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Prostate Specific Antigen-Based Cancer Screening in the United States

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Walden University
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Abstract

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

In 2012, the U.S. Preventive Services Task Force revised its prostate cancer screening recommendations to advocate against the routine use of prostate-specific antigen-based testing. This cross-sectional study of a large dataset from the Surveillance, Epidemiology, and End Results Program compared PSA-based diagnoses made from 2006 to 2011 to those from 2013 to 2018. The study aimed to address the impact of the change in recommendation on survival and stage at diagnosis in prostate cancer patients. The socioecological model was used as the theoretical foundation for the study. A total of 205,129 men diagnosed with prostate cancer comprised the study population. The study found a difference in the survival distributions of the two groups, with higher survival for men diagnosed before 2012 ($\chi^2(1) = 81.662$, $p < 0.001$). Cox regression showed a statistically significant 12.6% higher risk of death in those diagnosed after 2012 (HR = 1.126; 95% CI = 1.104, 1.148; $p < 0.001$), controlling for race and age. Regarding the stage at diagnosis, there was a statistically significant difference in the probability of being diagnosed with advanced stage (regional or distant) cancer ($\chi^2(1) = 1283.524$, $p < 0.001$) between the two groups, with higher probability in those diagnosed after 2012. Logistic regression demonstrated higher odds of being diagnosed with advanced-stage cancer in those diagnosed after 2012, controlling for race and age (OR=1.530; 95% CI = 1.496, 1.564; $p < 0.001$). These study findings could lead to positive social change by contributing to more effective prostate cancer screening practices, potentially reducing the high mortality linked to late prostate cancer diagnosis.

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Dedication

I dedicate this dissertation to Cecelia Dennis, my mother, who was also my first-grade teacher and taught me to always tackle assignments promptly. She passed away during my program and remains an inspiration to me.

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I want to acknowledge my parents for awakening, nurturing, and inspiring my thirst for learning. Their educational pursuits, despite many challenges, continue to inspire me. I especially want to thank my committee chair, Lee S. Caplan, PhD. whose remarkable patience, and excellent mentorship allowed me to complete this dissertation. A special thanks to my committee member, Clarence Schumaker, PhD, for your invaluable contributions and excellent feedback in the review of my proposal and dissertation. To my friend and colleague, Melissa Weidner, PhD, for her review and ongoing encouragement. I want to acknowledge Michael Floren, PhD, for his invaluable insights. I also want to express my profound appreciation to my family and friends for their encouragement, support, and understanding.

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Chapter 1: Introduction to the Study

By 1987, prostate-specific antigen (PSA) screening was adopted in the United States, changing the epidemiology of prostate cancer, with a rapid doubling of incidence and, by 2015, a 50% decrease in annual prostate cancer mortality (Basourakos et al., 2022). Before 2012, PSA-based screening had a significantly positive impact on diagnosing prostate cancer, with the incidence of males with non-organ-confined prostate cancer decreasing from 79.3% in 1984 to 24.7% in 2005 (King et al., 2020). PSA-based screening was the standard for prostate cancer screening, leading to the initiation of treatment (Benidir et al., 2022; Klein et al., 2017). PSA-based screening led to a decrease in the mean age of prostate cancer diagnosis. The lifetime risk of prostate cancer diagnosis in men 55–69 years old was 20%. The death rate was 3%, with two thirds of deaths occurring in men over 75 years old, NHBs having the highest death rate (37.5%) among all races (Hinata & Fujisawa, 2022; Surveillance, Epidemiology, and End Results Program [SEER], n.d.).

In May 2012, the U.S. Preventive Services Task Force (USPSTF, 2018) recommended against the routine use of PSA-based prostate cancer screening with a grade of D. The USPSTF uses five grades (A, B, C, D, and I). Grade A represents a high certainty of net benefit, B as a moderate certainty of benefit, C recommends offering or providing service to select patients based on individual circumstances, D recommends against the service with harm outweighing the benefits, and I represent insufficient evidence to assess. The USPSTF determined that although PSA-based screening was effective in detecting prostate cancer, the evidence was inconclusive on whether PSA

screening significantly improved survival outcomes and may have potential harm (Benidir et al., 2022; Kensler et al., 2021; Klein et al., 2017). Supporters of the USPSTF recommendation argued that harm from false positive results from early screening, follow-up biopsy, and treatment of asymptomatic prostate cancer outweighed the potential benefits, as it may take years or decades for symptomatic, metastasized cancer or death to occur (Benidir et al., 2022; Kensler et al., 2021; Klein et al., 2017; USPSTF, 2018). Based on 2016-2020 data, SEER (n.d.) reported that the age-adjusted incidence rate of new prostate cancer cases in the United States was 113.4% per 100,000 men per year. In this study, I evaluated whether there has been a significant difference in prostate cancer survival and staging since the USPSTF recommended against PSA-based prostate cancer screening in 2012 using secondary data. This chapter addresses the study's background, problem statement, purpose, research questions (RQs) and hypotheses, theoretical foundation, nature of the study, definitions, assumptions, scopes and delimitations, limitations, significance, and summary.

Background

The prostate is the largest of the accessory glands of the male reproductive tract (Tracy, 2023). Prostate cancer is a sex-specific cancer only affecting males. Most patients presenting with prostate cancer are asymptomatic or have non-specific symptoms (e.g., hematuria, urinary retention, erectile dysfunction; Boehm et al., 2023). A prostate cancer diagnosis is confirmed based on a transrectal ultrasound (TRUS) guided needle biopsy of the prostate. The diagnostic biopsy is informed by the combination of any of the following: elevated serum PSA, PSA kinetics, abnormal digital rectal exam (DRE),

family history, race, or previous abnormal biopsy (Boehm et al., 2023). It is important to note that no PSA level signifies the absence of prostate cancer. In contrast, increases in PSA levels signify increases in the risk of prostate cancer (e.g., PSA levels of 4-10 ng/ml = 25% risk, PSA levels over 10 ng/ml = 50% or higher). PSA levels are also elevated in other prostate-related diseases, such as benign prostatic hyperplasia and prostatitis (Boehm et al., 2023).

Prostate cancer is the fifth leading cause of cancer deaths in males worldwide, and approximately one in nine males will be diagnosed with prostate cancer during their lifetime (King et al., 2020). In the United States, the National Cancer Institute's (NCI) SEER (n.d.) reported that prostate cancer is the leading cancer among men, with 288,300 (14.7%) new cases in 2023. In the United States, prostate cancer is the second-highest cause of cancer-related death, with an estimated 34,700 deaths (5.7%) in 2023 (Kensler et al., 2021; SEER, n.d.; Zavala et al., 2021). In 2020, an estimated 3,343,976 men were living with prostate cancer in the United States, with a 5-year relative survival rate of 97.1% (SEER, n.d.).

The known non-modifiable risk factors for prostate cancer include age (over 65 years old), family history, and race/ethnicity (Elliott et al., 2018). Prostate cancer exhibits health disparities by race. Non-Hispanic Blacks (NHB) are more likely to develop prostate cancer and present with more aggressive disease than their non-Hispanic White (NHW) counterparts (Bickell et al., 2018; Jiang et al., 2018). NHBs also have a higher incidence (1.6. times) and survival (2.5 times) than NHWs. Furthermore, NHBs have the

highest prostate cancer survival despite effective treatments that can improve survival for clinically significant prostate cancer (Bickell et al., 2018; Jiang et al., 2018).

Problem Statement

After two decades of declining incidence of prostate cancer, there was a 3% annual increase from 2014 to 2019, with approximately half of the new cases being advanced disease (Siegel et al., 2023). By 2018, the USPSTF upgraded their prostate cancer screening guidelines for men aged 55 to 69 to a grade C recommendation, while men aged 70 and older remained with a grade D recommendation (Siegel et al., 2023; USPSTF, 2018). This change in the recommendation for 55- to 69-year-olds was fueled by continuing research, which suggested that the current prostate cancer screening guidelines did not appear to adequately address NHBs, a racial/ethnic group in the United States with a higher risk of prostate cancer incidence and mortality (Siegel et al., 2023; USPSTF, 2018).

Purpose of the Study

The purpose of this quantitative study was to utilize 1975-2021 data from the NCI's SEER Program to assess whether there has been a significant difference in prostate cancer survival and staging since the USPSTF recommended against PSA-based prostate cancer screening in 2012 (USPSTF, 2018). Since the USPSTF recommendation, there have been increases in metastatic and lethal prostate cancer among younger NHBs (Zavala et al., 2021). This study used 2012 as the demarcation point to compare SEER data on prostate cancer stage at diagnosis and survival rate from 2006 to 2011 against 2013 to 2018. The study variables included age (i.e., age recode with <1-year olds),

primary site, PSA values (i.e., PSA lab value Recode), race (i.e., race recode), sex, survival months, stage of disease (i.e., combined summary stage), year of diagnosis (SEER, n.d.).

Research Questions and Hypotheses

Identifying whether differences exist before and after the USPSTF 2012 recommendation against the routine use of PSA-based prostate cancer screening using a national database may help determine its usefulness in detecting early prostate cancer. The RQs and hypotheses for the study were as follows:

RQ 1: Is there a significant difference in the survival rate between individuals diagnosed with prostate cancer from 2006 to 2011 and individuals diagnosed with prostate cancer from 2013 to 2018 based on routine PSA-based prostate cancer screening tests?

$H_0$1: The null hypothesis for this research question is that there is no significant difference in the survival between individuals diagnosed with prostate cancer from 2006 to 2011 and individuals diagnosed with prostate cancer from 2013 to 2018 based on routine PSA-based prostate cancer screening tests.

