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Prostate Cancer Survival among Hispanics: A Surveillance, Epidemiology, and End Results (SEER) Population-Based Cohort Study

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PROSTATE CANCER SURVIVAL AMONG HISPANICS: A SURVEILLANCE,
EPIDEMIOLOGY, AND END RESULTS (SEER) POPULATION-BASED
COHORT STUDY

By

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2012

A thesis submitted in partial fulfillment
of the requirements for the

Master of Public Health

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Abstract

Hispanics are now the youngest, largest, and fastest growing minority group in the U.S. Prostate cancer (PC) is the most commonly diagnosed cancer in men and is the second-leading cause of cancer deaths among Hispanics. For the first time, we examined PC-specific survival among distinct Hispanic groups that include Mexicans, Cubans, Dominicans, Puerto Ricans, as well as Central and South Americans. We compared these groups to the main reference population in the U.S., non-Hispanic Whites (NHW), after adjustment for prognostic factor risk categories (prostate-specific antigen (PSA) level, Gleason score, and tumor stage), as well as sociodemographic covariates (e.g., health insurance, and marital status). Surveillance, Epidemiology, and End Results (SEER) data from 2004 to 2013 were used. Cox proportional hazards regression revealed that Hispanics, overall, show an increased risk of death in comparison to NHW HR = 1.17 (95% CI: 1.12-1.22), over time, but that difference disappears after adjustment for prognostic factors HR = 0.97 (95% CI: 0.93-1.02). This result is likely due to the known overdiagnosis of initial indolent PC cancers more common in the referent group (NHW). Moreover, among the subcategory of unknown stage (as opposed to known stage), Hispanics do relatively poorly which may account for some of the increased risk of death in relation to NHW. To further examine a more meaningful disparity, we restricted our analysis to those with localized stage and PSA larger than 9.9 ng/ml. Initially, for these intermediate risk stages that are more prone to disparities, due to differential treatment or access to quality healthcare, there were no differences between Hispanics and the referent group HR = 1.03 (95% CI: 0.96 – 1.09, p-value = 0.44); however, the HR appeared to improve after adjusting for

prognostic factors (HR = 0.95, 95% CI: 0.89 – 1.01, p-value = 0.09), which may indicate that Hispanics present marginally worse biological characteristics in comparison to NHW. Finally, after adjusting for all prognostic and social factors, Hispanics showed a theoretical survival advantage in comparison to NHW HR = 0.93 (95% CI: 0.87-0.99). Contrary to expected results, social factors that were included in this study did not appear to add a survival advantage for Hispanics. Among the different Hispanic groups, Puerto Rican men living in the U.S. (HR = 1.38, *p*-value <0.01, 95% CI: 1.17 – 1.63) showed the highest disparity in relation to NHW but this estimate may be impacted to some extent by the Not Otherwise Specified (NOS) bias. This bias may be large enough to significantly influence and artificially increase the risk of death among Puerto Ricans, as seen in our results. More should be done to improve stage at diagnosis and access to quality healthcare for all Hispanics to eliminate the persisting disparities.

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Chapter 1: Background

Cancer is a condition in which cells lose the ability to regulate cell division, producing uncontrollable cell proliferation that may invade healthy areas of the body, resulting in loss of function of cells, tissue and organ (Stewart, 2014). The prostate is an exocrine gland within the male reproductive system that produces an alkaline fluid that constitutes about 30% of semen volume. Its alkaline properties are vital in reproductive success by prolonging sperm lifespan and neutralize the vaginal tract acidity during intercourse. (Bethesda, 2016)

Prostate Cancer (PC) is the third most commonly diagnosed cancer among all cancer types, accounting for 10.7% of all new cancer cases in the United States (Surveillance, Epidemiology, and End Results [SEER], 2016). In men, PC is the most common cancer diagnosed and the second leading cause of cancer death nationwide (Siegel, 2016). In 2017, overall, it is estimated that 161,360 men in the US will be newly diagnosed and 26,730 men will have died from the disease (SEER, 2017). Relative 5-year survival is approximately 98.6%. Approximately 12% of American men will develop prostate cancer in their lifetime (SEER, 2017). PC median age at diagnosis is nearly 66 years, and the majority of cancer survivors are age 70 or greater (64%) (Chhatre, 2015; Miller, 2016).

The US age-adjusted 2012 - 2014 prostate cancer incidence rate was 119.8 per 100,000 men per year (SEER, 2017). Age-adjusted mortality was 20.7 deaths per 100,000 men per year (Siegel, 2015). In 2013, the prevalence numbers (survivors) of prostate cancer was approximately 2.85 million men. (SEER, 2016). Worldwide, PC is the most common cancer diagnosed in men with an estimated 1.6 million new cases occurring in 2015, and it is the 7th leading cause of death in men with about 366,000 deaths occurring annually (Fitzmaurice, 2016).

US cancer survival and incidence data are regularly collected from cancer registries that participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (SEER, 2014). Although PC incidence and survival rates have improved in recent years, minorities in the US often experience poorer cancer health outcomes than their non-Hispanic white (NHW) counterparts (Kish, 2014). Lower PC survival rates in African American men, compared to NHW, have been well documented. Although race/ethnicity is recognized as a strong prognostic factor for PC, there is limited published information regarding patient survival among Hispanic ethnic subgroups (Clegg, 2002). According to the 2010 US Census Bureau, 55 million self-identify as Hispanics, accounting for more than 17% of the US population (Colby, 2015). Hispanics are now the youngest, largest, and fastest growing minority group in the US. The population of Hispanics grew 57% or 4 times the rate of the entire US population from 2000 through 2014 (Siegel, 2015). The US Hispanic population is projected to reach 131.7 million by the year 2050 (Day, 1996). PC is the number one cancer among all Hispanic ethnic groups (Pinheiro et al., 2009).

Siegel et al. (2015) reported that the age-adjusted incidence for Hispanics is 112.1 per 100,000 population, approximately 9% less than the rate of non-Hispanics white men (123.0 per 100,000). This difference may be attributed to lower rates of prostate-specific antigen (PSA) testing among Hispanics. Nearly 79% of diagnosed PC cases are at a localized stage in non-Hispanic white men compared to only 75% in Hispanic men. For both groups, however, 5-year cause-specific survival is similar, about 98% (Siegel, 2015). Among Hispanic subgroups, PC is the leading cause of cancer death among Dominicans, and it is the second leading cause of cancer death among the remaining Hispanic groups, except for Puerto Ricans, for which it is the third. (Pinheiro et al, 2017). White et al. (2011) examined the survival disparities among

different racial/ethnic groups and found that both non-Hispanic black (aHR, 1.70; 95% CI, 1.58-1.83) and Hispanic men (aHR, 1.11 [95% CI, 1.02-1.20]) were more likely to die of prostate cancer compared to non-Hispanic white men in the state of Texas after adjustment for tumor stage, socioeconomic status (SES), and rural residence.

According to published literature, the typical determinants of PC survival include age, race/ethnicity, PSA level, Gleason score, tumor stage at diagnosis, receipt of treatment, health insurance status, marital status, and socioeconomic status (Moses et al., 2016). The major causes of PC itself remain undetermined, although several endogenous and exogenous risk factors have been suggested. Endogenous risk factors include: age, family history of PC, and race, particularly men with African ancestry (Bunting, 2002). Exogenous risk factors for PC include diet (e.g. consumption of polyunsaturated fatty acids), environmental agents (e.g. exposure to endocrine disruptive chemicals), and occupation (e.g. farming or rubber industry). Numerous other modifiable risk factors have been studied but reported limited or inconclusive evidence. These include smoking, sexual activity, marital status, vasectomy, physical activity, and socioeconomic status (Bostwick, 2004). Family history of PC and African descent are the two most widely accepted risk factors for PC and are characteristics physicians typically look for to assess if there is a need for PSA screening.

Literature Review

Age

The literature indicates that there is a strong relationship between PC and age. Hankey et al. (1999) showed that diagnosis rarely occurs prior to 40 years of age, with incidence increasing with age thereafter. Research results using SEER data from the mid-1990's demonstrated this relationship where annual incidence of non-Hispanic white men was estimated to be 1, 6, and 10

per 1000 persons stratified into 10-year age groups: 50-59, 60-69, and 70 years and older, respectively. Incidence rate declines for men aged 80-89 years a due to a lower frequency of PSA tests in men at this age. (Hankey, 1999) Among older men, PC is the most common malignancy, 64% of cases in the US were diagnosed in men 65 years or older, and account for 23% of cases in men older than 75 years (Bechis, 2010). Age has also been associated with an increase in diagnosis, for which diagnoses increase as men become older because they are more likely to be screened (Carter, 2013).

As men age, PC survival declines, as would be anticipated (Mariotto et al.,2014).. Additionally, older men in the US have a greater likelihood of being diagnosed with high-risk, late stage PC. As a result, they more likely to have lower PC-specific survival, and lower overall survival. The progression of PC of any given stage and grade seems to occur independent of age, thus, variation in managing the disease and lead-time at diagnosis may explain some of the observed differences in cancer-specific survival. Age, especially life expectancy, has also been shown to strongly influence treatment decision making (Buhmeida, 2006; Bechis, 2010).

