 (0.4- 0.4)	1.6 (1.5- 1.7)	0.5 (0.5- 0.6)	1.8 (1.7- 1.9)	0.5 (0.5- 0.6)
60	2.4 (2.3- 2.4)	1.0 (1.0- 1.0)	2.6 (2.5- 2.7)	1.2 (1.2- 1.2)	3.0 (2.9- 3.0)	1.4 (1.4- 1.4)
70	2.8 (2.7- 2.9)	1.8 (1.8- 1.9)	3.1 (3.0- 3.2)	2.1 (2.1- 2.2)	3.5 (3.4- 3.5)	2.5 (2.4- 2.5)
80	2.0 (2.0- 2.1)	1.9 (1.8- 1.9)	2.2 (2.2- 2.3)	2.1 (2.1- 2.2)	2.5 (2.5- 2.6)	2.5 (2.4- 2.5)
Males: 20 pack-years						
50	0.3 (0.3- 0.3)	0.2 (0.2- 0.2)	0.3 (0.3- 0.4)	0.3 (0.3- 0.3)	0.4 (0.4- 0.4)	0.4 (0.3- 0.4)
60	0.7 (0.7- 0.7)	0.6 (0.6- 0.6)	0.9 (0.8- 0.9)	0.8 (0.7- 0.8)	1.1 (1.0- 1.1)	0.9 (0.9- 1.0)
70	1.2 (1.2- 1.3)	1.1 (1.0- 1.1)	1.5 (1.4- 1.6)	1.3 (1.2- 1.4)	1.8 (1.7- 1.9)	1.6 (1.5- 1.7)
80	1.1 (1.1- 1.1)	1.0 (0.9- 1.0)	1.3 (1.3- 1.4)	1.2 (1.1- 1.3)	1.6 (1.5- 1.7)	1.5 (1.3- 1.5)
Males: 40 pack-years						
50	0.6 (0.5- 0.6)	0.4 (0.4- 0.4)	0.6 (0.6- 0.7)	0.5 (0.5- 0.5)	0.8 (0.7- 0.8)	0.6 (0.6- 0.7)
60	1.3 (1.2- 1.3)	1.0 (0.9- 1.0)	1.5 (1.4- 1.6)	1.2 (1.2- 1.3)	1.8 (1.6- 1.9)	1.5 (1.4- 1.6)
70	1.9 (1.8- 2.0)	1.6 (1.5- 1.6)	2.3 (2.1-2.4)	1.9 (1.8- 2.0)	2.7 (2.5- 2.9)	2.4 (2.2- 2.5)
80	1.5 (1.4- 1.6)	1.3 (1.2- 1.3)	1.8 (1.7- 1.9)	1.6 (1.5- 1.6)	2.1 (2.0- 2.2)	1.9 (1.8- 2.0)

*Former smokers stop smoking at age 50, 60, 70 or 80.

Chapter 5

Temporal Trends and Geographic Patterns of Lung Cancer Incidence by Histology in Thailand, 1990-2014

5.1 Abstract

Background: Lung cancer is one of the most common cancers in both males and females in Thailand, with some variations in distribution by histology and region. The etiology and survival of lung cancer differ greatly by histological type. Thus, it is important to characterize and forecast region-specific patterns of lung cancer incidence by histology.

Methods: We analyzed lung cancer incidence trends in Thailand by histology (adenocarcinoma, squamous-cell, large-cell, small-cell and other) from 1990 to 2014 in four geographic regions (North: Chiang Mai Province; Northeast: Lampang Province; Central: Khon Kaen Province; South: Songkhla Province). Annual percentage change (APC) was calculated to quantify the incidence rate trends over time using a joinpoint regression analysis. Age-period-cohort models were used to further examine the temporal trends of adenocarcinoma and squamous-cell lung cancer by age, calendar year and birth cohort. We finally projected the incidence of these two histologic types of lung cancer up to year 2030 using three independent approaches: joinpoint, age-period-cohort and Nordpred models.

Results: Incidence of adenocarcinoma significantly increased from 1990 to 2012 in Chiang Mai males (APC=1.3% [$p<0.05$]), Songkhla males from 2004-2014 (APC=2.5%, [$p<0.05$]), Songkhla females from 1990-2014 (APC=5.9%, [$p<0.05$]), and Khon Kaen females from 2005-2014 (APC=3.1%, [$p<0.05$]). Conversely, squamous-cell incidence significantly decreased from 1990-

2012 in Chiang Mai males and females (APC=-1.2% and -4.8%, respectively, [$p<0.05$]), Lampang males and females from 1993 to 2014 (APCs=-5.4% and -5.2%, respectively, [$p<0.05$]), and Songkhla females from 1990 to 2014 (APC=-2.1%, [$p<0.05$]). Trends of adenocarcinoma and squamous-cell lung cancer correlate in general better with birth-cohort rather than calendar-year. The three projection models suggested that incidence rates of adenocarcinoma of Songkhla will continue to increase until 2030, and to a lesser level in Chiang Mai and Khon Kaen.

Conclusion: Temporal trends of lung cancer by histology greatly varied between regions in Thailand. To reduce lung cancer incidence in Thailand may require prevention strategies tailored to each specific region.

5.2 Introduction

Worldwide, lung cancer has been one of the most common cancers for the last several decades. In 2012, an estimated 1.8 million new cases of lung cancer were diagnosed, 58% of which occurred in less developed regions.[1] Lung cancer in Thailand was ranked in 2012 as the second and third most common cancer type for males (32.0 cases per 100,000) and females (10.1 cases per 100,000), respectively.[2] Lung cancer mortality rates have peaked in many high-income countries (HICs), but are still on the rise in low- and middle- income countries (LMICs), including Thailand.[3] This reflects in part the different stages of the tobacco epidemic across countries, with developed countries in the decline of smoking prevalence, whereas LMICs are still on the rise.

It is well-known that lung cancer is mainly attributed to cigarette smoking. In Thailand, smoking is common in adults, with 46.6% of males and 2.6% females smoking cigarettes in 2011.[4] However, smoking prevalence has been decreasing; going from nearly 60% to 45% in males from 1991 to 2006, and from 5% to 2.5% in females.[5] Nonetheless, despite these reductions in smoking, the overall lung cancer incidence rate has been increasing continuously in Thailand since the 1990s.[6]

Lung cancer tumor histology can be classified into two major categories: small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma are the three main NSCLC subtypes. Cigarette smoking increases risk of all histologic types of lung cancer, but the degree of the association differs between types. Squamous-cell carcinoma and small-cell carcinoma are believed to be affected more profoundly by smoking than the other types, adenocarcinoma is associated with smoking, and most cases occur in smokers. Small-cell is unique because it does not occur in never

smokers.[7,8] Besides cigarette smoking, other factors such as secondhand smoking,[9] cooking fumes,[10] genetic predisposition,[11] hormones,[12] occupational exposure,[13] household radon,[14] and inflammatory processes can also contribute to the risk of lung cancer.[15]

As smoking patterns are changing in Thailand and elsewhere,[16] the relative lung cancer incidence between histologic types has shifted. In particular, while the incidence rates of squamous-cell carcinoma and small-cell carcinoma have decreased in general, the incidence of adenocarcinoma has increased, particularly in females.[17–21]

The objective of this study is to better understand trends of lung cancer incidence by histology and sex in different geographical regions in Thailand. We first analyze trends of age-adjusted lung cancer rates using joinpoint regression model. We then further investigate the trends of adenocarcinoma and squamous-cell carcinoma using age-period-cohort models. Finally, we used three projection methods to forecast lung cancer incidence rates by histology in different regions in Thailand until 2030.

5.3 Methods

Cancer registries and case ascertainment

Lung cancer data from four regional cancer registries were extracted for our analysis: Chiang Mai, Lampang, Khon Kaen and Songkhla Cancer Registries. These registries were chosen based on their geographical locations (Figure 5.1) and relatively high quality data. Case ascertainment in each registry catchment area is above 90%.[22] The Chiang Mai Cancer Registry was established in 1983 and actively collects cancer cases from all provincial hospitals in northeastern Thailand.[23] The Lampang Cancer Registry covers the province of Lampang in northern Thailand. Data is collected from 21 cancer centers, general hospitals, community

hospitals, private hospitals, university hospitals, the provincial public health service, and pathology laboratories.[24] The Khon Kaen Cancer Registry was established within the Faculty of Medicine, Khon Kaen University in 1985 in the central Thailand. It collects data from all hospitals within the region.[25] The Songkhla Cancer Registry is a population-based registry in the Songkhla province, and is located within the Faculty of Medicine, Prince of Songkla University in southern Thailand. The registry includes active case ascertainment from community hospitals, private hospitals, special hospitals, the provincial health office and the provincial population registration office.[26] All four registries provide data for the International Agency for Research on Cancer's (IARC) Cancer Incidence in Five Continents repository (CI5).[27]

Lung cancer case counts were obtained from Khon Kaen and Songkhla Cancer Registries (1990-2014), Chiang Mai Cancer Registry (1990-2012), and Lampang Cancer Registry (1993-2014), using the International Classification of Disease, 10th Edition (ICD-10) code, C33-C34. Case information included age, sex, date of diagnosis, and histology. Population counts by registry, age, sex and year were based on the 1990, 2000, and 2010 censuses published by the National Statistical Office in Thailand.[28,29] Age-adjusted rates of lung cancer incidence were standardized to the Segi world standard population.[30] Cases were classified by histology based on the ICD-O-3 code, squamous-cell carcinoma: 8050-8078, 8083-8084; adenocarcinoma: 8140, 8211, 8230-8231, 8250-8260, 8323, 8480-8490, 8550-8551, 8570-8574, and 8576; large-cell carcinoma: 8010-8012, 8014-8031, 8035, and 8310; small-cell carcinoma: 8041-8045 and 8246; non-small cell carcinoma: 8046; other histology: 8120, 8130, 8170, 8200, 8240–8249, 8340, 8430, 8525, 8551, 8560, 8562, 8580, 8940, 8972; and unknown histology: 8000-8009.