H_a1: The alternative hypothesis is that there is a significant difference in the survival between individuals diagnosed with prostate cancer from 2006 to 2011 and individuals diagnosed with prostate cancer from 2013 to 2018 based on routine PSA-based prostate cancer screening tests.

RQ 2: Is there a significant difference in the stage at diagnosis between

individuals diagnosed with prostate cancer from 2006 to 2011 and individuals diagnosed with prostate cancer from 2013 to 2018 based on routine PSA-based prostate cancer screening tests?

H_o2: The null hypothesis for this research question is that there is no significant difference in the stage at diagnosis between individuals diagnosed with prostate cancer from 2006 to 2011 and individuals diagnosed with prostate cancer from 2013 to 2018 based on routine PSA-based prostate cancer screening tests.

H_a2: The alternative hypothesis is that there is a significant difference in the stage at diagnosis between individuals diagnosed with prostate cancer from 2006 to 2011 and individuals diagnosed with prostate cancer from 2013 to 2018 based on routine PSA-based prostate cancer screening tests.

Theoretical Foundation

The theoretical foundation for this study was the socioecological model (SEM) by Urie Bronfenbrenner, which recognizes that factors of the individual, the community, and the environment affect health (Burkholder et al., 2020; Kilanowski, 2017; Krieger, 2014). The SEM describes factors influencing behavior at multiple levels, including the individual level characteristics (knowledge, attitudes, behavior, developmental history, demographics, and health literacy), interpersonal level (social networks and support systems), organizational/institutional level (operational rules and regulations), community level; and policy level (e.g., USPSTF guidelines). The SEM asserts that the individual is at the center, with all the other levels interconnected. This model provides a

framework for understanding the reciprocal interrelationships between individual and population-level determinants of behavior (Moore et al., 2015).

Many public health organizations (e.g., the Centers for Disease Control and Prevention) use the SEM as a framework to facilitate behavior change related to mental and physical health (Moore et al., 2015). Cancer-specific adaptations of the SEM are also used to encourage and support change at the individual, interpersonal, organizational, community, and policy levels for multilevel interventional design and implementation. These cancer-specific adaptation models have enhanced stakeholder communication, commitment, and collaboration to promote cervical and colorectal cancer screening, improve human papillomavirus vaccination uptake, and reduce adolescent indoor tanning.

The SEM is valid for comprehensive and critical identification of the level (micro, meso, or macro) of the research phenomena of interest, such as the impact of demographics (Kumar et al., 2022). This model is helpful in the research process deductively (from the outset) to inform the research aims, questions, data collection, and analysis or inductively (at the analysis stage). The SEM was used to explore demographic impact on survival and diagnosis stages to better inform prostate cancer screening guidelines for various races/ethnicities (see Krieger, 2014).

Nature of the Study

A quantitative approach addressed RQs 1 and 2. The specific research design to address the research questions in this quantitative study was a cross-sectional sample using a dataset from the SEER Program (NCI, n.d.). A secondary data analysis approach

using a SEER dataset addressed the research questions using measurable factors for comparison and contrast, with generalizable results for the national population.

Definitions

Control variable(s): An additional variable (e.g., age, race) introduced into a bivariate relationship and held constant so that the effect of the independent variable on the dependent variable can be observed more clearly (Frankfort-Nachmias, Leon-Guerrero & Davis, 2021).

Dependent variable(s): The outcome variable (e.g., survival months and combined summary stage) that can change due to the independent variable (Laerd Statistics, 2018a).

Digital rectal exam (DRE): A procedure in which a clinician inserts a gloved, lubricated finger through the rectum to check for abnormalities (e.g., enlarged prostate) (Boehm et al., 2023; Tracy, 2023).

Independent variable(s): An experimental or predictor variable (e.g., year of diagnosis) that is being manipulated in an experiment to observe the effect on a dependent (i.e., outcome) variable (Laerd Statistics, 2018a).

Primary site of diagnosis: The location of a primary cancer (SEER, n.d.).

Prostate cancer: The growth of cancer cells within the prostate (Boehm et al., 2023; Tracy, 2023).

Prostate-specific antigen (PSA): A protein produced by normal and cancerous cells in the prostate and released into the blood (Boehm et al., 2023; Tracy, 2023). A PSA level of zero signifies the absence of prostate cancer. PSA is measured in

nanograms/milliliters (ng/ml). The risk of disease increases as the PSA level increases:

- 1-3 ng/ml = risk < 25%,
- 4-10 ng/ml = 25% risk,
- Over 10 ng/ml = 50% or higher (Boehm et al., 2023; Tracy, 2023).

Race: The subject's racial/ethnic self-description (SEER, n.d.).

Tumor staging: T1 is not palpable during DRE or seen upon imaging (e.g., a computed tomography scan or TRUS) but may be found during surgery for another medical condition (Johns Hopkins Medicine, 2023). T2 is confined to the prostate, possibly palpable during DRE or seen on imaging. T3 is growth beyond the prostate, possibly spreading to the seminal vesicles. T4 is spread to adjacent tissues other than the seminal vesicles (e.g., the rectum, bladder, urethral sphincter, and pelvic wall.

Socioecological model (SEM): A theory developed by Urie Bronfenbrenner recognizes that factors of the individual, the community, and the environment affect health (Burkholder et al., 2020; Kilanowski, 2017; Krieger, 2014).

Surveillance, Epidemiology, and End Results Program (SEER): A national program that collects cancer data from population-based cancer registries covering approximately 48.0 % of the U.S. population (NCI, n.d.; SEER, n.d.).

U.S. Preventive Service Task Force (USPSTF): A panel of national disease prevention experts that provides evidence-based recommendations to help clinicians identify appropriate clinical preventive services (Klein et al., 2017). The panel provides periodic recommendations about multiple health disorders. Grade A: Recommends PSA-based prostate screening with the high certainty that the net benefit is substantial

(USPSTF, 2018). Grade B: Recommends PSA-based prostate screening with high certainty of benefit being moderate or a moderate certainty that the net benefit is moderate to substantial (USPSTF, 2018). Grade C: Recommends selectively offering or providing PSA-based prostate screening to individual patients based on professional judgment and patient preferences with at least moderate certainty that the net benefit is small (USPSTF, 2018). Grade D: Recommends against PSA-based prostate screening with moderate or high certainty of no net benefit and that harm outweighs the benefit (USPSTF, 2018). Grade I: Evidence is insufficient to assess the balance of benefit and harm of PSA-based prostate cancer screening (USPSTF, 2018).

Assumptions

This study's assumptions were that all data obtained from the SEER database were accurate to provide the necessary information for the cases who consented to participate and met inclusion criteria for participation in the database. The SEER program maintains rigorous data collection and quality control guidelines, including case finding, recoding, and reliability (SEER, n.d.). Every even number of calendar years, the program conducts an audit review in which a group of auditors travels to registries to collect data. The program also applies appropriate statistical procedures for obtaining measures to assess each registry's performance. In odd-numbered years, selected SEER registries conduct training programs with the National Cancer Registrars Association's (NCRA) annual meeting. The SEER program also utilizes a quality control tool, the Data Quality Profile, created for each registry to assess their respective data. Finally, extensive field edits are used to identify and correct errors in the data.

Scope and Delimitations

All men in the United States are at risk of developing prostate cancer (Rawla, 2019). Increasing age is a significant risk factor. The participants in this study were men obtained from the SEER database (SEER, n.d.). The SEER data represents registry information from across the United States on individuals of different national origins, socioeconomic statuses, and other demographic criteria. The SEER registry captures cancer data (e.g., prostate, lung, breast) across the United States. The database has specific inclusion and exclusion criteria established by the SEER program and the NCRA. The RQs were used to select the study variables (e.g., dates of PSA testing, PSA values, age at prostate cancer diagnosis, race/ethnicity, years of survival following diagnosis, the age at death, and the stage of prostate cancer diagnosis). This study's variables were in the dataset definitions provided by SEER.

Limitations

The limitations of this study include the uneven distribution between urban and rural demographics, the reliance on the SEER program to ensure oversight of the data collection process, lack of family history information, lack of dietary history, selection bias, information bias, and confounding. The limitations of SEER data include the incompleteness of individual-level data collected on specific cancer demographics and treatment, and the inaccuracies and incompleteness of the data collected from the source registries (Zavala et al., 2021). Also, self-identification for race and ethnicity posed an additional problem, as a large proportion of the U.S. population does not self-identify as a single race.

Selection bias is possible in population registry-based studies. Selection bias involves a systematic error in recruiting or retaining study participants (Soni, 2019; Szklo & Nieto, 2018). Selection bias may involve loss to follow-up, incomplete data records by the individual registries, unrecorded variables, or the potential for incomplete data from the migration of cases in and out of SEER registry sites (Soni, 2019). SEER's vigilant quality control system may attempt to reduce selection bias.

Missing data may be attributed to information bias and systemic distortions in the data collection process for exposure and disease status (Delgado-Rodríguez et al., 2004; Tripepi et al., 2010). SEER's quality controls may minimize problems associated with missing data, such as the binding contractual obligations of each registry, extensive field edits to prevent and correct data errors, and the collaborative efforts of the SEER stakeholders (SEER, n.d.)