Race/ethnicity

The relationship between race/ethnicity and PC survival has been well documented, with poorer health outcomes commonly found among non-Hispanic blacks (Clegg, 2002).

Racial/ethnic disparities in PC have been attributed to several factors including tumor stage at diagnosis, socioeconomic status, treatment, physician characteristics, and rural residence. Most studies examine the relationship between race/ethnicity and PC survival by comparing non-Hispanic white and non-Hispanic black men, few studies focus on other racial/ethnic groups. The few studies which do, have found that Hispanic men have slightly higher risk of death compared to the referent group (NHW) (White, 2012).

Prostate-Specific Antigen (PSA)

The PSA test is a screening tool that measures the level of PSA, a protein produced by prostate gland cells, present in the blood in men. PSA levels tend to increase over time with age. Men with PC often have elevated PSA levels present in their blood, however, benign medical conditions may also cause elevated PSA concentrations including benign prostatic hyperplasia (BPH) and prostatitis (Stenman, 1999). These incidental findings have not been associated with increased risk of PC, although, there is still the possibility of developing PC if a man is found to have either of these conditions. The PSA test was approved by the Food and Drug Administration (FDA) in 1986 to monitor disease status and permitted its use for diagnosis in 1992. By 1994, PSA was accepted to be used in conjunction with a digital rectal exam (DRE) to screen asymptomatic males for PC (Hankey, 1999).

Determinant of Incidence

PSA testing is used as a determinant of incidence which can result in early detection of PC. Since its approval, the test was associated with a dramatic increase in the incidence of PC in the early 1990's, but soon declined to rates similar to pre-PSA testing. PC mortality has been on a decreasing trend ever since (Fowke, 2005). Despite the disagreements regarding its benefits (Heidenreich, 2011), PSA testing is widely accepted in clinical practice and the general public.

The topic of PC screening is surrounded by controversy. Clinical trials report conflicting results regarding the benefit of PSA screening for reducing PC death rates. Screening is not regarded as the ultimate solution for this disease due to the fact that many cancers diagnosed and treated as a result of PSA testing would never have caused any symptoms nor would they have progressed into a life-threatening disease. Furthermore, some cancers are very aggressive in nature, which can often relapse, and prove fatal despite early detection and treatment. Therefore,

the value of early PC detection is not sufficient to advocate for or against screening with the PSA test for men who are have an average risk, based on the evidence that has been published (NCI, 2016).

The U.S. Preventive Services Task Force (USPSTF) recommends that men between the ages of 55 to 69 years, should consult with their physician to discuss the possible benefits and harms regarding PSA screening. There is a small potential advantage of reducing the chance of dying from PC. At the same time, PSA screening may lead to harm. This includes, an increase in false-positives that result in further unnecessary testing, and substantial over-diagnosis, which in turn inflate the rate of unnecessary treatment that may be accompanied by life-changing side-effects such as impotence and incontinence (Zargar, 2017).

Although, PSA screening has increased 7-fold since its approval in the mid-1980s, the increase was not seen uniformly throughout all race/ethnic populations (Fowke, 2005). Several factors such as access to healthcare, patient perception, and health literacy influence patient acceptance of PSA screening programs at the community-level (Hosain, 2012). Studies have found that PSA screening leads to earlier diagnosis by up to 13 years, resulting in increased survival for patients with PC (Albersten, 2011). More frequent PSA screening for high-risk populations, such as minorities and men with low-incomes, is recommended by some authors to reduce PC mortality through early detection of tumors before they may have become metastatic (Taksler, 2012). Furthermore, Hosain et al. (2012) revealed that Hispanic men are less likely to have had a PSA screening test than non-Hispanic white men. They also reported that having an annual check-up was the only significant predictor of PSA screening among Hispanic men. Previous studies have shown that cultural and language barriers are factors that prevent

Hispanics from establishing a proper link with health and preventative care services, thus significantly decreasing their PC screening rates (Hosain, 2012).

Prostate cancer screening is also an important prognostic factor. Normal PSA levels in the blood vary but it is widely accepted that men with PSA levels below 4.0 nanograms per milliliter of blood are considered normal. Some recommendations suggest that men with levels above 4.0 ng/mL should undergo a prostate biopsy to determine if PC is truly present. Studies have reported, however, that some men with PSA levels higher than 4.0 ng/mL did not have PC, while others with levels in the normal range had PC. In general, men with intermediate (10 – 19.9 ng/mL) to high (above 20 ng/mL) levels are more likely to be diagnosed with PC (Thompson, 2004).

Gleason Score

The Gleason score grading system was developed by Dr. Donald Gleason and his colleagues in the 1960's to aid in determining a prognosis for men with PC using prostate biopsy tissue samples (Gleason, 1992). In 2005, the Gleason grading system was modified to increase accuracy and performance by the International Society of Urological Pathology, and is presently the presumed standard (Epstein, 2005). Each PC biopsy tissue sample is graded and given a Gleason score ranging from 2 to 10, on the basis of its appearance under the microscope. Pathologists assign a primary grade or the dominant pattern ($\geq 50\%$) observed in the tumor and a secondary grade, which is the second most frequent observed pattern ($5\% \geq 50\%$). For example, a $3 + 4 = 7$ Gleason score would be interpreted as a primary grade of 3, a secondary grade of 4, with an overall grade of 7. Lower Gleason scores or well-differentiated tumors indicate PC tissue similar to that of what is considered normal prostate tissue signifying a better prognosis and cancer that is less likely to metastasize. Higher Gleason scores or poorly-differentiated tumors

are indicative of more aggressive cancer types and less favorable prognosis. Pathologists have been increasingly providing tertiary grades, generally, to more aggressive type cancer to more appropriately describe the cancer grade (Epstein, 2005).

Investigators at John Hopkins University have proposed combining Gleason scores and prognostic grades to be categorized under 5 main groups. Under their proposed prognostic grade, group I are assigned to tumors with Gleason scores of ≤ 6 ; Group II are intermediate-grade tumors with Gleason scores of 7 with primary grades lower than the secondary grade (e.g. $3 + 4 = 7$); Group III are also intermediate-grade tumor except the primary grade is higher than the secondary grade (e.g. $4 + 3 = 7$); Gleason scores of $4 + 4$ comprise group IV; and group V have scores of 9 – 10. (Billis, 2005).

Tumor Stage

Cancer staging refers to the process of determining the extent of the cancer, where it is located, and whether it has spread from its point of origin to other areas of the body. Cancer stage, together with PSA and Gleason score, are all important factors in selecting treatment options (e.g. type of surgery, radiation, hormone therapy or chemotherapy) and predicting a patient's prognosis (survival outlook). Cancer stage is based on tumor extent, and tumor metastasis to lymph nodes or other areas. SEER classifies prostatic carcinomas into 5 stages: *in situ*, localized, distant, and unknown stages (Epstein, 1994).

SEER staging applies all available information in the medical record and bases the criteria on cancer growth theory. Noninvasive cancer is described as "*in situ*". *In situ* tumors satisfy microscopic criteria necessary to be deemed malignant, however, they do not meet the criteria for the invasion of the basal membrane of the prostate. "Localized" tumors are confined and do not extend beyond the prostate. When the cancer has spread to remote parts of the body,

they are coded as “distant”. Tumors are recorded as “Unknown” when there is insufficient, ambiguous, or contradictory information (Partin, 1990).

Patients diagnosed with localized cancer have a 5-year relative survival rate of approximately 99% which significantly declines to 28% for those diagnosed with distant stage disease. Examining 5-year relative survival for all tumor stages combined shows a 16% increase, from 83% in the 1980s to about 99% in the 2000s. This may be a reflection of over-detection with more non-progressive cancers. The 10-year relative survival rate is 98% and the 15-year relative survival rate is 95%. (Miller, 2016) Hoffman et al. (2001) reported that Hispanic and African American men were more likely, to be diagnosed with advanced stage PC than their non-Hispanic white counterparts. Their findings suggest that stage at diagnosis is a strong predictor of survival.

PC Treatment

Treatment options for prostate cancer vary by several factors including extent of disease, risk of occurrence, personal preference, and patient sociodemographic and health characteristics (e.g. age, comorbidity). Men under 65 years are commonly treated with radical prostatectomy, while half of men over 75 years are likely to receive radiation or surgery. (Miller, 2016)

For patients with less aggressive tumors, those who have comorbidities and/or are older, patient monitoring is the most common recommended approach, rather than immediate treatment (Albersen, 2005). Men with more advanced tumors are treated with radiation, radical prostatectomy, chemotherapy, hormone therapy, bone-directed therapy, or a combination of these treatments (Miller, 2016).

A previous study reported that Hispanic and non-Hispanic black men were less likely to receive definitive therapy (radical prostatectomy, brachytherapy, external beam therapy, or any

combination) than their non-Hispanic white counterparts. In addition, higher tumor grade was associated with lower odds of definitive therapy among Hispanic men. However, this disparity in the receipt of definitive treatment decreased for Hispanic men from 1992 to 1999. (Underwood et al., 2004). A different study reported Hispanic men had a greater likelihood of receiving radical prostatectomy treatment, when compared to non-Hispanic white and Black men (Underwood et al., 2005).

