Current and Future Perspectives of Prostate Cancer in Thailand

by

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Dedication

To my parents, my brother,

and my fiancée Erin,

for their constant support and love.

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Preface

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List of Abbreviations

AAPC	Average annual percent change
APC	Age-Period-Cohort
ASR	Age-standardized incidence rate
ASMR	Age-standardized mortality rate
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention
BMI	Body mass index
BPH	Benign prostatic hyperplasia
CAP	Cluster Randomized Trial of PSA Testing for Prostate Cancer
CFR	Case fatality ratio
CI	Confidence intervals
DM	Diabetes mellitus
DRE	Digital rectal examination
EAPC	Estimated annual percent change
ERSPC	European Randomized Study of Screening for Prostate Cancer
GDP	Gross domestic product
HPFS	Health Professional Follow-Up Study
HR	Hazard ratios
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
LUTS	Lower urinary track symptoms
MIR	Mortality-to-incidence ratio
NCD	Non-communicable diseases
OECD	Organization for Economic Co-operation and Development
PI	Prediction intervals
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial
PSA	Prostate-specific Antigen
RR	Rate ratio
SCR	Songkhla Cancer Registry
SELECT	Selenium and Vitamin E Prevention trial
UHC	Universal Health Coverage
US	United States
USPSTF	US Preventive Service Task Force
UK	United Kingdom
WHO	World Health Organization

Abstract

Background

Prostate cancer is the second most common malignancy among men worldwide, representing a major public health burden mostly in developed countries. Nonetheless, the burden of the disease is expected to increase in developing countries. Currently, there is limited data available describing the current and future perspectives of prostate cancer in Thailand.

The aims of this dissertation were to: 1) Examine current trends and project incidence and mortality rates of prostate cancer over the next decade in Songkhla, Thailand; 2) Describe differences in prostate tumor characteristics and survival after diagnosis with prostate cancer between Buddhists and Muslims in Songkhla; 3) Evaluate the potential impact of screening for prostate cancer on the burden of the disease in Thailand.

Methods

Incident prostate cancer cases (1990-2014) from the Songkhla Cancer Registry, and census data from the Thai Statistical Office were used in this research. In aim 1, we used Joinpoint analysis to examine incidence and mortality trends of prostate cancer, and age-period-cohort (APC) models to assess the effect of age, calendar-year and birth-cohort on those trends. We used a comparative modeling approach to project the

incidence and mortality rates of prostate cancer. In aim 2, Wilcoxon and chi-square tests were used to compare differences in prostate tumor characteristics and sociodemographic factors between Buddhists and Muslims; in addition, Kaplan Meier methods and Cox proportional hazards models were used to assess differences in survival between both religious groups. In aim 3, we conducted a simulation analysis to project the incidence and mortality of prostate cancer under different screening scenarios for the Prostate-specific antigen (PSA) test and Digital rectal examination (DRE) in the 1960-birth cohort of Songkhla males.

Results

The incidence and mortality rates of prostate cancer have significantly increased since 1990, and the rates are projected to continue to increase in Songkhla. The APC models suggest that birth-cohort is the most important factor driving the increased trends of prostate cancer in this population. In the second aim, we found no significant differences in prostate tumor characteristics, age, or year at diagnosis between Buddhists and Muslims. However, we observed a longer survival time in Buddhists compared to Muslims (3.8 vs 3.2; p=0.09). In addition, we found that Muslim men are more likely to die after diagnosis with prostate cancer (HR:1.27, 95%CI:0.97,1.67). In aim 3, our model projects a 28% (and 21%) reduction in the number of prostate cancer deaths at age 70, under 100% uptake of PSA (and DRE) screening. The model projects that 13,000 and 9,000 deaths per 1,000 could be prevented with 100% PSA and DRE screening uptake, respectively.

Conclusions

Songkhla, Thailand is an ideal setting in which to examine the temporal evolution of prostate cancer as it has a long-standing, high-quality cancer registry that has collected data throughout Thailand's ongoing transition from low- to a middle-income country. These data demonstrate the increasing prominence of prostate cancer as a public health problem in lower-resource settings. This work further demonstrates that screening could reduce mortality due to prostate cancer in this population. Further studies should evaluate the potential barriers for the implementation of screening as well as aim to elucidate the underlying risk factors contributing to the increased incidence of prostate cancer. We hope that our study provides evidence that will help support the design of policies for the control of prostate cancer in Thailand.

Chapter 1. Introduction

Overview

The burden of cancer is expected to increase in developing countries as the population ages and as those countries undergo the epidemiologic transition. According to GLOBOCAN from the International Agency for Research on Cancer (IARC), 24 million cancer cases will be diagnosed by 2035 with most of the burden expected to be in developing countries. Despite this, to date most of the research on cancer has been conducted in developed, western countries, particularly among Caucasians. Prostate cancer is the second most common cancer and the fifth leading cause of cancer death in men worldwide. Currently there is a lack of research on the epidemiology of prostate cancer in Thailand. An evaluation of the temporal evolution and projection of the prostate cancer rates are important not only to characterize the disease in the population but also to help health authorities to allocate resources for the potential increased burden of this disease in the near future. Thus, the first aim of this dissertation examined current trends and projected incidence and mortality rates of prostate cancer in a southern province of Thailand over the next decade.

The survival rates for prostate cancer in many developing countries are lower compared to developed countries. For example, in the US, the percent of people surviving 5 year or more after being diagnosed with prostate cancer is 98.6%, partially explained by the widespread use of the prostate-specific antigen (PSA) test for the

screening of prostate cancer. Sociodemographic factors (e.g. ethnic group) and prostate tumor characteristics may influence survivorship. In Thailand, differences in prostate cancer incidence have been observed between Buddhists and Muslims, the two major religious groups in the country. There have been no studies examining the differences in cancer survivorship by religious group. The second aim of this dissertation examined differences in prostate tumor characteristics and survival after diagnosis with prostate cancer between Buddhists and Muslims from Songkhla, Thailand.

Screening for prostate cancer remains controversial because of the lack of definitive evidence of benefit in the reduction of prostate cancer mortality. In addition, most of the studies on prostate cancer screening have been conducted in Western populations, providing little evidence of the effect of screening for prostate cancer in non-Western populations. Although screening tests can detect cases in early stages when treatment may be effective, the early diagnosis of prostate cancer must be weighed against the risk of overtreatment, treatment side effects and subsequent impaired quality of life. Currently there are no official guidelines or recommendations for population-based screening for prostate cancer in Thailand. In the third aim we evaluated the potential impact of a screening program for prostate cancer on the incidence and mortality of the disease in Thailand.

Background

Prostate cancer incidence and mortality worldwide

Worldwide, prostate cancer is the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men.[1, 2] In 2012, an estimated 1.1 million cases of prostate cancer were diagnosed, composing 15% of the cancer diagnosed in men worldwide, with approximately 70% of the cases from developed regions.[1] In addition, an estimated 307,000 deaths occurred in 2012, representing 6.6% of the total male cancer deaths.[1, 2] By 2030, it is expected that 1.8 million new cases of prostate cancer and more than half-million prostate cancer related deaths will occur. The incidence and mortality rates of prostate cancer vary considerably worldwide, with the highest incidence rates in more developed regions such as North America, Western and Northern Europe, and Oceania.[3] For example, the current age-adjusted incidence rate (ASR) for prostate cancer in the United States (US) is 129.4 cases per 100,000 men per year;[4] in contrast, the ASR in South East Asia is only 11.0 cases per 100,000 men per year.[1] On the contrary, worldwide prostate cancer mortality rates are higher in less developed regions such as Sub-Saharan Africa and the Caribbean.[1] For instance, the age-adjusted mortality rate (ASMR) for prostate cancer in the Caribbean is 29.3 deaths per 100,000 men per year, whereas the age-adjusted mortality rate observed in the US is only 9.8 deaths per 100,000 men per year.[1] Differences in prostate cancer incidence and mortality rates across regions of the world are depicted in Figure 1.1.

Past and current trends of prostate cancer

Overall, prostate cancer incidence rates have increased worldwide, except in some developed countries,[1–3, 5] with an average annual percent change (AAPC) ranging from 1.5% in Sweden (2001-2010) to 19.3% in Lithuania (1998-2007).[5] In the US, prostate cancer cases have decreased on average 5.1% each year over the last 10 years,[4] a less pronounced decrease has been observed in Canada during 2007-2009 with an AAPC=0.5%.[6] Similarly, mortality rates for prostate cancer have increased in recent decades, particularly in less developed regions with a decline in most developed countries.[1–3, 5] For example, in the US prostate cancer death rates have decreased on average 3.5% each year over 2004-2013.[4] On the other hand, an increase in mortality rates has been observed in some Caribbean countries such as Cuba and Trinidad and Tobago with AAPC=1.5% and 4.5% respectively during the period 1993-2008.[5] It has been suggested that these varying incidence and mortality trends of prostate cancer worldwide have been influenced by screening, improvements in diagnostics, improved registration of cases, as well as other unknown factors.[2, 3, 5]

In Asia, the incidence rates of prostate cancer have shown a rapidly increasing trend. For example, the prostate cancer incidence rates in East Asia has increased by 7.2% per year during the period 2004-2009.[7] Furthermore, prostate cancer mortality rates show significant variations among countries with increasing trends observed in China (AAPC=1.8%), Kazakhstan (AAPC=1.2%), and South Korea (AAPC=13.4%); on the other hand, decreasing trends have been observed in Israel (AAPC=-3.7%) and Japan (AAPC=-1.6%).[7, 8] The mortality/incidence ratio (MIR) is remarkable higher in Asia (40%) in contrast to Europe (18%) or North America (25%).[7] As in the rest of the

world, less developed countries in Asia have higher mortality rates of prostate cancer, as well as more advanced disease compared to more developed countries,[7–9] Figure 1.2 shows the prostate cancer incidence (a) and mortality (b) rate trends for men of all ages and 50 to 79 years of age from 9 Asian-Pacific countries including Thailand from 1980 to 2009.

The rapid increase in incidence and mortality rates of prostate cancer in Asia is in part due to an increased life expectancy/ageing population of many Asian countries undergoing the epidemiological transition; in addition, the adoption of westernized lifestyles as a consequence of economic growth have been hypothesized as partly driving the increase.[7, 9, 10] This rapid increase in the burden of prostate cancer in Asia will be a serious challenge for the region because the average spending on health care in many Asian countries, particularly less developed nations is low compared to more developed countries.[7] For example, in Thailand the government invests only 4.1% of the gross domestic product (GDP) in healthcare, which is under the average percentage recommended by the Organization for Economic Co-operation and Development (OECD) (9.9%). However, Thailand established Universal Health Coverage (UHC) in 2002, in which individuals pay only 30 Baht (approximately US$1) to access any health care services.[10] In addition, this copayment is waived for higher-risk population groups such as children under 12 years of age or seniors over 60 years of age.[11]

The epidemiological transition in Thailand

The concept of the epidemiological transition has been recognized since 1950, particularly in industrialized countries.[12, 13] The theory was first postulated by Omran in

1971, and it describes changes in the population patterns of factors such as fertility, life expectancy, mortality and leading cause of death, and their relationship with other sociodemographic and economic changes in the population.[12, 13] Frequently, the epidemiological transition is characterized by a decrease in deaths of infectious diseases and increase in crude and proportional mortality attributable to non-communicable diseases (NCD) such as cancer, diabetes and vascular diaseses.[14] As less developed countries move through the epidemiologic transition, they are experiencing a double burden of infectious and NCDs.[14] Thailand has undergone social and economic transitions as well as changes in its disease profile over the last three decades.[15, 16] The life expectancy at birth has increased and the total fertility and infant mortality rates has decreased in the Thai population. Figure 1.3 shows the population pyramids in Thailand in 1960 and in 2010, demonstrating those changes.[15, 16] Several risk factors for NCDs such as obesity, diabetes, westernized diet, and a lack of physical activity have increased significantly among the Thai population.[15, 16] Consequently, cardiovascular disease and cancer have been the leading causes of death since the late 1980s.[15] Understanding whether and how the changes in these risk factors for NCDs are contributing to increase in their incidence and mortality will be important to design prevention strategies.

Etiology of prostate cancer

Despite the fact that prostate cancer is one of the most common cancers diagnosed among men worldwide, the etiology of prostate cancer remains unclear.[17] Currently, the well-established risk factors for the development of prostate cancer are

advancing age, race (African American) and family history of this disease.[18] However, the vast majority of epidemiological studies on prostate cancer have been conducted in Western countries, with predominantly Caucasian populations. No conclusive evidence has been observed for a role of traditional risk factors for cancer such as cigarette smoking, diet, obesity and others in the etiology of prostate cancer.[17] Since the introduction of PSA screening, which will be discussed in detail in a later section, overdiagnosis of prostate cancer has been an issue, particularly in the US. Thus, research on prostate cancer risk factors and survival predictors currently distinguishes between indolent disease and those cancers with clinical significance since they are thought to have distinct etiologies.[17]

Cigarette smoking

Smoking has been considered a major risk factor for cancer, particularly lung cancer; but the effect of smoking on prostate cancer is less clear. Epidemiological studies have not supported a causal relationship between smoking and the risk of total prostate cancer (i.e. all diagnosed disease which is a mixture of indolent and aggressive cases).[17] However, a consistent link between cigarette smoking and development of fatal prostate cancer (the most clinically relevant outcome) has been observed in epidemiologic studies including several large cohort studies;[17] cigarette smokers are estimated to be up to twice as likely as nonsmokers to die from prostate cancer.[17] A recent meta-analysis of tobacco use and prostate cancer mortality in prospective cohort studies found a statistically significant positive association with a dose-response relationship.[18] This study also found a positive association between cigarette smoking

and prostate cancer risk before the introduction of screening strategies in the US when the case distribution leaned toward fewer indolent cases.[18] Together these results may suggest that smoking is associated with more clinically relevant disease.[18] The prevalence of smoking in Thailand has steadily declined over the past 20 years, due to an effective tobacco control policy, however a slight increase in tobacco consumption in adolescents has been observed recently.[18]

Diet

Several epidemiological studies have been conducted to evaluate the effect of diet on prostate cancer with no conclusive results. A link between western diet, particularly fat intake and prostate cancer risk, has been observed in studies based on comparison of mortality rates and migrants from low- to high- risk countries.[17] Similarly, a meta-analysis found that saturated fat intake as well as red meat are associated with an increased risk of developing advanced or fatal prostate cancer, however other studies have not found any association. On the other hand, circulating lycopene in blood, a natural compound from tomato intake, has been observed to reduce the risk of developing aggressive prostate cancer in prospective studies.[19] In addition, two clinical trials have reported that lycopene supplementation reduced PSA levels in men with prostate cancer.[19] Other studies have reported no association between lycopene and prostate cancer development, however they have been conducted in heavily screened populations that likely include many indolent cases in their case population.[19] Furthermore, inconclusive findings have been reported for the association of whole grains and prostate cancer risk.[20] In Thailand, dietary patterns have shifted from a

traditional cereal-based and low-fat diet to a more Westernized diet characterized by high intake of fat, animal products and sugars.[15]

Micronutrients

Several micronutrients, including vitamins D and E have been studied in relation to prostate cancer risk without conclusive results. A recent meta-analysis of 19 prospective cohort and nested case-control studies reported that, contrary to the prevailing hypothesis, higher levels of circulating vitamin 25-hydroxyvitamin D are associated with an elevated risk of prostate cancer in a dose-response relationship.[21] However, another study has limited this elevated risk to prostate cancer of low grade,[22] while other studies have found more strongly positively associated for high-grade disease.[23, 24] Similarly, the Selenium and Vitamin E Prevention trial (SELECT) study found an elevated risk of prostate cancer with higher dose of vitamin E (400 IU daily) in a population free of subclinical disease at enrollment.[25] On the other hand, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study found a lower risk of prostate cancer with low-dose vitamin E supplementation (50 IU daily) among smokers with no baseline prostate cancer screening.[26, 27]

Obesity and physical activity

Obesity is a major risk factor for many NCDs, including cancer. It is becoming a serious problem worldwide as a consequence of economic and lifestyle changes. In Thailand, according to the National Thai Food consumption survey in 2011, approximately 24% of the population were overweight or obese, using standard BMI

cutoff points.[28] However, the prevalence of overweight/obesity is higher than that using ethnic-specific BMI cutoff points for Asian populations. Lower BMI cutoffs has been proposed to determine overweight/obesity among Asian individuals for public health interventions. Evidence suggests that Asians have a higher body fat percentage at low BMI compared to other groups (e.g. Caucasians), partially explained by differences in body composition.[29, 30] Thus, epidemiological research should take this into consideration to avoid underestimate the effect of obesity on prostate cancer in the Thai population.

Recent studies have observed that obesity is associated with an increased risk of fatal prostate cancer, but decreased risk of nonaggressive disease.[31] A meta-analysis of six cohort studies found a 15% increased risk (95%CI: 1.06, 1.25) of developing fatal prostate cancer for each 5 units increase in the body mass index (BMI).[31] The differences in the association between obesity and prostate cancer for aggressive and nonaggressive disease may be due to detection bias as prostate cancer detection can be complicated in obese men.[18, 31, 32] Moreover, vigorous physical activity (>29 Met-h/week) has been reported to reduce the risk for metastatic prostate cancer but the results were not statistically significant, according to the most recent Health Professional Follow-Up Study (HPFS).[33]

Diabetes

The global prevalence of diabetes mellitus (DM) is rapidly increasing as a result of population ageing, urbanization and associated lifestyle changes.[34] It is well-established that men with DM have a decreased risk of total prostate cancer.[35] A recent

meta-analysis found an inverse association between DM and prostate cancer regardless of clinical stage.[34] The risk ratio and 95%CI observed for the association of DM and localized disease was (RR: 0.72; 95%CI: 0.67, 0.76); similarly the association observed between DM and advanced disease was (RR: 0.85; 95%CI: 0.75, 0.97).[36] A potential mechanism that explain the reduction of the prostate cancer risk in men with DM is that insulin, a prostate tumor growth promoter declines with poor control of blood glucose or DM progression.[35]

Prostate cancer in Thailand

According to GLOBOCAN in 2012, the estimated ASR and ASMR of prostate cancer in Thailand were 7.2 cases and 3.7 deaths per 100,000 men per year respectively.[1] It is the fourth most commonly diagnosed cancer among Thai men, behind liver, lung and colorectal cancers.[1] A study reported that nationwide the incidence rates of prostate cancer in Thailand have increased continuously (AAPC: 2.7%) in the last two decades.[2] Furthermore, the Thai National Cancer Institute has reported regional differences in the incidence of prostate cancer, with higher incidence rates observed in southern Thailand.[37]

In addition, it is important to note that most of the cancer cases in Thailand are diagnosed at an advanced stage.[38] The stage of prostate cancer refers to the extent of spread of the tumor and it is one of the most important factors in selecting treatment options and predicting survival (e.g. advanced stages have the poorest survival because the cancer has spread to other organs, such as bones).[39] A study from the Chiang Mai cancer registry (northeastern part of Thailand) reported a higher rate of

advanced stage of prostate cancer at diagnosis compared to US, Europe and developed Asian countries such as Japan, South Korea and Taiwan in the early 2000's.[38] This study also reported that the distribution of cases that were staged at diagnosis was as follows, 67% stage C (cancer that has grown out of the prostate but not spread to lymph nodes or other places in the body), 23.7% stage D (cancer that has spread to lymph nodes or other places in the body), and only 8.6% stage A and B (cancer that are confined to the prostate).[38] In the US, 80% of the prostate cancer cases are diagnosed with localized stage (confined to primary site), which is in part due to the widespread use of PSA screening in the US population.[4, 12] There, is currently no recommended population-based screening program for prostate cancer in Thailand.[9]

Prostate cancer screening

The two available screening strategies for prostate cancer are: Prostate-specific antigen (PSA) test and digital rectal examination (DRE). In 1986, the U.S. Food and Drug Administration (FDA) approved the use of PSA in patients with prostate cancer to monitor the disease, and in 1994 the test was approved as a prostate cancer screening test for asymptomatic men in the US.[40] Use of the PSA test as a prostate cancer screening tool influenced the rapid increase in prostate cancer incidence and possibly survival in many Western countries during the 1990s.[41] For example, in the US, a study showed that the overall prostate cancer incidence increased rapidly at 12% per year after the introduction of PSA screening, reaching its peak at 237.2 cases per 100,000 men per year in 1992; subsequently rates were stabilized during the period 1995 to 2005, and decreased by 5.1% during the last 10 years.[4, 42] In addition during this "PSA

era" the proportion of patients having advanced disease at diagnosis has decreased by 80%.[41] Similarly, in Europe the incidence rates of prostate cancer increased and the proportion of advanced stage at diagnosis decreased during the "PSA era", notwithstanding that European countries do not do population-wide PSA screening.[43] In October 2011, the US Preventive Service Task Force (USPSTF) recommended against PSA screening for prostate cancer based on a review of the evidence that showed little or no evidence of prostate cancer-specific mortality reduction; the review also demonstrated that PSA screening is associated with harms related to overdiagnosis and, thus, unnecessary follow-up and treatment for some men diagnosed with prostate cancer.[44] This recommendation did not fully address screening via DRE which is still used by many practitioners in attempts to identify men with clinically significant prostate cancer.[45] In 2017, a draft with new recommendations for prostate cancer screening was released by USPSTF for public comments, in which it is recommended that men (ages 55-69) should discuss with their clinicians about the potential benefits and harms of PSA screening for prostate cancer in order to make an informed decision whether or not to be screened.[46] In addition, they still recommend against PSA screening for prostate cancer in men ages 70 years and older.[46]