Significance

This research is significant because it demonstrates if the updated USPSTF guidelines improve the effectiveness of diagnosing prostate cancer. The purpose of prostate cancer screening is to detect early prostate cancer, allowing for early treatment to reduce mortality. Studies on the impact of the USPSTF guidelines are limited (Burgess et al., 2022; Jeong et al., 2021; Kensler et al., 2021; Presti et al., 2020). However, more research to provide evidence on the usefulness of PSA-based prostate cancer screening can inform changes or updates to prostate cancer screening guidelines and policies (e.g., USPSTF recommendations), with the goal of earlier diagnosis and treatment, reduced mortality, and increased survival. Results from this study, in conjunction with PSA

improvements (e.g., IsoPSA assay), demonstrate to the USPSTF that changes to prostate cancer screening guidelines are needed.

Summary

The USPSTF recommendation against early and routine PSA screening needs to be re-evaluated to determine the potential benefits versus harm. In addition, recent advances (e.g., IsoPSA) in PSA-based prostate cancer screening (Benidir et al., 2022; Klein et al., 2017) warrant re-evaluating prostate cancer screening guidelines, especially for NHBs. The next chapter will elaborate on the literature review on prostate cancer, which provided relevance for this study.

Chapter 2: Literature Review

The USPSTF recommended changes to prostate cancer screening guidelines in 2012. However, prostate cancer cases experienced a 3% annual increase from 2014 to 2019, and approximately half of the new cases were advanced disease (Siegel et al., 2023). Metastatic and lethal prostate cancers have also increased among younger NHBs (Zavala et al., 2021). The purpose of this quantitative study was to utilize 1975-2021 SEER data to assess whether there has been a significant difference in prostate cancer survival and staging from 2006 to 2011 compared to 2013 to 2018. Although there are numerous studies on prostate cancer in the United States, there is limited literature addressing the survival and stage of diagnosis for individuals based on policy changes with the USPSTF recommendation guidelines against PSA-based prostate cancer screening. Some studies utilizing PSA-based prostate cancer screening are localized to specific geographic areas in the United States. In contrast, larger studies do not compare survival and stage at diagnosis for populations before and after the 2012 USPSTF recommendation.

This chapter will address the literature search strategy, and the literature review related to the key variables and concepts. The literature review related to the key variables and constructs will further address localized studies, SEER studies, studies on PSA-based screening, improved PSA-based testing, disease severity, survival and mortality, studies supporting USPSTF guidelines, and opposition to the USPSTF Guidelines. The chapter ends with a summary and conclusions.

Literature Search Strategy

A systematic literature review was conducted using multiple databases, including MEDLINE, CINHAL, EBSCO Discovery Service, ScienceDirect, and EMBASE with full text. The keywords searched included *prostate cancer screening*, *prostate cancer* or *prostatic neoplasms* or *prostate carcinoma*, *prostate-specific antigen* or *PSA*, *prostate screening*, *prostate*, *African Americans* or *American blacks* or *blacks*, *United States Preventive Services Taskforce* or *USPSTF*, and *Surveillance Epidemiology, and End Results* or *SEER*. African Americans or American Blacks or Blacks were chosen to select for articles focused on the United States. The literature review encompassed seminal literature and peer-reviewed articles within the last 5 years.

Literature Review Related to Key Variables and Concepts

The variables in this study were age (i.e., age recode with <1-year olds), primary site, PSA values (i.e., PSA lab value Recode), race (i.e., race recode), sex, survival months, stage of disease (i.e., combined summary stage), and year of diagnosis (SEER, n.d.).

Localized Studies

Since the USPSTF guideline changes, localized studies have been conducted in various municipalities across the United States. These studies reflect the increasing incidence of prostate cancer and the racial health disparity (Benidir et al., 2022; Jenkins et al., 2021; Jeong & Raman, 2021; Leung et al., 2018; Lewis-Thames et al., 2021). For example, Jenkins et al. (2021) studied 1,225 men at the Durham Veterans Administration Hospital after undergoing prostate biopsy due to an elevated PSA or abnormal DRE

between 2007 and 2018. They sought to determine the racial differences using a family history of prostate cancer and disease aggressiveness. The multivariable analysis showed that family history was associated with increased odds of high-grade prostate cancer in NHBs (odds ratio [OR] 1.85, $p = 0.041$). In all men, the multivariable analysis showed that family history was associated with increased odds of high-grade prostate cancer (OR 1.56, $p = 0.057$). The multivariable analysis also found that family history was unrelated to overall or low-grade prostate cancer diagnosis or stratified by race (all $p \geq 0.325$). As this study was specific to a local area (i.e., Durham Veterans Administration Hospital), studies using larger populations can yield more generalizable results due to a closer approximation of the general population (see Burkholder et al., 2020). Localized studies present an opportunity to provide data to support larger national research.

SEER Studies

More extensive national studies have utilized SEER data for prostate cancer analysis. For example, Iyengar et al. (2020) utilized SEER*Stat to evaluate recent prostate cancer incidence, distant stage diagnosis, and mortality rates by region, race/ethnicity, and age group for men diagnosed with ($n = 723,269$) and dying of ($n = 112,116$) prostate cancer between 2012 and 2015. The authors observed that for Hispanic and NHAIAN men, prostate cancer indicators (i.e., incidence, distant stage diagnosis, and mortality) varied by region, while NHB and API men consistently had the highest and lowest rates across regions. Hispanics had a lower incidence and mortality rates than NHWs in all regions except the Northeast, where they had a higher incidence (relative risk [RR] 1.16; 95% confidence interval [CI], 1.14-1.19) and similar mortality. Hispanics

had higher distant stage rates in the Northeast (RR, 1.18; 95% CI, 1.08-1.28) and South (RR, 1.22; 95% CI, 1.15-1.30) than NHW men, but similar rates in other regions. Non-Hispanic American Indian/Alaskan Native (NHAIAN) men had higher distant stage rates than NHWs in the West (RR, 1.38; 95% CI, 1.15-1.65). NHBs and Hispanics had higher distant stage rates than NHWs among those aged 55 to 69 (RR, 2.91; 95% CI, 2.81-3.02 and 1.24; 95% CI, 1.18-1.31, respectively), despite lower overall incidence for Hispanics in this age group. Iyengar et al. suggested that clinicians should be aware of regional and age differences in prostate cancer risk among populations in their respective regions to guide decision-making on prostate cancer screening.

Studies With PSA-Based Screening

Similar to the Durham veteran's study, localized studies continue to study PSA-based screening. Lewis-Thames et al. (2021) collected information on annual screening history via mail-in or onsite survey from 447 NHBs attending prostate cancer screening events in the St. Louis Metropolitan area (2007-2017) (Lewis-Thames et al., 2021). The study analyzed sociodemographic factors, family history of prostate cancer among first-degree relatives, healthcare utilization characteristics, and predictors of annual PSA screening. The study found that older NHBs and those with a primary physician were more likely to have an annual PSA screening regardless of sociodemographic and family history factors. Cancer family history status was unknown to one-third of the respondents. These study results support the influence that physicians, guided by USPSTF recommendation, can have to encourage annual PSA screenings among their patients. As this study was also localized to a specific geographic area (i.e., the St. Louis

metropolitan area), larger and national studies can provide more generalizable results to better approximate the general population (Burkholder et al., 2020).

Leung et al. (2018) conducted a retrospective study of 100 randomly selected patients out of 204 at a tertiary care safety-net hospital, Grady Memorial Hospital, in Atlanta from 2004-2011. Inclusion criteria included initial PSA ≥ 100 ng/ml. The majority of the men who presented with PSA ≥ 100 ng/ml were NHBs of lower socioeconomic status and had metastatic disease (Leung et al., 2018). Thus, these patients are less likely to receive regular care, such as routine medical visits or previous prostate cancer screenings care from private physicians, clinics, urgent care facilities and hospitals. As a safety net hospital, Grady Memorial Hospital is required to provide care to patients regardless of insurance. Based on their study, the authors state that the large number of non-Hispanics of lower socioeconomic status presenting with PSA ≥ 100 ng/ml and advanced disease suggest that the uniform absence of prostate cancer screening may expose more significant numbers of at-risk men to similar outcomes (Leung et al., 2018).

Misra-Herbert et al. (2017) retrospectively assessed prostate cancer screening practices since the issuing of the 2012 USPSTF recommendation. They studied 160,211 men aged ≥40 with at least one primary care clinic visit in an extensive integrated health system, Cleveland Clinic Health System (CCHS), from January 2007 to December 2014 (Misra-Herbert et al., 2017). They found that prostate cancer screening declined from 2007 to 2014, even in higher-risk groups, and follow-up screening rates were unrelated to previous PSA levels. The authors also found that there were higher rates of first prostate

biopsy in men with PSA tests and an increased risk for prostate cancer at a later age (Misra-Herbert et al., 2017). The study also found that variations in PSA testing existed among primary care physicians.

Nyame et al. (2021) sought to estimate the benefit and harm of intensified PSA screening of NHBs using two microsimulation models of prostate cancer calibrated to incidence. The authors utilized historical screening data from the National Health Interview Survey and the SEER-Medicare database, and biopsy data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial to assess the impact of screening strategies (varying screening intervals, starting and stopping ages, and biopsy utilization following an abnormal PSA) on disease-specific mortality and overdiagnosis (Nyame et al., 2021). Each strategy induced a mean lead time (MLT) for detected cases. MLT is the average time by which screening advances detection (Nyame et al., 2021). A longer MLT was associated with reduced mortality but increased overdiagnosis (based on combined estimates from US and European prostate cancer screening trials). Their results showed that NHBs had similar MLT to men of all races and similar mortality reduction (range between models = 21%-24% vs. 20%-24%), but a higher frequency of overdiagnosis (75-86 vs. 58-60 per 1000 men) (Nyame et al., 2021). Screening NHBs aged 40-84 annually would increase mortality reduction (29%-31%) and overdiagnosis (112-129 per 1000) (Nyame et al., 2021). Restricting screening to ages 45-69 would still achieve substantial mortality reduction (26%-29%) with lower overdiagnosis (51-61 per 1000) (Nyame et al., 2021). The authors determined that increasing biopsy utilization to 100% of abnormal tests would reduce mortality but substantially increase overdiagnosis

(Nyame et al., 2021). They observed that annual screening of NHBs decreases mortality more than that estimated under historical screening. Limiting screening to men younger than 70 years is expected to help reduce overdiagnosis (Nyame et al., 2021). These localized studies involving PSA-based testing suggest the need for further research at the national level for results to better approximate the general population (Burkholder et al., 2020).