Missing histology classification was substantial across registries, with about 30%-50% of unknown histology depending on the registry. Therefore, a multiple imputation method

previously developed by Sriplung *et al.* [31] was used to impute the unknown histology values. Specifically, multiple imputation was conducted using the "MICE" package in the R statistical software (version 3.2.0.).[32] Age, sex, year of diagnosis and registry were used as predictive variables of the unknown histology. Adenocarcinoma and squamous-cell carcinoma are the most common types in all registries, and the data for other types is sparse. Thus, our trend analyses focused primarily on adenocarcinoma and squamous-cell carcinoma.

For the analysis, we tabularized lung cancer cases by age groups (less than 50 years, 50–59 years, 60–69 years, 70–79 years, and 80 years and older) and year of diagnosis (1990-1994, 1995-1999, 2000-2004, 2005-2009, and 2010-2014), separately by sex.

Trend analysis

To identify any significant changes in trends of age-adjusted lung cancer rates by sex and histology, we performed joinpoint regression analysis using the statistical software Joinpoint, version 4.0.1 (Surveillance Research Program, US National Cancer Institute).[33] Due to data sparsity, we restricted the analysis to five data points as the minimum number observations between two joinpoints. Joinpoint regression identifies the annual percentage rate of change (APC) in each statistically significant trend interval. Average annual percentage rates of change (AAPCs) for the last ten years (2005-2014 for Lampang, Khon Kaen and Songkhla; 2003-2012 for Chiang Mai) were also estimated for comparison across demographic and histology groups.

Age-period-cohort analysis

Age-period-cohort models were used to estimate the separate effects of age, period (calendar year), and cohort (birth-year) on lung cancer incidence.[34] This assumes that the

incidence rates follow a Poisson distribution with mean equal to the product of age, period and cohort effects. The model can be written as:

$$\log \lambda_{a,p} = f(a) + g(p) + h(c),$$

where the expected log-incidence rates $\lambda_{a,p}$ are assumed to be equal to a linear combination of age (a), period (p), and birth-cohort (c) effects, with c=p-a. To deal with the well-known identifiability issue of age-period-cohort models,[34] we fitted the models with either cohort constrained to be 0 on average with 0 slope (AP-C) or period constrained to be 0 on average with 0 slope (AC-P). We used these age-period-cohort models to estimate age-specific incidence rates for selected years. The best fitted age-period-cohort models were determined based on the Akaike Information Criteria (AIC). Analyses were performed using the "Epi" package in the R statistical software (version 3.2.0).[32] The AP-C and AC-P models were fitted to adenocarcinoma and squamous-cell carcinoma data in each registry by sex. The number of cases was insufficient for other types of histology to build adequately powered models.

Lung cancer incidence projections

We projected lung cancer incidence by histology in each of the four registries from 2012 until 2030 using three different approaches: joinpoint, age-period-cohort, and Nordpred models,[35] and then compared the projections for the two major histologic types (adenocarcinoma and squamous-cell carcinoma) by sex across the three methods.

Joinpoint projections

For the joinpoint projections, because recent trends are likely to be the best predictors of future cancer incidence, the projection was obtained by carrying forward the APC estimate from

the last joinpoint period to the future years. Specifically, we kept the same trend for the first following five years, and then reduced it (de-trending) by 7% for each subsequent year until 2030.[36]

Age-period-cohort projections

For the age-period-cohort projections, we used both AP-C and AC-P models. For the AC-P approach, we estimated the linear component of the corresponding model cohort effects and projected it to 2030, while the age and period effects were kept constant. For the AP-C approach, we estimated the linear component of the corresponding model period effects and projected it to 2030, while the age and cohort effects were kept constant. A similar de-trending approach as for the joinpoint projections was applied to attenuate the linear period or the cohort effects trend when projecting these into the future.

Nordpred projections

Lastly, we used the R-package "nordpred" to project lung cancer incidence.[35] The data is fitted to an age-period-cohort model and then incidence rates for each 5-year age group and 5-year intervals are computed (1990-1994, …, 2010-2014). The estimated trends based on the observed data are extrapolated to four separate periods in the future, until 2030. To avoid potential overestimation of lung cancer cases, a power function in Nordpred was used to attenuate the linear trend (de-trending) by 0%, 21.6%, 48.3%, 65.9% and 77.6% for the corresponding five periods: 2012-2013, 2014–2018, 2019–2023, 2024–2028, and 2029-2030.

5.4 Results

Descriptive

From 1990 to 2012, there were 11,366 lung cancer cases reported in the Chiang Mai Cancer Registry (56.9% males). From 1993 to 2014, there were 7,727 cases in the Lampang Cancer Registry (63.3% males). From 1990 to 2014, there were 5,305 cases (71.5% males) in the Khon Kaen Cancer Registry, and 4,093 cases (70.7% males) in the Songkhla Cancer Registry. The distribution of age at diagnosis was similar across registries, with most cases diagnosed between 60-69 years old (Table 5.1). Table 5.2 shows the distribution of lung cancer cases by histology before and after multiple imputations were performed. Most unknown histology cases were re-classified as adenocarcinoma and squamous-cell carcinoma. Figure 5.2 shows the distribution of lung cancer cases by histology in each registry by year of diagnosis and sex. In Chiang Mai, Lampang and Songkhla Cancer Registries, the proportion of adenocarcinoma cases increased over time, while the proportion of squamous-cell carcinoma decreased. In Khon Kaen Cancer Registry, the histology proportions remained roughly constant over time.

Joinpoint regression (lung cancer trends)

Table 5.3 and Figure 5.3 show results of the joinpoint regressions by registry, sex and histology. Of the four regions, Chiang Mai had the highest incidence rates of adenocarcinoma in both males and females (12.5 and 13.3 per 100,000, respectively, in 1990). The incidence rate of adenocarcinoma significantly increased from 1990 to 2012 in Chiang Mai males (APC=1.3% [95% CI: 0.4%, 2.2%]), in Khon Kaen males from 2004-2014 (APC=2.5% [95% CI: 0.7%, 4.3%]), in Songkhla females from 1990-2014 (APC=5.9% [95% CI: 4.8%, 7.1%]), and in Khon Kaen females from 2005-2014 (APC=3.1% [95% CI: 0.2%, 6.2%]). In terms of average annual

percentage change over the last 10 years, Songkhla had the largest increases in adenocarcinoma (AAPCs, males: 2.5% and females: 5.9%). Conversely, decreasing AAPCs of the last 10 years for squamous-cell carcinoma were found in Chiang Mai males and females (AAPCs= -1.2% [95% CI: -2.0%, -0.4%], and -5.0% [95% CI: -7.1%, -2.8%], respectively), Lampang males and females (AAPCs= -5.4% [95% CI: -6.3%, -4.5%], and -5.2% [95% CI: -6.2%, -4.2%], respectively) and Songkhla females (AAPC= -2.1% [95% CI: -4.0%, -0.1%]). (Table 5.3, Figure 5.3). Joinpoint trend results for large-cell, small-cell and other lung cancers are shown in Table 5.4.

Age-period-cohort analysis

For males, the AC-P model, which gives predominance to cohort rather than period effects, fits better for all registries, except squamous-cell carcinoma in Khon Kaen and adenocarcinoma in Songkhla. For females, the AC-P model fits better for the adenocarcinoma and squamous-cell carcinoma incidence in Chiang Mai and Lampang Cancer Registries (Table 5.5).

Figure 5.4 shows the estimated age and cohort effects from the AC-P model, and age and period effects from the AP-C model for adenocarcinoma in males and females. Figure 5.5 shows similar figures for squamous-cell carcinoma. We anchored the birth cohort effect as 1 at the 1940 birth cohort (reference cohort), and the period effect at the 2000 calendar year (reference period). The period effects of adenocarcinoma increased from 2000 to 2010 for both Songkhla and Chiang Mai males and females, while the effects were relatively flat for others. We also observed an increase in the cohort effects for Songkhla males and females, while others remain

relatively constant. Conversely, for squamous-cell carcinoma, the cohort effects were lower in younger birth cohorts for both males and females in all regions.

Lung cancer incidence projection

Figure 5.6 and Figure 5.7 show the projected incidence rates of adenocarcinoma and squamous-cell carcinoma in four regions in Thailand by sex. For adenocarcinoma, using the joinpoint approach, incidence rates are projected to increase to 20.89 cases per 100,000 person-years for Chiang Mai males, to 20.59 cases per 100,000 person-years for Songkhla males, and to 19.25 cases per 100,000 person-years for Songkhla females in 2030. Both AP-C and AC-P models project that the incidence rates for Songkhla males will reach to 17.6 and 17.1 cases per 100,000 person-years respectively, and for Songkhla females to 10.0 and 9.6 cases per 100,000 person-years respectively, in 2030. The Nordpred model projects that incidence rates of adenocarcinoma will continue to increase to 16.7 and 12.3 cases per 100,000 person-years for Songkhla males and females, respectively. Conversely, rates of squamous-cell carcinoma are projected to decrease over the years to reach below 5 cases per 100,000 person-years in 2030 for both males and females in all regions.