To determine the effect of screening on prostate cancer mortality, two major randomized controlled trials of prostate cancer screening were conducted: the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the United States, and the European Randomized Study of Screening for Prostate Cancer (ERSPC) in several European countries.[47,48] The PLCO trial was associated with no reduction in prostate cancer mortality at 13 years of follow up between the intervention group (organized

annual screening) and the control group (opportunistic screening, which was part of usual care) (RR: 1.09; 95%CI: 0.87, 1.36).[49] On the other hand, the ERSPC trial found that the absolute risk reduction of death from prostate cancer at 13 years of follow up was 0.79 (95%CI: 0.69, 0.91).[48] Potential reasons for the discrepancy in the findings between the PLCO trial and the ERSPC are 1) the use of the PSA screening prior to randomization, particularly in the PLCO study population; 2) contamination of the control arm with men seeking PSA screening on their own (PLCO: 54.8%, ERSPC: 30%); and 3) non-compliance with biopsy when indicated which may have reduced the power of the trial by decreasing the incidence of cancers in the screened arm; in addition, it may have reduced the mortality reduction attributable to screening.[48, 50] The impact of the PLCO control arm contamination on perceived efficacy of the PSA screening was examined in a simulation study.[51] This study found that contamination increased the mortality rate ratio (from 0.68-0.77 to 0.86-0.91), and decreased the statistical power (from 40-70% to 9-25%) to distinguish a difference in mortality.[51] The authors concluded that contamination limited the ability of the trial to detect a significant benefit from the PSA screening.[51]

Importantly, the incidence rate for prostate cancer was significantly higher in the screening arm of both studies: PLCO (RR: 1.12, 95%CI: 1.07, 1.17) and ERSPC (1.63, 95%CI: 1.57, 1.69).[48, 49] Screening is beneficial for diagnosing cases in early stages when treatment may be effective, but this early detection must be weighed against the risk of overtreatment, side effects, and impaired quality of life.[52, 54] In Asia, nationwide PSA screening programs are not carried out, partially due to the lower incidence rate and/or the inadequate financial resources for healthcare in some Asian countries.[7]

Japan is the only country with official guidelines for prostate cancer screening approved by the national urological association, and there are population-based PSA screening programs in some of the municipalities in Japan.[7, 55] In a review article about prostate cancer in Asian men, the authors point out that recommendations for prostate cancer screening and treatment strategies are necessary and they should be tailored to the epidemiological and socioeconomic characteristics of each country.[56]

Prostate cancer control in Thailand

In Thailand, PSA and DRE are used as part of the diagnostic workup in patients with suspected prostate cancer (not used for screening purposes), particularly those with lower urinary tract symptoms (LUTS).[38] LUTS occur commonly in older men, and it can indicate urinary storage, voiding or post-voiding dysfunction.[57] These symptoms are often attributed to irritable or obstructive voiding conditions such as benign prostatic hyperplasia (BPH) or overactive bladder. In Thailand, transrectal ultrasound with a prostate biopsy is the recommended procedure for a diagnosis of prostate cancer after an abnormal PSA test (equal or above 4 ng/ml) and/or abnormal physical exam.[38] According to the guidelines from the National Comprehensive Cancer Network (Asian version), the treatment for prostate cancer may include active surveillance/watchful waiting, radical prostatectomy, radiation therapy and androgen deprivation therapy.[38, 58] In Thailand, radical prostatectomy is perhaps the most common treatment for the small proportion of localized prostate cancer diagnosed in the country. On the other hand, active surveillance/watchful waiting is not widely accepted in clinical practice because of anxiety induced in patients who are not being treated and/or lack the opportunity for a

cure.[38, 59, 60] In addition, patients may be burdened by periodic testing, particularly DRE and repeated biopsies. In prostate cancer cases diagnosed at an advanced stage or metastatic stage, which is the majority of cases in Thailand, third-line hormonal therapy, radiotherapy, chemotherapy, bone-targeted therapy and appropriate palliative care is recommended in Thailand.[38]

Prostate cancer survival in Thailand

Survival rates of prostate cancer are poor in many developing Asian countries.[58] This is consistent with the profile of stage at diagnosis and the high mortality to incidence ratio in this region of the world.[7, 9, 62] According to estimations from published reports, the 5-year survival rate for prostate cancer in Thailand is less than 50%, in contrast to the survival rates observed in Japan (>85%).[8, 63] In the US, the percentage of men surviving five years from prostate cancer is very high (98.6%) which is in part due to the influence of PSA screening.[4] Other developed western countries that do not conduct routine PSA screening, such as the United Kingdom (UK), also show higher rates of five year survival (84.8%).[64] Early detection of prostate cancer is important to provide timely treatment and improve prostate cancer survival. It is also important to understand differences in prostate cancer incidence and survival among populations, particularly in Asia where there is a lack of studies on risk factors and survival predictors for prostate cancer. As discussed above, most of the studies on prostate cancer have been conducted in Western countries where risk profile and tumor characteristics are most likely to be different than those Asian countries. A study that examined the ethnic differences in prostate cancer epidemiology between East Asians and Caucasians

found that PSA screening, medical practices and genetic factors may explain the lower prostate cancer incidence rates in Asian vs Caucasian men.[65]

Songkhla Thailand and prostate cancer statistics

Songkhla, Thailand is a southern province located on the eastern side of the Malasyian Peninsula and coast of the Gulf of Thailand (Figure 1.4). It has a total area of 7,393.9 km^2 (2,854.8 sq. mi) divided in 16 districts. According to the last census in 2010, the population of southern Thailand was 8.87 million people of which 4.39 million were males (the total population of Thailand in 2010 was 65.5 millions).[66, 67] Approximately, 15% of the population in Thailand are aged over 60 years and the life expectancy for Thai males is 72 years.[66] In addition, 25% of the population in Songkhla are Muslims. There is a lack of studies on the epidemiology of prostate cancer in southern Thailand. A recent study in the province of Songkhla examined differences in cancer incidence between Buddhist and Muslim populations, showing that incidence rates of several cancers, including prostate cancer, are lower in Muslims than Buddhists.[68] The authors concluded that diet and cultural practices among Muslim individuals may be related to the differences in cancer incidence rates found between these populations.[68]

Remaining questions:

This comprehensive literature review has led us to identify several remaining questions in relation to prostate cancer in Thailand, particularly in the southern region.

1. What are the current and future incidence and mortality trends of prostate cancer in the southern province of Songkhla, Thailand? In addition, what is the effect of age, calendar year and birth-cohort on those trends?
2. Is there any difference in prostate tumor characteristics and survival between Buddhists and Muslims in Songkhla, Thailand?
3. What would be the impact on prostate cancer incidence and mortality if population-based prostate cancer screening were introduced in Thailand?

Specific aims

Aim 1: Examine current trends and project incidence and mortality rates of prostate cancer over the next decade in Songkhla, Thailand (Chapter 2)

We hypothesized that incidence and mortality trends of prostate cancer have increased over time and they will continue to increase over the next decade. We used data from the population-based Songkhla Cancer Registry from 1990 to 2013 to examine the trends. In addition, we evaluated the effect of age, calendar year and birth-cohort on the prostate cancer trends in order to generate hypothesis that help us to understand potential factors that influence changes in prostate cancer trends in Songkhla, Thailand.

Aim 2: Describe the differences in prostate tumor characteristics and survival after diagnosis with prostate cancer between the two major ethnic/religious groups in Thailand: Buddhists and Muslims (Chapter 3)

We hypothesized that Buddhists and Muslims have different prostate tumor characteristics and that survival differs between these two populations. Here, we also used data from the Songkhla Cancer Registry from 1990 to 2014, as data was updated the following year (2016). We included a directed acyclic graph (DAG) to represent the causal assumption in this study (Figure 1.5). We also explored prostate cancer survival probability trends to examine the effect of the introduction of UHC in Thailand on the survival of prostate cancer between Buddhist and Muslims in Songkhla.

Aim 3: Evaluate the impact on prostate cancer incidence and mortality in Songkhla Thailand were screening strategies to be introduced, particularly DRE or PSA test, while taking into account the overdiagnosis issue.

We hypothesized that incidence of prostate cancer increases, while mortality decreases with the introduction of prostate cancer screening. We conducted a simulation analysis to evaluate the impact of screening, and used data from the population-based Songkhla Cancer Registry. In addition, we used data from other sources such as the Surveillance Epidemiology and End Results Program (SEER) and the ERSPC trial to estimate parameters and examine different scenarios.

Summary

The burden of cancer is increasing worldwide, particularly in less developed countries. In addition, the number of new cancer cases and cancer related deaths are expected to rise over the next decade. Planning cost-effective strategies to cope with this increased burden of the disease is an important task that many countries need to develop immediately.

Currently, there is a lack of studies on the epidemiology of prostate cancer in Thailand, and particularly in southern Thailand, which is characterized by different ethnic/religious groups with different socio-cultural characteristics and likely different cancer risk profiles. As in many other developing countries, Thailand is undergoing the epidemiological transition with an increased life expectancy and aging of the population that will increase the risk of prostate cancer.

Thailand is an interesting place to conduct this type of research for the following reasons. Most importantly, Thailand has a long-standing system of high-quality, population-based cancer registries throughout the country which allowed us to conduct this research. Thailand is one of only a few developing countries with this type of data available. Second, during this period when registry data has been available, Thailand has transitioned from a low-income country to a middle-income country. Therefore, Thailand represents an opportunity to directly observe the effects of the epidemiologic transition on the burden of cancer. Lastly, Thailand has high-quality UHC with access to care relatively consistent across the country. Thus, unlike in many low and middle income countries, differential access to care across population groups is unlikely to explain differences in disease risk and outcomes across the population.

The purpose of this dissertation is to examine prostate cancer in Songkhla, Thailand, including a trend analysis of current and future incidence and mortality rates of prostate cancer, and an analysis to examine differences in prostate tumor characteristics and cancer survival by religious groups. In addition, we plan to conduct a simulation analysis to evaluate the potential impact of the implementation of screening strategies on prostate cancer incidence and mortality in Songkhla, Thailand. Our ultimate goal is to inform Thai health authorities about the current and future burden of the disease, as well as identify potential disparities between religious groups, and to help to provide information that will help authorities make informed decisions about the introduction of prostate cancer screening in this population.

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Figure 1.1. Age-adjusted incidence and mortality rates of prostate cancer across world regions in 2012

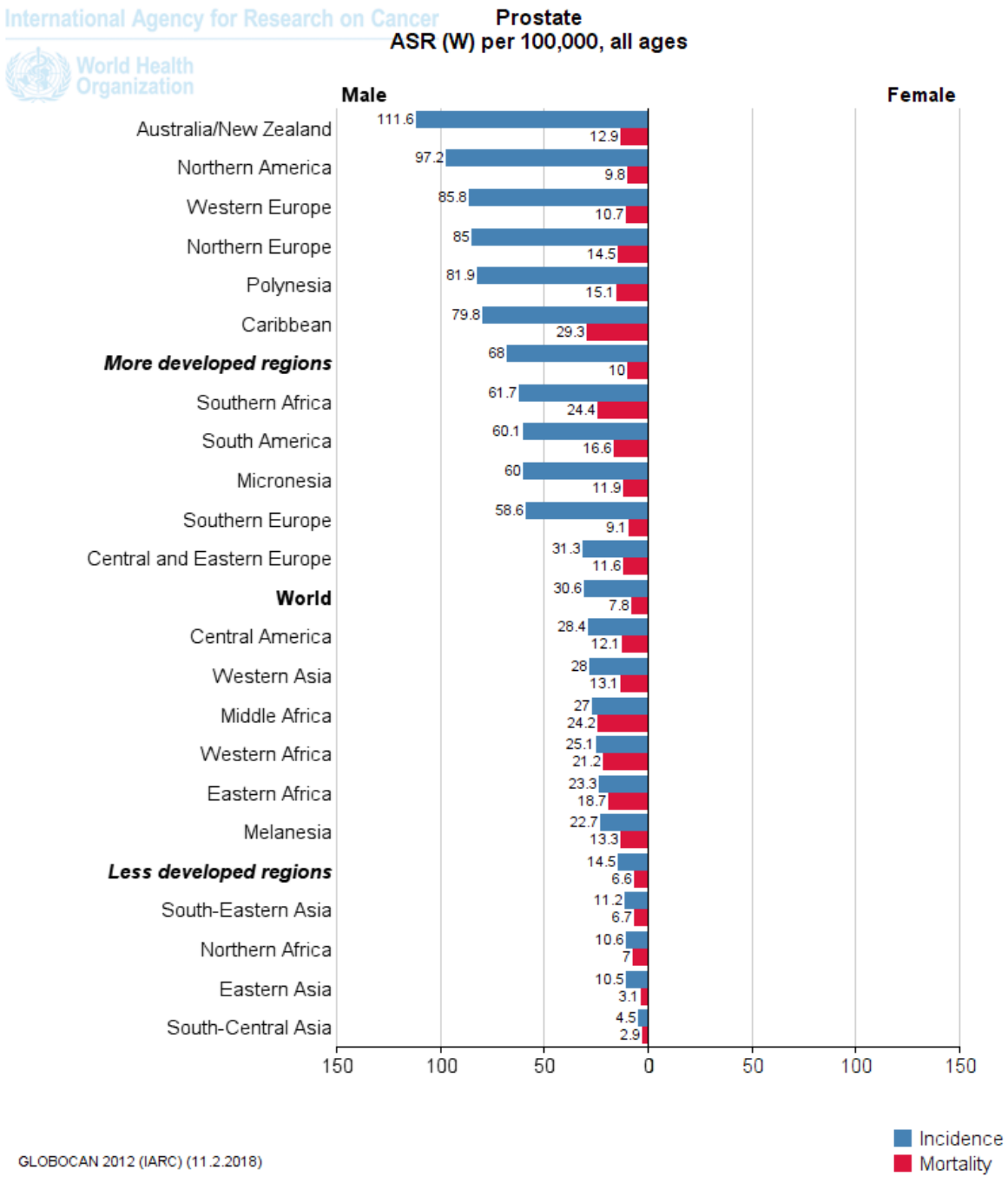
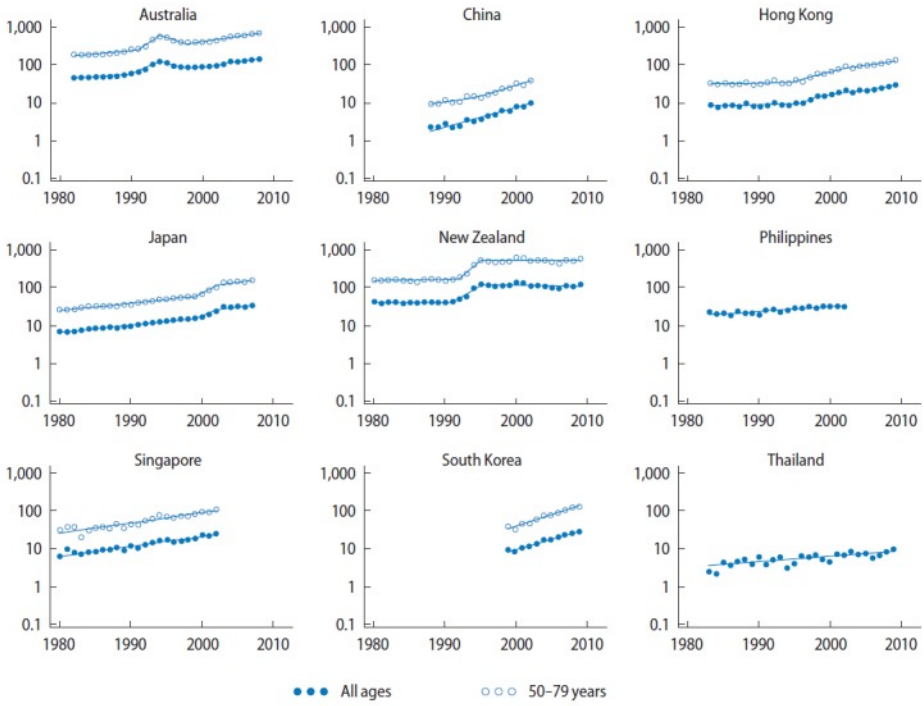


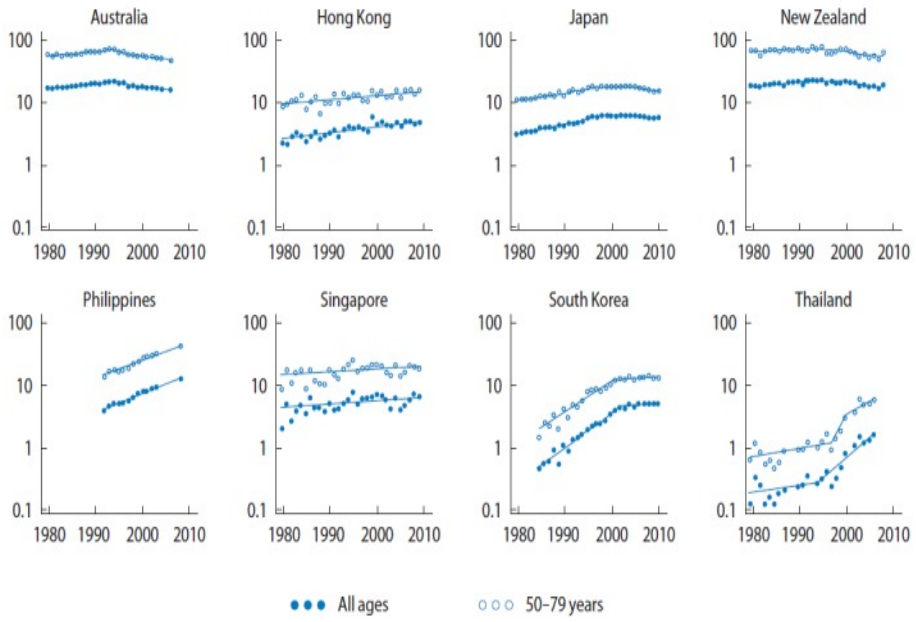
Figure 1.2. (a) Prostate cancer incidence rate trends for 9 Asian-Pacific countries from 1980 to 2009



X-axis represents the calendar year and Y-axis shown the age-standardized rates, according to the Segi's world standard population.

Source: Baade PD, Youlden DR, Cramb SM, et al: Epidemiology of prostate cancer in the Asia-Pacific region. Prostate Int 1:47-58, 2013.

Figure 1.2. (b) Prostate cancer mortality rate trends for 8 Asian-Pacific countries from 1980 to 2009



X-axis represents the calendar year and Y-axis shown the age-standardized rates, according to the Segi's world standard population.

Source: Baade PD, Youlden DR, Cramb SM, et al: Epidemiology of prostate cancer in the Asia-Pacific region. Prostate Int 1:47-58, 2013.

Figure 1.3. Population pyramids from 1960 and 2010 in Thailand

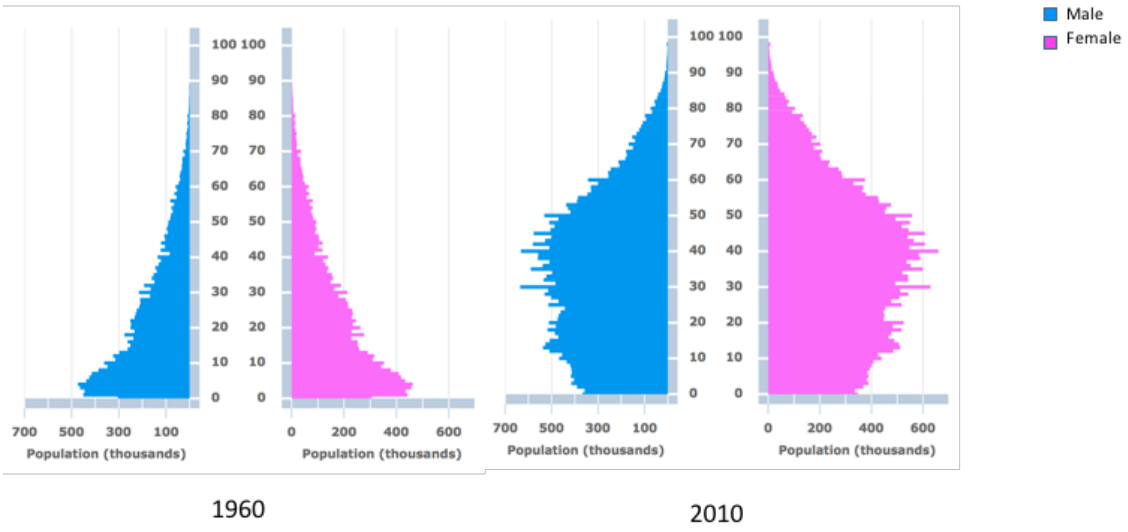
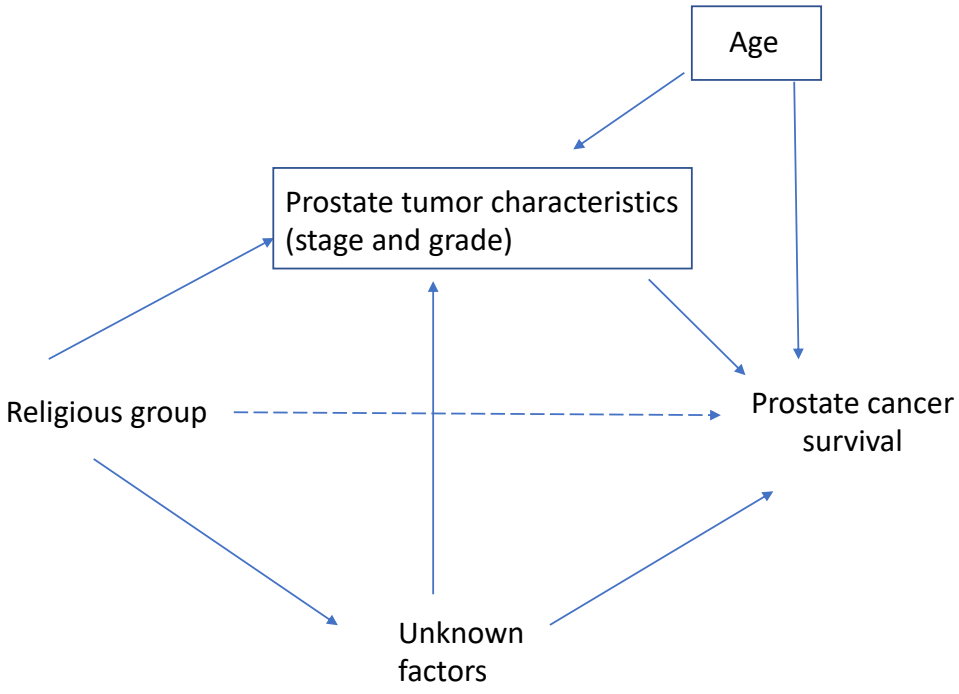


Figure 1.4. Map of Thailand (Songkhla province is shaded)

Source: by NordNordWest - self-made, using Thailand location map.svg, CC BY 3.0, https://commons.wikimedia.org/w/index.php?curid=6603273.