Improved PSA-Based Testing

Since the 2012 USPSTF recommendation, there have been significant advances in PSA-based testing (Benidir et al., 2022). In a single-center, retrospective study comparing 81 patients with prior IsoPSA testing, prostate biopsy, and radical prostatectomy to 44 patients (controls) with previous radical proctectomy (i.e., surgery to remove all or part of the rectum) and no preoperative IsoPSA from 2019 to 2021, Benidir et al. (2022) determined that elevated IsoPSA is an effective diagnostic tool to detect clinically significant prostate cancer at the time of biopsy which would then require further procedures, such as prostate MRI or radical proctectomy. Similarly, Klein et al. (2017) demonstrated in their multicenter prospective review of 261 men scheduled for prostate cancer biopsy between August 2015 and December 2016 that the IsoPSA assay performed above the concentration-based PSA measurement, providing a net benefit against other protocols. Thus, IsoPSA appears to provide improved PSA-based testing for prostate cancer screening.

Disease Severity, Survivability, and Mortality

Using the SEER registry, Sheng et al. (2021) evaluated the implications of the

USPSTF recommendation prostate cancer stage migration (i.e., advancing cancer through stages). They hypothesized that USPSTF recommendation against PSA screenings could delay the diagnosis of advanced prostate cancer. They identified 328,586 men (age 55-69) diagnosed with prostate cancer from 2004 to 2008 (group 1: 135,625), 2009 to 2012 (group 2: 117,979), and 2013 to 2015 (group 3: 74,982) (Sheng et al., 2021). These groups reflected USPSTF guideline changes, with data adjusted for population growth, and Group 1 serving as the control group. The average number of men diagnosed annually with N1M0 (group 1: 381; group 2: 477; group 3: 660) and M1 (group 1: 523; group 2: 761; group 3: 1037) disease increased (Sheng et al., 2021). The study found a decrease in localized disease incidence (group 2: 9.2%; group 3: 33.2%) (Sheng et al., 2021). However, the incidence of N1M0 (group 2: 5.3%; group 3: 30.1%) and M1 disease (group 2: 22.6%; group 3: 49.2%) increased (Sheng et al., 2021). A concurrent analysis of patients (aged 50-75) and NHBs showed similar trends. The authors stated that each USPSTF recommendation produced an increased incidence of de novo metastatic prostate cancer and that the sequelae of advanced disease include financial, emotional, and physical burdens (Sheng et al., 2021).

Shah and Ioffe (2020) conducted a retrospective comparative analysis of prostate biopsy characteristics for 1,703 sequential patients biopsied from 2010-2012 (Group A), against 383 biopsied in 2018 (Group B), and 310 in 2019 (Group C) (i.e., before and after the 2012 USPSTF guidelines). Data were collected on patient age, race, serum PSA level, DRE results, total biopsies performed, and Gleason sum scores (GSS) in a patient population of 73% NHBs, 16% NHWs, and 11% other races (Shah & Ioffe, 2020). The

prevalence of high-grade prostate cancer (GSS 7-10) in Groups A through C were 51.5%, 60.5%, and 60.0%, respectively (Shah & Ioffe, 2020). For serum PSA levels of 10 ng/mL or greater in Groups A through C, the prevalence was 25.4%, 29.3%, and 33% (Shah & Ioffe, 2020). Within in each group (i.e., A, B, and C), subjects aged 70 to 80 exhibited an increasing trend for serum PSA levels to be 10 ng/mL and higher (31% higher in Group A, 38% in Group B and 39% in Group C) compared to their counterparts aged ≤55, 56-69 (Shah & Ioffe, 2020). This age group had high-grade tumors occurring with a prevalence of 61%, 65%, and 68%, respectively (Shah & Ioffe, 2020). More than 50% positive biopsy cores were present in 46.3% of 70- to 80-year-olds and 36.6% of NHBs. The authors found decreased prostate biopsy, increased prostate cancer diagnosis, and increased high-grade prostate cancer, which supports recommending aggressive prostate cancer screening for men in high-risk categories (i.e., NHBs, family history, and healthy 70 to 80-year-olds) (Shah & Ioffe, 2020).

Presti et al. (2020) retrospectively studied whether the annual rates of PSA screening, prostate biopsy, incident prostate cancer detection, and stage IV at presentation in NHBs ages 45-69 at Kaiser Permanente in Northern California changed following the 2012 USPSTF guidelines. They discovered that after the change in 2012 USPSTF guidelines, screening rates declined 23.4% (95% CI 23.0-23.8%), biopsy rates declined 64.3% (95% CI 62.9-65.6%, and indolent prostate cancer detection rates declined 53.5% (95% CI 50.1-56.7%) (Presti et al., 2020). Since the 2012 USPSTF guideline changes, there were 1871 fewer incident cancers detected and an increase in metastatic cancer rates of 36.9% (95% CI 9.5-71.0%) (i.e., for every 25 fewer cancers detected, one

metastatic cancer was diagnosed) (Presti et al., 2020). The authors stated that major reductions in PSA screening coincided with lower overall incident cancer detection rates and higher metastatic disease rates in men under age 70 (Presti et al., 2020).

Burgess et al. (2022) sought to determine if the 2012 USPSTF Grade D recommendation against PSA screening was associated with prostate cancer-specific mortality (PCSM). This cross-sectional study used the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research to collect data on the cause of death for all individuals who died of prostate cancer in the US from 1999 to 2019 (Burgess et al., 2022). PCSM rates decreased before the recommendation and remained steady after the recommendation. The primary outcomes and measures, including the trends in PCSM rates, were calculated from 1999 to 2012 and from 2014 to 2019, with the washout year of 2013, using linear regression, with year and binary indicator of pre-2013 and post-2013 status as interaction terms (Burgess et al., 2022). Trends were further analyzed by age, race and ethnicity, urbanization category, and US census region. This study's results suggest that the change in the USPSTF PSA-based screening guideline to a Grade D recommendation may have been associated with the stagnancy of PCSM rates (Burgess et al., 2022).

Kensler et al. (2021) examined racial and ethnic variations in PSA testing and prostate cancer incidence following the 2012 USPSTF recommendation in the Behavioral Risk Factor Surveillance System (BRFSS). They studied 40- to 74-year-old men who self-reported routine PSA tests in the past year (2012-2018). Prostate cancer incidence rates and rate ratios (IRRs) by race and ethnicity were estimated using SEER registry data

(2004-2017). The results were that PSA testing frequencies were 32.3% (95% CI = 31.7% to 32.8%) among NHW, 30.3% (95% CI = 28.3% to 32.3%) among NHB, 21.8% (95% CI = 19.9% to 23.7%) among Hispanic, and 17.7% (95% CI = 14.1% to 21.3%) among API in 2012 (Kensler et al., 2021). From 2012 to 2018, the absolute screening frequency declined by 9.5%, with a more significant decline among NHBs (11.6%) than NHWs (9.3%) (Kensler et al., 2021). NHBs had a more significant relative annual decrease (OR = 0.86, 95% CI = 0.84 to 0.88) than NHW men (OR = 0.89, 95% CI = 0.89 to 0.90; Pheterogeneity = .005), driven by a more significant decline among NHB men ages 40-54 (Kensler et al., 2021). Driven by differences in localized tumor incidence, the NHB to NHW IRR for total prostate cancer increased from 1.73 (95% CI = 1.69 to 1.76) in 2011 to 1.87 (95% CI = 1.83 to 1.92) in 2012 and has remained elevated (Kensler et al., 2021). There was a significant increase in the incidence of metastatic prostate cancer across all racial and ethnic groups (Kensler et al., 2021). The authors observed that the frequency of prostate cancer screening varies by race and ethnicity, with a modestly steeper decline in PSA testing among younger NHBs relative to NHWs since 2012 (Kensler et al., 2021). The NHB to NHW IRR for localized prostate cancer modestly increased following 2012 (Kensler et al., 2021).