5.5 Discussion

Main results

In this study, we investigated lung cancer incidence trends in Thailand by region, histology, and sex using joinpoint and age-period-cohort models. We also projected lung cancer rates up to 2030 by using three models: joinpoint, age-period-cohort, and Nordpred. To our knowledge, this is the first study to examine lung cancer trends by histology in Thailand

comparing the trends in multiple registries. Lung cancer incidence trends vary by histology and region in Thailand. Overall, squamous-cell lung cancer in Thailand has been decreasing since the 1990s (most recent available data).[37] Our analyses suggest that the rates of adenocarcinoma were stable or increased moderately for both males and females in Chiang Mai and Lampang, while the rates of squamous-cell carcinoma have leveled off. Similar patterns were observed in Songkhla and Khon Kaen, but with a larger increase for adenocarcinoma. Projections from all three models suggest that the burden of lung adenocarcinoma for both males and females in Songkhla, and to a lesser extent in Chiang Mai and Khon Kaen, will continue to increase at least until 2030.

The shift in trends by region

The trends of lung cancer incidence by histology differ between regions in Thailand. The age-period-cohort analysis indicates that the decrease in incidence of squamous-cell carcinoma in all regions can be generally explained by decreases by birth-cohort. Since 1993, Thailand has implemented many tobacco control policies including taxation, packaging and labeling, advertising bans, and smoke-free public areas.[38] The effect of tobacco control thus may explain the significant drop in incidence of squamous-cell carcinoma in all regions. Nonetheless, we still observed regional differences in lung cancer incidence rates, which could be due to differential smoking rates by region. Table 5.6 shows the smoking prevalence vary by region.[4,39,40] According to the Thailand Global Adult Tobacco Survey (GATS), in 2011, the South has the highest number of daily smokers (29.9%) and Bangkok has the lowest (18.1%).[4] smoking rate is highest in the South (decreasing from 60.9% in 1994 to 49.9% in 2007) and lowest in Bangkok (decreasing from 45.7% in 1991 to 26.9% in 2007). For females, however, smoking is highest in

the North (decreasing from 12.5% in 1991 to 5% in 2007) and lowest in the Northeast (decreasing from 2.1% in 1991 to 0.7% in 2007).[41]

Conversely, for adenocarcinoma, we observed different period and cohort effects for each region. For the two regions in the North (Chiang Mai and Lampang), the trend of adenocarcinoma was better explained by cohort effect, whereas for Khon Kaen and Songkhla, both period and cohort effects were important. Although the reasons for these differences are unclear some contributing factors are listed next. First, during the early 1990s, due to the stigma associated with an HIV/AIDS diagnosis in Thailand, there might have been extensive misclassifications of HIV/AIDS malignancies as lung cancer. Given their similar symptomatology, many HIV/AIDS-related malignancies, with lower than expected rates given the relatively high HIV prevalence,[42] could have been misclassified as pulmonary malignancies. Chiang Mai and Lampang were especially affected by the HIV/AIDS epidemic,[42] therefore, adenocarcinoma incidence could have been artificially inflated in the 1990s and early 2000s in these provinces. Second, for Khon Kaen and Songkhla, the increasing trends by period could be also related to improvements in the diagnosis of adenocarcinoma since the registries in these two regions were established earlier and have better data quality than the other two registries.[23–26]

Comparison with other countries

Our study shows differential trends of lung cancer by histology in Thailand, with increasing rates of adenocarcinoma and decreasing rates of squamous-cell carcinoma over past 20 years in Songkhla and Khon Kaen. Similar patterns have been found in some high-income Asian regions, including Osaka (Japan), Hong Kong (China), and Tianjin (China).[19,20,43] Overall smoking prevalence has declined relatively early in these Asian countries. And in these

countries, incidence rates of squamous-cell carcinoma began to decline in the late 1980s, but incidence rates of adenocarcinoma was increasing or stable until the last decade.[19,20,43] In Japan, the aggressive tobacco products marketing campaigns targeting females have led to a doubling of the female smoking rates; however, smoking prevalence is still higher among Japanese males than females. Incidence of squamous-cell carcinoma has significantly decreased, but adenocarcinoma incidence has increased in both males and females in Japan.[19] In Hong Kong and Tianjin, China, incidence rates of lung cancer significantly decreased for both males and females after the 1980s.[20,43] In these two regions, squamous-cell carcinoma incidence rates are decreasing in both sexes whereas, adenocarcinoma incidence rates continue to increase.

The shift in trends by histology

The shift between histologic types in lung cancer incidence may be explained by several factors. First, some have hypothesized that the change in the composition of cigarettes to low-tar filtered cigarettes could change the prevalence of histologic types of lung cancer.[44–47] Newer filtered cigarettes might have promoted smokers to inhale more deeply, and led to more peripheral tumors such as adenocarcinoma.[48] Other changes in the chemical composition of cigarettes and design may explain the surge of adenocarcinoma. Cigarette makers increased the composition of tobacco-specific N-nitrosamines, which are adenocarcinoma inducers, and decreased the polycyclic aromatic hydrocarbons.[49] Future studies are needed to examine the composition of cigarettes used by the Thai population, especially with the increasing use of hand-rolled cigarettes.[50,51]

Second, there might be changes in exposure to environmental carcinogens. Previously, some studies have suggested that outdoor air pollution (particulate matter [PM] 2.5 and PM_{10}) is

a significant contributor to lung adenocarcinoma risk.[52] As Thailand is undergoing globalization, we speculate that air pollution from vehicle emissions, biomass burning and transboundary haze in rural and border areas could be a source of the increase of lung cancer adenocarcinoma. Particularly, the agricultural burning and forest fires in Chiang Mai have been major sources of high levels of PM_{10}.[53]

Third, changes in diagnostic criteria and advanced technology for the histopathology diagnosis of lung cancer may have led to increasing diagnoses of adenocarcinomas. With diagnostic procedures becoming safer, and improvements in treatment of adenocarcinomas,[54,55] an increasing number of tumors have been microscopically verified in the elderly. New classifications of tumors have decreased the proportion of unspecified lung cancers.[56] The changing trends by histology observed in our study occurred about the same period when the changes in the guidelines for classifying lung cancer histology were implemented.[56]

Future lung cancer incidence

We projected the incidence of adenocarcinoma and squamous-cell carcinoma up to 2030 using three different approaches. Joinpoint regression estimates annual percentage change in age-adjusted rate and uses the most recent trend period as the basis for prediction. Age-period-cohort and Nordpred models use the estimated period or cohort effects to project future incidence. All three methods suggested that the incidence of adenocarcinoma will potentially reach 10-20 cases per 100,000 person-years in 2030 for both males and females. On the contrary, all three methods projected that incidence of squamous-cell carcinoma will tail off to below 5 cases per 100,000 person-years in 2030. Thus, it is evident that incidence of adenocarcinoma will continue to

increase in some regions of Thailand, and may become an emerging public health issue. This is relevant given the differences in survival and treatment guidelines by histology.[54,55]

Strengths and limitations

There are some limitations in our study. First, the high proportion of lung cancer cases with missing histology (30%-50% depending on registry) might lead to unstable estimation of lung cancer incidence rates by histology. However, we utilized a multiple imputation method for missing histology data, which has already been validated for Thai Cancer Registries.[29] Second, the age-period-cohort models have an inherent non-identifiability issue which prevents the unique estimation of period or cohort effects. We resolved partially this non-identifiability problem by fitting models with either 0-period (AC-P) or 0-cohort (AP-C) trends.[57] The relative fit of these models gives an assessment of whether period or cohort is better correlated with lung cancer incidence. Smoking is largely a cohort-related behavior,[58] with most users beginning smoking as young adults and carrying out the behavior through adulthood. However, we cannot exclude the possibility of some underlying period-based trends due to increasing awareness of the health hazards of smoking supported by emerging tobacco control laws as these get implemented. Certainly, the documented changes in smoking patterns in Thailand are relatively recent and cannot then fully explain the lung cancer trends in the past two decades given the long lag time between smoking exposure and lung cancer.[9] Third, the registry data does not have information on biomarkers,[59] or environmental and lifestyle risk factors (e.g., tobacco use, asbestos exposure, COPD, family history, and diet). It is thus difficult to examine the causal relationship between these risk factors and observed lung cancer trends. Lastly, we did not have

information on tumor stage and size, which could be useful to examine the prognosis and survival of lung cancer by histology.

Our study has several strengths. This is the first study to examine the histology-specific lung cancer trends by age, calendar-year and birth-cohort in different regions in Thailand. The analysis of trends in lung cancer incidence was based on data from four population-based cancer registries in Thailand, which have sufficiently good quality with high completeness and validity (with the exception of histology).[22] The age-period-cohort approach allowed us to examine the influence of age, calendar-year and birth-cohort on the changing trends of lung cancer incidence by histology. Moreover, we used three alternative projection approaches which are based on different aspects of lung cancer incidence (age-adjusted rate, annual percentage change or period and cohort trends). And all three models projected relatively consistent trends for lung cancer incidence by histology in future years, which yield great credibility for our results.

Finally, our study also adds important contributions to the literature, which can serve as a basis for projecting the future burden of lung cancer in Thailand. Given the reductions in smoking prevalence, squamous-cell lung cancer incidence is expected to decrease further in next decades (which is partially captured by the decreasing trends by birth-cohort). Conversely, the trends in lung adenocarcinoma incidence vary by region, either remaining constant or continuing to increase. Future studies should focus on characterizing time-varying impact of smoking on lung cancer by histology, as well as understanding the impact of how other non-smoking risk factors are associated with lung cancer. The predicted changes in distribution of histologic types of lung cancer incidence in future years may also have some implications for prognosis and treatment options. In the US, there are no differences in treatment options by histology for those who are diagnosed with lung cancer in either Stage I or II. However, for patients with lung

cancer either in Stage III or IV, targeted therapy has been administered given their tumor histologic types.[54,55] For instance, patients with adenocarcinoma tend to have epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement, and treatments targeting these genetic changes have shown to improve patients' prognosis.[60] In Thailand, high prevalence of EGFR have been found in patients with lung cancer adenocarcinoma, which was projected to increase until 2030,[61] it is thus paramount to identify this group for targeted therapy and further reduce the lung cancer burden in the future.