Figure 1.5. Directed acyclic graph for the assumption of the causal relationship between prostate cancer survival and religious group



Chapter 2. The Current and Future Burden of Prostate Cancer in Songkhla, Thailand: Analysis of Incidence and Mortality Trends, 1990-2030

Christian S. Alvarez, Shama Virani, Rafael Meza, Laura Rozek, Hutcha Sriplung, Alison M. Mondul

Abstract

Purpose: Prostate cancer is the second most common malignancy among men worldwide, and it poses a significant public health burden that has traditionally been limited mostly to developed countries. However, the burden of the disease is expected to increase, affecting developing countries, including Thailand. We undertook an analysis to investigate current and future trends of prostate cancer in the province of Songkhla, Thailand, using data from the Songkhla Cancer Registry from 1990 to 2013.

Methods: Joinpoint regression analysis was used to examine trends in age-adjusted incidence and mortality rates of prostate cancer, and provide estimated annual percent change (EAPC) with 95% confidence intervals (CI). Age-period-cohort (APC) models were used to assess the effect of age, calendar year and birth-cohort on incidence and mortality rates. Three different methods (Joinpoint, Nordpred, and APC) were used to project trends from 2013 to 2030.

Results: Eight hundred fifty-five cases of prostate cancer were diagnosed from 1990 to 2013 in Songkhla, Thailand. The incidence rates of prostate cancer significantly increased since 1990 at an EAPC of 4.8% (95%CI, 3.6% to 5.9%). Similarly, mortality

rates increased at an EAPC of 5.3% (95%CI, 3.4% to 7.2%). The APC models suggest that birth cohort is the most important factor driving the increased incidence and mortality rates of prostate cancer. Future incidence and mortality of prostate cancer are projected to continue to increase, doubling the rates observed in 2013 by 2030.

Conclusions: It is critical to allocate resources to provide care for the men who will be affected by this increase in prostate cancer incidence in Songkhla, Thailand, and to design context-appropriate interventions to prevent its increasing burden.

Introduction

In 2012, prostate cancer was the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men worldwide.[1, 2] Prostate cancer incidence varies up to 25-fold across world regions, with the highest age-standardized rates (ASR) in Western developed countries, such as the United States.[1] However, prostate cancer mortality varies less across regions (approximately 10-fold) than incidence rates, with the largest age-standardized mortality rates (ASMRs) estimated from less developed regions such as Sub-Saharan Africa and the Caribbean.[1, 3] Accounting for growth and aging of the world population, the global burden of prostate cancer is expected to increase to 1.7 million new cases and nearly half a million deaths by 2030.[1, 4]

In Asia, reported incidence rates of prostate cancer are much lower than most Western developed countries.[3–8] However, over the past decade, prostate cancer incidence rates have increased rapidly in several Asian populations.[4–6, 8–10] For instance, the incidence rates in East Asia increased on average 7.2% per year from 2005 to 2009.[5] Similarly, mortality rates increased in some Asian countries, ranging from 5.3% per year in Shanghai, China (from 1985 to 2009), to 13.4% per year in South Korea (from 1985 to 2002).[6, 9] The rapid increase in the burden of prostate cancer in Asia may be partly a result of an aging population and adoption of Westernized lifestyles as a consequence of economic development.[5, 6, 8, 9]

In Thailand, the nationwide incidence rates of prostate cancer have increased at an average annual percent change of 2.7% over the past two decades.[2] The mean

annual ASR increased from 4.9 prostate cancer cases per 100,000 person-years in 1995 to 1999 to 7.1 prostate cancer cases per 100,000 person-years in 2010 to 2012.[11, 12] However, reports from the Thai National Cancer Institute show regional differences in the incidence of prostate cancer, with a higher incidence rate in southern Thailand compared to the northeast region (ASRs: 10.4 *v* 4.1 cases per 100,000 person-years, respectively).[12] Southern Thailand is a unique region as a result of its ethnic and cultural composition, where approximately 30% of the population is Muslims, mostly of Thai ethnicity.[13] It is clear that there is a need to comprehensively assess cancer incidence and mortality by region in Thailand, rather than just at the national level; to our knowledge, this has not been done, particularly in southern Thailand. We undertook an analysis investigating trends in the incidence and mortality of prostate cancer using data from the Songkhla cancer registry in southern Thailand from 1990 to 2013 and projecting prostate cancer rates to 2030.

Methods

Study population

Songkhla is a southern province of Thailand, located on the eastern side of the Malay Peninsula. In 2010, the population of Songkhla was approximately 1.5 million, of which 48.8% were male.[13, 14] Estimates from the Thai National Statistical Office show that 25% of the population in the Songkhla province is Muslim and 75% Buddhist.[14, 15] Furthermore, approximately 15% of the population in Thailand is older than age 60 years, with a life expectancy of 72 years for men.[16, 17]

Data source

Data on incident prostate cancers were obtained from the Songkhla Cancer Registry from 1989 to 2013. This registry has been described in detail previously.[13, 18–20] Briefly, the Songkhla Cancer Registry was established in 1989 and covers 16 districts in the province of Songkhla.[13] It actively captures cases of cancer from 23 sources, including the 3 tertiary referral hospitals for cancer in the province (Songklanagarind Hospital, Hat Yai Hospital, and Songkhla Hospital); community, private, and special hospitals; and the provincial health and population registration office.[13, 15, 18–20] Cancer case data are mainly collected from hospital and pathology records with the highest standard of quality, using strict protocols for case identification.[13] According to the cancer report in Thailand, volume VII (2007-2009), 87% of prostate cancers in the Songkhla Cancer Registry were histologically verified, and only 2.4% were obtained from death certificates.[21] Completeness is >95%, evaluated by capture-recapture methods.[22] This registry has been included in the International Agency for Research on Cancer's publication, Cancer Incidence in Five Continents since volume VIII (1993 to 1996).[18]

Data extraction and variables

Cancer cases were extracted using the International Classification of Diseases, 10th revision, code for malignant neoplasm of the prostate (C61). Complete information on cancer cases was available from 1990 to 2013 (n=855). Variables in the registry included: dates of diagnosis, last contact, and death; vital status; tumor grade, stage

and extent; age at diagnosis; religion; and district of residence.

Population denominators were obtained from decennial census data in 1990, 2000, and 2010 conducted by the Thai National Statistical Office. The annual intercensal population structure in Songkhla was estimated by 5-year sex-specific age groups, using a log-linear function between consecutive censuses. The population beyond 2010 was estimated by the Office of the National Economic and Social Development Board.[15, 19, 20]

Statistical analysis

Descriptive statistics (medians and percentages) were generated for the variables in the cancer registry. Age-specific incidence and mortality rates of prostate cancer were calculated for 24 calendar periods between 1990 to 2013 (1-year intervals) and 18 different 5-year age groups, and adjusted to the World standard Segi population.[23] Incidence and mortality rates used for comparison purposes in this study were also adjusted to the World standard Segi population.

Analysis of incidence and mortality trends

Joinpoint regression analysis was conducted to examine trends in ASRs and ASMRs for prostate cancer using the Joinpoint-Regression Program version 4.2.0.2 (https://surveillance.cancer.gov/joinpoint/). Joinpoint regression identifies statistically significant trend change points (joinpoints) and the rate of change (estimated annual percent change [EAPC]) in each trend segment using a Monte Carlo Permutation method.[13, 19] A maximum number of four joinpoints was allowed in the analysis to best

describe the trend of the data.

Age-period-cohort analysis

Age-period-cohort (APC) models were fitted to the incidence and mortality rates to assess the effects of age, calendar year and birth-cohort on the prostate cancer risk and mortality. APC analysis identifies patterns in cancer rates from population-based count and population data in order to gain insight about temporal trends.[24] The APC method fits a log-linear model with a Poisson distribution to the observed data to estimate age, period, and cohort effects in a multiplicative APC model.[13, 19, 25] This method is known as the "classical" approach and it is represented by the formula below,

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

This formula assumes that the expected log-incidence and/or mortality rates $\lambda_{a,p}$ is equal to a linear combination of time-related variables or effects that adjust for age (a), calendar year (p) and birth-cohort (c), where c=p-a.[13, 19, 25] In order to address non-identifiability due to the linear dependency of each time-related variable on the other two, two-effect models age-period (AP-C) and age-cohort (AC-P) were first selected and the remaining effect (cohort or period) was then fit to the respective model's residual using natural splines to reduce random variation.[13, 19, 25] The analysis of APC models was conducted with the Epi package in the R statistical software version 3.2.2.[26]

Prediction of prostate cancer incidence and mortality

To project the incidence and mortality rates of prostate cancer in Songkhla, Thailand through 2030, three independent models were used to compare the results

across these methods: these were Joinpoint, nordpred and APC model projections as performed by Virani *et al.* in her analysis of breast cancer in Songkhla, Thailand.[13] Ninety-five percent prediction intervals [PIs] and validation were conducted for the Joinpoint model only.

Joinpoint

For the entire trend of the joinpoint model, the linear and residual components were separated. The curvature of the trend is explained by the residual, and the secular drift is described by the linear component of the joinpoint model.[13] The incidence and mortality rates were extrapolated out to 2030. In order to reduce the effect of drift in project incidence and mortality rates, the cut trend system proposed by Olsen *et al.* [27] was used to attenuate the linear component of the trend by 0% in the first projected 5-year period (2014-2018), and after that by 5% per year. To provide the total age-adjusted incidence and mortality rates with linear attenuation, the residual and linear components of the joinpoint models were added.[13]

We conducted a sensitivity analysis for mortality excluding the first 2 years of registry data (1990-1991). Mortality is only ascertained for cancer cases included in the registry. Thus, at the beginning of data collection, deaths for prevalent cases not included in the registry would not be captured, making the mortality rates artificially low for the initial years of follow-up.

Prediction intervals were calculated to take into account the uncertainty of the parameter estimates and variation of the future incidence and mortality rates of prostate cancer, in which the upper and lower bound of the slopes of the linear trends (using

confidence intervals for the slope) were computed, and were used to project the incidence and mortality rates of prostate cancer through 2030 providing upper and lower bounds on the estimated rates.

A validation analysis was conducted, in which we fit the models for a five-year period (2006-2010) and predicted the incidence and mortality rates for the next 3 years (2011 to 2013). These predicted incidence and mortality rates were then compared with the observed rates of prostate cancer in Songkhla.

Nordpred

The second approach used the Nordpred R-package.[28] With this method, an APC model is fitted to the data and then the Segi world-standardized incidence and mortality rates were calculated for the eighteen five-year age groups and the 4-year interval periods between 1990 to 2013. An extrapolation of the trends based on the observed data was carried out for 4-year interval periods, through 2029. To prevent overestimation of prostate cancer cases from the multiplicative model, a power of 5 function was used to attenuate the linear drift as suggested by *Olsen et al*. (2008) and Mistry *et al* (2011).[27, 29]

AP-C and AC-P models

For the third approach, a spline model fit to the AP-C model period effect and AC-P model cohort effect were used. The linear and residual components of the period effects (for AP-C model) and cohort effects (for AC-P model) were individually separated and projected to 2030, similar to the joinpoint projection. The linear

component of each model was attenuated as performed in joinpoint.[13] Using the AP-C model age-effects, and the projected period effects, as well as projected populations counts by age, we calculated the incidence and mortality rates of prostate cancer from 2013 to 2030.

Results

Eight hundred fifty-five cases with prostate cancer were diagnosed from 1990 to 2013. The median age at diagnosis was 74 years (quartile 1 to quartile 3, 67 to 80 years). The majority of prostate cancer cases were Buddhist (89.6%) and the rest Muslim. Most of the prostate cancer cases were unstaged (79.8%); among those who were staged, 3.5%, 17.9%, 2.9%, and 75.7% had stage I, II, III, and IV disease, respectively. We observed a statistically significant change in the stage distribution over time ($p<0.0001$, Table 2.1). This change was largely due to the proportion of unstaged tumors decreasing with a concomitant increase in stage II tumors during 2005-2009 (Figure 2.1 a and b, and Table 2.1).

Joinpoint

Prostate cancer incidence rates in Songkhla increased significantly from 1990 to 2013 at an EAPC of 4.8% (95%CI: 3.6, 5.9, $p<0.05$) (Figure 2.2 a). The ASR increased approximately three-fold from 2.55 to 8.87 prostate cancer cases per 100,000 person-years in 1990 and 2013, respectively. Similarly, the mortality rate of prostate cancer in Songkhla increased significantly since 1990 at an EAPC of 5.3% (95%CI, 3.4% to 7.2%;

p< .05; Figure 2.2 b). The ASMR increased nearly six-fold from 0.80 to 4.93 deaths per 100,000 person-years in 1990 and 2013, respectively. In a sensitivity analysis excluding the first 2 years of data, the mortality EAPC was very similar (EAPC=4.72, 95% CI=2.9% to 6.6%; p< .05). Thus, subsequent mortality analyses did not exclude these data.

APC

Figure 2.3 shows the APC incidence trend analysis for each of the models (APC, AC-P [age-cohort model] and AP-C[age-period model]). The incidence trends in the models show that the incidence rates of prostate cancer increase exponentially (linear in log-scale) with age (Figure 2.3, left). We observed that younger cohorts have a higher risk of prostate cancer (Figure 2.3, center), and that the risk of prostate cancer increases with calendar year (Figure 2.3, right). The risk is approximately 2 times higher (95%CI: 1.68, 2.34) in 2010 versus 1995. The APC analysis for mortality yielded similar results for all models (Figure 2.4). The age-cohort model provides the best fit for the data in both incidence and mortality APC trend analysis, and the greatest difference of deviance residual is observed after cohort is removed from the full APC model, suggesting that birth-cohort is the most important factor driving the increased incidence and mortality rates of prostate cancer (Table 2.2).

Projections

Prostate cancer incidence and mortality are estimated to continue increasing in the next decade (Figure 2.5). By 2030, incidence rates are expected to double from the

2013 rates, increasing from 8.9 to 16.4 cases per 100,000 person-years (95%PI: 14.0 to 18.7) (Figure 2.5 a). Incidence projections were similar using APC and Nordpred (Figures 2.6). By 2030, mortality rates will increase from those observed in 2013, from approximately five to 11.0 deaths per 100,000 person-years (95%PI: 8.7 to 13.4). Mortality projections were similar across the methods used (Figure 2.7).

Results for incidence and mortality projections were validated using data from 2006 to 2010 to project rates for 2011 to 2013. The projected data for 2011 to 2013 closely matched the observed data for both incidence and mortality (Figures 2.8 and 2.9).

Discussion

This first in-depth look at the trends of prostate cancer in Songkhla, Thailand, demonstrates that there has been a significant increase in prostate cancer incidence and mortality since 1990 (Figure 2.2 a and 2.2 b) likely as a result of changes in sociodemographic and lifestyle factors of the Thai population. In addition, the burden of prostate cancer is expected to continue to increase through 2030 (Figure 2.5).

The increased trends of prostate cancer in Songkhla are similar to those observed in other areas of Thailand as well as across Asia. In Chiang Mai (northern Thailand), the incidence and mortality rates of prostate cancer increased at an EAPC of 3.3% (95%CI, 2.2% to 4.4%) from 1983 to 2009 and 2.7% (95%CI, -4.4% to 10.4%) from 1980 to 1994, respectively.[6] Similarly, in Shanghai, China, the prostate cancer incidence and mortality EAPCs were 3.2% (95%CI, 0.3% to 6.8%) from 1991 to 2004,

and 5.3% (95%CI, 4.7% to 6.0%) after 1985, respectively.[9] Other Asian countries have reported similar results.[6] However, in the United States, the incidence and mortality of prostate cancer have decreased at a rate of 1.1% (95%CI, 0.4% to 1.8%) and 3.4% (95%CI, 3.3% to 3.6%) from 1990 to 2013, respectively.

Although prostate cancer incidence rates are increasing in Thailand, the rates remain low compared with developed Western countries.[6] In 2013, the ASR of prostate cancer in the United States was 74.8 cases per 100,000 person-years, approximately nine-fold higher than the rate in Songkhla, Thailand in the same year (ASR: 8.87 prostate cancer cases per 100,000 person-years).[30] This difference in incidence rates between the United States and Thailand is partially explained by the use of prostate-specific antigen (PSA) for prostate cancer screening in the United States.[31, 32] However, the use of PSA screening does not completely explain these differences because rates in Western countries that do not routinely do population-based PSA screening, such as the United Kingdom, are still substantially higher than those in Thailand (ASR: 73.2 prostate cancer cases per 100,000 person-years).[1] There are no official guidelines on population-based screening for prostate cancer in Thailand or any other Asian countries, except for Japan, where screening rates remain low (12.2% in 2011).[33]

Asian men may also be at a reduced genetic risk of prostate cancer. Asian Americans have lower prostate cancer rates compared with white Americans (37.2 and 69.0 prostate cancer cases per 100,000 person-years, respectively).[34] Furthermore, genetic studies on prostate cancer have observed substantial racial differences between white and Asian populations. Importantly the TMPRSS2-ERG fusion, which is associated with poorer prognosis,[35] is more prevalent in whites (approximately 50%)

than Asian populations (8% to 21%).[5, 35]

Prostate cancer incidence and mortality rates in Songkhla increased at approximately the same EAPC during the study period. It should be noted that the increase in mortality over time occurred despite a slight downward shift in the stage distribution at diagnosis in later periods. The mortality-to-incidence ratio (MIR) of prostate cancer is remarkably higher in Songkhla (0.56) compared with the United States (0.09), even though the difference in prostate cancer mortality rates is currently small (US and Songkhla mortality rates: 8.5 and 5.57 deaths per 100,000 person-years, respectively). However, if prostate cancer mortality rates remain stable in the United States, the projected mortality rate in Songkhla will surpass the US rate by 2030 (10.99 *v* 8.5 deaths per 100,000 person-years). The higher MIR in Songkhla is partially a result of the large proportion of prostate cancer tumors diagnosed at advanced stages. Our study found that 75.7% of staged tumors were diagnosed at an advanced stage versus only 4% of tumors diagnosed in the United States.[36] PSA screening contributes to diagnosing patients at early stages in the United States; however, PSA screening remains controversial, and the benefits of early detection must be weighed against the risk of overtreatment, adverse effects, and impaired quality of life.[37–39] Nonetheless, even in Western countries where population-wide PSA screening is not conducted, the stage distribution is still much lower than in Thailand (e.g. 17% of patients diagnosed at advanced stage in United Kingdom).[40] Designing interventions to diagnose prostate cancer at earlier stages in Thailand will be instrumental in reducing prostate cancer mortality in this population.

The adoption of a more Western lifestyle, particularly poorer diet and less physical activity, has been speculated to increase the incidence of cancer in this region. This is supported by the increase in rates observed by birth-cohort in the APC analyses and the cohort effects from the AC-P (age-cohort) model. Thailand has undergone both social and economic transition over the past three decades that have shifted dietary patterns toward a diet high in fat, meat, and total energy intake as well as lowered physical activity.[41] Furthermore, studies have suggested that environmental factors may play a role in the risk of progression of prostate cancer to adverse outcomes.[42] In fact, several risk factors (e.g. higher body mass index, smoking, reduced lycopene intake) have been observed for lethal or aggressive prostate cancer, but not for indolent disease.[42] Because more prostate cancer cases in Songkhla are diagnosed with advanced-stage disease, it is likely that etiologic factors in this population are similar to those identified for aggressive or lethal prostate cancer in the US.

We also considered whether introduction of universal health coverage by the Thai National Health Security Office in 2002 may have contributed to the increase in incidence and mortality. However, we observed a linear increase in both incidence and mortality over time that did not differ between the periods before and after introduction of universal health care. In addition, the stage distribution at diagnosis remained similar before and after this introduction. If improved access to healthcare was strongly influencing rates, we would expect to see an increase or no change in incidence with a stage shift toward lower stages at diagnosis and, perhaps, reduced mortality as a result of improvements in treatment. Thus, the pattern we observed is not consistent with the introduction of universal health coverage having a strong influence on prostate cancer

incidence or mortality. We also considered whether awareness of prostate cancer as a possible diagnosis by health care providers may have increased in recent decades, potentially contributing to increased trends. However, again, we did not observe any substantial downshift in the staging of prostate cancer at diagnosis as we might expect under this scenario. Further research is necessary to address these hypotheses.

This study was, to our knowledge, the first to explore the current and future trends of prostate cancer in Songkhla. Each of the methods we used for the projection analysis (Joinpoint, Nordpred, and APC) has different limitations, including the assumption of a Poisson distribution for the method presented in the main findings (i.e. the Joinpoint method). However, our results were essentially the same no matter which model was used, indicating the robustness of our findings. Our data come from a population-based cancer registry, which allows us to extrapolate the results to the entire province of Songkhla; in addition, the data has been collected with the highest standard of quality in order to obtain accurate estimates.[13] Nonetheless, it is difficult to estimate the number of cases not captured by the registry in the province of Songkhla. Although universal health care has been available since 2002, some individuals residing in rural villages may not choose to access health care services and may prefer to use traditional medicine.[13]

Another limitation of this study is that mortality rates represent all-cause mortality (not prostate cancer-specific mortality), which might have led to prostate cancer mortality estimates that were slightly too high. However, it should be noted that the resulting rates are similar to those estimated in other studies in Asia, suggesting that our results are reasonably accurate.[9] An alternative strategy for identifying deaths would

have been to use data from death certificates from the Thai Ministry of Health. However, death certificate data in Thailand is relatively poor quality with considerable misclassification.[43] A study conducted in 2003 found that the agreement between cause of death recorded in hospital records and that from death certificates was only 25%.[43] Had we used death information from these records instead, we likely would have substantially underestimated the prostate cancer mortality rate in this population.