In a more recent study, Moses et al. (2016) reported incongruous findings to the aforementioned reports; Hispanic men had 11% and 21% lower odds of receiving treatment when diagnosed with intermediate or high-risk D'Amico classification (a classification system intended to assess the risk of disease recurrence following treatment of PC), respectively. This suggests the possibility of a diminishing survival over time, which could translate to increasing mortality risk in Hispanic men (Moses, 2016). The Hispanic paradox, also known as the epidemiologic paradox, suggests that Hispanics have favorable health and mortality outcomes relative to their US non-Hispanic white counterparts, despite having lower education and SES status (Markides, 2005).

Sociodemographic Variables

Marital status, health insurance status and socioeconomic status (SES) variables have been inconsistently shown to have a significant effect on prostate cancer stage at diagnosis. Yet, these variable have an impact on PC survival, however, it is unclear whether these variables are independent prognostic factors of PC after adjustment for prognostic factors such as tumor stage, Gleason score, and PSA levels (Buhmeida, 2006).

Marital Status

Several studies have shown an association between marital status and PC survival. Unmarried men, including those never married, have unfavorable effects on PC stage. Xiao et al. showed that married men are less likely to be diagnosed with late stage prostate cancer when compared to unmarried men (Xiao et al., 2011). Separated, divorced or widowed men had more advanced stages of prostate cancer at surgery and higher prostate cancer specific mortality (Abdollah et al., 2011). These findings suggest being married provides a protective effect when it comes to being diagnosed with PC and PC survival. Moses et al. (2016) reported married men were over twice as likely to receive treatment. Marital status is commonly categorized into married, widowed, divorced/separated, and single (never married) groups.

Health Insurance Status

Compared to men with health insurance, men who were uninsured experienced more severe diagnoses (Bennet et al., 1998). Disparities have been documented even among patients with health insurance. A more recent study found that patients who were uninsured or received Medicaid were more likely to be diagnosed with advanced-stage PC and were less likely of receiving definitive treatment when compared to patients who used either Medicare or private insurance. (Walker, 2014). Fedawa et al. (2010) confirmed that access to health insurance is key in receiving adequate medical care and cancer screening.

Socioeconomic Status

SES plays a crucial role in PC outcomes. Low SES and individuals residing in more deprived neighborhoods, have lower rates of survival when compared to their more affluent counterparts (Singh, 2017). Schwartz et al. (2009) examined AA and non-Hispanic white men with PC in Detroit, Michigan from 1988 to 1992. Their findings showed that low SES and

nonsurgical treatment were associated with PC survival and increased the risk of PC-specific mortality. White et al. (2011) reported 32.4% Black and 34.1% Hispanic men diagnosed with PC tended to reside in very low socioeconomic areas in Texas compared to white males (7.9%). Low income has been associated with a higher chance of being diagnosed with PC; Clegg et al. (2009) found that men that have a lower family income are more at risk. At the census level, higher income status was linked to a lower possibility of being diagnosed with late stage PC (Clegg et al., 2009). Low SES was reported to play a significant role in healthcare accessibility as well (Bennet et al., 1998). There are fewer opportunities to detect PC early for men with low income due to cultural, social, and financial reasons (Barbiere et al., 2012).

Study Significance

The proposed investigation will contribute to the body of knowledge of the field of cancer health disparities research among the understudied Hispanic community experiencing different incidence, mortality, and survival rates among its several distinct ethnic groups (e.g. Mexicans, Cubans, Puerto Ricans, Dominican, Central Americans and South Americans). Statistical patterns are vital to help guide researchers, healthcare professionals, policy makers, and governments to understand the true impact of prostate cancer. These efforts could aid in developing appropriate strategies necessary for navigating the challenges created by prostate cancer, and measure the effectiveness of prevention and control efforts (NCI, 2016). A better understanding of prostate cancer disparities will be advantageous in tailoring and directing preventative and treatment resources to at-risk ethnic populations in an effort to reduce their burden.

Study Purpose

The purpose of this study is to analyze SEER population based data to examine prostate cancer survival by race, Hispanic groups, and age after adjusting for clinical factors, PSA level risk categories and Gleason score risk categories, as well as marital and insurance status in men living in the United States from 2004 to 2013. The following hypotheses were evaluated:

Research Question 1: How Does Risk of Death among Hispanics Compare to the Referent Group?

H₀: The risk of death over time among all Hispanics is similar to that of non-Hispanic white men after controlling for covariates.

H_a: The risk of death over time among all Hispanics is not similar to non-Hispanic white men after controlling for covariates.

Research Question 2: Are There Differences in Risk of Death between Hispanic Subgroups?

H₀: There will be no difference in the risk of death over time among Mexican men compared to non-Hispanic white men after adjusting for covariates in the model.

H_a: There will be a difference in the risk of death over time among Mexican men compared to non-Hispanic white men after adjusting for covariates in the model.

* Research hypothesis 2 will be assessed for all Hispanic groups included in this study.

Chapter 2: Methods

Study Design

A population-based retrospective cohort study was conducted using data obtained from National Cancer Institute's SEER database. Due to the lack of availability for complete data regarding PSA values, two SEER datasets were merged. The resulting dataset that includes all-inclusive information of patients diagnosed with PC from January 1st, 2004 to December 31st, 2013 was used in our survival analyses. The first dataset contains complete information from 2004 to 2009, with one year of follow-up to December 31st 2010. The second dataset includes comprehensive information from 2010 to 2012, with one year of follow-up to December 31st 2013. Cause of death from death certificates were used to identify prostate cancer-specific deaths. Cox proportional hazard modeling was used to estimate prostate cancer-specific risk of death hazard ratios for race and Hispanic ethnic groups with adjustment for all other covariates. Cause-specific survival time was calculated from the time of prostate cancer diagnosis to the date of death or last date of follow-up (December 31st, 2014), whichever occurred first. Cases that were reported alive at the end of each of the follow-up times were censored. Hazard ratios were used to compare racial groups and to assess the relationship between covariates (age, race/ethnicity, PSA risk, and Gleason score risk categories). To provide a more accurate assessment and to avoid excluding cases with informative survival experience, cases with missing information regarding date of diagnosis were assigned the median day of the month (day 15), or the median month of the year (June).

Characterization of Variables

For the purposes of this study, age at diagnosis was stratified into 5 age (in years) categories: 0 – 54, 55 – 64, 65 – 74, 75 – 84, 85+. Race was stratified into 5 mutually exclusive

groups: non-Hispanic White, non-Hispanic Black, American Indian/Alaskan Native, Asian/Pacific Islander, and Hispanic. Hispanics were further stratified into 6 ethnic populations: Mexican, Puerto Rican, Cuban, South/Central American, not otherwise specified (NOS) and Dominican.

All prognostic factor were classified in accordance with The National Comprehensive Cancer Network (NCCN) standard. PSA levels were recoded: low risk (0 – 9.9 ng/ml), intermediate risk (10 – 19.9 ng/ml), or high risk (20 – 98 ng/ml) levels. Gleason scores were reclassified as: low-grade (Gleason \leq 6), intermediate (Gleason = 7), and high-grade (Gleason = 8 – 10). Tumor stage was categorized as: low risk (T1-T2a), intermediate risk (Tc) and high risk (T2d-T4NOS) (Mohler, 2017).

Insurance status was recoded into patients with private insurance, Medicare or Medicaid, or uninsured. Marital status was recoded and categorized into single (never married), married, widowed, and divorced/separated.

Study Population and Data Source

The study included approximately 513,499 patients in 5 racial groups and 8 distinct Hispanic ethnic groups residing in 19 different geographic areas, which report cases to SEER. All men diagnosed with a first PC from January 1st, 2004 to December 31st, 2013, were included in the study.

The cohort was identified through SEER, a network of statewide population based registries that collect data on newly diagnosed cancers to support cancer-related research covering approximately 28% of the US population from 19 states (NCI, 2014). SEER routinely collects data on patient demographics, course of treatment, tumor morphology, stage of cancer at diagnosis, and conducts active patient vital status follow-up for 95% of all cases. The SEER

participant coverage is representative of the nation's vast array of racial and ethnic groups of all cancer types. These groups include 25% of non-Hispanic white, 26% of non-Hispanic black, 38% of Hispanic, 50% of Asian/Pacific Islander and 44% of American Indian/Alaskan Native (NCI, 2010).

Statistical Analysis

Survival Statistics Overview

Generally, survival rates measure the percentage of patients that remain alive after a specified period of time, following diagnosis. Survival rates are advantageous for monitoring the progression of treatment and early detection advancements of the majority of cancers. However, they do not take into account the proportion of patients that are cured from cancer because death may occur after the time period in question after a diagnosis. Relative survival is the most common cancer survival indicator used for the general population. It is expressed as the percentage of patients alive after a given period of time subsequent to diagnosis, over the percentage of patients expected to live based on normal life expectancy in the absence of cancer.