Conclusion

Our study showed the shift in lung cancer trends by histology in Thailand, which varies by sex and geographic region. Overall, while the incidence of squamous-cell lung cancer has been decreasing since the 1990s, adenocarcinoma has been increasing or stable in recent years in Thailand. Three independent models consistently projected increasing trends of adenocarcinoma incidence until 2030 for both Songkhla males and females. The changing patterns of lung cancer by histology in different regions of Thailand suggest that the profile of non-tobacco risk factors and smoking patterns might vary by region. This highlights the need for surveillance systems for both risk factors and cancer to evaluate how non-tobacco risk factors in synergy with cigarette smoking determine lung cancer rates. Furthermore, the prognosis for lung cancer may vary by histology, and the histologically tailored treatment may effectively improve patient's survival. Projections of lung cancer rates by histologic type can help the cancer control community to plan for treatment needs and highlight the need for additional prevention efforts against lung cancer.

5.6 References

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Figure 5.1 Maps of Thailand with four registries: Chiang Mai (red), Lampang (black), Khon Kaen (blue) and Songkhla (green).

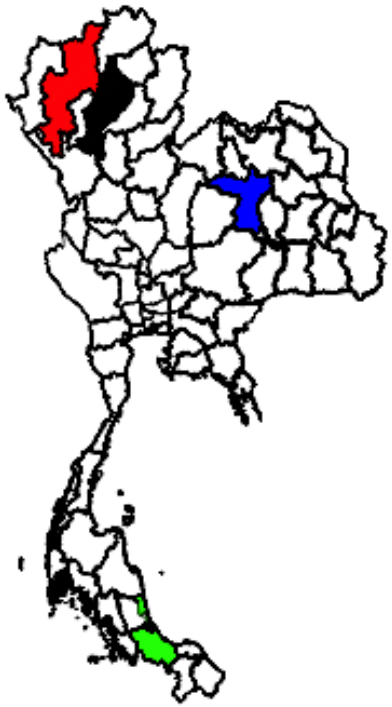

Table 5.1 Characteristics of lung cancer cases in females and males across registries, 1990-2014.

	Males				Females			
	Chiang Mai	Lampang	Khon Kaen	Songkhla	Chiang Mai	Lampang	Khon Kaen	Songkhla
Diagnosis period	1990-2012	1993-2014	1990-2014	1990-2014	1990-2012	1993-2014	1990-2014	1990-2014
Number of cases	6463	4891	3795	2895	4903	2836	1510	1198
Age at diagnosis (y) (%)								
<50	12.4	8.9	13.8	12.2	10.7	10.7	19.1	17.1
50-59	23.2	20.3	23.1	20.5	22.8	19.4	25.2	20.1
60-69	32.8	32.1	32.9	30.7	33.9	34.2	37.7	34.3
70-79	25.2	28.6	24.0	27.1	25.6	28.0	22.0	26.3
≥80	6.4	8.2	6.1	9.5	7.0	7.7	6.0	12.2
Year of diagnosis (%)								
1990-1994*	18.2	8.3	12.0	10.3	19.7	8.2	11.3	7.9
1995-1999	18.0	22.6	16.4	11.2	17.0	20.5	17.5	11.7
2000-2004	21.5	23.7	20.5	17.8	21.9	23.3	17.9	15.4
2005-2009	25.2	22.5	21.9	27.8	24.4	23.6	22.7	25.1
2010-2014**	17.3	23.0	29.3	33.0	17.0	24.5	30.6	39.8
Histology (%)								
Adenocarcinoma	27.6	22.0	22.2	34.1	30.9	26.4	35.6	54.1
Squamous-cell carcinoma	18.9	19.0	7.4	20.8	13.3	15.9	3.4	7.9
Small-cell carcinoma	6.2	7.4	2.2	6.5	6.5	7.0	0.8	1.9
Large-cell carcinoma	7.1	14.9	6.5	4.5	6.2	14.4	6.5	2.8
NSCLC	1.0	0.5	3.5	5.1	0.9	0.7	3.1	3.6
Other lung cancer	0.5	0.3	0.5	0.4	0.5	0.3	0.4	1.3
Unknown	38.8	35.9	57.6	28.7	41.7	35.4	50.3	28.4

NSCLC: Non-small cell lung cancer

* For Lampang, data is available from 1993-1994; ** For Chiang Mai, data is available from 2010-2012

Table 5.2 Distribution of lung cancer cases by histologic types in males and females, pre-multiple imputation (pre-MI) and post-multiple imputation (post-MI).

	Chiang Mai				Khon Kaen				Lampang				Songkhla			
	Male		Female		Male		Female		Male		Female		Male		Female	
Histological type	Pre-MI	Post-MI	Pre-MI	Post-MI	Pre-MI	Post-MI	Pre-MI	Post-MI	Pre-MI	Post-MI	Pre-MI	Post-MI	Pre-MI	Post-MI	Pre-MI	Post-MI
Adenocarcinoma	27.62	45.6	30.94	53.5	22.24	57.1	35.56	78.9	22.02	34.4	26.38	40.9	34.09	51.9	54.09	79.4
Small-cell carcinoma	6.16	10.3	6.53	11.5	2.19	5.6	0.79	1.7	7.36	11.6	7.02	11	6.46	9.8	1.92	2.9
Squamous-cell carcinoma	18.85	31.5	13.26	23.5	7.4	19.1	3.38	7.4	19.01	29.9	15.87	25	20.76	31	7.93	11.8
Large-cell carcinoma	7.12	11.8	6.2	10.7	6.51	16.9	6.49	14.1	14.9	23.6	14.35	22.6	4.46	6.6	2.84	4.2
Other lung cancer	0.53	0.87	0.47	0.78	0.5	1.2	0.4	0.89	0.31	0.48	0.32	14.1	0.41	0.64	1.25	1.8
NSCLC *	0.97	-	0.88	-	3.53	-	3.05	-	0.49	-	0.67	-	5.08	-	3.59	-
Unknown	38.76	-	41.73	-	57.63	-	50.33	-	35.9	-	35.4	-	28.74	-	28.38	-

*NSCLC was treated as Unknown and also re-distributed to a specific histologic type through multiple imputation.

Figure 5.2 Distribution of lung cancer cases by histologic types over diagnosis year, for males and females in all registries: a) Chiang Mai (b)Khon Kaen (c) Lampang (d) Songkhla. (SCC: Squamous-cell carcinoma; Adeno: Adenocarcinoma; Large: Large-cell carcinoma; Small: Small-cell carcinoma; Other: Other histology)

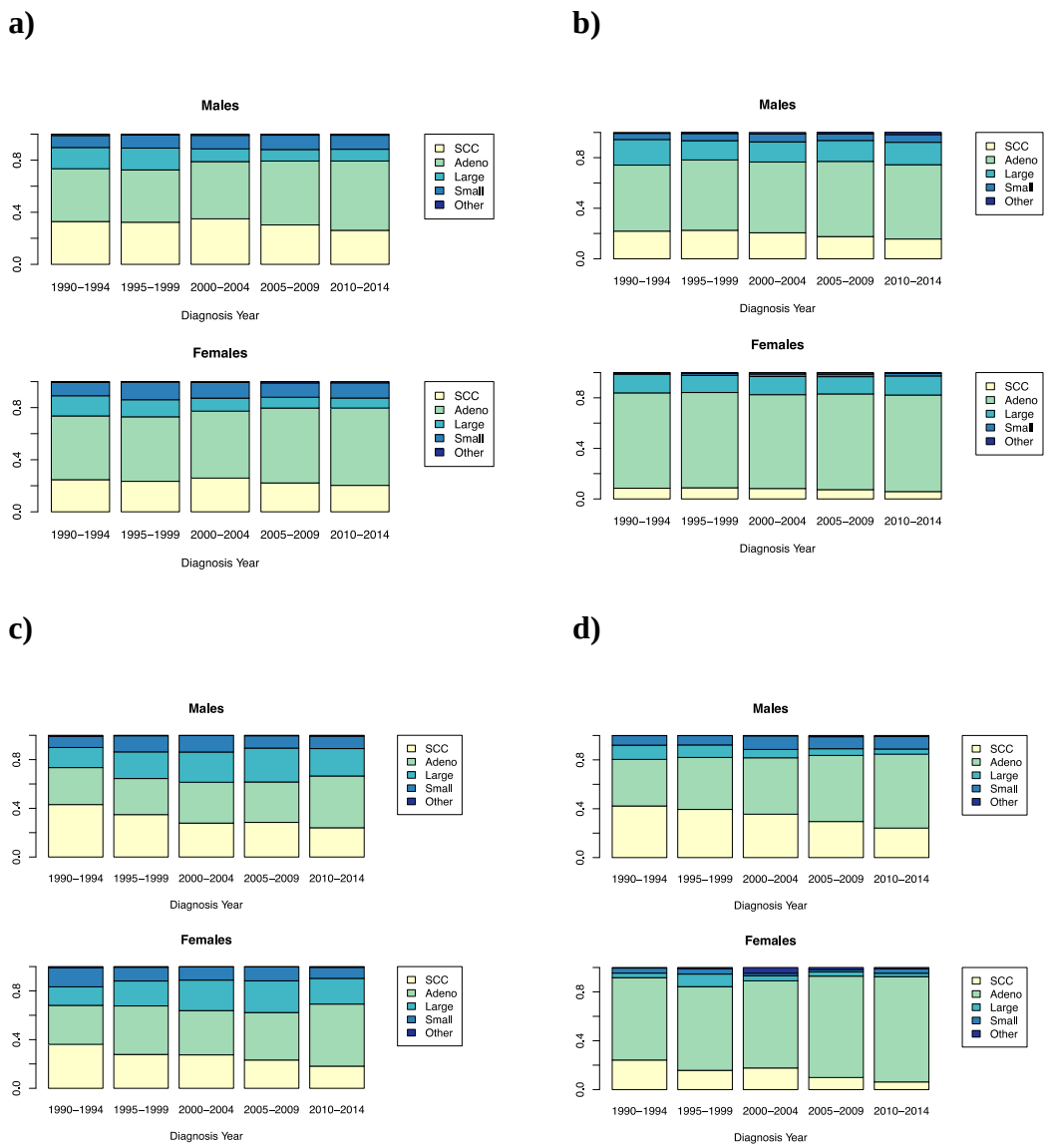

Table 5.3 Annual Percent Change (APC), Average Annual Percent Change (AAPC) and 95% confidence interval (CI) in age-adjusted incidence in all histology, adenocarcinoma, and squamous-cell carcinoma