In conclusion, prostate cancer incidence and mortality have increased in Songkhla, Thailand, since 1990 and are expected to continue to increase through 2030. Lifestyle changes may be the most important factors driving the increased incidence and mortality of prostate cancer in Songkhla. Additional studies should evaluate the role of the improvement in access to health care as well as awareness of prostate cancer in Thailand. It is critical to allocate resources to provide care for men who will be affected by the increased burden of disease in this population. In addition, further research is important to identify strategies for the control of prostate cancer in Songkhla, Thailand, including the impact of the introduction of screening programs.

Acknowledgements

We would like to thank the Songkhla cancer registry team for the collection and provision of this data. Also, Dr. Andrew Brouwer for his support in modeling and debugging the APC analysis. Mr. Alvarez was supported by the Fogarty/LIFESPAN Program (D43 TW009315) and the Office of Global Public Health at University of Michigan.

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Table 2.1. Prostate cancer stage distribution across 5-year periods for staged tumors (n=175)

Calendar period	Stage			
	I	II	III	IV
1990-1994	0 (0%)	1 (9.1%)	0 (0%)	10 (90.9%)
1995-1999	0 (0%)	0 (0%)	1 (6.2%)	15 (93.8%)
2000-2004	0 (0%)	0 (0%)	0 (0%)	26 (100%)
2005-2009	4 (5.8%)	28 (40.6%)	1 (1.4%)	36 (52.2%)
2010-2013	2 (3.8%)	3 (5.6%)	3 (5.7%)	45 (84.9%)

p value<0.0001 (Fisher's exact test, stage IV vs. stages I to III).

Figure 2.1. Prostate cancer stage distribution across 5-year periods for (a) all tumors (N=855) and (b) tumors that were staged only (n=175)

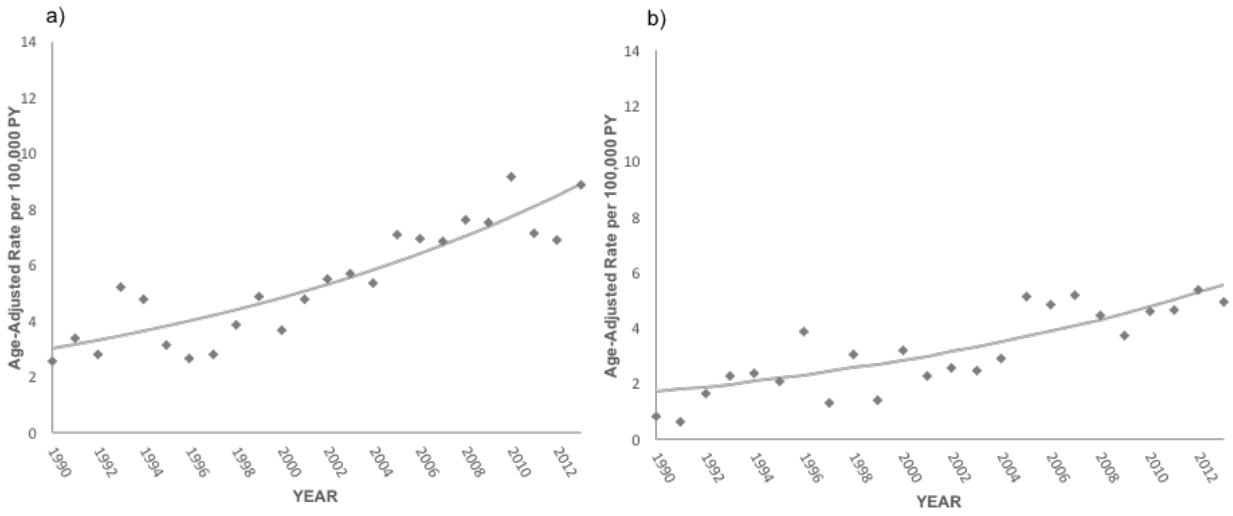

Figure 2.2. Age-adjusted incidence (a) and mortality (b) rates of prostate cancer in Songkhla, Thailand from 1990 to 2013 for males all ages by Joinpoint analysis

Estimated annual percent change: 4.8% (95%CI, 3.6%, 5.9%; $p<0.05$) and 5.3% (95%CI, 3.4%, 7.2%; $p<0.05$), respectively. The points show the observed rates, and the lines indicate the incidence and mortality trends.

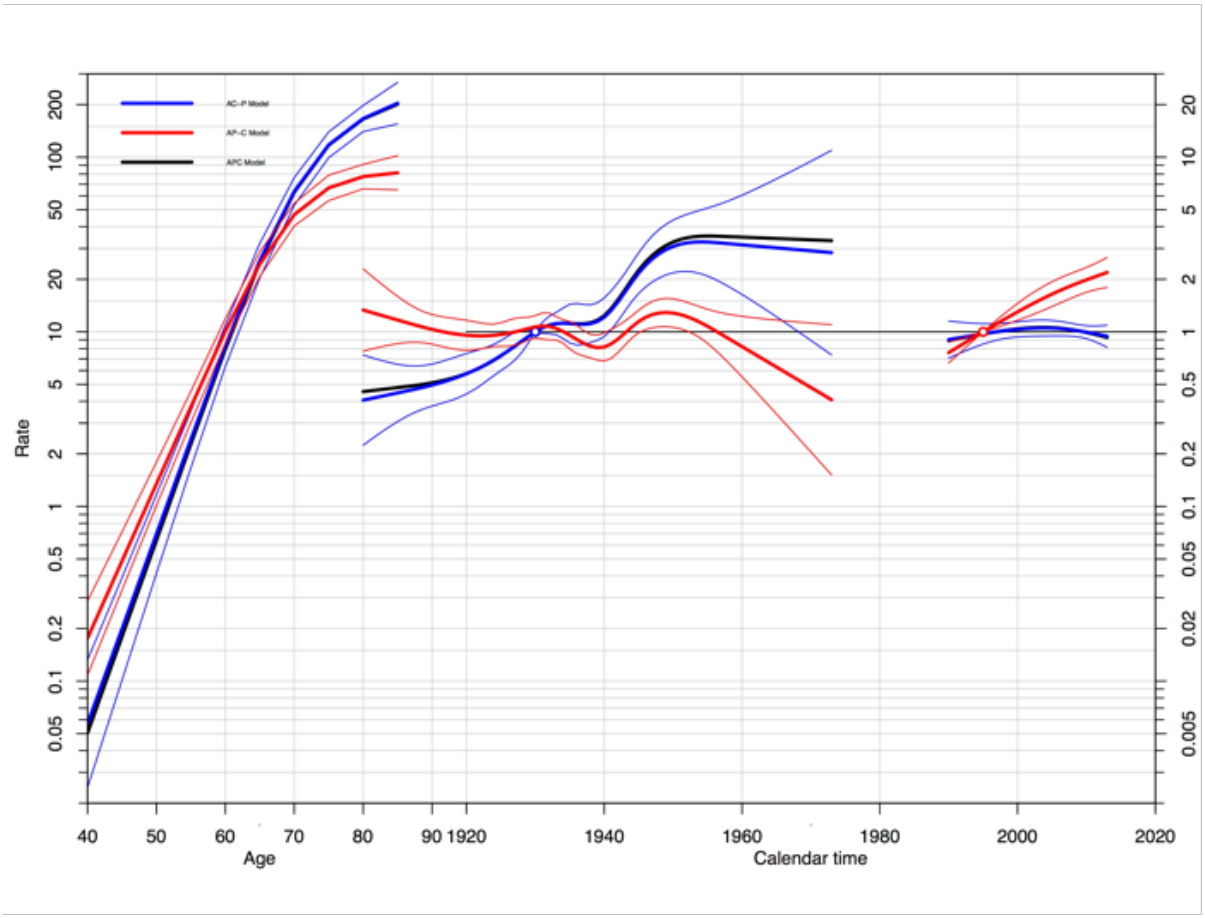

Figure 2.3. Age-period-cohort trend analysis for incidence of prostate cancer (1990-2013) in men of all ages in Songkhla, Thailand. A, age; C, cohort; P, period

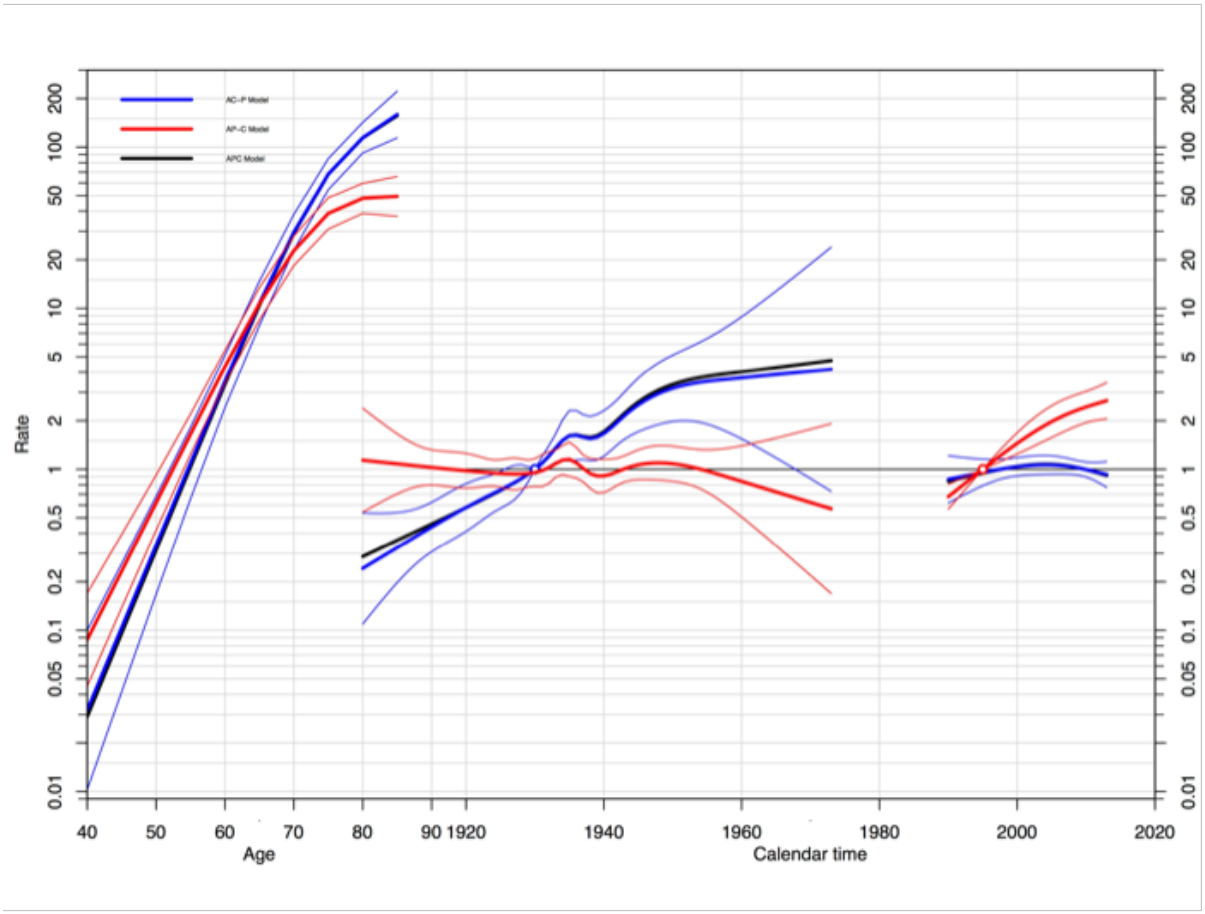

Figure 2.4. Age-period-cohort trend analysis for mortality of prostate cancer (1990-2013) in men of all ages in Songkhla, Thailand. A, age; C, cohort; P, period

Table 2.2. AIC values for the AC, AP, and APC models relative (difference) to the age-only model for the incidence and mortality of prostate cancer in Songkhla, Thailand

	APC trend for incidence	APC trend for mortality
Model	AIC*	AIC*
AC	237.96	190.59
APC	240.28	192.93
AP	240.75	192.96

Note. Relative values that weight the goodness of fit of the model to empirical data. A better model fit is indicated by lower AIC values.
Abbreviations: A, age; AIC, Akaike information criteria; C, cohort; P, period.
*-2 x log(likelihood) + 2 x number of estimated parameters.

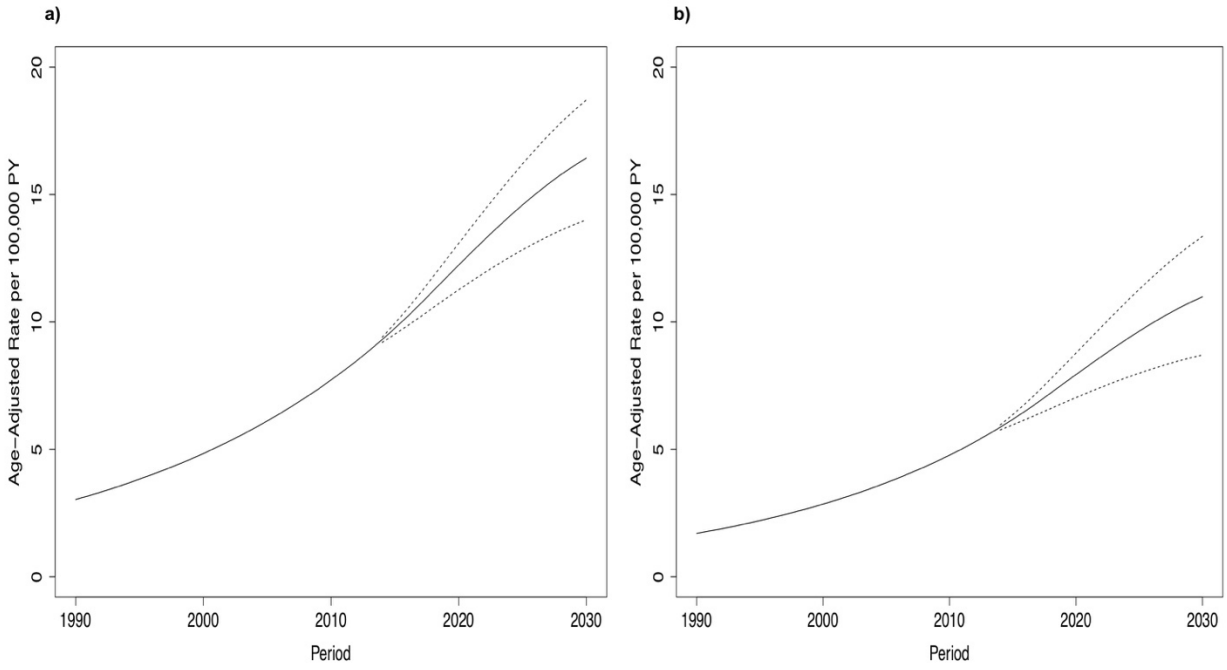

Figure 2.5. Prostate cancer incidence (a) and mortality (b) trend projections to 2030. Joinpoint method with 95% prediction intervals (PI)

The continuous lines are the projected incidence and mortality trends and the dashed lines show the 95%PI.

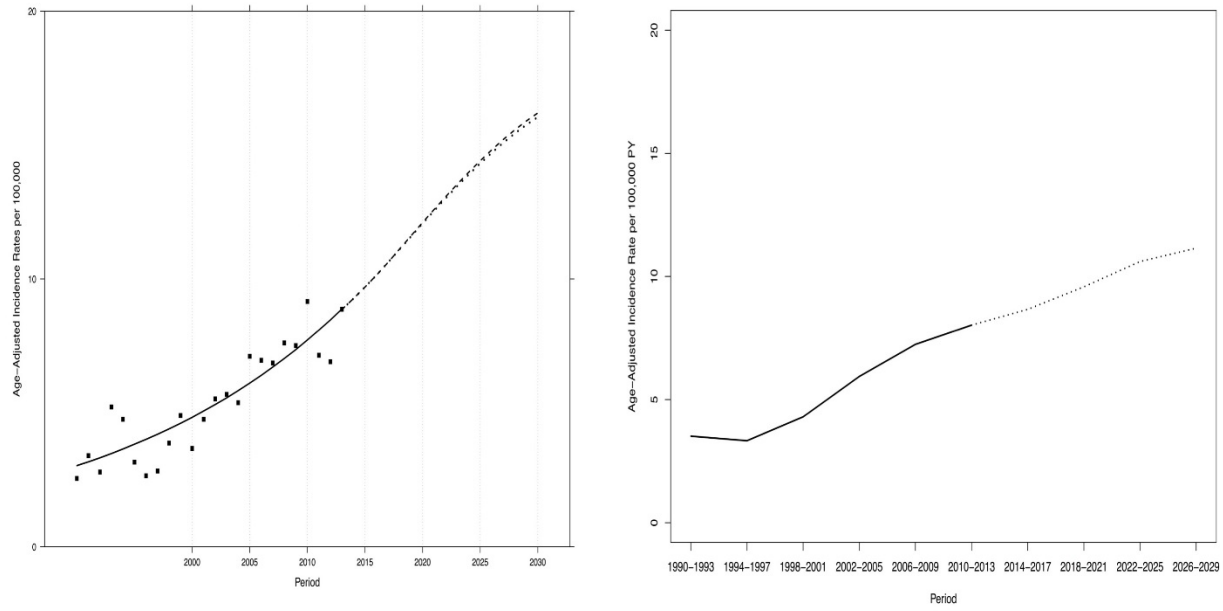

Figure 2.6. Prostate cancer incidence trend projection to 2030. APC method (left) and Nordpred method (right)

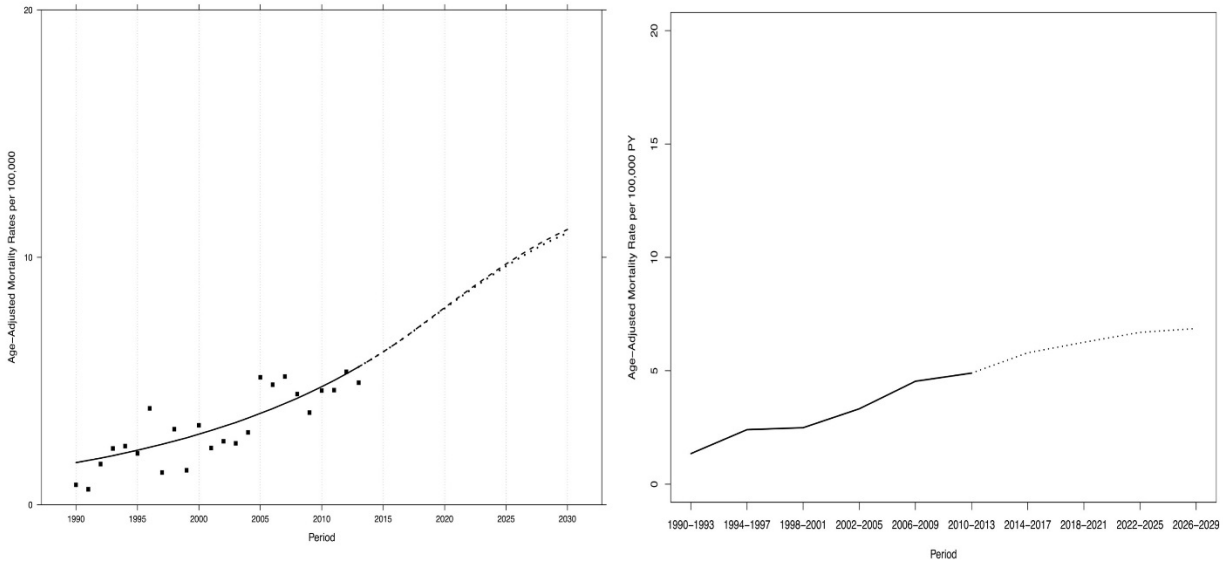

Figure 2.7. Prostate cancer mortality trend projection to 2030. APC method (left) and Nordpred method (right)

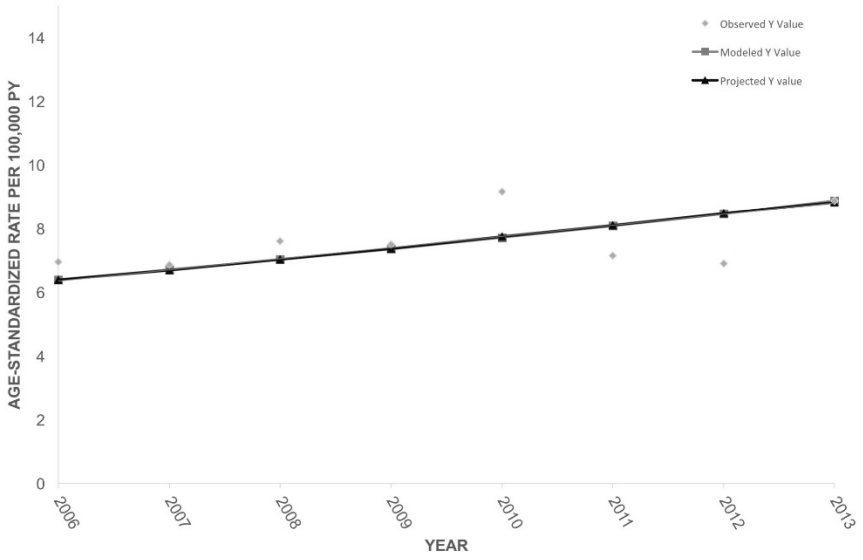

Figure 2.8. Validation of Joinpoint projection model for incidence of prostate cancer in Songkhla, Thailand (2006-2013)

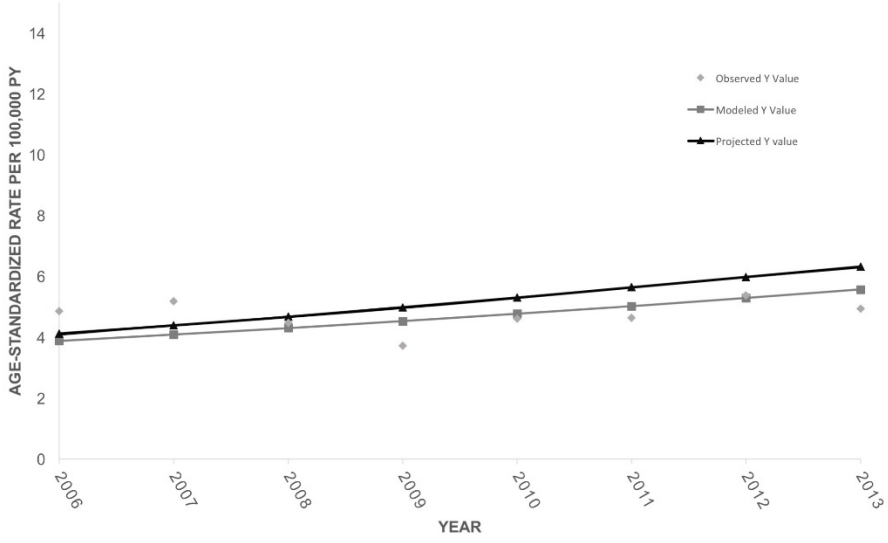

Figure 2.9. Validation of Joinpoint projection model for mortality of prostate cancer in Songkhla, Thailand (2006-2013)

Chapter 3. Differences in Prostate Tumor Characteristics and Survival among Religious Groups in Songkhla, Thailand

Christian S. Alvarez, Eduardo Villamor, Rafael Meza, Laura S. Rozek,
Hutcha Sriplung, Alison M. Mondul

Abstract

Background: The incidence and mortality from prostate cancer is expected to increase in the next decade in Thailand. Despite the perceived lower risk in this population vs. developed, western countries, it is becoming an important public health issue. Prostate cancer incidence varies between the most predominant religious groups in Thailand, Buddhists and Muslims. However limited data is available describing the prostate cancer survival in these two populations. Here we examine differences in prostate tumor characteristics and survival between Buddhists and Muslims in the province of Songkhla, Thailand.