Historically, life expectancy data is limited for minority groups in the US including Hispanics. For this reason, cause-specific survival is a more appropriate survival measure used to compare among racial/ethnic groups. Cause-specific survival is defined as the percentage of patients that have not died from a disease during a specific time period after being diagnosed with the disease. Survival differences between populations are prone to bias and may be influenced by several factors. They include differences in the use of screening tests (PSA test), access to treatment, and accuracy of patient follow-up. These biases are prominent in populations that consist largely of foreign-born individuals, such as the Hispanic population in the US, due to difficulties in follow-up among these populations (Pinheiro, 2014).

Analysis

Multivariate survival analyses were conducted to estimate the cause-specific risk of death among race and Hispanic ethnicity. Adjusted and unadjusted hazard ratios (HR), with their corresponding 95% confidence intervals (CI), were measured using Cox proportional hazard regression models to assess relative disparities. These statistical models provide the means to evaluate differences in cause-specific survival while allowing for covariate adjustment of race, Hispanic ethnicity, age, year/month of diagnosis, insurance status, marital status, as well as PSA, tumor stage and Gleason score risk categories. Descriptive statistics were used to summarize sociodemographic and clinical characteristics by race/ethnicity. The proportional hazards assumption was assessed and satisfied for each variable included in the analysis. The p-values were set to the significance level of less than or equal to 0.05. The data was analyzed using SPSS statistical software version 23.

Chapter 3: Results

	N	%
Race/Ethnicity		
Non-Hispanic White	354375	69
Non-Hispanic Black	74582	14.5
American Indian/Alaskan Native	1593	0.3
Asian/Pacific Islander	23790	4.6
Hispanic	42113	8.2
<i>Mexican</i>	8998	21.4
<i>Puerto Rican</i>	1424	3.4
<i>Cuban</i>	809	1.9
<i>South/Central American</i>	3282	7.8
<i>NOS</i>	27223	64.6
<i>Dominican Republic</i>	377	0.9
Unknown	17046	3.3
Total	513499	100

Table 1. SEER Race/Ethnicity Characteristics, SEER 2004-2013.

Table 1 provides race/ethnicity characteristics in 513,499 men diagnosed with PC from 2004 – 2013, in the geographical areas covered by SEER. The majority of the PC population were White (69%), followed by Black (14.5%), Hispanic (8.2%), Asian/Pacific Islander (4.6%), American Indian/Alaskan Native (0.3%), and Unknown (3.3%). In total, 42,113 Hispanic men included in this study. The distribution of Hispanic men by ethnic subgroup was: 21.4% Mexican, 3.4% Puerto Rican, 1.9% Cuban, 7.8% South/Central American, 64.6% NOS, and 0.9%. Dominicans.

	Censored	Cause-Specific Death	Total
Race			
Non-Hispanic White	332600	17293	349893
Non-Hispanic Black	70052	4514	74566
American Indian/Alaskan Native	1457	136	1593
Asian/Pacific Islander	22705	1059	23764
Hispanic	44168	2457	46625
Total	487793	25706	513499

Table 2. Prostate Cancer-Specific Death & Censored Cases by Race, SEER 2004 – 2013.

Table 2 describes prostate cancer-specific deaths, and censored cases by race up to the date of last follow-up (December 31, 2014). The total study population was 513,499. Cases that were diagnosed with PC, as a second or higher order cancer, were excluded from the original sample. In total, the survival analyses included 25,706 cause-specific deaths and excluded 487,793 censored cases.

PSA Level Risk Categories	Low (0-9.9 ng/ml)		Intermediate (10 – 19.9 ng/ml)		High (20–98 ng/ml)		Unknown		Total	
	N	%	N	%	N	%	N	%	N	%
Race/Ethnicity										
Non-Hispanic White	226323	63.9	42042	11.9	33249	9.4	52761	14.9	354375	100
Non-Hispanic Black American	42482	57	10817	14.5	10946	14.7	10337	13.9	74582	100
Indian/Alaskan Native	797	50	260	16.3	303	19	233	14.6	1593	100
Asian/Pacific Islander	13524	56.8	3979	16.7	3241	13.6	3046	12.8	23790	100
Hispanic	22159	56.1	5770	14.6	5129	13	6461	16.3	39519	100
<i>Mexican</i>	4709	52.3	1425	15.8	1506	16.7	1358	15.1	8998	100
<i>Puerto Rican</i>	817	57.4	162	11.4	189	13.3	256	18	1424	100
<i>Cuban</i>	440	54.4	124	15.3	104	12.9	141	17.4	809	100
<i>South/Central American</i>	1869	56.9	489	14.9	470	14.3	454	13.8	3282	100
<i>NOS</i>	15420	56.6	3774	13.9	3125	11.5	4904	18	27223	100
<i>Dominican Republic</i>	197	52.3	46	12.2	49	13	85	22.5	377	100
Unknown	7700	45.2	1656	9.7	1185	7.0	6505	38.2	17046	100
Total	314278	61.2	64774	12.6	54367	10.6	80080	15.6	513499	100

Table 3. Race/Ethnicity by Prostate Specific Antigen (PSA) Level Risk Categories, SEER 2004 – 2013.

Table 3 presents characteristics for race/ethnicity by PSA level risk categories. Low, intermediate, and high PSA level risk categories accounted for 61.2%, 12.6%, and 10.6% of the cases studied respectively. White men were found to have a higher percentage of low PSA levels (63.9%), with lower intermediate (11.9%), and high (9.4%) levels compared to other races. Asian/Pacific Islanders had the highest percentage of intermediate risk PC (16.7%). Within the Hispanic ethnicities, Puerto Ricans (57.4%), South/Central Americans (56.9%), and NOS (56.6%) experienced higher percentage of low PSA levels relative to other groups. Mexicans (15.8%) and Cubans (15.3%) had the highest percentages of intermediate PSA levels. Mexicans (16.7%) also experienced the largest percentage of high PSA levels compared to any other race or Hispanic ethnic group.

Gleason Score Risk Categories	Low grade (≤6)		Intermediate grade (7)		High grade (8-10)		Unknown		Total	
	N	%	N	%	N	%	N	%	N	%
Race/Ethnicity										
Non-Hispanic White	157946	44.6	126422	35.7	51983	14.7	18024	5.1	354375	100
Non-Hispanic Black American	30037	40.3	28586	38.2	11768	15.8	4191	5.6	74582	100
Indian/Alaskan Native	603	37.9	556	34.9	270	16.9	164	10.3	1593	100
Asian/Pacific Islander	9246	38.9	8316	35	4892	20.6	1336	5.6	23790	100
Hispanic	19055	45.2	13849	32.9	6631	15.7	2578	6.1	42113	100
<i>Mexican</i>	3697	41.1	2903	32.3	1634	18.2	764	8.5	8998	100
<i>Puerto Rican</i>	590	41.4	447	31.4	256	18	131	9.2	1424	100
<i>Cuban</i>	366	45.2	254	31.4	132	16.3	57	7	809	100
<i>South/Central American</i>	1470	44.8	1097	33.4	545	16.6	170	5.2	3282	100
<i>NOS</i>	12764	46.9	9033	33.2	4002	14.7	1424	5.2	27223	100
<i>Dominican Republic</i>	168	44.6	115	30.5	62	16.4	32	8.5	377	100
Unknown	8752	51.3	5223	30.6	2068	12.1	1003	5.9	17046	100
Total	225639	43.9	182952	35.6	77612	15.1	27296	5.3	513499	100

Table 4. Race/Ethnicity by Gleason Score Risk Categories, SEER 2004 – 2013.

Table 4 provides characteristics for race/ethnicity by Gleason level risk categories. Low, intermediate, and high Gleason level risk categories accounted for 43.9%, 35.6%, and 15.1% of the cases studied respectively. Among race, White (44.6%) and Hispanic (45.2%) men were found to have a higher percentage of low risk Gleason scores. Hispanic men had a lower

proportion of intermediate risk Gleason scores (32.9%). Asian/Pacific Islander had a larger percentage of cases in the high risk category (20.6%). Within Hispanic ethnic subgroups, NOS (46.9%) and Cubans experienced higher percentage of low risk Gleason scores compared to other groups. South/Central Americans (33.4%), NOS (33.2%), and Mexicans (32.3%) also experienced the highest percentage of intermediate risk Gleason scores. Mexicans (18.2%) and Puerto Ricans (18%) experienced the highest percentages of high risk Gleason scores.