	Trend 1		Trend 2		Trend 3		Last 10 years
	Year	APC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)	AAPC (95% CI)
Males							
All histology							
Chiang Mai	1990-2012	-0.3 (-1.0, 0.4)					-0.3 (-1.0, 0.4)
Lampang	1993-2014	**-2.9 (-3.6, -2.2) ***					**-2.9 (-3.6, -2.2) ***
Khon Kaen	1990-2001	**3.7 (1.5, 6.0) ***	2001-2005	-6.6 (-18.2, 6.6)	2005-2014	1.6 (-0.6, 3.8)	1.6 (-0.6, 3.8)
Songkhla	1990-1999	-0.8 (-4.5, 3.1)	1999-2005	**10.1 (2.7, 18.1) ***	2005-2014	-0.2 (-2.3, 2.0)	-0.2 (-2.3, 2.0)
Adenocarcinoma							
Chiang Mai	1990-2012	**1.3 (0.4, 2.2) ***					**1.3 (0.4, 2.2) ***
Lampang	1993-2014	-0.9 (-1.8, 0.0)					-0.9 (-1.8, 0.0)
Khon Kaen	1990-1997	5.3 (-0.1, 11.0)	1997-2014	0.2 (-0.8, 1.2)			0.2 (-0.8, 1.2)
Songkhla	1990-2000	0.8 (-2.7, 4.5)	2000-2004	19.6 (-0.1, 43.3)	2004-2014	**2.5 (0.7, 4.3) ***	**2.5 (0.7, 4.3) ***
Squamous-cell carcinoma							
Chiang Mai	1990-2012	**-1.2 (-2.0, -0.4) ***					**-1.2 (-2.0, -0.4) ***
Lampang	1993-2014	**-5.4 (-6.3, -4.5) ***					**-5.4 (-6.3, -4.5) ***
Khon Kaen	1990-2000	**5.5 (2.0, 9.1)**	2000-2004	-12.1 (-26.4, 5.1)	2004-2014	-0.8 (-3.5, 2.0)	-0.8 (-3.5, 2.0)
Songkhla	1990-2014	0.0 (-1.1, 1.1)					0.0 (-1.1, 1.1)
Females							
All histology							
Chiang Mai	1990-1998	**-3.7 (-6.2, -1.2) ***	1998-2012	-0.4 (-1.4, 0.7)			-0.4 (-1.4, 0.7)
Lampang	1993-2014	**-2.2 (-2.7, -1.7) ***					**-2.2 (-2.7, -1.7) ***
Khon Kaen	1990-1998	**7.3 (3.3, 11.6) ***	1998-2003	-7.2 (-15.2, 1.6)	2003-2014	**2.8 (1.1, 4.5) ***	2.1 (-0.2, 4.4)
Songkhla	1990-2014	**4.5 (3.6, 5.4) ***					**4.5 (3.6, 5.4) ***
Adenocarcinoma							
Chiang Mai	1990-2012	-0.2 (-1.0, 0.6)					-0.2 (-1.0, 0.6)
Lampang	1993-2014	-0.3 (-1.2, 0.6)					-0.3 (-1.2, 0.6)
Khon Kaen	1990-1993	29.9 (-0.4, 69.5)	1993-2005	-1.8 (-4.4, 0.9)	2005-2014	**3.1 (0.2, 6.0) ***	**3.1 (0.2, 6.0) ***
Songkhla	1990-2014	**5.9 (4.8, 7.1) ***					**5.9 (4.8, 7.1) ***
Squamous-cell carcinoma							
Chiang Mai	1990-1999	**-4.8 (-7.1, -2.3) ***	1999-2003	6.0 (-6.6, 20.3)	2003-2012	**-5.0 (-7.1, -2.8) ***	**-5.0 (-7.1, -2.8) ***
Lampang	1993-2014	**-5.2 (-6.2, -4.2) ***					**-5.2 (-6.2, -4.2) ***
Khon Kaen	1990-2014	-1.0 (-2.8, 0.9)					-1.0 (-2.8, 0.9)
Songkhla	1990-2014	**-2.1 (-4.0, -0.1) ***					**-2.1 (-4.0, -0.1) ***

* Annual percent change and average annual percent change are significantly different from zero $p < 0.05$.

Figure 5.3 Histology-specific age-adjusted incidence rates of lung cancer per 100,000 population in (a) Adenocarcinoma (b) Squamous-cell carcinoma

(a) **(b)**

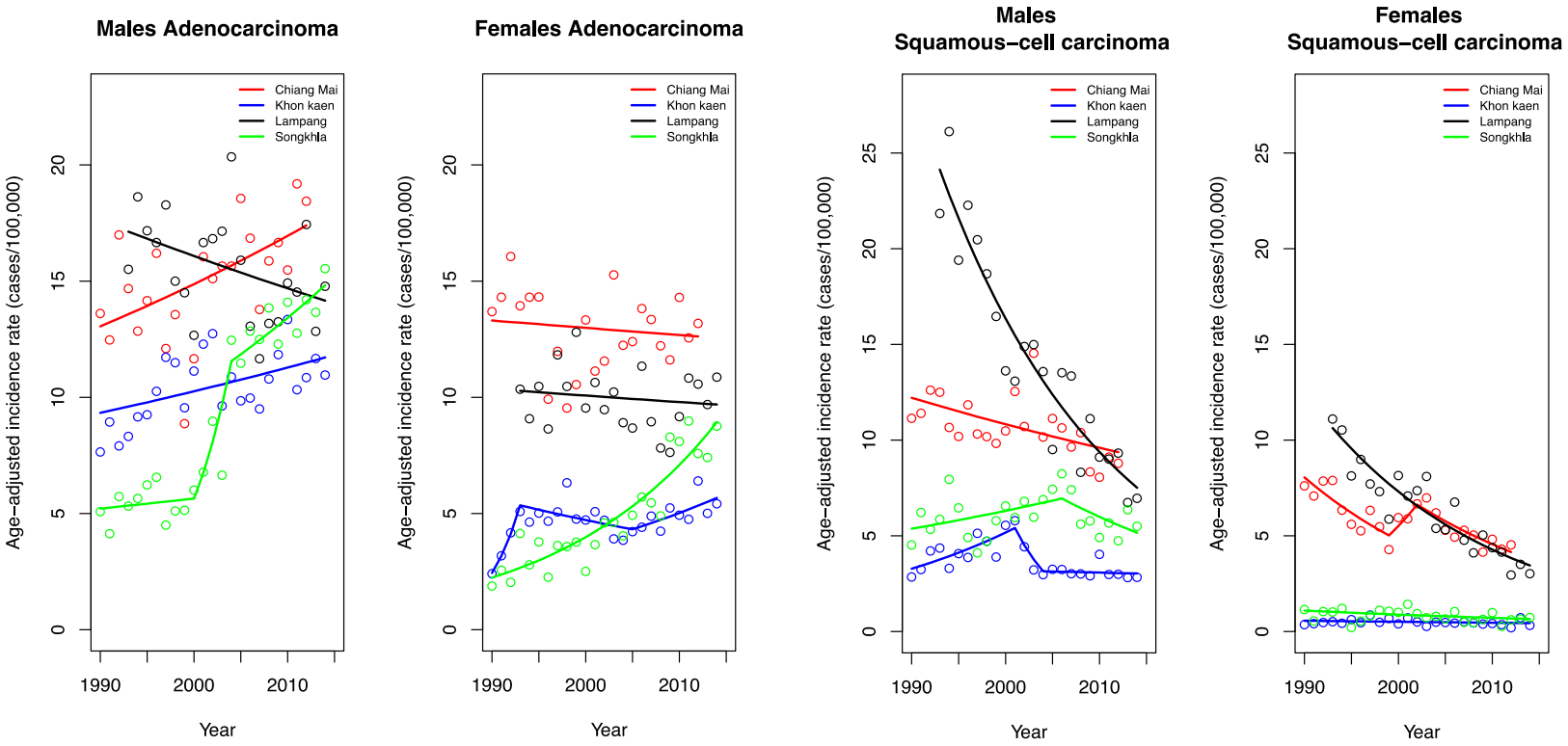

Table 5.4 Annual Percent Change (APC), Average Annual Percent Change (AAPC) and 95% confidence interval (CI) in age-adjusted incidence in small-cell carcinoma, large-cell carcinoma and other histology.