Methods: 945 incident prostate cancer cases (1990-2014) from the population-based Songkhla Cancer Registry were used in this analysis. Age, grade, stage, and year at diagnosis were compared across religious groups, using Wilcoxon or Chi-square tests. Kaplan Meier methods were used to estimate the median survival time and 5-year survival probabilities. Cox proportional hazards models were used to estimate hazard ratios (HR) between religious groups and 95% confidence intervals (CI) for mortality in crude and adjusted models.

Results: Prostate tumor characteristics, age, and year at diagnosis were similar across religious groups. The median survival time after diagnosis of prostate cancer was longer in Buddhists 3.8 years compared with Muslims 3.2 years (p=0.08). The age-adjusted risk of death after prostate cancer diagnosis was higher in Muslims compared with Buddhists (HR: 1.31; 95%CI: 1.00, 1.72). After adjustment by stage and grade, results were slightly attenuated (HR: 1.27, 95%CI: 0.97, 1.67).

Conclusion: Muslims have shorter survival after prostate cancer diagnosis than do Buddhists in Thailand. The reasons underlying this difference require additional investigation in order to design targeted interventions for both populations.

Introduction

Worldwide, the overall burden of prostate cancer has increased substantially over the last three decades, with geographical variation in incidence and mortality.[1–3] The highest incidence rates of prostate cancer are observed in Western, developed countries such as the United States (US), (age-standardized incidence rate (ASR): 98.2 prostate cancer cases per 100,000 person-years).[4] This high incidence can be partially explained by the implementation of population-based screening programs using the prostate-specific antigen (PSA) test in the US population.[5] However, even Western developed countries that do not conduct population-based PSA screening have relatively high incidence rates of prostate cancer (e.g. Canada: 88.9 and the UK: 73.2 prostate cancer cases per 100,000 person-years).[4] On the other hand, incidence rates of prostate cancer are relatively low in non-Western, less developed regions such as South-East Asia (ASR: 5.5 prostate cancer cases per 100,000 person-years).[4]

Despite these current lower rates in South-East Asia, the burden of disease is expected to increase in this region and other low and middle income countries worldwide.[1, 2, 6–8] In Thailand, prostate cancer is the fourth most common diagnosed cancer and the fourth leading cause of cancer death among Thai men.[4] In southern Thailand, incidence and mortality rates of prostate cancer have increased significantly from 1990 to 2013 at an estimated annual percent change of 4.8% and 5.3% respectively.[9] In addition, prostate cancer rates are projected to continue increasing through 2030, doubling the rates observed in 2013.[9]

Unlike the lower incidence rates in Southeast Asia, prostate cancer mortality rates are quite high;[10] the mortality-to-incidence ratio (MIR) in Thailand is 0.51,

compared to more developed countries such as the US (MIR: 0.09).[4, 9] The lower survival rates of prostate cancer in many Asian countries is consistent with the large proportion of prostate cancer diagnosed at advanced stages, mostly due by the lack of population-based PSA screening.[11, 12] However, we cannot rule out other factors, such as genetics, access to care, and sociocultural characteristics of Asian populations that may influence disparities in prostate cancer outcomes not only between- but also within-countries.[13]

Songkhla is a province in southern Thailand, located on the eastern side of the Malay Peninsula.[14] It has 16 districts with a population of 1.5 million inhabitants.[15] The composition of the population in Songkhla is unique because of the diversity in ethnic/religious groups.[14] Approximately, 25% of the people are Muslims and 75% Buddhists. There are documented health disparities between Buddhists and Muslims in Songkhla, Thailand. These differences are thought to be due, in part, to variability in lifestyle factors because of cultural differences between these groups;[16, 17] for example, studies have reported differences in risk of cancer at several sites, including prostate cancer, as well as differences in risk of other chronic conditions and risk factors, such as metabolic syndrome, cardiovascular diseases and diabetes.[17–19] Prostate cancer incidence rates in Muslims are lower compared to Buddhists (ASR: 8.7 prostate cancer cases per 100,000 person-years in Buddhists vs <5 in Muslims).[17] However, to our knowledge, no studies have examined if these differences extend to differential cancer survival between these two religious groups. Therefore, the purpose of our study was to compare the prostate tumor characteristics and the survival time after diagnosis with prostate cancer between Buddhist and Muslim men in Songkhla, Thailand.

Methods

Study population

We extracted incident prostate cancer cases from the Songkhla Cancer Registry (SCR) from 1989 to 2014. A detailed description of this registry has been provided elsewhere.[20, 21] Briefly, the SCR is a population-based cancer registry that has actively collected cancer cases in the Songkhla province since 1989. It captures cancer cases from 23 data sources, including governmental and private hospitals as well as the population registration office.[20, 21] The SCR also collects information on age and year at diagnosis, religion, stage, grade as well as date of last contact, date of death, and vital status. The completeness of case ascertainment is greater than 95%, evaluated by capture-recapture methods.[22] This registry delivers high quality data and has contributed data to the International Agency for Research on Cancer (IARC), Cancer Incidence in Five Continent publications since volume VIII.[23]

Data extraction and variables

The 10th revision of the International Classification of Disease (ICD-10) code for malignant neoplasm of the prostate (C61) was used for the extraction of prostate cancer cases. We restricted our analysis to prostate cancer cases diagnosed after 1989, because we assumed that data was incomplete during the first year of registration. In total, 945 prostate cancer cases were diagnosed between January 1, 1990 and December 31, 2014. We further excluded four prostate cancer cases because of missing information on religion.

Religious group (Buddhist or Muslim) is routinely collected in the SCR. Age at diagnosis is recorded as continuous variable (in years). We categorized grade as moderately/poorly differentiated, undifferentiated, or unknown; and stage as localized/regional, distant and unknown. Year at diagnosis was categorized in 5-year groups (e.g. 1990-1994, 1995-1999, 2000-2004, 2005-2009 and 2010-2014). In addition, vital status is recorded as dead or alive. Deaths are only ascertained for cancer cases included in the registry by hospital records, and they represent all-cause mortality, not prostate cancer-specific mortality.

Statistical Analysis.

Age at diagnosis and prostate tumor characteristics such as grade and stage, as well as year at diagnosis were compared between Buddhists and Muslims. We used the Wilcoxon test to compare median age at diagnosis between the two religious groups, as age was not normally distributed. The chi-squared test was used to compare the distribution of prostate cancer cases by grade, stage and year at diagnosis in Buddhists and Muslims. All tests were considered statistically significant at $p<0.05$.

The main outcome of interest was survival time, defined as the number of years between date of diagnosis and either date of death or date of last contact. Median survival time as well as 5-year survival probability of prostate cancer were estimated using the Kaplan-Meier method, and differences by religious group were assessed using the log-rank test. Kaplan-Meier survival curves of prostate cancer were obtained for the overall study population and stratified by religious group. To confirm the proportional hazard assumption, we examined Kaplan-Meier plot of survival (S) versus

time (T) and log (-log(S)) versus log (T) for Buddhists and Muslims, finding that there was no evidence of violation of the proportional hazard assumption from visual inspection of the survival functions for exposure groups. Further, we included an interaction term between religious group and follow-up time and evaluated its significance using the Wald test; this variable was not statistically significant (p=0.76).

Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for mortality. The main exposure considered was religious group as recorded in the registry (Buddhist or Muslim). Models were compared with and without using the following covariates in the model: age, and tumor grade and stage. In addition, we assessed for interaction between religious group and age, grade and stage using product terms. All statistical analyses were conducted in SAS software v 9.4 (SAS Institute, Cary NC).

Sensitivity Analysis.

Because of the large number of unstaged and ungraded tumors (78.9% and 46.9%, respectively), we conducted a multiple imputation analysis to impute stage and grade for those missing this information, including age, religion, follow-up time and vital status to predict the missing data. We used the PROC MI statement in SAS to conduct the multiple imputation. We obtained parameter estimates from the multivariable-adjusted Cox proportional hazards regression models for 100 imputed datasets. The parameter estimates were combined for inference using PROC MIANALYZE statement in SAS. We assumed that data were missing completely at random.

To evaluate the effect of period pre- and post-introduction of the universal health coverage by the Thai National Health Office in the early 2000s we examined the religious group-specific median survival time, 12-months, 2- and 5-year survival probabilities, partitioning follow up time as follows: 1990-1999, 2000-2004, 2005-2009 and 2010-2014. Finally, to more tightly control for age and calendar year, we conducted sensitivity analyses using age and calendar year as the time scale in our models.

Results

Of the 945 prostate cancer cases, 89.2% were Buddhists and the rest Muslims, with a median age at diagnosis of 74 (Interquartile range (IQR)=67, 79) and 72 (IQR=68, 77) respectively (Table 3.1). Of tumors with known grade at diagnosis the majority were moderately/poorly differentiated. Similarly, among tumors with known stage at diagnosis, the majority were distant. In addition, Muslims seem to have a slightly higher proportion of undifferentiated and distant tumors compared to Buddhists. On the other hand, the proportion of ungraded and unstaged tumors is slightly higher in Buddhists compared to Muslims. Furthermore, more than 80% of the cases have been diagnosed since the year 2000 when universal health coverage was introduced in Thailand. We observed no statistically significant differences by religious group for any of the variables examined (Table 3.1).

The overall median survival time after diagnosis of prostate cancer was 3.7 years (95%CI: 3.4, 4.2), and the overall 5-year survival probability was 40.6% (95%CI: 37.0%, 44.2%) (Figure 3.1). Despite the small number of Muslim prostate cancer cases (n=98),

we found a borderline significant difference in prostate cancer survival between Buddhists and Muslims (log-rank test, p=0.08). The median survival time was longer in Buddhists 3.8 years (95%CI: 3.4, 4.3) compared to Muslims 3.2 years (95%CI: 2.0, 4.4) (Figure 3.2, and Table 3.2). Similarly, Buddhists have a higher 5-year survival probability of prostate cancer than Muslims, 41.3% (95%CI: 37.4%, 45.0%) vs 34.7% (95%CI: 23.8, 45.8%), respectively (Table 3.2).

We next estimated differences in survival after diagnosis between religious groups. After adjustment for age at diagnosis, Muslim men were more likely to die post-diagnosis with prostate cancer compared to Buddhist men (HR: 1.31, 95%CI: 1.00, 1.72; p=0.04). This finding was only slightly attenuated after further adjustment for stage and grade at diagnosis (HR: 1.27, 95%CI: 0.97, 1.67; p=0.06). There was no evidence of statistically significant interactions between religious group and age (p=0.64), grade (p=0.22) or stage at diagnosis (p=0.29). In addition, our multiple imputation analysis from 100 imputed datasets yielded similar results for the multivariable-adjusted Cox regression model, the estimated HR for death in Muslims vs Buddhists was 1.28 (95%CI: 0.97, 1.66). Furthermore, the overall stage distribution and by religious groups remain similar after multiple imputation (Table 3.3).

Estimates from the overall median survival time (years) by period after partitioning follow-up time show that although overall, there are modest increases in the median survival time and 12-months, 2- and 5-years survival probabilities pre- and post-introduction of universal health access, these increases appear limited to Buddhist men. The 1-year survival probability increases from 77.9% in 1990-1999 to 83.6% in 2010-2014 in Buddhists. On the other hand, among Muslims the 1-year survival probability

remained unchanged during 1990-1999: 75.0% and 2010-2014: 75.5% (Table 3.4). Finally, the three methods used to account for time (number of years, calendar time, and age) yielded similar results in both the age adjusted and fully adjusted models (Table 3.5).

Discussion

We compared prostate cancer characteristics and survival after diagnosis between Muslim and Buddhist men in Songkhla Thailand. We found that Muslim men had a higher risk of death after diagnosis of prostate cancer compared to Buddhists, finding which was not fully explained by differences in tumor characteristics at diagnosis. However, the large number of unstaged and ungraded tumors in both groups does not allow for complete adjustment for these factors even when imputation was used to attempt to assign stage and grade to those with missing information. Differences in the distribution of tumor characteristics among those with missing information by religious groups might still explain the observed survival differences.

Our findings are consistent with those from several published studies that suggest that Muslim populations have poorer cancer survival after diagnosis compared to other ethnic and religious groups.[23–28] In Songkhla, Thailand, lower survival rates for oral, breast and cervical cancer have been observed among Muslims compared to Buddhists.[24] Another study conducted in Asian populations found that breast cancer survival is higher among Indian (54%) and Chinese (49%) women compared to Malay women (45%), which is a predominantly Muslim population.[25] In addition, Malay women

are more likely to be diagnosed at advanced stages of breast cancer than other ethnic/religious groups.[26] It should be noted that the Muslims in Songkhla, Thailand are predominantly of Malay descent. Similarly, a study conducted in Northern Israel found that Arab women are more likely to be diagnosed at advanced stage for breast cancer, and with more aggressive disease compared to their Jewish counterparts, likely due to differences in genetic susceptibility as well as socioeconomic factors.[27] In the US, a prostate cancer survival study found that risk of death after diagnosis of the disease is 40% higher among South Asian men compared to Whites.[29]

It remains unclear why Muslims may experience poorer cancer outcomes. In Thailand, access to healthcare is relatively consistent across the country, and there are ongoing efforts to integrate Muslims in Songkhla into communities along with Buddhists. The Thai government has established policies for cultural assimilation of minority religious groups (e.g. promotion of Thai language and identity). However, there has been resistance to these policies, and cultural differences do persist. For example, some Muslims in southern Thailand speak Yawi (a Malay dialect) as their first language, creating barriers to communicating with healthcare providers who largely speak Thai.[24] In addition, cultural beliefs could be an important barrier for individuals to seek and/or receive healthcare.[30] This may cause delay in diagnosis and treatment for cancer. For example, one study found that Thai Muslims experienced delays in the time from diagnosis to treatment for oral cancer compared to Buddhists, which the authors concluded was likely due to differences in health attitudes, among Muslims in Thailand.[31, 32] Another study that evaluated knowledge and health belief attitudes for oral cancer among Thai Muslims found that they are more likely to use traditional

medicine to prevent and treat oral cancer, even if diagnosis of oral cancer was confirmed in a hospital setting.[32]

Several studies have reported that the perspectives of sickness and death among Muslims are different than other religious groups.[33] In some studies about health attitudes and knowledge, Muslims have reported a perception of sickness as a God's proof of their faithfulness.[34] This belief may lead individuals to delay seeking medical care for their cancer, which may partially explain the poorer survival from prostate cancer among Muslim men in Songkhla. Anecdotal evidence from physicians practicing in Songkhla, Thailand suggests that Muslims may be less likely to accept treatment after a diagnosis with cancer, despite having equal access to high quality care. Supporting this, our findings have shown that survival has not improved among Muslims after the introduction of universal health care. Although, reports from a recent WHO report (CONCORD-3) show that prostate cancer survival in Thailand appear to increase by 10% from 1995 to 2014.[35] In addition, the risk of death after prostate cancer diagnosis appear to increase in Muslims compared to Buddhists after the introduction of the universal healthcare access, e.g. 1990-1999 HR: 0.96, 95%CI: 0.21, 4.19; 2010-2014 HR: 1.52, 95%CI: 1.00, 2.30 (Table 3.6). However, this increase is not statistically significant and the number of deaths were small for the earliest period. Further research is warranted to identify what factors may play a role in the increased risk of death among Muslim men diagnosed with prostate cancer in Thailand and whether similar disparities in cancer survival exist for other cancer sites or chronic conditions.

Strengths and Limitations.

Our findings are based on a high quality population-based cancer registry, which allows us to extrapolate the results to the province of Songkhla and the rest of southern Thailand; in addition the completeness of follow up for this cancer registry is very high (>95%).[22] Another strength is that the SCR consistently collects information on religious groups that allows us to conduct this type of analysis and identify patterns of the disease in specific groups.

An important limitation of this study is that deaths are not prostate cancer-specific mortality as SCR only collects information on all-cause mortality. This might bias our results by overestimating the prostate cancer deaths. We could have used data from death certificates from the Thai Ministry of Health to identify prostate cancer specific deaths. However, the quality of death certificates is poor in Thailand.[36] Another limitation of this study is that the number of undetected cases are unknown due to distant communities that may have poor access to health centers, but the capture rate for prostate cancer in Songkhla has been very high. One more limitation is that complete adjustment for stage and grade was not possible because of the large number of unknowns. To address this limitation we conducted sensitivity analyses where we imputed missing stage and grade. The multiple imputation analysis showed similar results for the risk of death between Buddhists and Muslims.

Conclusions.

Muslim men had a higher risk of death after diagnosis of prostate cancer compared to Buddhist men. In contrast with Buddhists, prostate cancer survival has

remained constant in Muslims even after the introduction of universal health care access. It is important to understand what risk factors may underlie the poorer survival observed in Muslims to design targeted interventions in both populations.

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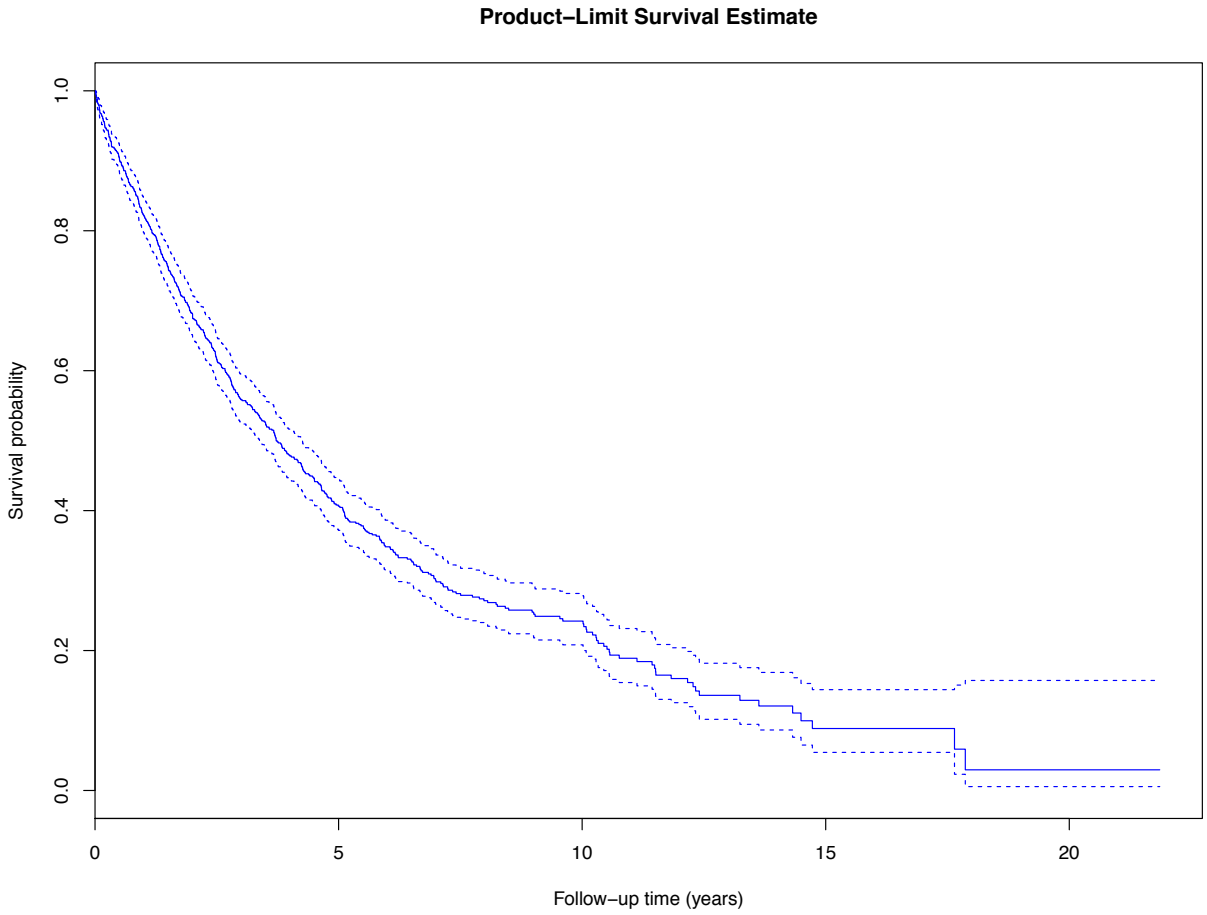
Table 3.1. Demographic and prostate tumor characteristics among religious groups in Songkhla, Thailand

