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Association Between Androgen Deprivation Therapy for Prostate Cancer and Alzheimer's Disease

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MS, New York Medical Health Sciences University, 2003

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Alzheimer's disease (AD) is the most common progressive, neurodegenerative disease and form of dementia. The hallmarks of AD are extracellular accumulation of amyloid beta protein, resulting in neuritic, senile plaques and intracellular accumulation of tau protein. AD mainly arises from imbalance of amyloid beta protein production and its clearance in the brain. Testosterone modulates production of amyloid beta protein by decreasing its accumulation. Prostate cancer remains a substantial public health challenge in the United States. While androgen deprivation therapy (ADT) is an effective treatment for prostate cancer, it may be associated with cognitive impairment due to decreased levels of testosterone. The purpose of this study was to explore the association between ADT and the development of AD. This study was a retrospective, quantitative cohort study of subjects diagnosed with prostate cancer from a large population database, SEER Medicare-linked database. Data were analyzed using descriptive statistics along with correlation and multiple logistic regression analysis to evaluate the association between ADT use for prostate cancer and AD risk. The sample consisted of 27,913 men with a mean age of 72 years, majority being Caucasian with multiple comorbidities. Subjects who had received ADT were 20% more likely to develop AD than subjects who had not received ADT (OR, 1.20; 95% CI, 1.09, 1.32; $p < .001$) after controlling for race, ethnicity, prostate cancer stage, prostate cancer risk groups, and comorbidities. This association did not appear to vary by race or PCa risk group. Given an aging population and increased incidence and prevalence of prostate cancer and AD, these results may lead to positive social change by furthering AD prevention.

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Chapter 1: Introduction to the Study

Alzheimer's disease (AD) is the most common progressive, neurodegenerative disease and form of dementia (Centers for Disease Control and Prevention [CDC], 2015; Mayeux & Stern, 2012). It affects regions of the brain implicated in learning and memory, such as the hippocampus and cortex, gradually destroying a person's ability to remember, learn, and ultimately carry out activities of daily living (Rubio-Perez & Morillas-Ruiz, 2012). It is the sixth leading cause of mortality in the United States and the fifth leading cause of death among those aged 65 and older (CDC, 2015; Selkoe, 2012; Tejada-Vera, 2013). Aging, family history, decrease in sex hormones, and cardiovascular disease appear to be the main risk factors for AD; however, the exact cause is unknown.

Similarly, prostate cancer (PCa) remains a substantial public health challenge in the United States (Brawley, 2012; National Cancer Institute, 2015a). It is the most common malignancy and the second leading cause of cancer death in men in the United States, preceded only by lung cancer (Brawley, 2012; National Cancer Institute, 2015a; Siegel, Miller, & Jemal, 2016). The National Cancer Institute (2015a) indicated that approximately 220,800 new cases of PCa and 27,540 deaths were reported in 2015. Moreover, a United States male has a 1 in 6 lifetime risk of developing PCa (Delahunt, Miller, Srigley, Evans, & Samaratunga, 2012; Zheng & Tyner, 2013). Worldwide, PCa remains the third leading cause of cancer death in men (Buschemeyer & Freedland, 2007).

Androgen deprivation therapy (ADT) remains the standard treatment for locally advanced, high risk, and/or metastatic PCa. ADT decreases concentrations of circulating testosterone substantially, as androgens have been associated with PCa growth and recurrence (Ciocca et al., 2016; Martins & Gandy, 2016). ADT administration has increased significantly over the last few decades due to its effectiveness as sole or adjunct therapy for PCa subjects (Martins & Gandy, 2016). Approximately 500,000 men currently utilize ADT in the United States for PCa, and this number is increasing (Nead et al., 2016). While it is an effective treatment for PCa, ADT reduces concentrations of circulating androgens to extremely low levels (< 350ng/ml) and may be associated with cognitive impairment (Martins & Gandy, 2016). However, the association between ADT and cognitive dysfunction, particularly AD, has not been well studied and results are conflicting.

Given the significant patient, familial, and economic burden and increased morbidity and mortality from AD, it is imperative to further investigate the association between ADT and AD in order to prevent further morbidity and mortality and effect positive social change. In addition, given the morbidity and mortality from PCa and the ubiquitous and increasing use of ADT, it is essential to understand the side effects of this treatment, such as cognitive dysfunction, to limit morbidity (Ahmadi & Daneshmand, 2013).