	Trend 1		Trend 2		Trend 3		Last 10 years
	Year	APC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)	AAPC (95% CI)
Males							
Small-cell							
Chiang Mai	1990-2012	0.6 (-0.7, 1.9)					0.6 (-0.7, 1.9)
Lampang	1993-1999	**11.1 (0.2, 23.2) ***	1999-2014	**-7.3 (-9.6, -4.9) ***			**-7.3 (-9.6, -4.9) ***
Khon Kaen	1990-2014	0.6 (-1.0, 2.2)					0.6 (-1.0, 2.2)
Songkhla	1990-2014	**4.1 (2.3, 5.9) ***					**4.1 (2.3, 5.9) ***
Large-cell							
Chiang Mai	1990-2012	**-4.6 (-6.1, -3.0) ***					**-4.6 (-6.1, -3.0) ***
Lampang	1993-1999	**11.0 (2.0, 20.7) ***	1999-2014	**-4.8 (-6.5, -3.0) ***			**-4.8 (-6.5, -3.0) ***
Khon Kaen	1990-2014	0.0 (-1.0, 0.9)					0.0 (-1.0, 0.9)
Songkhla	1990-2014	**-2.1 (-4.0, -0.2) ***					**-2.1 (-4.0, -0.2) ***
Other histology							
Chiang Mai	1990-2012	-0.8 (-4.8, 3.4)					-0.8 (-4.8, 3.4)
Lampang	1993-2014	-3.3 (-7.4, 0.9)					-3.3 (-7.4, 0.9)
Khon Kaen	1990-2014	3.6 (0.9, 6.2)					3.6 (0.9, 6.2)
Songkhla	1990-2014	**9.0 (3.2, 15.0) ***					**9.0 (3.2, 15.0) ***
Females							
Small-cell							
Chiang Mai	1990-2012	**-1.5 (-2.5, -0.5) ***					**-1.5 (-2.5, -0.5) ***
Lampang	1993-2014	**-4.2 (-5.6, -2.7) ***					**-4.2 (-5.6, -2.7) ***
Khon Kaen	1990-2014	2.7 (-0.4, 6.0)					2.7 (-0.4, 6.0)
Songkhla	1990-2008	-7.1 (-13.9, 0.3)	2008-2014	**33.7 (8.1, 65.4) ***			**18.4 (3.5, 35.6) ***
Large-cell							
Chiang Mai	1990-2012	**-5.5 (-6.7, -4.4) ***					**-5.5 (-6.7, -4.4) ***
Lampang	1993-2004	**3.5 (0.6, 6.5) ***	2004-2014	**-6.5 (-9.3, -3.7) ***			**-6.5 (-9.3, -3.7) ***
Khon Kaen	1990-2014	0.6 (-0.8, 2.1)					0.6 (-0.8, 2.1)
Songkhla	1990-1996	**66.1 (18.7, 132.4) ***	1996-2000	-34.7 (-83.3, 155.2)	2000-2014	2.9 (-3.3, 9.4)	2.9 (-3.3, 9.4)
Other histology							
Chiang Mai	1990-2012	**3.1 (0.3, 5.9) ***					**3.1 (0.3, 5.9) ***
Lampang	1993-2014	-2.5 (-7.9, 3.1)					-2.5 (-7.9, 3.1)
Khon Kaen	1990-2014	1.7 (-4.6, 8.3)					1.7 (-4.6, 8.3)
Songkhla	1990-2014	-2.0 (-8.6, 5.1)					-2.0 (-8.6, 5.1)

* Annual percent change is significantly different from zero $p < 0.05$.

Table 5.5 Akaike information criteria (AIC)* values for the Age-Period, Age-Cohort, Age-Period-Cohort

	Age-Period	Age-Cohort	Age-Period-Cohort
Males			
Adenocarcinoma			
Chiang Mai	412.47	**336.9**	301.53
Khon Kaen	275.2	**274.3**	261.88
Lampang	255.15	**241.2**	221.53
Songkhla	**317.15**	324.94	305.74
Squamous-cell carcinoma			
Chiang Mai	332.69	**258.1**	247.35
Khon Kaen	**164.1**	168.7	155.76
Lampang	283.08	**235.5**	230.88
Songkhla	294.76	**281.5**	270.56
Female			
Adenocarcinoma			
Chiang Mai	380.73	**329.79**	298.85
Khon Kaen	**309.85**	317.15	301.71
Lampang	265.45	**262.78**	253.07
Songkhla	**343.54**	344.46	335.13
Squamous-cell carcinoma			
Chiang Mai	255.73	**217.16**	204.53
Khon Kaen	**121.56**	123.32	121.07
Lampang	202.64	**187.22**	183.42
Songkhla	167.79	**167.28**	163.49

* -2 x log(likelihood) +2 x number of parameter estimates

Figure 5.4 Age-Period-Cohort trend analysis for adenocarcinoma in males and females, a) AC-P model, b) AP-C model

a) **b)**

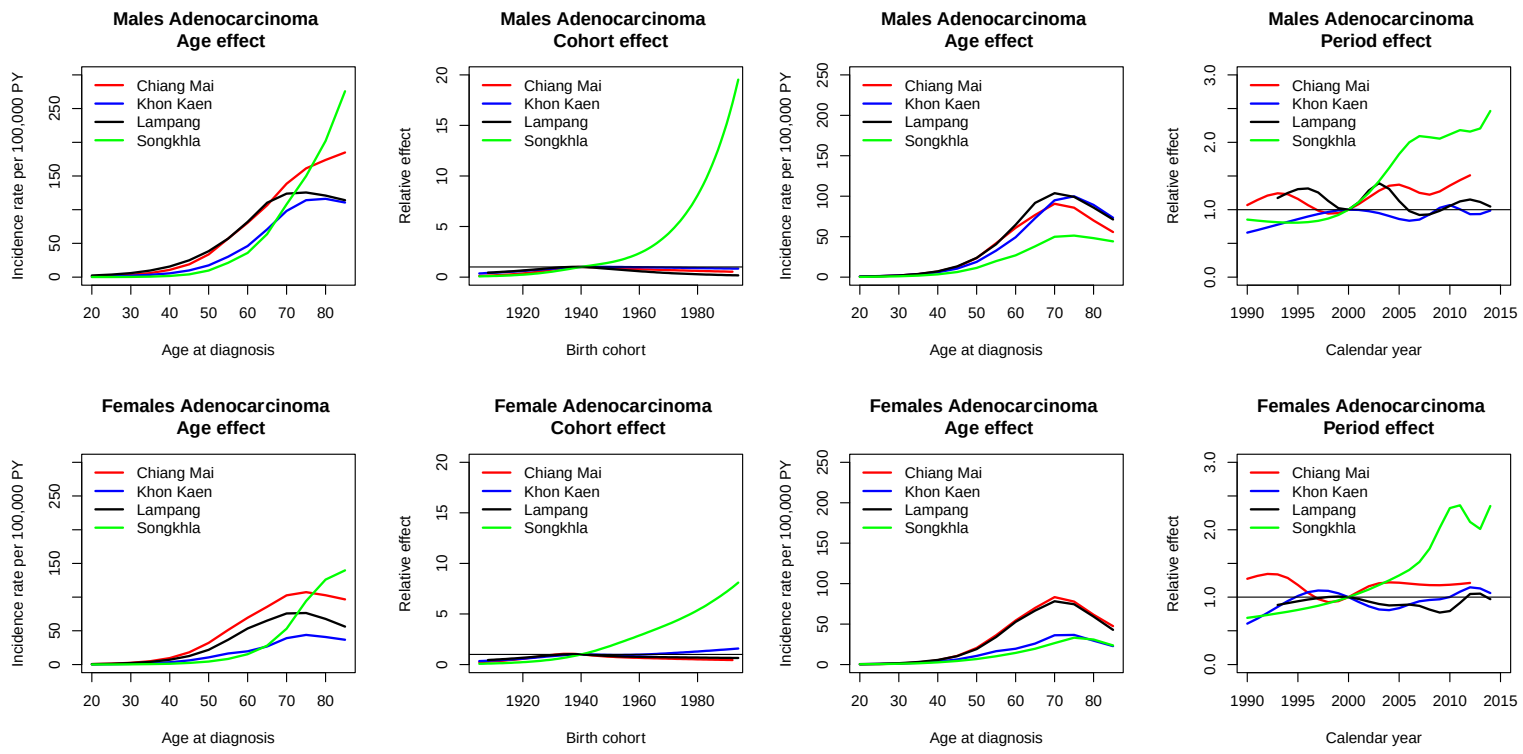

Figure 5.5 Age-Period-Cohort trend analysis for squamous-cell carcinoma in males and females, a) AC-P model, b) AP-C model