Opposing Guidelines

Qiao et al. (2022) examined the impact of PSA screening and primary care provider utilization on prostate cancer outcomes in young (aged 40-55) NHBs diagnosed with prostate cancer between 2004 and 2017 at the Veterans Health Administration. The authors utilized an inverse probability of treatment-weighted (IPTW) propensity scores to

measure the baseline covariates and more accurately estimate the average treatment effect of PSA screening on disease severity endpoints (Qiao et al., 2022). The treatment effect of PSA screening refers to the outcome of a patient's PSA screening for those individuals who had PSA levels higher than 20, GSS of 8 or higher, and metastatic disease at diagnosis. The IPTW propensity scores were used in multivariable models to assess PSA screening when PSA levels are higher than 20, GSS is 8 or higher, and metastatic disease is present at diagnosis (Qiao et al., 2022). Lead-time adjusted Fine-Gray regression evaluated PSA screening on PCSM, with noncancer deaths as competing events. The study had a cohort of 4726 patients (Qiao et al., 2022). The mean age was 51.8, with an 84-month median follow-up. There were 1057 (22.4%) with no PSA screening before diagnosis (Qiao et al., 2022). PSA screening was associated with statistically significantly reduced odds of PSA levels higher than 20 (OR = 0.56, 95% CI = 0.49 to 0.63; P < .001), GSS of 8 or higher (OR = 0.78, 95% CI = 0.69 to 0.88; P < .001), metastatic disease at diagnosis (OR = 0.50, 95% CI = 0.39 to 0.64; P < .001), and decreased PCSM (sub-distribution hazard ratio = 0.52, 95% CI = 0.36 to 0.76; P < .001) (Qiao et al., 2022). There were similar effects in primary care provider visits. The authors observed that among young NHBs diagnosed with prostate cancer, PSA screening was associated with a statistically significantly lower risk of PSA levels higher than 20, GSS of 8 or higher, metastatic disease at diagnosis, and PCSM. NHBs possessed the highest PCSM rate among the racial groups (Qiao et al., 2022).

Rodriguez et al. (2019) conducted a SEER analysis of 2005-2015 data to assess prostate cancer screening guidelines on different racial and ethnic populations. The

researchers observed that the odds of regional-stage prostate cancer diagnosis in 2013-2015 were 1.3 times higher for NHBs, 1.3 times higher for APIs, and 1.2 times higher for NHWs compared to 2005-2008 (Rodriguez et al., 2019). The odds of distant-stage prostate cancer diagnosis in 2013-2015 were 1.6 times higher for NHBs, 1.8 times higher for APIs, and 2.1 times higher for NHWs compared to 2005-2008 (Rodriguez et al., 2019). For the years 2005-2008, 2009-2012, and 2013-2015, respectively, the odds of distant-stage prostate cancer diagnosis were 1.8 times, 1.7 times, and 1.4 times higher for NHBs compared to NHWs ($p < .001$) (Rodriguez et al., 2019). Similarly, APIs were 1.5 times, 1.5 times, and 1.4 times higher compared to NHWs ($p < .001$) (Rodriguez et al., 2019). They observed that the proportion of late-stage prostate cancer has increased significantly across the United States regardless of race and ethnicity. From 2013-2015, there was a higher chance of all men being diagnosed with regional or distant stage disease than in previous years. Newly diagnosed regional-stage disease increased the most in APIs and NHBs, while distant prostate cancer increased the most in white men (Rodriguez et al., 2019).

Researchers that compared populations before and after the 2012 recommendation found increased rates of more aggressive prostate cancer at diagnosis (Gleason 4+4: 4.7% vs. 10.5%; higher: 3.2% vs. 11.2%; increased, $p=0.045$ and greater percentage of core involvement at $p=0.039$) and metastatic disease (1.8% vs. 6.7%, $p=0.009$) (Silva et al., 2020). In a retrospective observational study, Silva et al. (2020) assessed the impact of the USPSTF recommendation release on prostate cancer detection rates and disease aggressiveness and described the treatment patterns pre- and post-USPSTF 2012

guidelines. From men submitted to prostate biopsy from January 2010 to December 2016 at a tertiary care center, Silva et al. (2020) compared patient demographics, comorbidities, presenting PSA, biopsy characteristics, grade and stage of disease and treatment for 518 patients: 245 before and 273 after USPSTF recommendation (a mean value of 98 and 61 PBs per year, respectively). Additionally, Silva et al. (2020) observed a significantly lower percentage of patients receiving curative-intent treatments for localized disease post-2012 (37.9% vs. 32.9%, p=0.021).

Summary and Conclusions

Prostate cancer remains a serious public health concern in the United States. Early diagnosis is critical to effective treatment. Results of localized studies provide support for the need for larger studies at the national level to assess PSA-based testing as an effective screening tool for prostate cancer (Benidir et al., 2022; Jenkins et al., 2021; Jeong & Raman, 2021; Leung et al., 2018; Lewis-Thames et al., 2021). Although current guidelines recommend shared decision-making for PSA screening, this recommendation depend on studies that included fewer NHBs, which limited their generalizability (Qiao et al., 2022). Health disparities among races also indicate more lethal cancer for NHBs (Zhang et al., 2020). IsoPSA shows potential for improved prostate cancer screening (Benidir et al., 2022; Klein et al., 2017). To validate early detection, further research is warranted to address PSA-based prostate cancer screening, especially among NHBs.

Chapter 3: Research Method

The purpose of the study was to determine the impact of the 2012 USPSTF recommendation against PSA-based prostate cancer screening utilizing SEER data from 1975-2021. An extensive literature review showed limited research on prostate cancer survival and stage of disease at diagnosis for individuals with PSA-based prostate screening compared to those with PSA-based prostate cancer screening. The PSA-based test is a widely available and relatively inexpensive lab test for prostate cancer screening. PSA-based test results are readily captured by cancer registries and included in the SEER database. There is a need to investigate whether PSA-based prostate cancer screening affects survival and stage of disease at diagnosis. This study aimed to assess whether there has been a significant difference in prostate cancer survival and staging between patients receiving PSA-based prostate cancer screening and those not receiving PSA-based prostate cancer screening

In this chapter, I will explain the research methodology for this study, including the research design and rationale, methodology, data analysis plan, and threats to validity to address the research questions for this study. Under the Methodology section, I will further explore the population, the sampling and sampling procedures, data collection, and finally, the instrumentation and operationalization of constructs. Under the section on the threats to validity, I will explain the ethical procedures.

Research Design and Rationale

This was a cross-sectional study conducted using an existing database. A cross-sectional analysis of an existing database is the most appropriate approach to provide an

observational perspective on the measure of the exposure and health outcome in a given population at a certain time. This study utilized a population-based cancer registry. The study included two dependent variables (survival months and stage of diagnosis), two independent variables (year of diagnosis), and two control variables (race and age) (SEER, n.d.).

Methodology

Population

The target population was males in the United States. Utilizing population-based cancer registries, the SEER database covers approximately 48.0% of the U.S. population (NCI, n.d.; SEER, n.d.). The SEER registry captures cancer data from across the United States of people of different races/ethnicities, socioeconomic statuses, and other demographic criteria.

Sampling and Sampling Procedures

Inclusion criteria for this study were males aged 40 and above, having prostate cancer as a primary cancer, and diagnosis years 2006 to 2011 and 2013 to 2018. Females were excluded. Males under the age of 40 were excluded. Subjects with the prostate as a secondary cancer site were excluded.

A priori power analyses were performed to estimate the minimum sample sizes needed to evaluate the hypotheses associated with the research questions of this study (Pallant, 2016). To calculate the sample size needed to compare the stage at diagnosis of the prostate cancer patients diagnosed prior to 2012 to the stage at diagnosis of those diagnosed after 2012 for RQ 2 using a chi-squared analysis, the G*Power software

(version 3.1.9.7) was utilized. Using an alpha of 0.05, a power of 80%, and a small effect size (w=0.10), the power analysis resulted in a minimum sample size requirement of 785 patients. For RQ 1, since power analysis for the Logrank test was not available in G*Power, it was calculated using the cpower function from the Hmisc package (Harrell, 2024) in R (R Core Team, 2024). To detect a difference between a post-2012 annual mortality rate of 3% and a pre-2012 annual mortality rate of 2.7% (a 10% drop) with 80% power, a sample size of 17619 participants was required.

Data Collection

SEER data are collected from population-based cancer registries throughout the United States. SEER data are widely used and accepted by researchers with publications in peer-reviewed journals. The SEER program has existed for almost 50 years and adheres to rigorous guidelines on data collection and quality control (SEER, n.d.). The program performs quality control checks, including case finding, recoding, and reliability checks during even calendar years (e.g., 2018, 2020; SEER, n.d.). Case finding and recoding are done by a group of auditors traveling to a registry to collect data and using appropriate statistical procedures to assess the registry's performance. Reliability quality checks are through a web-based process that evaluates the skills of central and hospital registry personnel and measures consistency in coding applications and rules across a program. Selected SEER registries, in conjunction with the annual meeting of the National Cancer Registrars Association, conduct training programs during odd calendar years (e.g., 2019, 2021). A quality control tool, the Data Quality Profile, is created for each registry to assess it. The SEER program also does extensive field edits to identify

and correct errors in the data.

Access to the SEER data was possible through online registration. SEER data are available to researchers, clinicians, public health professionals, and the public (SEER, n.d.). Access was granted through institutional access (i.e., Walden University). The SEER database is maintained for researchers and research purposes and adheres to the highest standard of good research practices.

Instrumentation and Operationalization of Constructs

The variables extracted from the 1975-2021 SEER database include age (i.e., age recode with <1-year olds), primary site, PSA values (i.e., PSA lab value Recode), race (i.e., race recode), sex, stage of disease (i.e., combined summary stage), survival months, and year of diagnosis (SEER, n.d.). The determination to extract these specific variables was aligned with the research question and hypotheses.

Age recode with <1-year olds: Refers to age at diagnosis in the SEER dataset. It is a categorical variable coded in years 15-54, 55-64, 65-74, 75-84, and 85+.

Combined summary stage: Refers to stage of disease at diagnosis in the SEER dataset. The combined summary stage is a categorical variable with four categories: localized, regional, distant, and unstaged.

Primary site: A categorical variable with the only selection in this study being the prostate. The primary site designates the location of the primary cancer, and not a secondary cancer or metastatic site.

PSA lab value recode: A continuous variable that refers to the PSA value in the SEER dataset, coded in ng/ml.