Tumor Stage Risk Categories	Low (T1c-T2a)		Intermediate (T2b-c)		High (>T3)		Unknown		Total	
	N	%	N	%	N	%	N	%	N	%
Race/Ethnicity										
Non-Hispanic White	229467	64.8	26664	7.5	80570	22.7	17674	5	354375	100
Non-Hispanic Black	51317	68.8	5385	7.2	13852	18.6	4028	5.4	74582	100
Amer. Indian/Alaskan Native	925	58.1	103	6.5	411	25.8	154	9.7	1593	100
Asian/Pacific Islander	15494	65.1	1609	6.8	4886	20.5	1801	7.6	23790	100
Hispanic	25997	68.8	2590	6.9	6631	17.5	2578	6.8	37796	100
<i>Mexican</i>	5436	60.4	499	5.5	2219	24.7	844	9.4	8998	100
<i>Puerto Rican</i>	903	63.4	135	9.5	252	17.7	134	9.4	1424	100
<i>Cuban</i>	529	65.4	66	8.2	149	18.4	65	8	809	100
<i>South/Central American</i>	2206	67.2	240	7.3	667	20.3	169	5.2	3282	100
<i>NOS</i>	16660	61.2	1614	5.9	6441	23.7	2508	9.2	27223	100
<i>Dominican Republic</i>	263	69.8	36	9.5	44	11.7	34	9	377	100
Unknown	7262	42.6	417	2.4	5830	34.2	3537	20.7	17046	100
Total	330462	64.4	36768	7.2	115321	22.5	30948	6	513499	100

Table 5. Race/Ethnicity by Tumor Stage Risk Categories, SEER 2004 – 2013.

Table 5 summarizes characteristics for race/ethnicity by tumor stage risk categories. Low, intermediate, and high tumor stage risk categories accounted for 64.4%, 7.2%, and 22.5% of the total cases studied respectively. Both Hispanic and Black men were found to have a higher percentage of low risk tumor stage (68.8%). White and Black men had the highest percentage of intermediate risk PC accounting for 7.5% and 7.2 % respectively. American Indian/Alaskan Native men were found to have the highest proportion of High risk tumor stage (25.8%). Within the Hispanic ethnicities, Dominicans (69.8%) and South/Central Americans (67.2%) experienced a higher percentage of low risk tumor stage relative to other ethnicities. Dominicans (9.5%),

Puerto Ricans (9.5%), and Cubans (8.2%) had the highest percentages in the intermediate risk tumor stage category. Mexicans (24.7%) and NOS (23.7%) also experienced the largest percentage of high risk tumor stage compared to any other Hispanic ethnic group.

Tumor Stage	Localized		Distant		Unknown		Total	
	N	%	N	%	N	%	N	%
Race/Ethnicity								
Non-Hispanic White	326470	92.1	14970	4.2	12935	3.7	354375	100
Non-Hispanic Black	67532	90.5	4175	5.6	2875	3.9	74582	100
American Indian/Alaskan Native	1352	84.9	149	9.4	92	5.8	1593	100
Asian/Pacific Islander	21158	88.9	1275	5.4	1357	5.7	23790	100
Hispanic	36791	87.4	2348	5.6	2974	7.1	42113	100
<i>Mexican</i>	7656	85.1	760	8.4	582	6.5	8998	100
<i>Puerto Rican</i>	1210	85	120	8.4	94	6.6	1424	100
<i>Cuban</i>	713	88.1	48	5.9	48	5.9	809	100
<i>South/Central American</i>	2951	89.9	200	6.1	131	4	3282	100
<i>Dominican Republic</i>	326	86.5	26	6.9	25	6.6	377	100
<i>NOS</i>	23935	87.9	1194	4.4	2094	7.7	27223	100
Unknown	13371	78.4	184	1.1	3491	20.5	17046	100
Total	466674	90.9	23101	4.5	23724	4.6	513499	100

Table 6. Race/Ethnicity by SEER Historic Stage, SEER 2004 – 2013.

Table 6 describes characteristics for race/ethnicity by SEER historic stage. Localized, distant and unknown stage categories account for 90.9%, 4.5%, and 4.6% of the cases studied respectively. Non-Hispanic white men were found to have a highest percentage of localized tumors (92.1%), and the lowest distant stage proportion (4.2%) compared to other race/ethnicities. American Indian/Alaskan Natives (9.4%) showed the highest percentage of distant stage PC. Within the Hispanic ethnic groups, South/Central Americans (89.9%), and Cubans (88.1%) experienced highest percentages of localized tumors relative to other groups, while, the unknowns experienced the lowest proportion. Mexican (8.4%) and Puerto Rican (8.4%) men both experienced the largest percentage of distant stage tumors compared to any other Hispanic ethnic group.

	Model 1A*			Model 1B†			Model 2A‡			Model 2B‡		
	HR	p-value	CI	HR	p-value	CI	HR	p-value	CI	HR	p-value	CI
Race/Ethnicity												
Non-Hispanic White	-	-	-	-	-	-	-	-	-	-	-	-
Non-Hispanic Black	1.57	<0.01	1.51 - 1.62	1.09	<0.01	1.05 - 1.27	1.56	<0.01	1.5 - 1.61	1.08	<0.01	1.04 - 1.12
American Indian/Alaskan Native	1.64	<0.01	1.38 - 1.95	1.03	0.74	.87 - 1.23	1.58	<0.01	1.33 - 1.89	1.01	0.9	0.85 - 1.21
Asian/Pacific Islander	0.87	<0.01	0.81 - 0.93	0.75	<0.01	0.7 - 0.8	0.86	<0.01	0.81 - 0.92	0.75	<0.01	0.7 - 0.8
Hispanic	1.17	<0.01	1.12 - 1.22	0.97	0.25	0.93 - 1.02						
<i>Mexican</i>	-	-	-	-	-	-	1.47	<0.01	1.36 - 1.59	1.03	0.45	0.95 - 1.11
<i>Puerto Rican</i>	-	-	-	-	-	-	2.02	<0.01	1.71 - 2.39	1.38	<0.01	1.17 - 1.63
<i>Cuban</i>	-	-	-	-	-	-	1.49	<0.01	1.19 - 1.88	1.24	0.07	0.98 - 1.56
<i>South/Central American</i>	-	-	-	-	-	-	1.24	<0.01	1.06 - 1.44	0.94	0.45	0.81 - 1.1
<i>NOS</i>	-	-	-	-	-	-	0.81	<0.01	0.76 - 0.87	0.78	<0.01	0.73 - 0.83
<i>Dominican Republic</i>	-	-	-	-	-	-	1.7	<0.01	1.16 - 2.5	1.02	0.91	0.7 - 1.5
Unknown	0.34	<0.01	0.3 - 0.38	0.42	<0.01	0.37 - 0.47	0.33	<0.01	0.29 - 0.38	0.41	<0.01	0.36 - 0.47
Age at diagnosis												
0-54	-	-	-	-	-	-	-	-	-	-	-	-
55-64	1.08	<0.01	1.02 - 1.15	1.03	0.36	0.97 - 1.1	1.08	0.01	1.02 - 1.15	1.03	0.37	0.97 - 1.1
65-74	1.54	<0.01	1.45 - 1.63	1.25	<0.01	1.17 - 1.32	1.53	<0.01	1.44 - 1.63	1.25	<0.01	1.17 - 1.32
75-84	4.2	<0.01	3.96 - 4.45	1.96	<0.01	1.84 - 2.08	4.19	<0.01	3.95 - 4.45	1.96	<0.01	1.84 - 2.08
>85+	10.91	<0.01	10.25 - 11.62	2.55	<0.01	2.39 - 2.73	10.83	<0.01	10.17 - 11.54	2.54	<0.01	2.38 - 2.72
PSA Value												
Low (0 – 9.9 ng/ml)	-	-	-	-	-	-	-	-	-	-	-	-
Intermediate (10 – 19.9 ng/ml)	-	-	-	2.19	<0.01	2.08 - 2.3	-	-	-	2.19	<0.01	2.08 - 2.31
High (20 – 98 ng/ml)	-	-	-	6.7	<0.01	6.43 - 6.98	-	-	-	6.71	<0.01	6.44 - 6.99
Unknown	-	-	-	1.95	<0.01	1.86 - 2.05	-	-	-	1.95	<0.01	1.86 - 2.05
Gleason Score												
Low grade (≤6)	-	-	-	-	-	-	-	-	-	-	-	-

Intermediate grade (7)	-	-	-	1.16	<0.01	1.1 - 1.21	-	-	-	1.16	<0.01	1.1 - 1.21
High grade (8-10)	-	-	-	4.55	<0.01	4.36 - 4.75	-	-	-	4.54	<0.01	4.35 - 4.74
Unknown	-	-	-	4.51	<0.01	4.27 - 4.76	-	-	-	4.48	<0.01	4.25 - 4.73
Tumor Stage Risk												
Low (T1a - T2a)	-	-	-	-	-	-	-	-	-	-	-	-
Intermediate (T2b - T2c)	-	-	-	1.35	<0.01	1.28 - 1.43	-	-	-	1.35	<0.01	1.28 - 1.43
High (T3a -T4)	-	-	-	2.16	<0.01	2.09 - 2.24	-	-	-	2.16	<0.01	2.09 - 2.24
Unknown	-	-	-	3.82	<0.01	3.64 - 4.0	-	-	-	3.82	<0.01	3.64 - 4.01
Insurance Status												
Private Insurance	-	-	-	-	-	-	-	-	-	-	-	-
Medicare/Medicaid	-	-	-	1.35	<0.01	1.27 - 1.44	-	-	-	1.36	<0.01	1.28 - 1.45
Uninsured	-	-	-	1.53	<0.01	1.38 - 1.7	-	-	-	1.54	<0.01	1.38 - 1.71
Unknown	-	-	-	0.7	<0.01	0.67 - 0.74	-	-	-	0.7	<0.01	0.67 - 0.74
Marital Status												
Married	-	-	-	-	-	-	-	-	-	-	-	-
Single/Unmarried	-	-	-	1.34	<0.01	1.29 - 1.39	-	-	-	1.34	<0.01	1.29 - 1.39
Widowed	-	-	-	1.19	<0.01	1.15 - 1.24	-	-	-	1.19	<0.01	1.15 - 1.24
Divorced/Separated	-	-	-	1.32	<0.01	1.27 - 1.38	-	-	-	1.32	<0.01	1.26 - 1.38
Unknown	-	-	-	0.87	<0.01	0.83 - 0.91	-	-	-	0.88	<0.01	0.84 - 0.92