a) **b)**

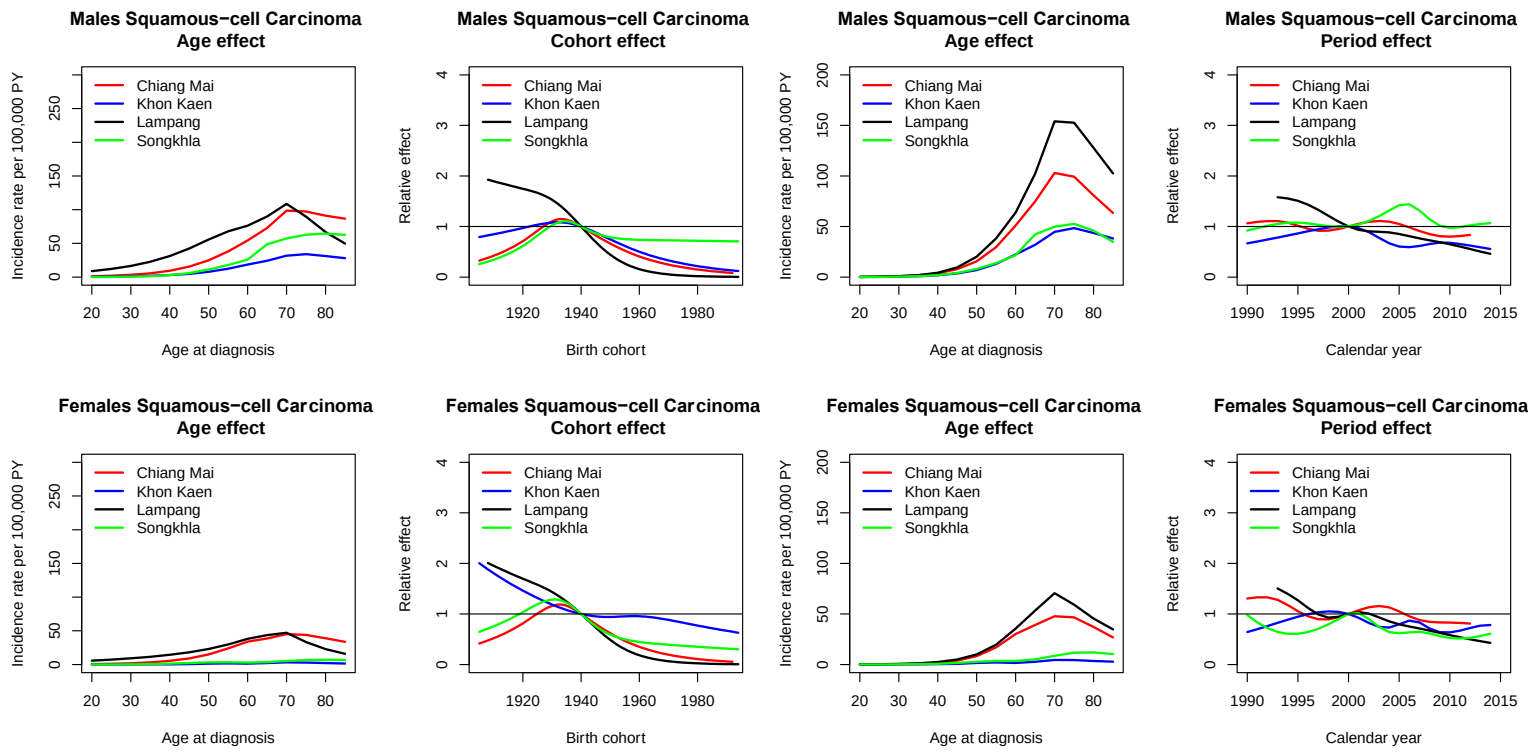

Figure 5.6 Age-adjusted incidence rates of adenocarcinoma until 2030 using 3 projection models; Joinpoint analysis, Age-period-cohort, and Nordpred by sex. The dashed line represents model projection.

(a) (b)

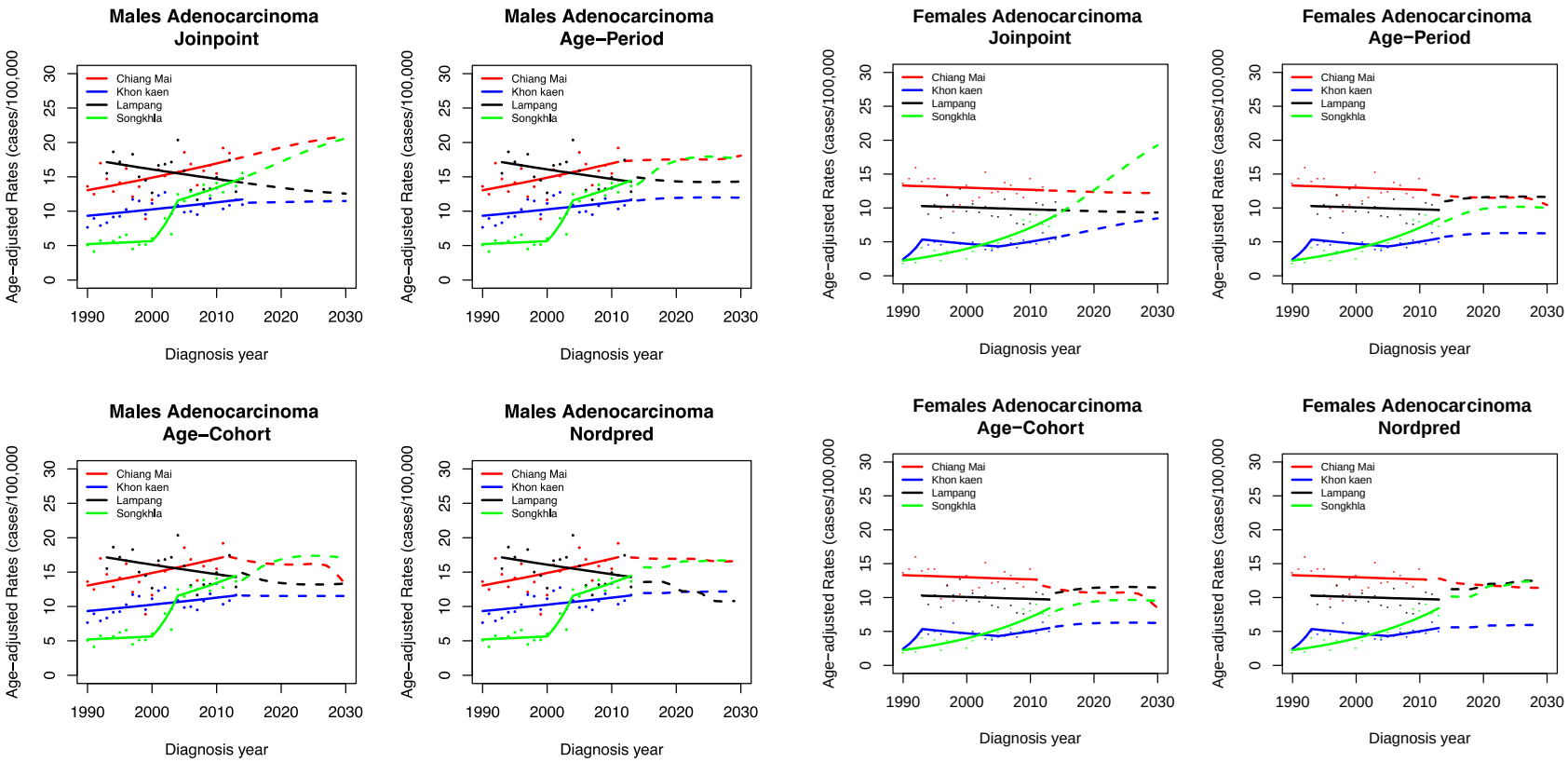

Figure 5.7 Age-adjusted incidence rates of squamous-cell carcinoma (SCC) until 2030 using 3 projection models; Joinpoint analysis, Age-period-cohort, and Nordpred by sex. The dashed line represents model projection.

(a) (b)

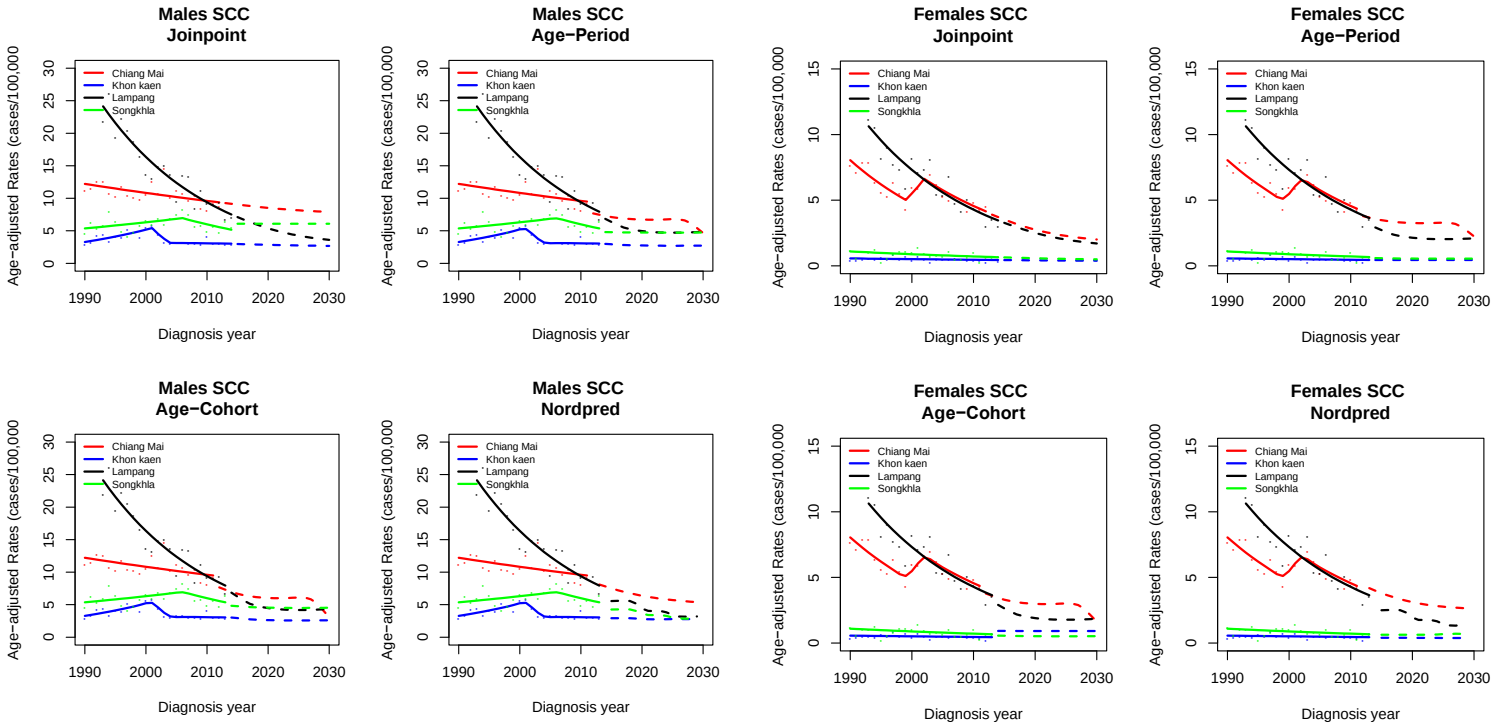

Table 5.6 Smoking prevalence by region in Thailand.