Moreover, racial health disparity in ADT use remains a public health dilemma. African American men are less likely to be offered aggressive treatment options for PCa and less likely to desire treatments, which have side effects (Chornokur, Dalton,

Borysova, & Kumar, 2011). African American men are also less likely to receive ADT for advanced disease compared to Caucasian men (Chornokur et al., 2011). This often leads to higher mortality rates and decreased quality of life among African American men, compared to Caucasian men (Chornokur et al., 2011). Tyson and Castle (2014) indicate that the largest health disparities occur in African American men, who do not undergo treatment (Tyson & Castle, 2014). Even after adjustment for treatment effects, African American men exhibit the lowest overall and PCa-specific survival among all racial groups (Tyson & Castle, 2014). It is possible race and/or ethnicity may modify the association between ADT and AD (Chornokur et al., 2011). In addition, Schlesinger et al. (2013) showed that African ancestry is inversely associated with neuritic plaques or beta amyloid accumulation, which is the hallmark of AD, even after controlling for several potential confounding factors, such as age and cardiovascular disease. This may indicate that genetics and possible unknown environmental factors protect African American men from developing AD.

The magnitude of the expected rise in AD is significant due to an aging population and will be an even more costly public health problem in the years to come (Mayeux & Stern, 2012). This research is significant because AD incidence and prevalence are increasing and there is no cure for this degenerative disease. With increasing healthcare costs and extensive burden on subjects and their caregivers, it is important to learn more about AD risk factors to prevent AD or slow its progression (Vest & Pike, 2013).

Background of the Problem

AD is the most common chronic, degenerative disease (CDC, 2015; Mayeux & Stern, 2012). People aged 85 years and older have a 5.4 times greater risk of dying from AD than people aged 75-84 years old (Mayeux & Stern, 2012). Caucasians have a 26% higher mortality risk from AD compared to African Americans (Mayeux & Stern, 2012).

Physiologically, AD is characterized by increased extracellular accumulation of amyloid beta protein in the form of senile plaques and intracellular formation of neurofibrillary tangles composed of tau protein, a component of the cell's cytoskeleton, particularly in the hippocampus and cortex of the brain, areas implicated in memory and executive function (Vest & Pike, 2013).

Both genetics and environmental factors are implicated in AD. Certain risk factors, such as cardiovascular disease and diabetes, are highly associated with AD. Moreover, age and factors attributed to aging, such as low androgen levels, are significant risk factors for cognitive decline and possibly AD (Mayeux & Stern, 2012).

Vest and Pike (2013) discussed that the brain is an androgen-responsive tissue and is affected by age-related androgen loss leading to impairment in cognition and increased AD risk. Androgens are neuroprotective and attenuate neuronal cell injury against insults such as oxidative stress and amyloid beta toxicity, which are also significant risk factors for AD.

Lv et al. (2015) conducted a systematic meta-analysis of seven prospective cohort studies to explore and confirm the association between low testosterone levels and risk of AD. Results showed that low plasma testosterone in elderly men was significantly

associated with higher risk of AD. For all studies, follow-up data spanned at least one year, which is minimal given that AD development can takes several years. After controlling for a moderate degree of heterogeneity among the studies, low testosterone levels were still significantly associated with an increased risk of AD in elderly men (N = 240) across all seven prospective cohort studies. Moreover, Martins and Gandy (2016) discussed that ADT decreases levels of testosterone to well below physiological low levels or less than 350ng/ml, and its use has increased significantly over the last few decades. While ADT has enhanced PCa treatment and increased survival, it exhibits a myriad of side effects, such as cognitive impairment.

Wu, Diefenbach, Gordon, Cantor, and Cherrier (2013) presented the results of a small, qualitative study that supported an association between ADT and cognitive impairment. Eight out of eleven participants administered ADT reported impairments in concentration, information processing, visuospatial processing, memory, and executive functioning. While results of this study may help clinicians become more aware of how subjects verbalize cognitive dysfunction, the sample size was too low to draw definite conclusions. Moreover, as it was a qualitative and not a quantitative study, it was difficult to test associations and hypotheses.

Nead et al. (2016) presented the first large, retrospective cohort study of 2,397 hospital-based subjects diagnosed with PCa who received ADT for less than, equal to, or greater than 12 months. Results support an association between the use of ADT for the treatment of PCa and higher risk of AD, especially when treatment duration was 12 months or longer. However, Chung, et al. (2016) conducted a larger retrospective

population based study (n = 5,340) of PCa subjects and matched controls and followed this cohort for 5 years to assess AD incidence. The hazard ratio was not statistically significant. In addition, researchers assessed participants who took ADT and those who did not, and the results were the same—no statistically significant hazards ratio between the groups (Chung et al., 2016). Although the sample size was adequate, this study may be flawed in that subjects were only followed for 5 years, and the onset of AD could take several years to manifest.