Race recode: Refers to race in the SEER dataset. It is a categorical variable. Race recode will include White, Black, or Other, and defines the subject's racial/ethnic self-report.

Sex: A nominal variable extracted to validate that the data extraction is male-specific for prostate cancer.

Survival months: A continuous variable signifying the number of months that the subject lives after diagnosis.

Year of diagnosis: A categorical variable that ranges from 1975 to 2018, with only 2006 to 2011 and 2013 to 2018 being selected.

Data Analysis Plan

The dataset was analyzed using Statistical Package for the Social Sciences (SPSS), version 28, which is available through Walden University for students and researchers. I performed a descriptive analysis of the demographic characteristics, including race, age, year of diagnosis, survival months, and stage of disease. The descriptive statistics displayed frequencies and percentages of the categories for race, age, year of diagnosis, and stage of disease. The descriptive analysis included the use of frequency tables and figures for the visual representation of the results.

Kaplan-Meier survival analysis and Cox proportional hazards regression analysis were used to address RQ 1. Kaplan-Meier survival analysis is nonparametric and was used to estimate the probability of survival of men diagnosed with prostate cancer before 2012 and the probability of survival of men diagnosed after 2012 at given time points (i.e., survival distributions; Laerd Statistics, 2018c). In order to compare the Kaplan-

Meier survival curve for men diagnosed with prostate cancer before 2012 with the survival curve for men diagnosed after 2012, the Logrank test was used, which generates a chi-square statistic (Pallant, 2016). The Logrank test is a nonparametric test to compare two survival distributions. Cox proportional hazards regression analysis is semi-parametric and was used to determine which group of men (those diagnosed before 2012 or those diagnosed after 2012) had a higher hazard rate (risk or probability of suffering the event of interest, which in this case was death, given that the participant had survived up to a specific time, while controlling for race and age (Adelian et al., 2015; LaMorte, 2016).

The chi-square test and logistic regression were used to address RQ 2. The chi-square test is a nonparametric statistical test which was used to determine whether there was an association between the two categorical variables year of prostate cancer diagnosis and stage of prostate cancer at diagnosis (Pallant, 2016). Logistic regression is a parametric test which was used to compare the odds of advanced prostate cancer at diagnosis between those diagnosed before 2012 and those diagnosed after 2012, while controlling for race and age. All the statistical analyses used a p value of <0.05 to indicate statistical significance.

Assumption of the Kaplan-Meier Survival Analysis

There are six assumptions of the Kaplan-Meier survival analysis (Laerd Statistics, 2018c). The first assumption is that the event status should consist of two mutually exclusive and collectively exhaustive states—censored or event. The second assumption is that the time to an event or censorship (i.e., survival time) should be clearly defined

and precisely measured. Assumption 3 is that left censoring should be minimized or avoided, where possible. The fourth assumption is that there should be independence of censoring and the event. The fifth assumption is that there should be no secular trends. The sixth assumption is that there should be a similar pattern of censorship per group. All assumptions were met, permitting the use of Kaplan-Meier survival analysis to address RQ 1.

Assumptions of the Logrank Test

The assumptions of the Logrank test are basically the same as the assumptions of the Kaplan-Meier survival analysis (Bland & Altman, 2004). The assumptions are that censoring is unrelated to prognosis, the survival probabilities are same for subjects recruited early and late into the study, and the events happened at the times specified. The assumptions for the Logrank test were met.

Assumptions of the Cox Proportional Hazards Regression Analysis

There are two assumptions for the Cox proportional hazards regression analysis (IBM, 2023). The first assumption is that the observations should be independent. The second assumption is that the hazard ratio should be constant across time. Both assumptions were met, permitting the use of Cox proportional hazards regression analysis to address RQ 1.

Assumptions of the Chi-Square Test

There are two assumptions of the chi-square test (Laerd Statistics, 2018b). The first assumption is that two variables should be measured at an ordinal or nominal level (i.e., categorical data). The second assumption is that two variables should consist of two

or more categorical, independent groups. Both assumptions were met, permitting the use of the chi-square test to address RQ 2.

Assumptions of Simple Logistic Regression Analysis

There are four assumptions for simple logistic regression analysis (Laerd Statistics, 2018a). The first assumption is that the dependent variable should be measured on a dichotomous scale. The second assumption is that one or more independent variables are either continuous or categorical. The third assumption is that there is an independence of observations, and the dependent variable should have mutually exclusive and exhaustive categories. The fourth assumption is that there needs to be a linear relationship between any continuous independent variables and the logit transformation of the dependent variable. These assumptions have all been met, permitting the use of simple logistic regression to address RQ 2.

Threats to Validity

Threats to validity may be internal or external. Internal validity is the extent to which the observed results represent the truth in the study population (Patino & Ferreira, 2018). External validity refers to the extent to which the results of a study are generalizable to the population that the sample is thought to represent. Confounding variables may pose a threat to internal and external validity (Laerd Statistics, 2018a). Confounders are extraneous variables that affect both the independent and dependent variables, making it challenging to determine their true relationship (Pourhoseingholi et al., 2012). Confounding can be addressed at the study design and analysis stages. Randomization, restriction, and matching address confounding in the study design phase.

This study applied restriction by focusing only on cases with a primary cancer site of the prostate.

Stratification and multivariate models are techniques used to control confounding during the analysis stage of the study through stratification of group data based on the levels of the confounder, allowing for separate analysis within each stratum (Pallant, 2016; Pourhoseingholi et al., 2012). The Cochran-Mantel-Haenszel method is used to provide adjusted results according to strata (Pallant, 2016). A significant difference between crude and adjusted results suggests the presence of confounding. The SEER program recognizes the potential for age as a potential confounder through age-adjustment, as a statistical technique to account for confounding factors related to age (Dess et al., 2019).

Ethical Procedures

This study did not require identifying data; thus, no identifying data were obtained. Furthermore, the SEER database does not collect, store, or make available any identifying data. The limited dataset was unidentifiable, anonymous, and confidential. The limited SEER dataset was used for this study. The limited data will only be available to the researcher, statisticians, and advisors. No attempts were made to contact the participants or uncover their identity by the researchers. This limited dataset was deleted upon study completion. This research study obtained Institutional Review Board (IRB) approval from Walden University (approval no. 01-04-24-1001537). IRB approval was sought prior to receiving SEER data from NCI. The limited dataset was not shared with anyone else (NCI, 2021). Additionally, participant protection was also covered by

research guidelines at the NCI and the National Institutes of Health (NIH), which provides for the protection of human subjects and the highest ethical standards by researchers. This study complied with the Health Insurance Portability and Accountability Act (HIPPA) regulations. There were no other foreseeable ethical considerations for this study.

Summary

This was a secondary data analysis using a cross-sectional study design of a SEER database. A cross-sectional study is the most appropriate approach to provide an observational epidemiologic perspective on the measure of the exposure and health outcome in a given population at a certain time. The SEER dataset was used to compare diagnosed cases of prostate cancer reported from 2006 to 2011 to cases from 2013 to 2018 regarding survival rates and stage of disease, while controlling for race and age. This chapter explored the research design and rationale, methodology, data analysis plan, and threats to validity to address the research questions for this study. Upon IRB approval, data analysis commenced, and Chapter 4 presents the results of the analysis, and Chapter 5 provides a discussion on the interpretation of the study's findings.

Chapter 4: Results

The quantitative research design utilized secondary data analysis of SEER data to assess whether there has been a significant difference in prostate cancer survival and staging since the USPSTF recommended against PSA-based prostate cancer screening in 2012. The data were analyzed using SPSS statistical software, version 28.0.1.0, and the results are presented using tables and figures for illustration. This chapter covers the findings from testing the hypotheses of the two research questions formulated for this study:

- RQ 1: Is there a significant difference in the survival rate between individuals diagnosed with prostate cancer from 2006 to 2011 and individuals diagnosed with prostate cancer from 2013 to 2018 based on routine PSA-based prostate cancer screening tests?
- RQ 2: Is there a significant difference in the stage at diagnosis between individuals diagnosed with prostate cancer from 2006 to 2011 and individuals diagnosed with prostate cancer from 2013 to 2018 based on routine PSA-based prostate cancer screening tests?

Data Collection

The secondary data for this study were obtained from the Incidence-SEER Research Plus Data, 8 Registries, November 2023 Submission (1975-2021). Through an agreement between the NCI and Walden University, I was granted permission to access the SEER Research Plus database as a noninstitutional user with a verified email account. I downloaded and installed the SEER*Stat 8.4.3 software to my laptop. I logged on to

SEER*Stat 8.4.3, which allowed me access to the current version of the SEER*Stat program. In SEER*Stat 8.4.3, I selected Incidence-SEER Research Plus Data, 8 Registries, November 2023 Submission (1975-2021). I created a dataset by selecting the variables for age (i.e., age recode with <1-year olds), primary site, PSA values (i.e., PSA lab value Recode), race (i.e., race recode), sex, survival months, stage of disease (i.e., combined summary stage), year of diagnosis (SEER, n.d.). I extracted the data from SEER*Stat 8.4.3 to a text file.

Using Microsoft ACCESS, the data in the text file were filtered to only include prostate cancer as a primary site (i.e., primary site code was 619) and later filtered again to only include the years 2006 to 2011 and 2013 to 2018. Further filtering was performed using SPSS. For the PSA lab values, blanks, "not documented", and "results not in" (though the test was ordered) were recoded as missing. Additionally, the PSA lab values of "0.1 or less" were set to 0, and "98.0 or greater" were set to 98. "Unknown" race was coded as missing. "Unknown" and "in situ" summary stages were coded as missing. I did not include age groups from smaller sample age bands under age 40 (e.g., <1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39 years).