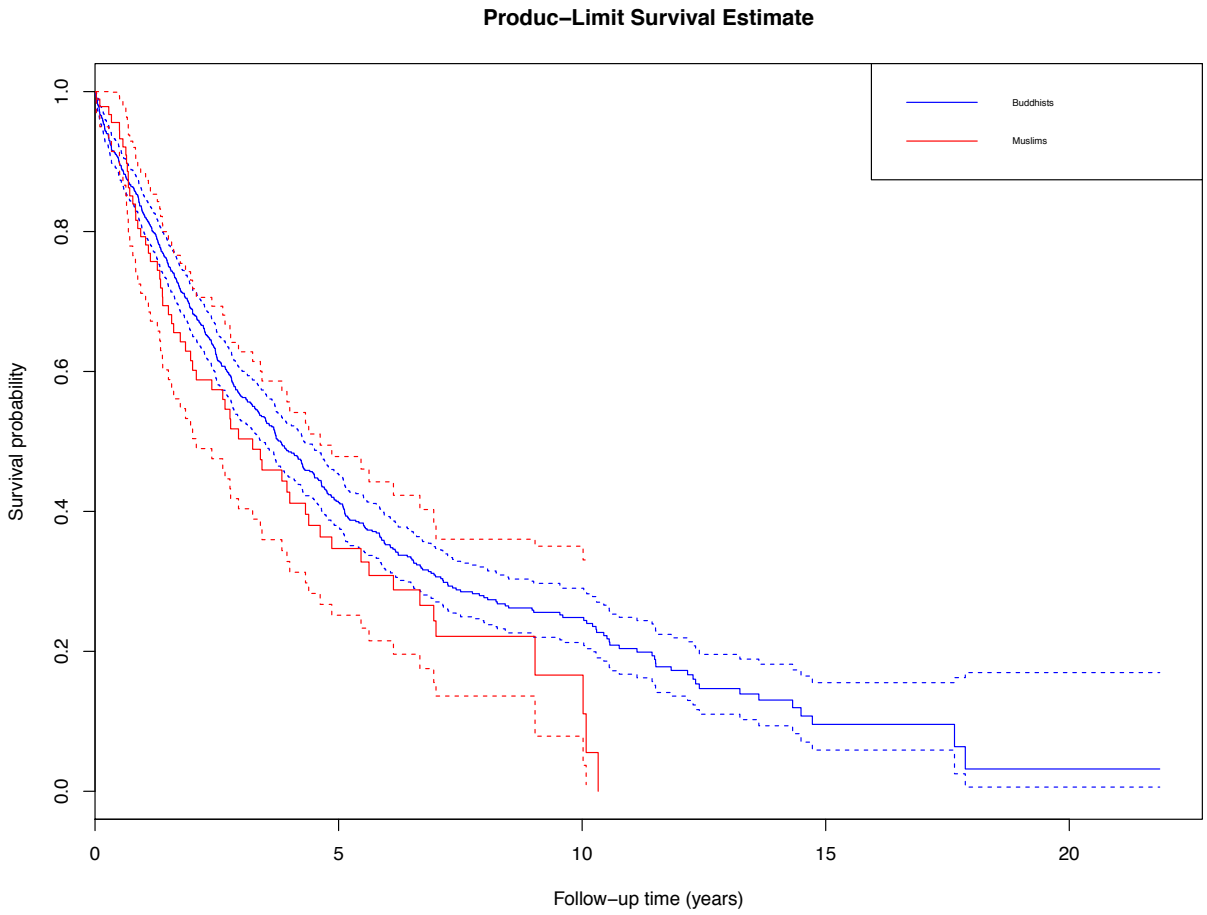
Characteristic	Total N=945 n (%) or Median (Q1-Q3)	Religion		
		Buddhists N=843 n (%) or Median (Q1-Q3)	Muslims N=98 n (%) or Median (Q1-Q3)	p-value
Age	73 (67,79)	74 (67,79)	72 (68, 77)	0.3836
Grade				
Well differentiated	186 (19.7%)	163 (19.3%)	23 (23.5%)	0.6466
Moderately/Poorly differentiated	247 (26.1%)	221 (26.2%)	26 (26.5%)	
Undifferentiated	69 (7.3%)	60 (7.1%)	9 (9.2%)	
Unknown	443 (46.9%)	399 (47.3%)	40 (40.8%)	
Stage				
Localized/Regional	50 (5.3%)	42 (5.0%)	8 (8.2%)	0.3514
Distant	149 (15.8%)	132 (15.7%)	17 (17.4%)	
Unknown	746 (78.9%)	669 (79.4%)	73 (74.5%)	
Year of diagnosis				
1990-1999	177 (18.7%)	155 (18.4%)	21 (21.4%)	0.7512
2000-2004	147 (15.6%)	133 (15.8%)	14 (14.3%)	
2005-2009	264 (27.9%)	237 (28.1%)	25 (25.5%)	
2010-2014	357 (37.8%)	318 (37.7%)	38 (38.8%)	

Figure 3.1. Kaplan-Meier survival curve of prostate cancer in Songkhla, Thailand



Overall median survival time: 3.7 (95%CI: 3.4, 4.2)
Overall probability surviving after 5 years: 40.6% (95%CI: 37.0%, 44.2%)

Figure 3.2. Kaplan Meier survival curves of prostate cancer by religious group in Songkhla, Thailand



Log-rank p value: 0.0840

Table 3.2. Survival probabilities and hazard ratios for death of prostate cancer by religious group in Songkhla, Thailand

Religious group	Deaths	Person-years	Median survival time In years (95%CI)	5-year survival probability (95%CI)	Model 1	Model 2
					HR (95%CI)	HR (95%CI)
Buddhists	520	3020.4	3.8 (3.4, 4.3)	41.3% (37.4%, 45.0%)	1.0 (ref)	1.0 (ref)
Muslims	62	279.4	3.2 (2.0, 4.4)	34.7% (23.8%, 45.8%)	1.31 (1.00, 1.72)	1.27 (0.97, 1.67)

Model 1: Adjusted by age
Model 2: Adjusted by age, grade and stage

Table 3.3. Overall stage distribution and by religious groups comparing observed vs imputed data

Stage	Observed data*			Imputed data (MI=100)**		
	Total	**Buddhists**	**Muslims**	**Total**	**Buddhists**	**Muslims**
Localized	7 (3.5%)	7 (4.7%)	0 (0.0%)	4158 (4.4%)	4725 (5.0%)	0 (0%)
Regional	43 (21.6%)	9 (6.1%)	8 (32.0%)	22114 (23.4%)	21263 (22.5%)	29012 (30.7%)
Distant	149 (74.9%)	132 (89.2%)	17 (68.0%)	68229 (72.2%)	68513 (72.5%)	65489 (69.3%)

*Total missing (unknown stage)=746
**100 imputed datasets, n=945 in each dataset

Table 3.4. Median survival time (years) by period after partitioning follow up time by religious group

	Buddhists				**Muslims**			
Period	**Median survival time (y)**	**12-month survival prob.**	**2-year survival prob.**	**5-year survival prob.**	**Median survival time (y)**	**12-month survival prob.**	**2-year survival prob**	**5-year survival prob**
1990-1999	3.0	77.9%	61.0%	30.5%	6.1	75.0%	*	*
2000-2004	4.3	86.2%	71.6%	43.2%	3.1	74.7%	56.1%	30%
2005-2009	3.8	78.9%	65.4%	42.2%	3.4	76.3%	61.8%	21.8%
2010-2014	4.4	83.6%	71.6%	45.1%	2.6	75.5%	58.2%	*

*Unable to calculate.

Table 3.5. Hazard ratios for death of prostate cancer using 3 different methods to account for time: person-years, calendar period and age

Religious group	Model 1:			Model 2:		
	Person-years	Calendar period	Age	Person-years	Calendar period	Age
	HR (95%CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Buddhists	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Muslims	1.31 (1.00, 1.72)	1.27 (0.97, 1.66)	1.31 (1.00, 1.72)	1.27 (0.97, 1.67)	1.24 (0.94, 1.63)	1.25 (0.95, 1.64)

Table 3.6. Hazard ratios for death of prostate cancer by religious groups after partitioning follow up time

Period	Deaths	Person-years	Model 1 HR (95% CI) Muslims vs Buddhists	Model 2 HR (95% CI) Muslims vs Buddhists
1990-1999	86	382.4	1.05 (95%CI: 0.25, 4.51)	0.96 (95%CI: 0.21, 4.19)
2000-2004	81	476.6	1.29 (95%CI: 0.66, 2.50)	1.26 (95%CI: 0.64, 2.51)
2005-2009	170	837.1	1.26 (95%CI: 0.77, 2.06)	1.09 (95%CI: 0.66, 1.82)
2010-2014	234	1380.49	1.55 (95%CI: 1.03, 2.34)	1.52 (95%CI: 1.00, 2.30)

Chapter 4. The potential impact of a population-based screening program on the increased burden of prostate cancer in Thailand: A simulation study

Christian S. Alvarez, Alison M. Mondul, Laura S. Rozek, Hutcha Sriplung, Rafael Meza, Jihyoun Jeon

Abstract

Background: Prostate cancer incidence and mortality are expected to increase considerably in the next decade in Thailand. There is thus an urgent need to establish prevention measures, such as screening to reduce the increasing burden of prostate cancer in the country. Currently there are no official guidelines or recommendations for prostate cancer screening in the Thai population. Here we conducted a simulation analysis to assess the potential impact of screening on the incidence and mortality of prostate cancer in the southern province of Songkhla, Thailand.

Methods: The target population was Thai males from Songkhla born in 1960, and they were followed-up from ages 50 to 70. Data for this simulation analysis was drawn from several sources including the Songkhla Cancer Registry and the census data from Thailand. We assumed 4 different scenarios for the Prostate-specific antigen (PSA) test and the Digital Rectal Examination (DRE) screening, including no screening, 15%, 60% and 100% uptake rates. The number of prostate cancer cases were projected using a population model of cancer incidence adjusted for incidence trends by year, and we accounted for the excess of cases under screening scenario by

incorporating estimates from the European Randomized Study of Screening for Prostate Cancer (ERSPC). In addition, deaths from prostate cancer were projected using survival probabilities from Songkhla and the United States.

Results: The model projects that the incidence of prostate cancer for the 1960 birth-cohort would increase from 88,000 to 150,000 cases per 1,000 (with mostly localized disease), and mortality would decrease from 37,000 to 24,000 deaths per 1,000, under 100% PSA screening uptake . Furthermore, our model projects a 28% reduction in the number of prostate cancer deaths at age 70, under 100% PSA screening (case fatality ratio [CFR]=0.16), and 21% decrease with 100% DRE screening uptake (CFR=0.29). In addition, 13,000 deaths per 1,000 could be prevented with 100% PSA screening, and 9,000 deaths per 1000 under 100% DRE screening uptake.

Conclusion: Screening for prostate cancer could substantially reduce the large proportion of advanced disease in Thailand. In addition, it would decrease the number of prostate cancer deaths, contributing to reduce the escalating burden of the disease in the Thai population. However, our results depend on the assumed survival rates under screening, which could vary depending on the quality of the implementation.

Introduction

Prostate cancer is emerging as a significant public health problem in many developing countries.[1–4] In Thailand, there has been a significant increase in the incidence and mortality rates of prostate cancer over the last few decades,[4–6] with a large proportion of prostate cancer cases diagnosed at advanced stages. In Songkhla, approximately 75% of staged tumors are stage IV at diagnosis.[6] In contrast, in the United States (US), the vast majority of prostate cancer cases are diagnosed at early stages (79% localized),[7] which is partially explained by the widespread use of the prostate-specific antigen (PSA) test for prostate cancer screening in the US population.[8]

Screening for prostate cancer is controversial as it leads to a considerable increase in incidence while the benefit for prostate-specific mortality remains unclear.[9, 10] Two major randomized clinical trials have been conducted to assess the effectiveness of PSA screening in the reduction of prostate cancer mortality and have reported conflicting results.[11, 12] The European Randomized Study of Screening for Prostate Cancer (ERSPC) conducted in several European countries showed a statistically significant reduction in prostate cancer mortality of 21% (Rate ratio [RR]: 0.79; 95%CI: 0.69, 0.91) among men who underwent PSA screening after 13-years of follow-up.[12] On the other hand, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the US showed no reduction of prostate cancer mortality among men who screened during the same follow-up period (RR: 1.09; 95%CI: 0.87, 1.36).[13] To our knowledge no randomized trial has been conducted assessing the effectiveness of DRE as a prostate cancer screening test, although it remains widely used in clinical practice. Importantly, PSA screening is associated with potential harms as a result of

overdiagnosis and subsequent overtreatment, that leads to adverse effects, particularly in older men.[10–12, 14]

Currently, there is no population-based screening program for prostate cancer in Thailand, where the burden of the disease is expected to continue to rise.[6] Therefore, assessing the impact of screening strategies for the control of prostate cancer is necessary in this country. We, therefore, conducted a simulation analysis to evaluate the potential impact of screening, using either the PSA test or the DRE on the incidence and mortality of prostate cancer, while taking into account the potential for overdiagnosis.

Methods

Data sources:

Incident prostate cancer cases from the Songkhla Cancer Registry (SCR) and census data from the National Statistical Office of Thailand were used in this analysis. The Songkhla Cancer Registry collects information on age, year of diagnosis, religion, stage, and grade, as well as the date of last contact, date of death, and vital status. A total of 945 prostate cancer cases were diagnosed in Songkhla, Thailand between 1990 and 2014, and 61.9% of these cases died during the same period. We obtained population denominators from decennial census data in 1990, 2000 and 2010. The annual intercensal population structure in Songkhla was obtained by 1-year sex-specific group. The population beyond 2010 was estimated by the Thai Office of the National Economic and Social Development Board.[6] Our simulation analysis included population data from Songkhla males up to 2030.

Assumptions:

We assigned the number of screened and unscreened individuals in the Songkhla male population who were born in 1960 (ages 50 to 70 years old), assuming the following screening uptake rates: 100%, 60%, and 15%. The last two screening scenarios are based on reports of prevalence of PSA screening in the US and other Asian countries. In 2010, the Behavioral Risk Factor Surveillance System (BRFSS), a nationally representative survey on health-related risk behaviors and use of preventive services in the US,[15] reported that approximately 60% of US males aged 50 years and older had undergone PSA screening for prostate cancer in the past 2 years.[15] On the other hand, a Japanese study reported a PSA screening prevalence of 12% in males aged 55-69 from Kanazawa city in 2010.[16] We compared the results based on those screening scenarios with no screening. Our simulation study was done separately by screening modality: PSA and DRE.

Our target population was males from Songkhla born in 1960. We followed this cohort from ages 50 to 70, which spans years 2010-2030. We started at age 50 because of the recommendations in existing prostate cancer screening guidelines, such as, the Japanese Urologic Association (50 years and older), the PLCO trial (50 to 74 years), the ERSPC trial (55 to 74 years), and the US Preventive Service Task Force (USPSTF) (55 to 69). On the other hand, the USPSTF recommends against the use of PSA screening for prostate cancer in men aged 70 and older.[14]

Model overview:

Projections of prostate cancer:

To project the number of prostate cancer cases under different screening scenarios, first we used the population rates of prostate cancer in Songkhla. The prostate cancer rates were modified to account for the excess of cases among PSA or DRE screened population. Therefore, the prostate cancer rates were multiplied in our baseline scenario by 1.71, which reflects the 71% excess of cases under PSA screening observed in the ERSPC trial;[12] and 1.10 to account a 10% excess of cases for DRE screening, which we assumed occurred pre-PSA era. The prostate cancer rates were computed by age and period using the previously developed age-period-cohort model using prostate cancer incidence data in Songkhla Cancer Registry:[6] For age a and calendar year p, the prostate cancer incidence rate is computed by

$$C_{(a,p)} = K \times \beta_a \times \beta_p \times N_{(a,p)},$$

where β_a and β_p are the age effect coefficient and the period effect coefficient, and $N_{(a,p)}$ is the number of population at age a and calendar year p. K is an adjusting factor related to screening, which set as 1.71 under PSA screening, 1.10 under DRE, and 1 otherwise (no screening).

For the stage distribution of prostate cancer cases among the screened population in the simulation, we applied the stage distribution of prostate cancer observed in the US in 2010 to our cases under the PSA screening scenario; on the other hand, we applied the stage distribution of prostate cancer diagnosed in the US in the pre-PSA era (1985) to our cases under the DRE screening scenario. For the distribution of prostate cancer cases under the no screening scenario, we used the

stage distribution from Songkhla. The stages of prostate cancer were classified as: localized, regional, and distant. We used SEER data from 9 registries (1973-2014) to obtain the stage distribution from the US.

Projection of prostate cancer deaths:

To project the number of prostate cancer deaths under different screening scenarios, we first fit Weibull survival models to obtain annual survival probabilities by tumor stage (localized, regional, and distant) from the Songkhla Cancer Registry data. We then used the Weibull survival models to project the number of prostate cancer deaths among unscreened cases. Because of the large number of unstaged tumors in the Songkhla Cancer Registry, we used a multiple imputation analysis with chained equations to impute the missing information.[17] Two parameters were obtained from the Weibull survival model: scale and shape (or slope).[18] The model adequacy was assessed by inspecting empirical-based Kaplan-Meier curves models (Figure 4.1).

To project deaths from the screen-detected prostate cancer cases, we used the survival probabilities from SEER 9 registries for US men aged 50 and older from 1990 to 2014, representing the survival probabilities during the PSA era. Those survival probabilities were applied to PSA to account for the benefit of screening, assuming that the quality of care would be similar to that received by men in the US. In addition, there is limited information on survival probabilities in the context of DRE in SEER, therefore we used the annual survival probabilities from Songkhla to project deaths from screen-detected prostate cancer cases under DRE.

The total number of deaths from prostate cancer between age 50 and n for the 1960 birth cohort is calculated by

$$\sum_{j}\sum_{a=50}^{n}\sum_{i=a}^{n} C^{j}_{(a,p)} \times S^{j}_{i-a} \times (S^{j}_{i-a} - S^{j}_{i-a+1}),$$

where j corresponds to the tumor stage (localized, regional, and distant), C(a,p) is the number of prostate cancer cases at age a and calendar year p, and S_t corresponds to the survival probability at time t. R statistical software was used for this analysis.

We computed case fatality ratios (CFR) to estimate the overall impact of prostate cancer screening on deaths across screening scenarios. The CFR was calculated by dividing the total number of deaths by the total number of prostate cancer cases in the 1960 birth cohort. In order to take into account overdiagnosis in the CFR calculations, we removed either 23% (lower bound) or 42% (upper bound) of prostate cancer cases that were screen-detected, because this range corresponds to the overdiagnosis rates observed in the US during the PSA era.[19]

Finally, our projections were multiplied by 1,000 cases because of the small number in the birth cohort. Figures 4.2 and 4.3 show the flowcharts for the procedures used in this simulation analysis for PSA and DRE, respectively.

Results

Figure 4.4 illustrates the stage distribution of prostate cancer cases under different screening scenarios with PSA (left) and DRE (right) in our modeled cohort. There is a shift in the stage distribution of prostate cancer towards more localized

stages, particularly under 100% and 60% uptake rates. This reflects the difference in the assumed stage distribution between the no screening (Songkhla) and the screening (SEER) scenarios. In total, we projected 125,000 cases per 1,000 with localized disease and only 5,000 cases per 1,000 with distant stage under 100% PSA screening uptake. On the other hand, with no screening we projected 3,000 cases per 1,000 with localized disease and 70,000 cases per 1,000 with distant stage. Similar patterns in the stage distribution for prostate cancer as a function of screening coverage are observed with the DRE screening strategy.

Impact of screening on prostate cancer incidence

The incidence of prostate cancer increases by age in our modeled cohort. Under the model assumptions, at age 70, we projected approximately 9,600 cases per 1,000 in excess under 100% PSA screening compared to no screening (Figure 4.5, top). In contrast we expect only 1,300 cases per 1,000 in excess under 100% DRE screening compared to no screening at the same age (Figure 4.5, bottom).

Figure 4.6 shows the number of prostate cancer cases by stage under PSA and DRE screening scenarios with different uptake rates. At age 70, we projected between 3,000 to 19,000 more prostate cancer cases diagnosed at localized stage under 15% and 100% uptake rates of PSA, respectively. On the contrary, we expect from 1,300 to 9,000 more prostate cancer cases under the same screening scenarios with DRE. Furthermore, the model projects a large number of cases diagnosed at distant stage under no screening compared to any of our modeled screening scenarios over the follow-up time for both screening modalities. Moreover, at age 70, there would be 8,600

and 7,800 fewer cases with distant stage under 100% PSA and DRE screening uptakes, respectively.

Impact of screening on prostate cancer mortality

Overall, under the model assumptions the number of deaths decreases with higher PSA (Figure 4.7, top) and DRE (Figure 4.7, bottom) uptake. At age 70, we project that the number of deaths would decrease approximately 28% under 100% PSA screening uptake, and 16% under 60% PSA screening uptake (a more realistic scenario). On the other hand, the reduction in the number of deaths is slightly lower in DRE compared to PSA at age 70 (e.g. 21% and 13%, under 100% and 60% DRE screening uptakes).

In addition, the model projects that the number of total deaths that could be prevented in our cohort with 100% PSA screening is 12,683 per 1,000, and the total number of deaths that could be prevented under 60% PSA screening is 7,600 per 1,000. Similarly, we expect 8,800 deaths per 1,000 that could be prevented under 100% DRE screening scenario, and 5,300 deaths averted under 60% DRE screening scenario. Table 4.1 shows the case fatality ratios (CFRs) for the different scenarios of PSA and DRE screening. We observed that the CFR decreases from 0.42 (with no screening) to 0.23 and 0.16 with 60% and 100% PSA screening uptakes, respectively. Similarly, the CFR decreases from 0.42 (under no screening) to 0.34 and 0.29 with 60% and 100% DRE screening uptakes, respectively. In addition, table 4.2 shows the CFRs with and without adjustments for overdiagnosis (23% and 42%). In overall, we observe that CFR is lower if overdiagnosis is not taken into account. For example, under 100%

PSA screening uptake, the adjusted CFR is 0.16, in contrast to 0.12 and 0.09 without adjustment for 23% and 42% overdiagnosis, respectively. In a similar manner, under 100% DRE screening scenario, the adjusted CFR is 0.29, compared to 0.22 and 0.17 without adjustment for 23% and 42% overdiagnosis (Table 4.2).