	Data Source				
Region	CSDBS: 2007	GATS 2009	GATS 2011	CSDBS 2011	CSDBS 2014
Bangkok	13.9	19.0	18.1	14.7	16.6
Central	15.1	23.2	23.4	18.0	18.9
North	17.6	22.6	21.9	19.3	20.4
Northeast	17.9	23.9	20.9	21.8	21.9
South	25.0	29.7	29.9	23.7	27.1
GATS: Global Adult Tobacco Survey; CSDBS: Cigarette Smoking and Drinking Behavior Survey					

Chapter 6

Conclusion

Although tobacco consumption has declined greatly in most developed countries, the incidence of tobacco-related diseases remains an extremely large economic and health burden worldwide. This dissertation extends current knowledge regarding temporal aspects of tobacco use and its related disease risks. The results demonstrate that understanding the complex time relationships between exposures and disease is important to better assess and predict the burden of tobacco-related illnesses. Moreover, the analyses of surveillance data on both tobacco use and NCDs such as cancer and COPD can be a powerful tool for planning and evaluating individual and population-based prevention and control interventions.

The current drastic changes in the tobacco use landscape both globally and domestically will likely further complicate the complex relationship between tobacco exposure and outcomes. This is paramount to understand and investigate; as new tobacco products emerge, we do not know their impacts on cancer and other NCDs (if any) and their potential synergistic effects with cigarette smoking and other more traditional forms of tobacco products, such as chewing tobacco and snuff. As we seek to reduce the burden of tobacco use on health risk, we need to adapt and develop innovative methods to characterize temporal patterns of polytobacco use by multiple time dimensions, such as age, calendar-year and birth cohort, and understand how these shape disease incidence and mortality, both at the individual and population levels. In Chapter 2, I used a rigorous and yet simple time trends approach, a joinpoint regression analysis, to extend our

current understanding of SLT use and cigarette smoking trends. I found that smoking prevalence decreased significantly from 1990 to 2011 in the US, while the prevalence of SLT use remained steady since the early 2000s. Additionally, SLT use is associated with former smoker status, younger age, white race, living in rural areas, residing in the South, lower education, and being unemployed.[1] Focused tobacco control efforts to these demographic groups are needed to reduce SLT prevalence to under 0.3%, which is the Healthy People 2020 goal.[2]

Since analyses in Chapter 2 are based on cross-sectional surveys, I was unable to capture longitudinal use behaviors, such as product switching or cessation. Therefore, to examine the transition rates between cigarette smoking and SLT use, I took advantage of the nested one-year longitudinal designs within the TUS-CPS (2002-2003 and 2010-2011 longitudinal cohorts) in Chapter 3. Individuals in these two cohorts were followed for one-year, providing the opportunity to capture transitions between tobacco products. I found that the one-year quit rate for cigarette smoking doubled from 2002 to 2010, while the corresponding quit rate for SLT use remained roughly constant. This finding supports the results in Chapter 2, in part. That is, while smoking has continued to decrease, SLT use has remained constant. Furthermore, I noticed that smokers were less likely to switch to other forms of tobacco compared to SLT users. Additionally, the smoking cessation rate was slightly higher in dual users than in exclusive smokers, but this finding was not statistically significant, likely due to the small sample size of dual users. However, if this is true, the potentially higher smoking cessation rate in dual users has implications to understand how smokers might be using SLT and other alternative products to quit smoking.[3,4] Yet, more epidemiological research in this area is needed.

The temporal relationship between tobacco exposure and health outcomes is complex. Specifically, Chapter 4 in this dissertation and other studies[1,5] have demonstrated the complexity

of the relationship between cigarette smoking and the risk of COPD and lung cancer. A simple metric such as "smoking status" only captures a snapshot of an individual's smoking exposure at a given time point, and may not be sufficient to assess properly the effect of smoking on diseases. Utilizing more detailed smoking information such as intensity of the exposure, duration of use, time since quit, and the time (age) of exposure would provide more accurate assessments. In Chapter 4, I developed a Cox regression model with time-varying smoking covariates constructed based on individual smoking histories, and investigated the association of each smoking parameter with COPD risk. This model was then used to predict COPD risk given individual smoking profiles. To my knowledge, this is the first COPD risk prediction model that uses detailed smoking histories. The analyses found that inclusion of detailed time-varying smoking information increased significantly the predictive power and discriminatory accuracy of COPD incidence risk models. Our model can be useful for multiple potential applications. For instance, our COPD risk prediction model incorporates detailed individual level smoking information, which may be useful to identify individuals at high risk of COPD more accurately compared with using a simple summary measure, such as smoking status or pack-years. It thus provides a tool for clinicians to identify individuals at high risk for COPD, and could also be used as an aid for discussions between clinicians and patients about the benefits of smoking cessation and lifestyle changes for disease progression.[6] Secondly, as smoking patterns at the population level continue to change over time, the burden of COPD is likely to change. This model could be integrated with smoking population simulation models, such as SimSmoke[7] or the CISNET models,[8–10] to project the future burden of COPD in the US and elsewhere as tobacco patterns continue to change.

Most of the future tobacco-related diseases are expected to occur in LMICs.[11] In Chapter 5, I addressed the importance of the availability of high quality population-level data to describe and project the rates of tobacco-related diseases in developing countries. Using data from four population-based cancer registries in Thailand, I applied joinpoint regression, age-period-cohort and Nordpred models to characterize and project the incidence of lung cancer by histology, sex and region in this country. To the best of my knowledge, this is the first study to characterize and predict time trends of lung cancer incidence in such detail in Thailand. These analyses highlight regional differences in lung cancer incidence by histology; while the rates of adenocarcinoma remain, stable or increasing in males and females in Chiang Mai and Lampang (registries in the North), the rates of squamous-cell carcinoma have been leveled off. Similar patterns were observed in Songkhla (South) and Khon Kaen (Central), but with more considerable increases in the rates of adenocarcinoma. These results also emphasize the importance of understanding the profile of lung cancer risk factors in addition to smoking, and how these factors may vary across regions within the same country. We find that consistently with other studies, trends of lung cancer correlate better with birth-cohort or generation rather than with calendar-year. This is not surprising since smoking patterns are known to vary in a cohort fashion.[12,13] In addition, the projections suggest that the rates of lung adenocarcinoma in both males and females are expected to continue to increase at least until 2030 in Songkhla province, and perhaps in Chiang Mai and Khon Kaen. These results demonstrate that the availability of cancer registration data is important to examine past and current trends and project future cancer patterns, which could help researchers to make hypotheses for future epidemiologic studies and for policymakers to better allocate resources for targeted-treatment options for specific histologic types. The results also suggest that regional specific tobacco control policies might be needed to reduce the future

burden of lung cancer in Thailand more effectively compared to uniform interventions across the entire nation.

There are many challenges ahead in tobacco control. Since every country is at a different stage in the tobacco epidemic, country-specific surveys should be tailored to their specific situations. Local longitudinal information on tobacco use from multiple perspectives, such as tobacco use-related behaviors (frequency, intensity and age at initiation), attitudes, patterns by age, calendar-year and importantly birth-cohort, knowledge about the effects of different tobacco products and tobacco-related illness needs to be collected to better understand how the changes in temporal patterns of tobacco use will impact the related health risks. For example, the US smoking prevalence is at its lowest, and adolescents are less likely to smoke compare to the older adult population.[14,15] However, with emerging tobacco products are coming into the market targeting young people, such as ENDS, e-cigarettes, hookah, and heat-not-burn (HNB) products, we are facing a significant shift in the tobacco use landscape. This shift on new tobacco use could induce important differences by birth cohorts as new generations face a completely different landscape than those ahead. In addition, the health implications of these new products are not yet clear. One study has shown that e-cigarettes and other vaping products may reduce smoking-related deaths by 21% for those born after 1997.[14] However, the long-term cumulative effect of these new products or polytobacco use remains debatable. Future studies are needed to address how single and combined use of different tobacco products impact health, and examine the dynamics of single or multiple products usages and how they affect each other. In 2013, the NIH and the FDA-CTP launched a longitudinal study of tobacco behaviors in the US population,[16] which serves an excellent example of the data needed to address these research gap. However, additional epidemiological studies are needed to better understand the associations

between polytobacco use and health, examining tobacco exposures comprehensively, including information on duration, intensity, age at start, and time since quitting, and not only focusing in summary measures such as smoking status or cumulative pack-years.

Final remarks

In the US, a remarkable progress has been made in tobacco control, which has led to a decrease in smoking prevalence to 15.1% in 2015.[17] Yet tobacco use remains the leading cause of preventable premature deaths in the US and globally, and this pattern is expected to continue at least for the next few decades.[12,18] As the tobacco landscape and the related cultural norms continue changing, so will the tobacco industry strategies to market and place their products, the patterns of use of novel and traditional tobacco products, as well that as other related non-tobacco risk factors. Therefore, it is not guaranteed that the current progress in the reductions of smoking will continue. Collecting data on cigarette smoking exposure and measuring the synergistic effects of polytobacco use on disease risk are thus critical. This dissertation shows the benefits, and need, of accounting for the temporal aspects of tobacco exposure and disease outcomes, and provides examples of methodological approaches that can be used for the analysis of epidemiological time trends. Use of these and other methods is critical to properly assess the current and future burden of tobacco, and the impact of interventions to reduce its burden.

6.1 References

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