* Model 1A was adjusted for race, and age

† Model 1B was adjusted for model 1 variables plus Insurance Status, Marital Status, PSA, Gleason score, and Tumor Stage Risk Categories

‡ Model 2A was adjusted for Race, Hispanic ethnicity and age

‡ Model 2B was adjusted for model 2A variables plus Insurance Status, Marital Status, PSA, Gleason Score, and Tumor Stage Risk Categories

Table 7. Risk of Death from Prostate Cancer by Race/Ethnicity, Sociodemographic and Prognostic Factors, SEER 2004 – 2013.

Table 7 details the results of 4 Cox proportional hazard models that were created to analyze the risk of death by race, Hispanic ethnicity, age, insurance status, marital status, and prognostic factors in patients diagnosed with PC from 2004 to 2013. Hispanic men had a 17% (HR = 1.17, $p < 0.01$, CI [1.12 – 1.22]) higher risk of death when compared to White men. However, after adjustment for age, race, sociodemographic, and prognostic factors (Model 1B), the increased risk of death for Hispanics disappeared and was no longer significant (HR = 0.97, $p = 0.25$, CI [0.93 – 1.02]). However, after stratifying Hispanics into their corresponding ethnicity and adjusting for all variables of interest, Puerto Rican men were found to have 38% higher risk (HR = 1.38, $p < 0.01$, CI [1.17 – 1.63]) of death compared to any other ethnic group (Model 2B). Additionally, Black men had a 57% (HR = 1.57, $p < 0.01$, CI [1.51 – 1.62]) higher risk of death when compared to White men (Model 1A). Prostate cancer survival disparity among Black men decreased to 9% (HR = 1.09, $p < 0.01$, CI [1.05 – 1.27]) after adjusting for all variables of interest. Furthermore, there appears to be a significant survival advantage among Asians/Pacific Islanders (HR = 0.87, $p < 0.01$, CI [0.81 – 0.93]) in model 1A that increases (HR = 0.75, $p < 0.01$, CI [0.7 – 0.8]) after all variables are adjusted for in model 2B.

	Model 1A [*]			Model 1B [†]			Model 2A [†]			Model 2B [‡]		
	HR	<i>P</i> -value	CI	HR	<i>P</i> -value	CI	HR	<i>P</i> -value	CI	HR	<i>P</i> -value	CI
Race/Ethnicity												
Non-Hispanic White	-	-		-	-		-	-		-	-	
Non-Hispanic Black	1.55	<0.01	1.46 - 1.64	1.3	<0.01	1.22 - 1.38	1.54	<0.01	1.45 - 1.63	1.2	<0.01	1.13 - 1.27
American Indian/Alaskan Native	1.46	0.02	1.06 - 2.03	1.17	0.36	0.84 - 1.62	1.41	0.04	1.02 - 1.96	1.1	0.59	0.79 - 1.52
Asian/Pacific Islander	0.8	<0.01	0.71 - 0.91	0.7	<0.01	0.62 - 0.79	0.79	<0.01	0.7 - 0.89	0.7	<0.01	0.62 - 0.79
Hispanic	1.07	0.11	0.99 - 1.15	0.93	0.07	0.86 - 1.01	-	-	-	-	-	-
<i>Mexican</i>	-	-		-	-	-	1.31	<0.01	1.13 - 1.53	1.04	0.66	0.89 - 1.21
<i>Puerto Rican</i>	-	-		-	-	-	1.95	<0.01	1.43 - 2.65	1.65	<0.01	1.21 - 2.25
<i>Cuban</i>	-	-		-	-	-	1.59	0.01	1.1 - 2.29	1.4	0.07	0.97 - 2.02
<i>South/Central American</i>	-	-		-	-	-	1.06	0.69	0.8 - 1.4	0.89	0.4	0.67 - 1.17
<i>NOS</i>	-	-		-	-	-	0.72	<0.01	0.64 - 0.81	0.66	<0.01	0.59 - 0.74
<i>Dominican Republic</i>	-	-		-	-	-	1.68	0.15	0.84 - 3.36	1.21	0.59	0.61 - 2.43
Unknown	0.48	<0.01	0.4 - 0.57	0.47	<0.01	0.39 - 0.56	0.47	<0.01	0.4 - 0.57	0.46	<0.01	0.38 - 0.55
Age at diagnosis												
0-54	-	-		-	-		-	-		-	-	
55-64	1.29	<0.01	1.16 - 1.44	1.19	<0.01	1.07 - 1.33	1.29	<0.01	1.16 - 1.44	1.21	<0.01	1.08 - 1.34
65-74	2.18	<0.01	1.96 - 2.41	1.71	<0.01	1.54 - 1.89	2.17	<0.01	1.96 - 2.41	1.75	<0.01	1.58 - 1.95
75-84	5.79	<0.01	5.22 - 6.42	3.21	<0.01	2.89 - 3.56	5.78	<0.01	5.21 - 6.41	3.27	<0.01	2.94 - 3.63
>85+	21.37	<0.01	19.12 - 23.89	7.11	<0.01	6.35 - 7.97	21.35	<0.01	19.09 - 23.86	7.11	<0.01	6.33 - 7.97
PSA Value												
Low (0-9.9 ng/ml)	-	-		-	-		-	-		-	-	
Intermediate (10 – 19.9 ng/ml)	-	-		1.69	<0.01	1.59 - 1.8	-	-		1.69	<0.01	1.59 - 1.8
High (20 – 98 ng/ml)	-	-		3.17	<0.01	3.0 - 3.36	-	-		3.18	<0.01	3.0 - 3.36
Unknown	-	-		2.29	<0.01	2.15 - 2.43	-	-		2.29	<0.01	2.15 - 2.44
Gleason Score												
Low grade (≤6)	-	-		-	-		-	-		-	-	

Intermediate grade (7)	-	-	-	1.75	<0.01	1.64 - 1.87	-	-	-	1.75	<0.01	1.64 - 1.87
High grade (8-10)	-	-	-	6.91	<0.01	6.5 - 7.34	-	-	-	6.89	<0.01	6.49 - 7.32
Unknown	-	-	-	4.99	<0.01	3.38 - 6.23	-	-	-	4.99	<0.01	4.53 - 5.51
Tumor Stage Risk												
Low (T1a - T2a)	-	-	-	-	-	-	-	-	-	-	-	-
Intermediate (T2b - T2c)	-	-	-	1.25	<0.01	1.16 - 1.84	-	-	-	1.24	<0.01	1.16 - 1.33
High (T3a -T4)	-	-	-	1.62	<0.01	1.54 - 1.69	-	-	-	1.61	<0.01	1.53 - 1.68
Unknown	-	-	-	4.78	<0.01	3.52 - 6.48	-	-	-	4.51	<0.01	3.33 - 6.012
Insurance Status												
Private Insurance	-	-	-	-	-	-	-	-	-	-	-	-
Medicare/Medicaid	-	-	-	1.39	<0.01	1.23 - 1.56	-	-	-	1.39	<0.01	1.24 - 1.57
Uninsured	-	-	-	1.65	<0.01	1.31 - 2.08	-	-	-	1.66	<0.01	1.31 - 2.09
Unknown	-	-	-	1.1	0.06	1.0 - 1.22	-	-	-	1.11	<0.01	1.0 - 1.22
Marital Status												
Married	-	-	-	-	-	-	-	-	-	-	-	-
Single/Unmarried	-	-	-	1.48	<0.01	1.38 - 1.58	-	-	-	1.48	<0.01	1.38 - 1.58
Widowed	-	-	-	1.44	<0.01	1.34 - 1.54	-	-	-	1.44	<0.01	1.34 - 1.54
Divorced/Separated	-	-	-	1.5	<0.01	1.39 - 1.62	-	-	-	1.49	<0.01	1.38 - 1.61
Unknown	-	-	-	1.08	0.02	1.01 - 1.16	-	-	-	1.09	0.01	1.02 - 1.17

* Model 1A was adjusted for race, and age

† Model 1B was adjusted for model 1 variables plus Insurance Status, Marital Status, PSA, Gleason score, and Tumor Stage Risk Categories

‡ Model 2A was adjusted for Race, Hispanic ethnicity and age

‡ Model 2B was adjusted for model 2A variables plus Insurance Status, Marital Status, PSA, Gleason Score, and Tumor Stage Risk Categories

Table 8. Risk of Death from Localized Prostate Cancer by Race/Ethnicity, Sociodemographic and Prognostic Factors, SEER 2004 – 2013.