The dataset was transferred into SPSS for further analysis. Using the transform feature in SPSS to recode variables, a binary variable for "combined summary stage" (i.e., localized, regional, distant, and unstaged) was recoded with two categories, "Localized" and "Regional/Distant." Similarly, a binary variable indicating whether the initial diagnosis was before or after 2012 was created from the continuous variable year of diagnosis. The following table illustrates the sample size after the various data filtering

steps.

Table 1

Sample Size After Various Filtering Steps

n	Description
5,094,540	Starting sample size (all cancers)
624,979	Sample size after removing all non-prostate cancer patients
205,129	Sample size after removing prostate cancer patients not diagnosed in 2006-2011 or 2013-2018
205,019	Sample size after removing individuals with age >= 40 *

* This step performed in SPSS.

Descriptive Data Analysis

The sample in this study consisted of 205,129 men with prostate cancer, with 79.1% White (*n* =162,551), 11.8% Black (*n* = 24,189), and 7.6% Other (American Indian/Alaska Native, Asian/Pacific Islander; *n* = 15,495). Age distributions are presented by age groups in Table 2. This study met external validity due to the large sample size and diversity of race and age groups. The results of this study are generalizable to the population that the sample is thought to represent.

Table 2

Age Distribution of Men with Prostate Cancer

	n	%
40-44 years	804	0.40%
45-49 years	4086	2.00%
50-54 years	13666	6.70%
55-59 years	27079	13.20%
60-64 years	39039	19.00%
65-69 years	44668	21.80%
70-74 years	33706	16.40%
75-79 years	21586	10.50%
80-84 years	11598	5.70%
85+ years	8787	4.30%

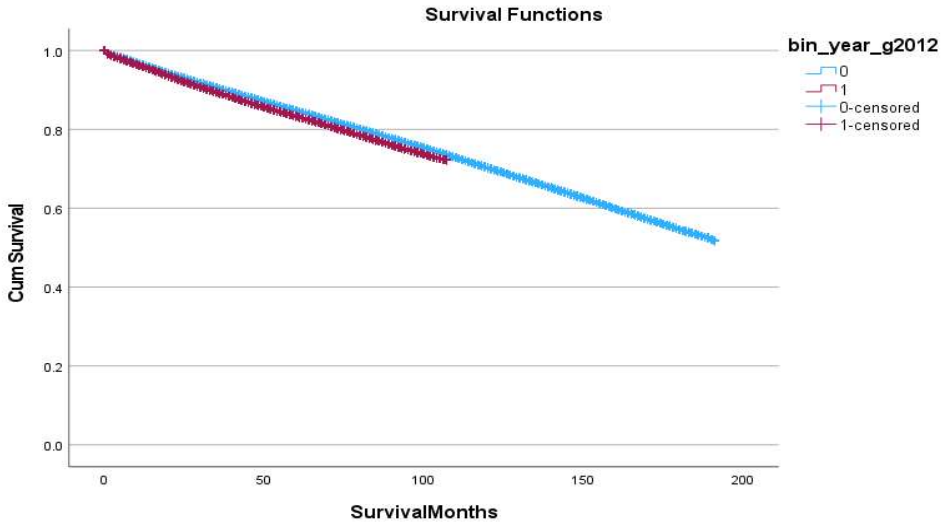
Results

Research Question 1: Comparing Survival Rates

The Logrank test, which was used to compare the Kaplan-Meier survival curves in Figure 1, indicated that there was a statistically significantly higher probability of survival for individuals diagnosed prior to the year 2012 (i.e., years 2006 to 2011) compared to individuals diagnosed after year 2012 (i.e., years 2013 to 2018) ($\chi^2(1) = 81.662$, $p < 0.001$).

Figure 1

Kaplan-Meier Survival Function



A Cox proportional hazards regression analysis was performed to compare the hazard rates for individuals diagnosed prior to the year 2012 to those diagnosed after year 2012, controlling for race and age. The Cox proportional hazards regression analysis is a regression model used to determine the association between the hazard rates and one or more predictor variables (LaMorte, 2016). The parameter estimates for race were

calculated with “White” as the reference group, for age were calculated with “40-44” as the reference group, and for year of diagnosis were calculated with “before 2012” as the reference group.

As seen in Table 3, there was a statistically significant association between hazard rate and year of diagnosis, after controlling for race and age, with individuals diagnosed after 2012 having a 12.6% higher risk of death than those diagnosed before 2012 (HR = 1.126; 95% CI = 1.104, 1.148; $p < 0.001$). Race and age were also significantly related to hazard rate, with Blacks and older age groups having higher hazards. Blacks had a 43.2% higher hazard compared to Whites, which was statistically significant. Oher races had a 9.1% lower hazard compared to Whites, which was also statistically significant. Hazard rates increased with increasing age, reaching a high in the 85+ group, which had a 36 times higher hazard rate than the 40–44-year-old group.

Table 3

Cox Proportional Hazards Regression Model for Research Question 1

	Est	HR	SE	Z	P-Value	Low 95	High 95
After 2012	0.119	1.126	0.01	11.913	< .001	1.104	1.148
Race: Black	0.359	1.432	0.013	27.778	< .001	1.396	1.469
Race: Other	-0.097	0.908	0.015	-6.408	< .001	0.881	0.935
Age: 45-49 years	0.057	1.059	0.123	0.466	0.641	0.832	1.348
Age: 50-54 years	0.235	1.265	0.115	2.038	0.042	1.009	1.587
Age: 55-59 years	0.454	1.575	0.114	3.994	< .001	1.26	1.969
Age: 60-64 years	0.744	2.105	0.113	6.573	< .001	1.686	2.628
Age: 65-69 years	1.161	3.193	0.113	10.273	< .001	2.558	3.984
Age: 70-74 years	1.633	5.121	0.113	14.458	< .001	4.104	6.39
Age: 75-79 years	2.162	8.693	0.113	19.136	< .001	6.966	10.848
Age: 80-84 years	2.804	16.515	0.113	24.778	< .001	13.23	20.617
Age: 85+ years	3.585	36.043	0.113	31.638	< .001	28.865	45.005

Research Question 2: Comparing Stage at Diagnosis

The results of the chi-square test demonstrated a statistically significant association between the two categorical variables year of prostate cancer diagnosis and stage of prostate cancer at diagnosis. ($\chi^2(1) = 1283.524$, $p < 0.001$). There was a higher percentage of those diagnosed after 2012 being diagnosed with regional or distant prostate cancer compared to those diagnosed before 2012 (23.6% vs. 17.1%).

As seen in Table 4, the odds of being diagnosed with advanced stage cancer were statistically significantly higher in those diagnosed after 2012 compared to those diagnosed before 2012 after controlling for race and age (*OR*=1.530; 95% *CI* = 1.496, 1.564; p < 0.001). Blacks had lower odds (*OR* = 0.802) of being diagnosed with advanced stage disease compared to Whites. Other races had a slightly higher odds (*OR* = 1.107) of being diagnosed at a later stage. Those aged 70-74 (*OR* = 0.783) and 75-79 (*OR* = 0.729) had lowers odds of being diagnosed at an advanced stage of disease, while those aged 85+ had much higher odds (*OR* = 2.387) of advanced stage of disease at diagnosis than those aged 40-44.

Table 4

Logistic Regression Model for Research Question 2

	Est	OR	SE	Z	P-Value	Low 95	High 95
Constant	-1.527	0.217	0.092	-16.571	< .001	0.181	0.26
After 2012	0.425	1.53	0.011	37.259	< .001	1.496	1.564
Race: Black	-0.22	0.802	0.019	-11.849	< .001	0.773	0.832
Race: Other	0.102	1.107	0.021	4.858	< .001	1.063	1.154
Age: 45-49 years	0.081	1.085	0.1	0.814	0.416	0.892	1.319
Age: 50-54 years	0.052	1.054	0.094	0.555	0.579	0.876	1.268
Age: 55-59 years	-0.005	0.995	0.093	-0.053	0.958	0.829	1.195
Age: 60-64 years	0.015	1.015	0.093	0.164	0.87	0.846	1.218
Age: 65-69 years	-0.098	0.907	0.093	-1.056	0.291	0.756	1.087
Age: 70-74 years	-0.245	0.783	0.093	-2.629	0.009	0.652	0.94

Age: 75-79 years	-0.316	0.729	0.094	-3.362	0.001	0.607	0.877
Age: 80-84 years	0.12	1.127	0.095	1.265	0.206	0.936	1.358
Age: 85+ years	0.87	2.387	0.095	9.133	< .001	1.98	2.877

Figure 2 illustrates the significant difference in the probability of being diagnosed with advanced stage disease before 2012 and after 2012. Table 5 illustrates the significant change in the percentage of stage of disease at diagnosis associated with the year 2012 change in prostate cancer screening.