Discussion

Our simulations suggest that the incidence of prostate cancer would increase from 88,000 to 150,000 cases per 1,000, and mortality would decrease from 37,000 to 24,000 deaths per 1,000 under 100% coverage PSA scenario in the Songkhla 1960 birth-cohort. As expected per our assumptions, screening would shift the stage distribution of prostate cancer at diagnosis towards earlier stages, with an increase from 3,300 to 75,000 localized cases per 1,000 when going from the no screening to the 60% PSA screening scenarios.

In the US, the proportion of men diagnosed at localized disease increased from 30% to 42% during the earliest period of the PSA era, and the rate of advanced prostate cancer decreased by 75% between 1989-1992 to 1999-2002.[20] Similarly, a Japanese study reported that the proportion of metastatic disease decreased with increasing use of PSA screening in a population-based screening cohort.[16] They observed a 10% reduction in metastatic disease by increasing exposure rate for PSA screening from lesser or equal than 10% to more or equal than 30.1%.[21] A clear benefit of prostate cancer screening is to diagnose cases at early stages when treatment may be more effective, and thus potentially reduce mortality. However, the benefit of detecting more localized disease

must be weighed against the risk of harm related to overdiagnosis and, thus, unnecessary follow-up and treatment for some men diagnosed with prostate cancer.[9, 14, 22, 23]

Under the screening scenarios, we expect an excess in the number of prostate cancer cases, which are likely to be overdiagnosed and/or overtreated. This would create an unnecessary burden not only in the patients but also in the Thai healthcare system. Overdiagnosis is defined as screen-detected cancer that would not have been clinically diagnosed during a patient's lifetime in the absence of screening (i.e. indolent disease).[24] Therefore, it is an important issue in the control of prostate cancer because it increases the risk of harm to those patients that do not benefit from having their cancer detected by screening.[24] They receive unnecessary follow up (biopsies) and treatment for their cancers that cause harm.[24] For example, studies have reported that men who receive prostatectomy (the most common treatment for early cases of prostate cancer) experience up to 80% and 25% of erectile dysfunction and urinary incontinence, respectively.[25, 26] In the US, a recent report showed that the proportion of screen-detected prostate cancers that were overdiagnosed during the time of the introduction of PSA screening was between 23% and 42%, according to modeling studies.[24]

On the other hand, we expect 53,367 less cases in excess with DRE compared to PSA. In the US, studies have reported that abnormal findings with DRE is associated with the detection of more clinically significant prostate cancer cases (e.g. high grade disease).[27, 28] However, it is not recommend as a primary screening test for prostate cancer because there is a lack of evidence from randomized controlled trials supporting its effectiveness in reducing prostate mortality.[27]

According to our analysis, and our assumptions of excess incidence, stage-shift and prostate cancer survival under screening, the number of prostate cancer deaths would be reduced with either PSA or DRE screening. The model projects a reduction of 28% under 100% PSA screening uptake at age 70. Similarly, the CFR decreases considerable for no screening vs 100% PSA screening (0.42 vs 0.16). This is consistent with the reduction in prostate cancer mortality observed in the ERSPC trial at 13 years of follow up (Mortality RR: 0.79 [95%CI: 0.69, 0.91]).[12] On the other hand, no mortality reduction was observed in the PLCO trial (Mortality RR: (1.09 [95%CI: 0.87, 1.36]), which has called into question the efficacy of screening on the survival of prostate cancer.[13] Several studies have concluded that the use of PSA screening prior to randomization, contamination (subjects in the control arm who received screening), and non-compliance limited the ability to demonstrate the efficacy of screening in the PLCO trial.[10, 22, 29–33] Similarly, a recent randomized trial (the Cluster Randomized Trial of PSA Testing for Prostate Cancer [CAP]) found no significant difference in prostate cancer mortality with a single PSA screening after 10 years of follow up.[34] However here we are modeling annual screening during the period of eligibility.

Our analysis also demonstrated a reduction in the number of prostate cancer deaths with DRE screening (21%). This strategy, if implemented, would be less costly than PSA, although we project a lower reduction in the number of deaths compared to PSA. The infrastructure already exists within the Thai national healthcare system to provide preventive care and men are already seeking such care in large numbers (in 2013, 77.3% of the Thai population reported use of preventive services in the past month).[35] It would be important to understand potential barriers that prevent men from

undergoing screening for prostate cancer in the Thai population. Anecdotal evidence from physicians in Thailand indicates that Thai men are embarrassed to talk about urinary problems with providers. In addition, they may feel uncomfortable with the performance of a rectal examination. Those factors may prevent men from receiving prostate cancer screening using the DRE.

Several groups in Asia have started the discussion about prostate cancer screening in the region. In 2010, the Japanese Urological Association recommended the use of PSA screening for men at risk of prostate cancer, explaining the potential risks and benefits of screening.[36] There is no official guidelines on screening for prostate cancer in Asian countries, except in Japan; therefore it has been recognized as an important need for the control of prostate cancer in the region.[16, 36–39] In general, the prevalence of prostate cancer screening is very low in Asian countries.[16] A study conducted in China reported a 10% prevalence of PSA screening among men aged 50 and older;[40] the study also suggested that screening recommendations by health care providers was positively associated with the screening uptake.[40] We hope that our study will advance the evidence necessary to make an informed decision about screening for prostate cancer in the region.

Strengths and limitations

One of the most important strengths of this study is that we used parsimonious models that allows to simplify our analysis and create real world conditions. Therefore, they are simpler to translate for healthcare authorities and policy makers, with the purpose of help them to take an informed decision to plan screening strategies for the

control of prostate cancer. Another strength is that we used data from the Songkhla Cancer Registry to project the incidence and mortality of prostate cancer under the screening scenarios. Therefore, the results can be extrapolated to the province and the rest of southern Thailand.

A limitation in our study is that we use all-cause mortality, which may underestimate the survival probabilities computed for the unscreened population. We may have used data from death certificates in Thailand, but the quality of the information is poor.[41] Another important limitation is that we used survival assumptions under PSA screening from the US that may not be appropriate to the Thai population. This could overestimate the reduction on the number of deaths with screening because the survival probabilities could be higher in the US than Thailand, in general because differences in healthcare system. However, the majority of studies on prostate cancer screening has been conducted in Western populations, and there is limited data in non-Western countries. We used the best available evidence to conduct our simulation analysis. In addition, the DRE scenarios assume stage-specific survival as observed in the Songkhla province, so these serve as a measure of the benefits that could be gained just from the stage-shifting of clinically relevant cancers due to screening, even if screening does not lead to additional improvements in survival as assumed for PSA. Lastly, the CFR estimations may get deflated, providing overly optimistic impact of screening in reduction of prostate cancer death if they are not adjusted for overdiagnosis. Therefore, we examined the CFRs adjusted by 23% and 42% of overdiagnosis (Table 4.2). Overdiagnosis wouldn't be an issue if they wouldn't treat aggressively all cancers found. So with "watchful waiting" one could possibly get all the benefits without the harms.

Conclusions

Screening for prostate cancer in Thailand could have an important impact on the burden of the disease, diagnosing prostate cancer cases at earlier stages when treatment may be effective. Our study shows that there could be a significant reduction in the number of prostate cancer deaths by implementing a screening program in the population, although it is important to take into account any potential risk associated with those screening strategies. The infrastructure currently exists to conduct at least population-based DRE screening, so introduction of this strategy in Thailand would incur minimal cost. Further studies should be conducted to understand the barriers to implementing this strategy in the male population of Thailand, and also potential benefits and harms by introducing PSA screening in this country given limited resources.

Acknowledgements

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Figure 4.1. Weibull (dashed lines) vs Kaplan-Meier (solid lines) survival curves by stage for prostate cancer incidence in the Songkhla Cancer Registry

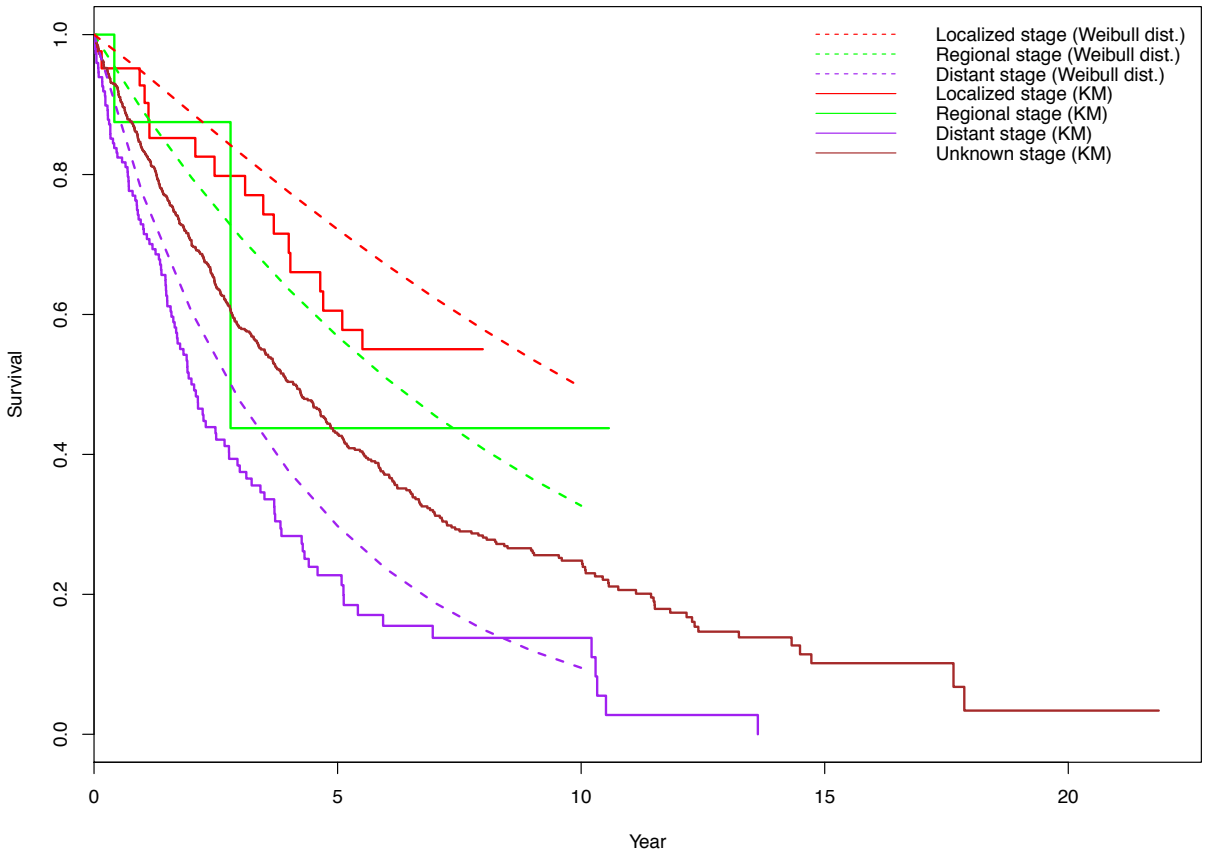


Figure 4.2. Flowchart of the simulation analysis for PSA screening

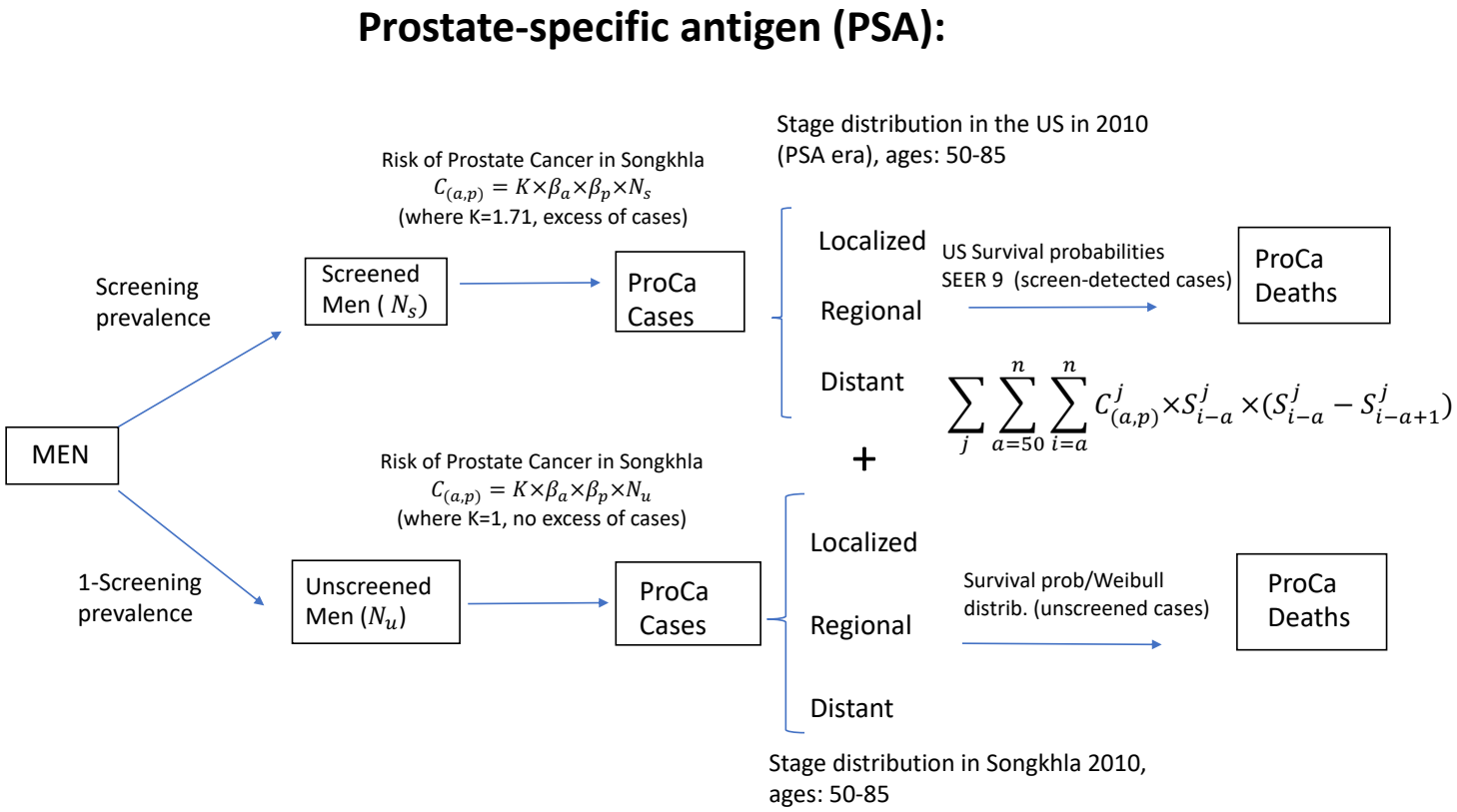


Figure 4.3. Flowchart of the simulation analysis for DRE screening

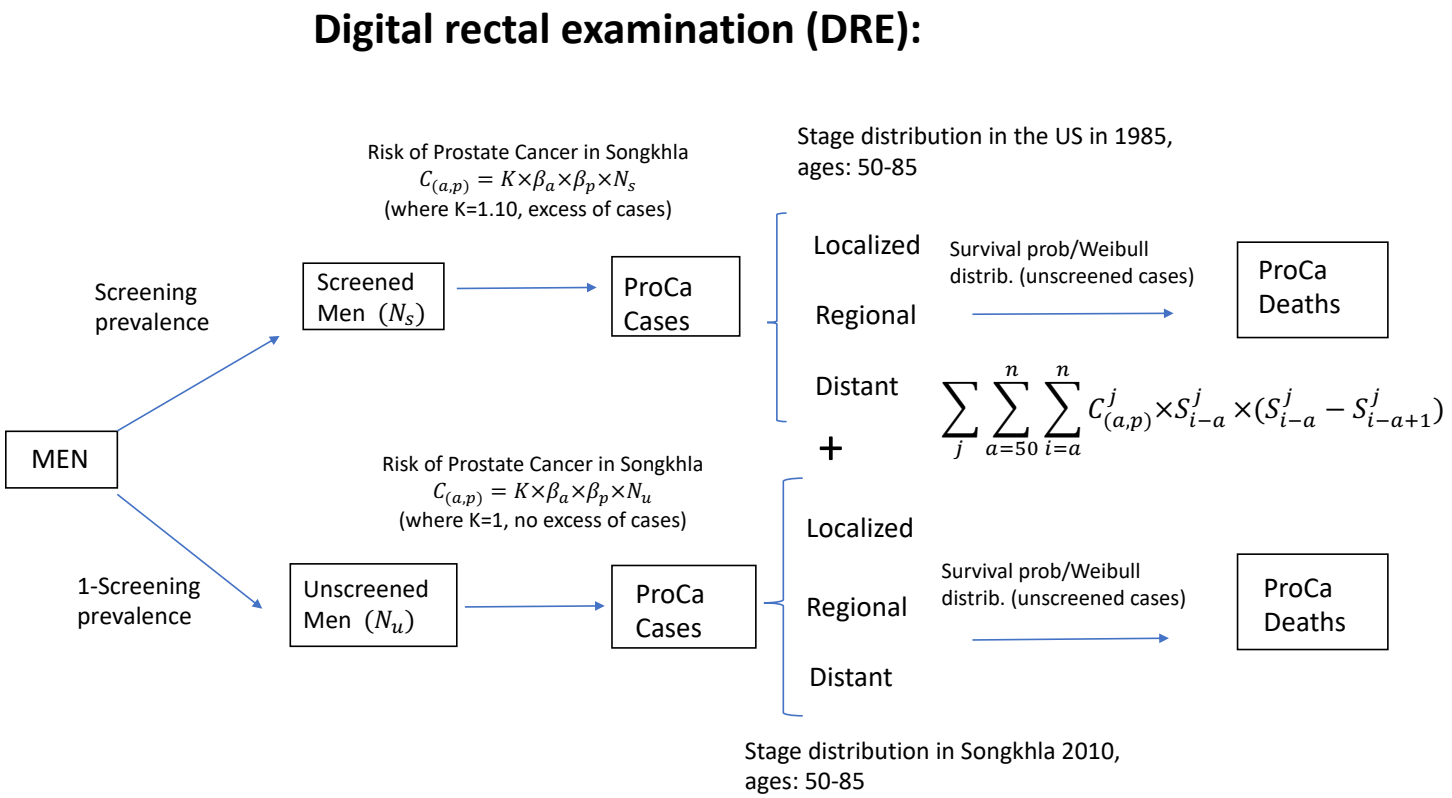


Figure 4.4. Prostate cancer stage distribution under different scenarios of PSA (left) and DRE (right)

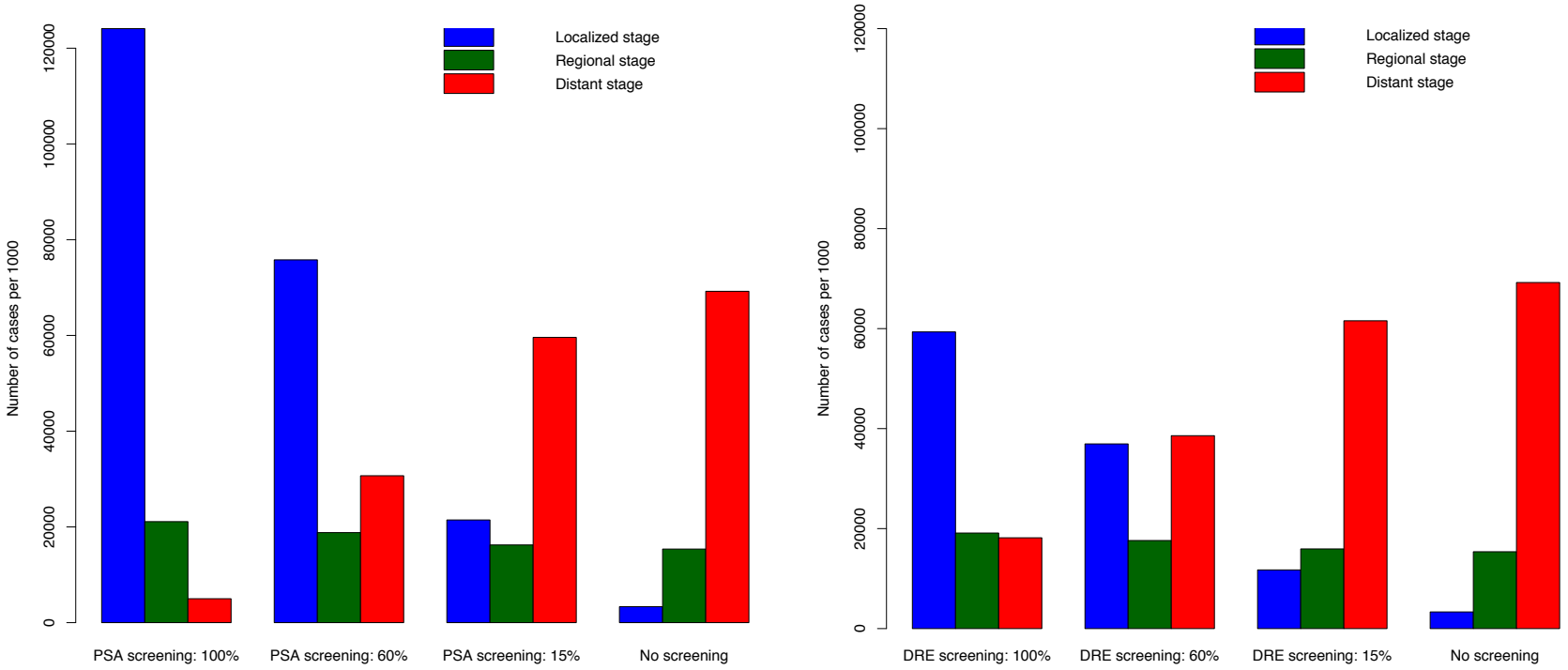
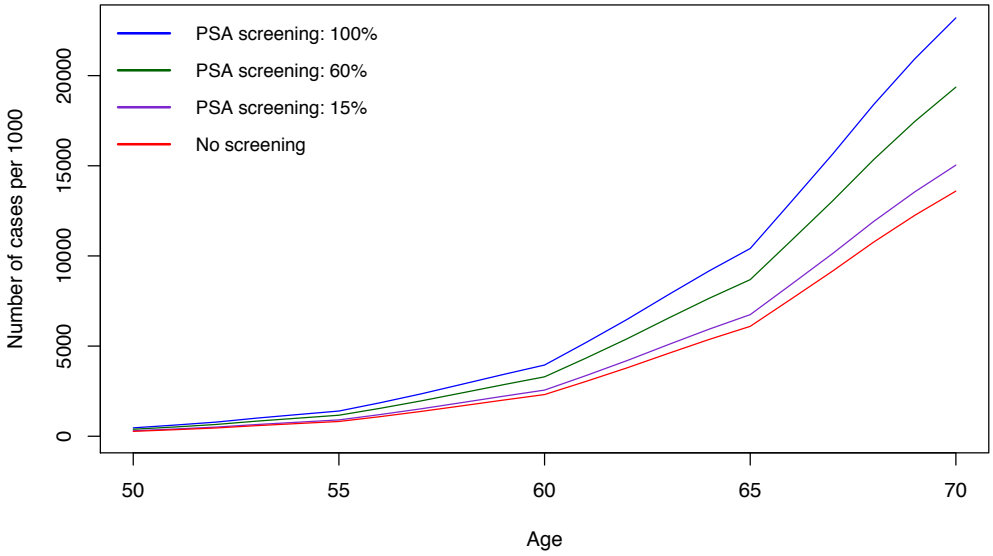