Table 8 describes the results of 4 models to assess the risk of death from localized PC by race, Hispanic ethnicity, sociodemographic, and prognostic factors in patients diagnosed with PC from 2004 to 2013. Survival disparities for Hispanic men disappeared when examining localized PC cases only. After adjusting for race and age, the risk of death in Hispanics (HR = 1.07, $p = 0.11$, CI [0.99 – 1.15]) was not significantly different than the referent group (model 1A). After stratifying Hispanics into their corresponding ethnic subgroups and adjusting for age, and ethnicity, Mexican (HR = 1.31, $p < 0.01$, CI [1.13 - 1.53]) and Puerto Rican men (HR = 1.95, $p < 0.01$, CI [1.43 – 2.65]) had a higher risk of death compared to any other ethnic group (Model 2A). However, after adjusting for age, sociodemographic and clinical prognostic factors (Model 2B), localized PC survival disparities in Mexican men disappeared (HR = 1.04, $p = 0.66$, CI [0.89 – 1.21]), while survival disparities persisted among Puerto Rican men (HR = 1.65, $p < 0.01$, CI [1.21 – 2.25]). Additionally, Black men had a 55% (HR = 1.55, $p < 0.01$, CI [1.46 – 1.64]) higher risk of death when compared to White men (Model 1A). Prostate cancer survival disparity among Black men reduced to 30% (HR = 1.30, $p < 0.01$, CI [1.22 – 1.38]) after adjusting for all variables of interest. Furthermore, there appears to be a survival advantage among Asians/Pacific Islanders (HR = 0.8, $p < 0.01$, CI [0.71 – 0.91]) in model 1A that increases (HR = 0.7, $p < 0.01$, CI [0.62 – 0.79]) after all variables are adjusted for in model 2B.

	Model 1A*			Model 1B [†]			Model 2A [†]			Model 2B [‡]		
	HR	<i>p</i> -value	CI	HR	<i>p</i> -value	CI	HR	<i>p</i> -value	CI	HR	<i>p</i> -value	CI
Race/Ethnicity												
Non-Hispanic White	-	-	-	-	-	-	-	-	-	-	-	-
Non-Hispanic Black	1.05	0.08	0.99 - 1.11	0.98	0.47	0.93 - 1.04	1.05	0.1	0.99 - 1.11	0.98	0.44	1.13 - 1.27
American Indian/Alaskan Native	0.98	0.86	0.76 - 1.26	0.87	0.3	0.68 - 1.13	0.97	0.84	0.75 - 1.26	0.87	0.29	0.79 - 1.52
Asian/Pacific Islander	0.72	<0.01	0.65 - 0.79	0.71	<0.01	0.65 - 0.79	0.72	<0.01	0.65 - 0.79	0.71	<0.01	0.62 - 0.79
Hispanic	0.97	0.34	0.91 - 1.03	0.95	0.16	0.89 - 1.02	-	-	-	-	-	-
<i>Mexican</i>	-	-	-	-	-	-	0.95	0.33	.84 - 1.06	0.89	0.06	0.89 - 1.21
<i>Puerto Rican</i>	-	-	-	-	-	-	1.28	0.05	1.0 - 1.64	1.21	0.14	1.21 - 2.25
<i>Cuban</i>	-	-	-	-	-	-	0.9	0.62	0.61 - 1.35	0.95	0.82	0.97 - 2.02
<i>South/Central American</i>	-	-	-	-	-	-	0.96	0.69	0.78 - 1.18	0.98	0.86	0.67 - 1.17
<i>NOS</i>	-	-	-	-	-	-	0.91	0.06	0.83 - 1.0	0.92	0.08	0.59 - 0.74
<i>Dominican Republic</i>	-	-	-	-	-	-	0.86	0.61	0.47 - 1.55	0.86	0.61	0.61 - 2.43
Unknown	0.42	<0.01	0.32 - 0.55	0.5	<0.01	0.38 - 0.66	0.42	<0.01	0.32 - 0.55	0.5	<0.01	0.38 - 0.55
Age at diagnosis												
0-54	-	-	-	-	-	-	-	-	-	-	-	-
55-64	0.95	0.22	0.88 - 1.03	0.98	0.63	0.91 - 1.06	0.95	0.21	0.88 - 1.03	0.98	0.63	0.91 - 1.06
65-74	0.96	0.36	0.89 - 1.04	1.02	0.7	0.94 - 1.1	0.96	0.35	0.89 - 1.04	1.02	0.71	0.94 - 1.1
75-84	1.31	<0.01	1.21 - 1.42	1.29	<0.01	1.19 - 1.4	1.31	<0.01	1.21 - 1.41	1.29	<0.01	1.19 - 1.4
>85+	2.12	<0.01	1.95 - 2.3	1.88	<0.01	1.73 - 2.05	2.12	<0.01	1.95 - 2.3	1.88	<0.01	1.73 - 2.05
PSA Value												
Low (0-9.9 ng/ml)	-	-	-	-	-	-	-	-	-	-	-	-
Intermediate (10 – 19.9 ng/ml)	-	-	-	1.09	0.09	0.99 - 1.19	-	-	-	1.09	0.08	0.99 - 1.2
High (20 – 98 ng/ml)	-	-	-	1.4	<0.01	1.3 - 1.5	-	-	-	1.4	<0.01	1.3 - 1.5
Unknown	-	-	-	1.25	<0.01	1.15 - 1.36	-	-	-	1.25	<0.01	1.15 - 1.37

Gleason Score												
Low grade (≤6)	-	-	-	-	-	-	-	-	-	-	-	-
Intermediate grade (7)	-	-	-	0.55	<0.01	0.5 - 0.6	-	-	-	0.55	<0.01	0.5 - 0.6
High grade (8-10)	-	-	-	0.9	<0.01	0.84 - 0.95	-	-	-	0.9	<0.01	0.84 - 0.95
Unknown	-	-	-	1.25	<0.01	1.17 - 1.33	-	-	-	1.25	<0.01	1.17 - 1.33
Tumor Stage Risk												
Low (T1a - T2a)	-	-	-	-	-	-	-	-	-	-	-	-
Intermediate (T2b - T2c)	-	-	-	1.13	<0.01	1.03 - 1.23	-	-	-	1.13	<0.01	1.03 - 1.23
High (T3a -T4)	-	-	-	1.26	<0.01	1.2 - 1.33	-	-	-	1.26	<0.01	1.2 - 1.33
Unknown	-	-	-	1.45	<0.01	1.36 - 1.55	-	-	-	1.45	<0.01	1.36 - 1.55
Insurance Status												
Private Insurance	-	-	-	-	-	-	-	-	-	-	-	-
Medicare/Medicaid	-	-	-	1.09	0.02	1.01 - 1.18	-	-	-	1.1	0.02	1.02 - 1.19
Uninsured	-	-	-	1.11	0.1	0.98 - 1.25	-	-	-	1.11	0.09	0.98 - 1.26
Unknown	-	-	-	1.17	<0.01	1.05 - 1.3	-	-	-	1.17	<0.01	1.06 - 1.3
Marital Status												
Married	-	-	-	-	-	-	-	-	-	-	-	-
Single/Unmarried	-	-	-	1.16	<0.01	1.1 - 1.23	-	-	-	1.16	<0.01	1.1 - 1.23
Widowed	-	-	-	1.16	<0.01	1.09 - 1.23	-	-	-	1.16	<0.01	1.09 - 1.23
Divorced/Separated	-	-	-	1.17	<0.01	1.1 - 1.24	-	-	-	1.16	<0.01	1.09 - 1.24
Unknown	-	-	-	0.85	<0.01	0.78 - 0.92	-	-	-	0.85	<0.01	0.78 - 0.92

* Model 1A was adjusted for race, and age

† Model 1B was adjusted for model 1 variables plus Insurance Status, Marital Status, PSA, Gleason score, and Tumor Stage Risk Categories

‡ Model 2A was adjusted for Race, Hispanic ethnicity and age

‡ Model 2B was adjusted for model 2A variables plus Insurance Status, Marital Status, PSA, Gleason Score, and Tumor Stage Risk Categories

Table 9. Risk of Death from Distant Stage Prostate Cancer by Race/Ethnicity, Sociodemographic and Prognostic Factors, SEER 2004 – 2013.

Table 9 summarizes the results of 4 models that were created to examine the risk of death by race, Hispanic ethnicity, sociodemographic, and prognostic factors in patients diagnosed with distant stage PC from 2004 to 2013. It appears that survival disparities among Hispanic men diagnosed with distant stage PC were non-significant in all models, after adjusting for all variables that include race, Hispanic ethnicity, age, insurance status, marital status, PSA, Gleason score, and tumor stage risk categories (Models 1A, 1B, 2A, and 2B).