Figure 2

Probability of Regional/Distant Prostate Cancer Diagnosis by Year of Diagnosis

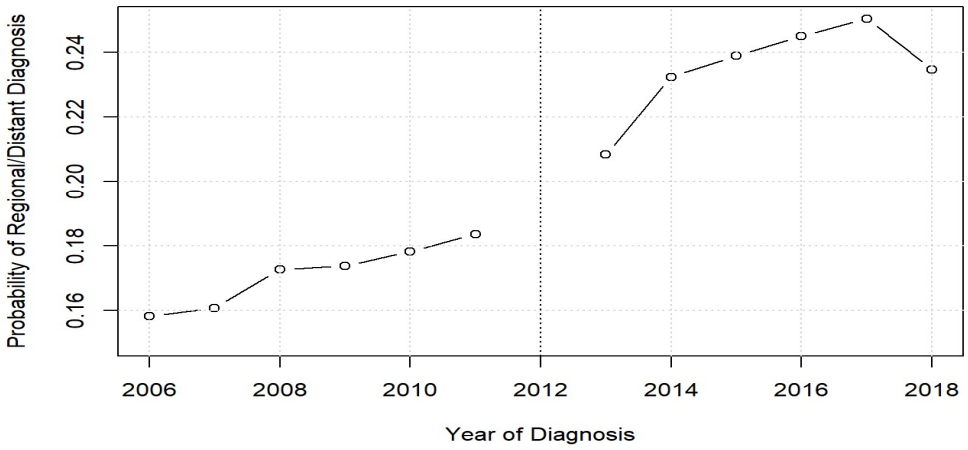


Table 5

Stage at Diagnosis by Year of Diagnosis for Research Question 2

Year	Localized (%)	Regional/Distant (%)
2006	84.2	15.8
2007	83.9	16.1
2008	82.7	17.3
2009	82.6	17.4
2010	82.2	17.8
2011	81.7	18.3

2012	80.2	19.8
2013	79.2	20.8
2014	76.8	23.2
2015	76.1	23.9
2016	75.5	24.5
2017	75	25
2018	76.5	23.5

Summary

Based on the data analysis for RQ 1, I rejected the null hypothesis that there is no significant difference in survival between individuals diagnosed with prostate cancer using routine PSA-based prostate cancer screening tests from 2006 to 2011 and individuals diagnosed from 2013 to 2018. Also, based on the data analysis for RQ 2, I rejected the null hypothesis that there is no significant difference in the odds of being diagnosed at an advanced stage between individuals diagnosed with prostate cancer using routine PSA-based prostate cancer screening tests from 2006 to 2011 and individuals diagnosed from 2013 to 2018.

In this chapter, I described the data collection and the results of the data analysis, providing tables and figures to support the results. In Chapter 5, I will interpret these results and compare them to those in related studies and describe the study's strengths and limitations, make recommendations for future research, and describe the study's implications for social change.

Chapter 5: Discussion, Conclusions and Recommendations

The purpose of this quantitative study was to utilize secondary data to assess whether there was a significant difference in prostate cancer survival and stage at diagnosis since the USPSTF recommended against PSA-based prostate cancer screening in 2012. This cross-sectional study utilized the most current national epidemiologic data on prostate cancer from the SEER program. The study sample included 205,129 men diagnosed with prostate cancer from 2006 to 2011 and 2013 to 2018. Overall, men diagnosed with prostate cancer before 2012 had a significantly higher probability of survival than those diagnosed after 2012. Furthermore, men were significantly more likely to be diagnosed with advanced (e.g., regional, or distant) prostate cancer after 2012.

Interpretation of the Findings

At the core of this quantitative study was the utilization of SEER data to assess whether there was a significant difference in prostate cancer survival and stage of prostate cancer at diagnosis before and after the USPSTF recommended changes to prostate cancer screening guidelines in 2012. RQ 1 addressed the potential difference in survival rate between these two groups, while RQ 2 addressed the potential difference in stage of the disease at diagnosis between the two groups.

Previous research showed higher incidences of advanced prostate cancer diagnosed after 2012 (Sheng et al., 2021; Siegel et al., 2023; Silva et al., 2020). For example, Sheng et al. (2021) found an increased incidence of metastatic prostate cancer at stage of diagnosis between 2013 to 2015 (i.e., after 2012) compared to the control

group (i.e., 2004-2008), which was in line with the findings of the current study, though they did not assess survival rates. Further, Silva et al. (2020) assessed the impact of the 2012 USPSTF recommendation on 518 patients and found increased rates of more aggressive prostate cancer at diagnosis, with higher Gleason scores and greater core involvement in biopsies after the 2012 recommendation. Biopsy involves core samples from various regions of the prostate, with core involvement referring to the number of cores involved by the tumor, and the length or percentage of tumor involvement of the core (Antonelli et al., 2013; Harvard Prostate Knowledge, 2009). These results aligned with the current study's findings of increased severity of disease at diagnosis, suggesting a shift towards more advanced and aggressive disease presentation after the 2012 recommendation.

The current study also found that Black men had a 43.2% higher hazard rate than White men after 2012. Similarly, Iyengar et al. (2020) utilized SEER data and found that NHBs and APIs exhibited the highest and lowest incidence and mortality rates, respectively, with increasing trends in distant stage diagnosis in men post-2012. Nyame et al. (2021) also found benefits (e.g., reduced mortality and lower risks of overdiagnosis) of intensified PSA screening, particularly among NHBs, suggesting that targeted screening might be beneficial. However, their study utilized modeling which had a number of limitations, such as the underrepresentation of Blacks (0-3%). The current study offered a different perspective without the utilization of modeling, as in the study by Nyame et al., and with a significantly larger percentage of Blacks (11.80%) than in the PCLO Cancer screening trial.

The SEM, which was the theoretical foundation for the current study, recognizes that factors of the individual, the community, and the environment affect health (Burkholder et al., 2020; Kilanowski, 2017; Krieger, 2014). This model was helpful in the research process to inform the research aims, questions, data collection, and analysis which can potentially influence prostate cancer screening recommendations to promote PSA-based screening (Kumar et al., 2022). The current study builds on the localized studies within the framework of the national discussion of the effects of prostate cancer screening on stage at diagnosis and survival. Past research underscores the potential negative consequences of the USPSTF's 2012 decision to recommend against routine PSA screenings for all men regardless of individual risk factors. The overall increase in late-stage diagnoses and mortality observed in several post-2012 studies suggest that the findings of the current study were not isolated findings. Some earlier research involved localized studies that were regional with smaller sample sizes (Jenkins et al., 2021; Lewis-Thanes et al., 2021; Leung et al., 2018; Misra-Herbert et al., 2017) while other studies involving SEER data only assessed survival (Iyengar et al. 2020) or involved microsimulation modeling (Nyame et al., 2021). The current study also builds on the larger study that involved SEER data by assessing survival and stage of diagnosis. The evidence in the current study advocates for re-evaluating screening guidelines.

Limitations of the Study

This study utilized data from the SEER program, a national cancer registry comprised of valid and reliable information on prostate cancer survival and stage of disease. A national cancer registry like the SEER program offers significant sample size

and representativeness advantages, allowing for reliable and generalizable results of study subjects from 2006 to 2011 and 2013 to 2018 (Soni, 2019). One limitation of this study is that the SEER program does not collect data on family history, a non-modifiable risk factor for prostate cancer, which could have potentially caused confounding of the results of the current study (Delgado-Rodríguez et al., 2004; Elliott et al., 2018; Tripepi et al., 2010).

Recommendations for Future Research

Research findings of the current study showed an increase in the stage of prostate cancer at diagnosis and a decrease in survival in prostate cancer patients following the 2012 USPSTF recommendation regarding screening for prostate cancer. Further research is needed to elucidate the causal associations for more aggressive prostate cancer diagnoses and reduced survival since the implementation of the 2012 USPSTF recommendations against PSA-based prostate cancer screening. Future studies should consider including additional variables to allow to study their effects and perhaps control these effects to minimize the likelihood of confounding and eliminate alternate potential explanations. Other research opportunities exist in studying age and race in advanced-stage prostate cancer. The current study showed fluctuating odds with increasing age groups. For example, the 80-84 age group had an increased *OR* of 1.127. For race, Black men had a lower *OR* of 0.802 compared to Other, which had an *OR* of 1.107.

Implications

Prostate cancer carries a significant national burden. As prostate cancer is the leading cancer in men (e.g., 1 out of 9 males being diagnosed), and the second leading

cause of cancer mortality overall in the United States, reversing the increased incidence in prostate cancer stage at diagnosis and decreased survival rate is an imperative public health concern (Kensler et al., 2021; King et al., 2020; SEER, n.d.; Zavala et al., 2021). Positive social change may result from a change in USPSTF prostate cancer screening informed by the findings of relevant research, and this could lead to earlier prostate cancer diagnoses, resulting in more early-stage disease, earlier treatment, longer survival, and decreased mortality.

The theoretical foundation of the SEM supports the potential for positive social change, particularly in influencing the USPSTF recommendation at the national level to impact the health of individuals and communities. The SEM supports the need for PSA-based testing to be effectively integrated into prostate cancer screening through changes in USPSTF recommendations. The findings of the current research study could encourage clinicians to advocate for PSA-based testing as a screening tool for their patients, leading to reduced mortality and increased survival. Thus, the SEM guides the support for changing the USPSTF recommendation to include PSA-based screening, which will affect the individual and the community to produce increased prostate cancer survival rates and less aggressive disease presentation.

Conclusion

This research addressed a significant public health concern, the potential negative impact of the 2012 USPSTF issuance of a new recommendation against routine PSA-based prostate cancer screening. A quantitative study was performed using the most recent SEER dataset to compare survival rates and stage of disease at diagnosis in

individuals diagnosed with prostate cancer over the 5 years (2006-2011) prior to the change in recommendation and individuals diagnosed with prostate cancer over the 5 years (2013-2018) following the change in recommendation. The results of the current study were consistent with those of earlier studies, showing decreased survival and increased disease severity at the time of diagnosis after the USPSTF changed its prostate cancer recommendation in 2012. Evaluating the USPSTF recommendation is essential in safeguarding public health by ensuring that the best evidence-based practices are used to provide optimal protection.

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