Figure 4.5. Number of prostate cancer cases under different screening scenarios of PSA (top) and DRE (bottom)



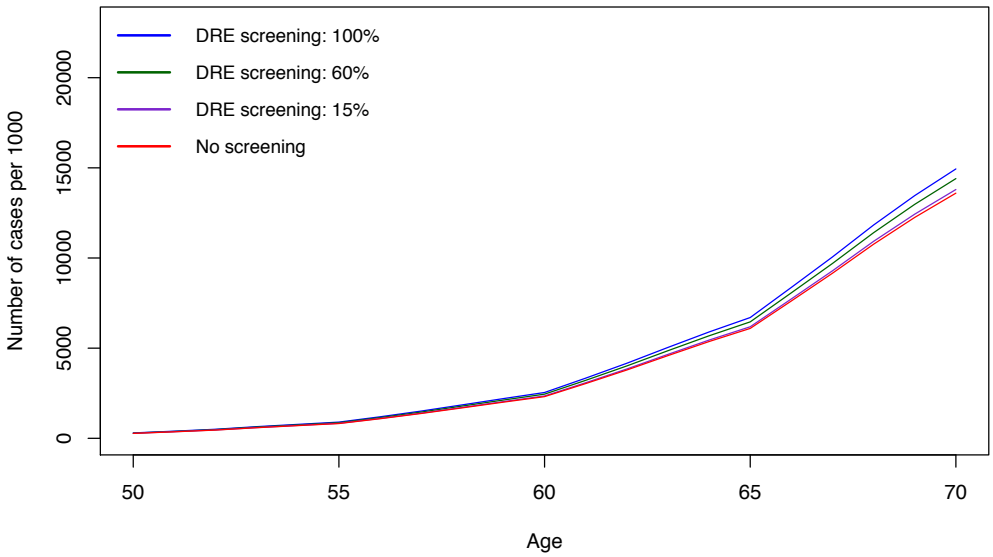


Figure 4.6. Number of prostate cancer cases by stage distribution under different screening scenarios PSA (top) and DRE (bottom)

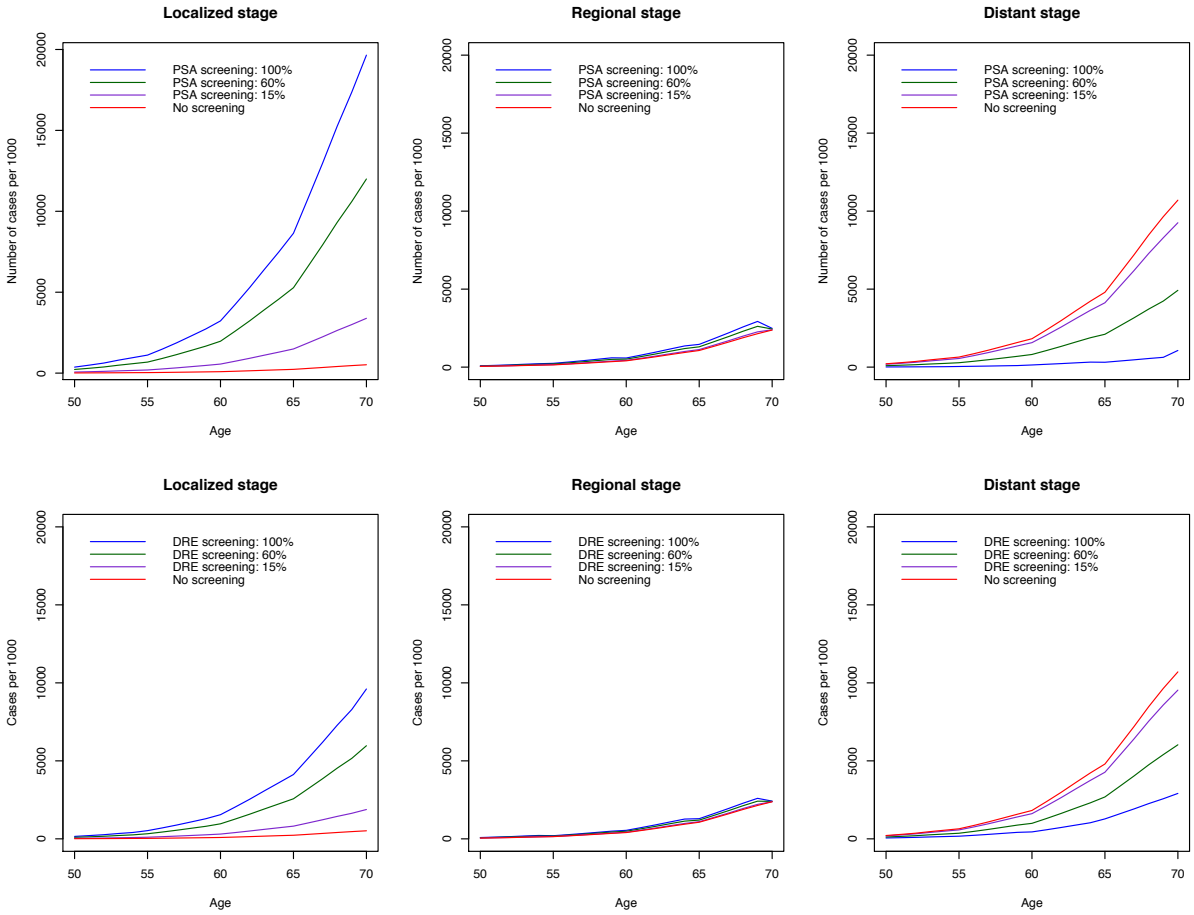
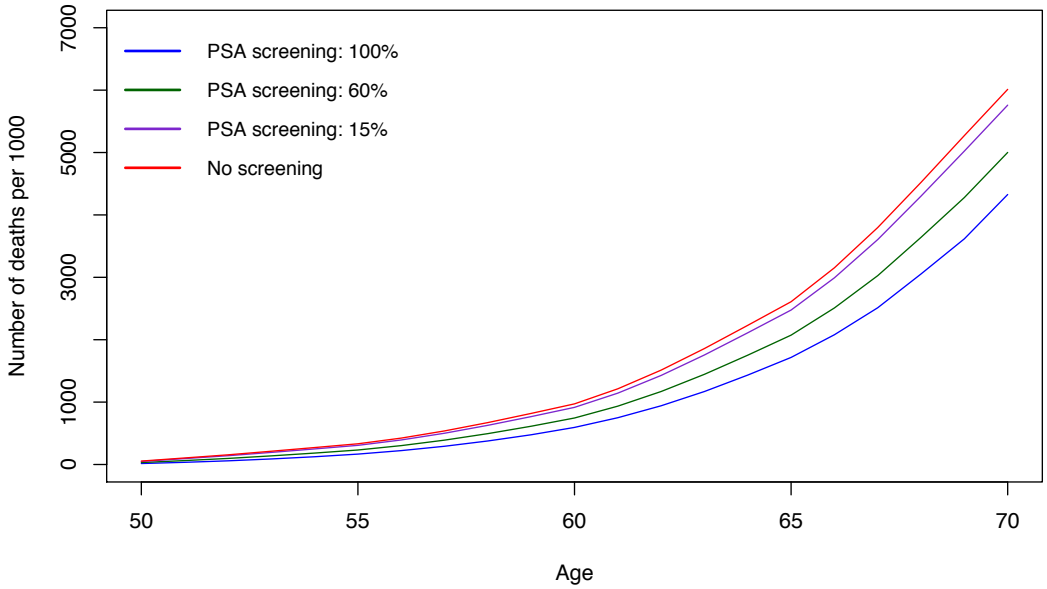


Figure 4.7. Number of prostate cancer deaths under different screening scenarios of PSA (top) and DRE (bottom)



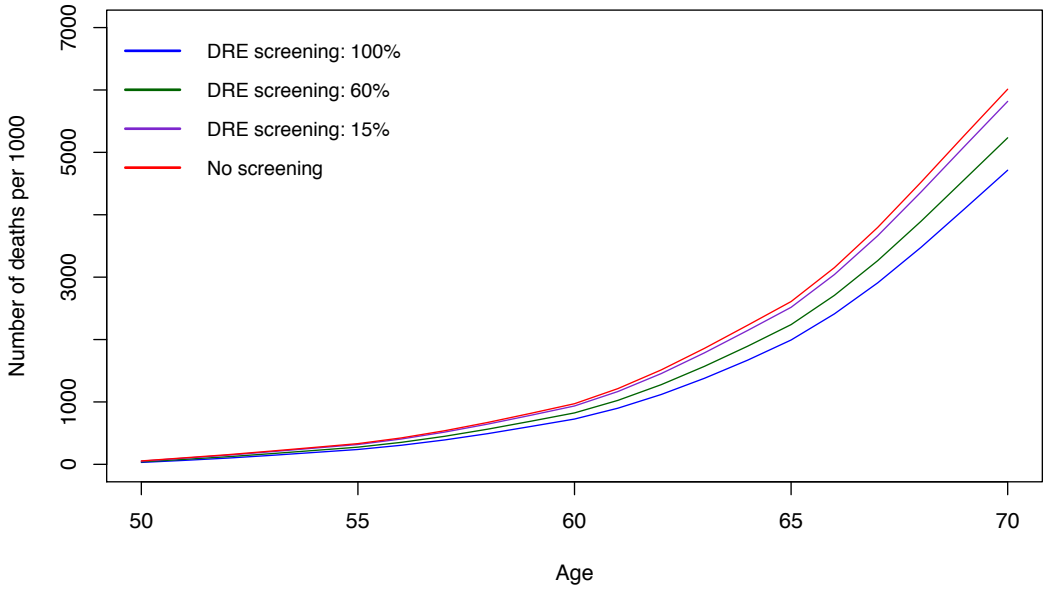


Table 4.1. Case fatality ratio (CFR) under PSA and DRE screening scenarios

Screening uptake	PSA	DRE
No screening	0.42	0.42
15%	0.36	0.40
60%	0.23	0.34
100%	0.16	0.29

Table 4.2. Case fatality ratios (CFRs) without and with adjustment for overdiagnosis (23% and 42%) under PSA and DRE screening

	PSA				DRE			
	23%		42%		23%		42%	
Screening uptake rate	CFR^1	CFR^2	CFR^1	CFR^2	CFR^1	CFR^2	CFR^1	CFR^2
15%	0.35	0.37	0.34	0.38	0.39	0.40	0.38	0.41
60%	0.21	0.25	0.18	0.26	0.30	0.35	0.26	0.36
100%	0.12	0.16	0.09	0.16	0.22	0.29	0.17	0.29

CFR^1: CFR without adjustment for overdiagnosis; CFR^2: CFR with adjustment for overdiagnosis

Chapter 5. Conclusions

Summary of Findings

Prostate cancer is emerging as a significant public health problem in less developed countries.[1–3] The burden of the disease has been stabilized in developed western countries, but it is expected to increase in other parts of the world, including Thailand.[4] Currently, there is limited data available describing the profile of prostate cancer in the Thai population. Therefore, this dissertation aimed to investigate the current and future perspectives of prostate cancer in a southern province of Thailand (Songkhla).

In chapter 2, we examined past and current trends of prostate cancer and projected the incidence and mortality rates over the next decade (up to 2030) in Songkhla. In addition, we assessed the effect of three time-related variables on the prostate cancer trends: age, calendar-year and birth-cohort. We used data from the population-based Songkhla Cancer Registry from 1990 to 2013. In this analysis, we have employed methods that have been widely used in cancer epidemiology to evaluate the temporal evolution of the disease (see chapter 2). We found that the incidence and mortality rates of prostate cancer have significantly increased since 1990 in Songkhla, which is consistent with the increase reported in other Asian countries.[5, 6] Furthermore, we observed a large proportion of prostate cancer cases with no stage at diagnosis, and among those who were staged, the vast majority of cases were diagnosed at advanced

stages. In addition, we found that the increase in the prostate cancer trends are predominantly influenced by a birth-cohort effect, suggesting that the adoption of more Western lifestyle has been contributing to the increasing burden of the disease in the Thai population. Lastly, we project that the rates of prostate cancer will continue to increase remarkably in the next decade in Songkhla. In fact, the mortality rates will exceed the current US mortality by 2030. Similarly, the burden of breast cancer in Songkhla was projected to continue to increase in the same period.[7] Therefore, there is an urgent need to establish cancer control measures to address the future burden of the disease in Songkhla, Thailand.

In chapter 3, we examined differences in prostate tumor characteristics such as stage and grade, sociodemographic characteristics, and survival between Buddhists and Muslims in Songkhla, using data from the Songkhla Cancer Registry. The southern region of Thailand has a distinctive population makeup, where approximately 30% of the population is Muslim and the rest Buddhist. Differences in the risk of cancer (including prostate cancer) has been reported between both religious groups.[8] No studies have reported differences in prostate cancer survival in this population. We found slight variability in prostate tumor characteristics and age between Buddhists and Muslims, but the differences were not statistically significant. In addition, despite the small number of prostate cancer cases in Muslims (n=98), we found a borderline significant difference in prostate cancer survival between these religious groups. Muslim men have a lower probability of surviving after a diagnosis of prostate cancer than Buddhist men. In addition, we observed that, unlike Buddhists, prostate cancer survival in Muslims has not improved after the introduction of the universal healthcare in Thailand. Lastly, we estimated that

Muslim men are 27% more likely to die compared to Buddhist men. Our results were consistent with those observed in other Muslim populations. For example, a study in several Asian countries showed that breast cancer survival is lower among Malay women (with a predominantly Muslim population) compared to Chinese or Indian women. Similarly, in Songkhla, a study reported a lower survival rate for oral, breast and cervical cancer among Muslims. It remains unclear why Muslims have a poorer survival. It has been speculated that differences in cultural beliefs and perception of sickness play a role in those cancer disparities, through delaying the time of diagnosis and treatment.

In chapter 4, we conducted a simulation analysis to evaluate the potential impact of a population-based screening program for prostate cancer on the incidence and mortality of the disease in Songkhla. Our target population was Thai males from Songkhla born in 1960, and they were followed-up from ages 50 to 70. We used data from different sources, including the Songkhla Cancer Registry, the National Statistical Office of Thailand, the Surveillance, Epidemiology, and End Results Program (SEER) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial. We used parsimonious models to project the number of prostate cancer cases and deaths under different scenarios of screening: 100%, 60%, and 15% uptake rates compared to no screening, in two screening modalities: Prostate specific-antigen (PSA) test and Digital Rectal Examination (DRE). The model projects that the incidence of prostate cancer for the 1960-birth cohort would increase from 88,000 to 150,000 cases per 1,000 (with mostly localized disease), and mortality would decrease from 37,000 to 24,000 deaths per 1,000, under 100% PSA screening uptake. Moreover, our model projects a 28% (and 16%) reduction in the number of prostate cancer deaths at age 70, under 100% (and 60%) PSA

screening; and 21% (and 13%) decrease with 100% (and 60%) DRE screening uptake. Therefore, our analysis demonstrated that screening for prostate cancer would help to reduce the future burden of the disease in Thailand.

In order to decide which screening modality is the most appropriate in this context, it is important to take into consideration the criteria for a suitable screening strategy, including costs, the easiness of the test/exam administration, minimal risk of harm, validity and reliability.[9] For instance, DRE is less costly than PSA screening ($31.77 [including medical fees in the US] vs $37.23 [with no medical fees]),[10] which would be an advantage for low-resource settings such as Thailand. On the other hand, DRE has a lower sensitivity and specificity to detect prostate cancer than PSA (e.g. 60% vs 80% [for PSA levels >4 ng/mL).[9] Overall, the high sensitivity of PSA trade off with the high false positive rate, and cases with indolent disease, which may cause harm due to unnecessary follow-up (possibly men undergo repeat biopsies) and treatment. For example, radical prostatectomy performed in those localized prostate cancer cases may cause serious side effects such as urinary incontinency and sexual dysfunction as well as psychological distress.[11, 12] Finally, other potential barriers (e.g. acceptability of DRE) should be taken into account for the selection and implementation of the screening strategy for prostate cancer in this population.

In addition, we speculate that the implementation of screening for prostate cancer may exacerbate the disparities in incidence and survival of prostate cancer between Buddhists and Muslims reported in our previous chapters. We have discussed that Muslims are less likely to accept diagnosis/treatment for cancer; thus, they may be less receptive to prostate cancer screening than Buddhists, increasing the prostate cancer

disparities in this population. A previous study in Songkhla reported that Muslim women are less likely to receive screening for breast and cervical cancer than Buddhists due to differences in cultural and religious characteristics between both groups.[13] The adoption of population-based prostate cancer screening in Thailand should consider regional differences in incidence and mortality, as well as potential barriers in the population. We suggest to begin the implementation in southern Thailand (as they have a higher incidence of the disease, and have a unique population composition), subsequently, the screening programs should be extended to other regions in the country.

We expect that our evidence will help Thai health authorities to make an informed decision about the implementation of a prostate cancer screening program in the country.

The strengths of this dissertation include; first, we used data from a population-based cancer registry, which enable us to extrapolate the result to the province of Songkhla, and the rest of southern Thailand, where the population composition is similar to that in Sonkghla. Second, the Songkhla Cancer Registry collects high quality data, with >95% of completeness, which allows us to obtain accurate estimates. In addition, data from this registry has been included in the Cancer Incidence in Five Continent (CI5) since the mid-nineties.[14] Furthermore, the Songkhla Cancer Registry routinely collects information on religion that allows us to conduct analysis to explore cancer disparities among religious groups in Thailand. Lastly, an important strength of our simulation analysis is that we used parsimonious model to simplify the analysis and create more real world conditions that help us to translate the evidence of screening easily to health authorities and policy makers in Thailand.

On the other hand, this dissertation has several limitations. For example, the deaths reported in the cancer registry represent all-cause mortality, they are not prostate cancer-specific mortality, which may overestimate the prostate cancer-specific death rates and could potentially bias the results. We would have used data from death certificates instead, but the quality of death registration in Thailand has been reported to be low.[15] Furthermore, the limited number of variables collected in this cancer registry did not allow us to explore determinants of prostate cancer outcomes in Songkhla (e.g. lifestyles) or adjust for additional confounders. In addition, our data has a large proportion of unstaged and ungraded tumors that limited our ability to completely adjust for those factors in the survival analysis. We used multiple imputation analysis to impute the missing information, yielding similar results. Another limitation is that we might have underestimated prostate cancer cases in Songkhla of those cases with limited access to health centers, however the capture rate for prostate cancer in Songkhla has been very high. Finally, a limitation in the simulation analysis is that we used data from Western population to estimate some parameters. However, there is limited data on prostate cancer screening in non-Western populations instead we used the best available evidence to conduct our simulation study.

Public Health Implications and Future Directions

This dissertation presents several implications for public health in Thailand, as this study is the first in-depth look at the current burden of prostate cancer in the country. In chapter 2 we learned that prostate cancer trends have been increased in Songkhla since 1990 and they will continue to increase. Our projection analysis of prostate cancer is important to inform public health authorities about the future burden of the disease in Songkhla. In fact, the Minister of Health of Songkhla expressed interest in our findings, potentially to allocate resources to provide care for men who will be affected by the increased burden of the disease, and to plan cost-effective strategies to reduce the impact of prostate cancer in this population. Furthermore, we speculate that the increase in prostate cancer incidence and mortality is likely due to the adoption of more western lifestyles in Thailand; therefore, further research is warranted to investigate this hypothesis. In addition, it is necessary to investigate reasons for the large proportion of unstaged and ungraded tumors in order to improve data collection for prostate cancer in the Songkhla Cancer Registry.

In chapter 3, we found that Muslim men have a higher risk of death after diagnosis of prostate cancer. It is important to further investigate this population in order to understand what risk factors may underlie the poorer survival in Muslims and design targeted interventions in both populations. A breast cancer case-control study is underway to evaluate behavioral/clinical risk factors which influences breast cancer risk and outcomes in southern Thailand; therefore, a similar study should be undertaken for prostate cancer in this population.

Lastly, in chapter 4 we presented the potential benefits of prostate cancer screening in this population. With this evidence, we hope to provide information that will guide health authorities in making an informed decision on the implementation of prostate cancer screening in the Thai population, and contribute to the control of prostate cancer in Songkhla. In addition, research is needed to understand potential barriers for prostate cancer screening among Thai men in order to implement screening strategies that take into consideration those barriers.

In summary, this dissertation demonstrates that prostate cancer is emerging as a significant public health problem in Thailand. In addition, we highlighted disparities in prostate cancer outcomes that should be addressed. Lastly, we provided evidence that screening for prostate cancer may be an important strategy to implement in this population. We hope that our work contributes to plan and implement control measures for prostate cancer to reduce the escalating burden of the disease in Thailand.

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