Chapter 4: Discussion

Cox proportional hazards regression revealed that Hispanics, overall, show an increased risk of death in comparison to NHW HR = 1.17 (95% CI: 1.12-1.22) over time. That difference disappears after adjustment for prognostic factors HR = 0.97 (95% CI: 0.93-1.02; p -value = 0.25). These results suggest three notions: Firstly, the known overdiagnosis of initial indolent PC cancers is much higher in the referent group (NHW) due to more prevalent PSA screening among them. Secondly, Hispanics are experiencing worse PSA risk categories. Lastly, among those with unknown stage, Hispanics do relatively poorly, which may also account for some of the increased risk of death in relation to NHW. Although the proportion of Hispanic men with unknown stage is only 7.1%, when examining unknown stage cases only and in comparison to the referent group, they are experiencing an increased risk of death (HR = 4.7; 95 % CI: 3.57 – 6.19) that may be large enough to skew the overall risk of death among Hispanic men as a whole. Moreover, when examining Hispanic groups, NOS men had the largest proportion of unknown stage (7.7%).

The results call attention to members of the Hispanic population living in the U.S. who may be undocumented or homeless. Due to the heterogeneity among Hispanics, there is also an underlying need for information that is both accurate and up-to-date to appropriately assess any health disparities that take into account their growing diversity. Unfortunately, undocumented Hispanic immigrants in the U.S. represent a “hidden” population that is challenging to sample, in part, because there is a great deal of stigma and fear of deportation associated with this immigrant status. Being undocumented is also a known risk factor for the lack of access to healthcare among undocumented Hispanics (Pérez-Escamilla, 2010).

Language barriers are also a major risk factor known to cause deleterious effects, especially when it comes to access to healthcare. These barriers are associated with patients being less likely to have a usual source of healthcare. In addition, these patients are less likely to obtain preventive services and return to follow-up appointments at reduced rates (Flores, 2006). *Machismo* is a term used to describe cultural attitudes and identities related with the concept of masculinity according to the Hispanic culture. *Machismo* can influence health behavior and be a cultural barrier to health care. Hispanic men often have the belief that enduring pain is necessary to “prove manhood” and consulting a physician can be viewed as an indication of weakness. Another cultural concept seen among Hispanic men is known as *fatalismo*. *Fatalismo* is the belief that people cannot change the progression of their disease because it is intimately linked with their life destiny. Because of *fatalismo*, Hispanic individuals are often less likely to follow prescribed treatment and preventive care (Caballero, 2011). These barriers, alone or in combination, can prevent some Hispanic men from obtaining the adequate healthcare and preventive services they require. As a result, Hispanic men are more likely to be diagnosed at a more progressive stage of disease, with higher risk PSA levels. More should be done to improve stage at diagnosis and access to quality healthcare for all Hispanics to eliminate the persisting disparities.

To further examine a more meaningful disparity, we restricted our analysis to those with localized stage and PSA larger than 9.9 ng/ml. For these intermediate risk stages that are more prone to disparities, due to differential treatment or access to quality healthcare, there were no differences seen between Hispanics and the referent group HR = 1.03 (95% CI: 0.96 – 1.09, p-value = 0.44); however, the HR appears to improve after adjusting for prognostic factors (HR = 0.95, 95% CI: 0.89 – 1.01, p-value = 0.09), which may indicate that Hispanics present marginally

worse biological characteristics (e.g. PSA levels, Gleason scores, tumor stage). After adjusting for all prognostic and social factors, Hispanics show a theoretical survival advantage in comparison to NHW HR = 0.93 (95% CI: 0.87-0.99). Contrary to anticipated results, social factors included in this study – marital status and insurance status – did not appear to add a significant survival advantage for Hispanics.

Among the different Hispanic groups, Puerto Rican men living in the U.S. (HR = 1.38, p -value <0.01, 95% CI: 1.17 – 1.63) showed the highest disparity in relation to NHW but this estimate may be impacted to some extent by bias. Unfortunately, in U.S. cancer surveillance data, not all Hispanics have a specified ethnic group recoded. Often, these data come from death certificates which may yield bias when it comes to PC survival among Hispanic ethnic populations. As referred in the literature, those with a specified Hispanic ethnicity will have an artificially higher risk of death compared to those without one, also known as the NOS bias (Pinheiro, 2013). This bias may be large enough to significantly influence and artificially increase the risk of death among Puerto Ricans, as seen in our results (model 2B of tables 6 & 7). Moreover, SEER data has also been identified as having a higher likelihood of incomplete follow-up (specifically missing death information) among Hispanics when compared to NHW and blacks. Therefore, it cannot be assumed that random censoring is occurring throughout race/ethnicity. Cases with worse prognosis will tend to have incomplete follow-up than cases with better prognosis (Pinheiro, 2014). Since Puerto Ricans are U.S. citizens, their deaths will be captured in totality (Pinheiro, 2011) and will have a higher likelihood of a complete follow-up. The same will not necessary apply other Hispanic groups. Thus, survival may be inflated among other Hispanic groups in comparison to Puerto Ricans.

Generally, Hispanic immigrants who have lived in the U.S. for over ten years are more likely to experience less favorable health outcomes than recent immigrants. However, in comparison to other Hispanic heritage groups, Puerto Ricans tend to have more adverse health outcomes, whether they were born in Puerto Rico or not. This could be due to differing experiences of an array of risk factors that include racial discrimination, acculturation, and structural barriers that yield disparities in health care access, quality of care, and overall health (Greer, 2017). However, when it comes to prognostic factors, the situation is less clear. Our results suggest a SES driven disadvantage for US-born or US-related minorities that translates into worse survival as well as mortality rates (Pinheiro et al., in press.)

Strengths and Study Limitations

The uniqueness of the groups assessed in the study have added new knowledge about survival disparities among men of Hispanic, black, white and Asian descent living in the United States. This study has over a ten-year span and is population-based, avoiding selection issues from hospital-based only samples. Lastly, the data used in the study is highly rated among cancer epidemiology researchers.

A drawback of this study, however, was the unavailability of the data regarding patient, provider and system level variables. Thus, patient treatment preference, quality of care and the type training physicians based their diagnosis on could not be included in the analysis. This study was also limited in clinical data. Information on comorbidity and other data, which have the potential to create bias, are not collected by SEER (Moses et al, 2016). Future research could examine the distinction between race and ethnicity by further investigate survival in ethnic subgroups, while accounting for additional variables that are known determinants for PC survival

but could not be accounted for here (mentioned in the literature review). Another limitation is the high proportion of Hispanic NOS cases as previously mentioned.

There are also limitations regarding the dataset that were used in our analysis. As mentioned in the study design, there is a bipartition in the dataset that resulted in two follow-up times. The fact that we adjusted for year of diagnosis in the multivariate analysis eliminated any bias that could have resulted. Moreover, in the dataset that includes data from 2004 to 2009, PSA values are likely underestimated. However, it is unlikely that this could lead to misclassification and bias our main results when examining various race/ethnic groups.

Chapter 5: Conclusion

This study is the first study, to our knowledge, that examine racial/ethnic differences in prostate cancer survival with focus on distinct ethnic Hispanic groups in the US, while assessing the impact of clinical diagnostic factors used to determine treatment options and diagnosis: PSA level and Gleason score risk categories. The data analyzed was obtained through SEER from 2004-2013. In total 513,499 PC cases were analyzed, 9.1% (46,625 men) of which were of Hispanic ethnicity.

Cox proportional hazards models were used to calculate disease-specific hazard ratios to determine the risk of death for men with PC. Upon the addition of all covariates including age, race/ethnicity, and diagnostic factors, the study revealed racial/ethnic significant survival disparities for men diagnosed with prostate cancer.

Initially, Hispanic men were found to have a 17% higher risk of death compared to non-Hispanic White men (HR = 1.17; 95% CI: 1.12-1.22). After adjusting for sociodemographic and prognostic factors; that disparity disappeared. When evaluating the outcome of the main hypothesis of this study, it was determined that the null hypothesis can be accepted and the alternative hypothesis rejected: the risk of death over time among all Hispanics is similar to that of non-Hispanic white men, after controlling for covariates. Furthermore, the null hypothesis for the secondary hypothesis was also accepted, based on the results: there will no difference in the risk of death over time among Mexican men compared to non-Hispanic white men after adjusting for covariates in the model. After examining all Hispanic groups, the same can be said about all other subgroups except Puerto Rican men, which may be experiencing PC-survival disparity (HR = 1.38, p -value <0.01, CI [1.17 – 1.63]) compared to any other ethnic group. Further study is needed to validate our findings.

Cancer survival studies are a method of measuring the collective progress that has been made against cancer. A heightened sense of attentiveness is needed to continue using statistical methods to identify disparities in the populace and to monitor changes in risk factors that may impact cancer survival, mortality, and incidence. The SEER cancer monitoring program is a useful tool for filling the gaps in the literature and identify areas that require attention to improve social justice and overall health.

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