As discussed, the association between ADT and cognitive impairment, especially AD, has been less well studied, and results are conflicting in that some studies showed an association between cognitive impairment and ADT and some did not. This study, therefore, builds upon the methodological flaws of previous studies and adds to the literature by further investigating the association between ADT and AD because AD is a disease without cure, and ADT has been an increasingly popular sole or adjuvant treatment for PCa.

Problem Statement

AD is the most common form of dementia (CDC, 2015; Mayeux & Stern, 2012). It manifests as cognitive or mental decline and loss of intellectual ability (CDC, 2015). As AD progresses, it often leads to dysfunction in daily living, poor judgment, changes in mood and/or personality, and difficulty with executive functions, such as making decisions (Mayeux & Stern, 2012).

AD is the sixth leading cause of mortality in the United States and the fifth leading cause of death in those aged 65 and older (CDC, 2015; Tejada-Vera, 2013).

Globally, there are approximately 24 million people living with dementia and approximately 34 million with AD; this number is expected to triple to over 100 million by 2050 due to an aging population (Lv et al., 2015; Mayeux & Stern, 2012; Selkoe, 2012). In the United States, there are approximately 5 million persons living with the disease, and this number is expected to triple to 13.8 million by 2050 (Mayeux & Stern, 2012; Tejada-Vera, 2013).

As heart disease incidence, prevalence, and mortality have declined over the last few decades, incidence, prevalence, and death from AD have increased by 39% from 18.1% to 25% of the population in the United States (Tejada-Vera, 2013). Moreover, the cost of healthcare for those with AD was approximately $200 billion in 2012 and will reach 1.1 trillion by 2050 as the population continues to age (Mayeux & Stern, 2012; Tejada-Vera, 2013).

Because there is no cure for this degenerative and debilitating disease, and current treatments do not halt its progression, it is imperative to understand the risk factors, especially modifiable risk factors, that predict AD for prevention (Lv et al., 2015; Nead et al., 2016). Scientists agree that secondary prevention, or diagnosing and treating the disease before symptoms manifest, as well as overall prevention, are essential to slow neuropathology and cognitive decline (Selkoe, 2012).

Age, for example, is one of the main risk factors for AD, and several studies suggest that androgen loss as a result of aging may promote cognitive decline in older men and increase risk of AD due to low levels of circulating testosterone (Ciocca et al., 2016; Martins & Gandy, 2016; Nead et al., 2016; Vest & Pike, 2013). Physiological low

levels of testosterone due to aging have been associated with increased risk for AD by both in vitro and in vivo studies; however, data are often conflicting (Martins & Gandy, 2016; Verdile et al., 2014).

Testosterone is normally neuroprotective, helping to mitigate oxidative stress, and preventing amyloid beta neurotoxicity (Verdile et al., 2014). Because androgen receptors reside in the hippocampus and prefrontal cortex, low levels of testosterone, the primary male androgen, result in a decline in cognition, memory, and visuospatial ability leading to dementia and often AD (Verdile et al., 2014). Moreover, some studies show that low testosterone levels resulting from ADT are responsible for decreased cognitive functioning in men; however, results are equivocal (Ciocca et al., 2016; Lv et al., 2015).

ADT treatment for locally advanced, high risk, and/or metastatic PCa decreases testosterone levels to well below normal physiological low levels, or below 350 ng/mL total testosterone (Ciocca et al., 2016; Martins & Gandy, 2016). The use of ADT has increased significantly over the last few decades due to its effectiveness as sole or adjunct therapy for PCa subjects (Martins & Gandy, 2016). Approximately 500,000 men currently utilize ADT in the United States for PCa, and this number is increasing (Nead et al., 2016). While it is an effective treatment, ADT reduces androgens to extremely low levels and is likely associated with cognitive impairment (Martins & Gandy, 2016). With the number of PCa subjects expected to increase due to population growth and an aging population, and given the burden that cancer places on subjects, family members, and healthcare, understanding treatment outcomes and side effects remains crucial (Ambs et al., 2008).

Results from a large, retrospective cohort study indicate that ADT may be associated with AD (Martins & Gandy, 2016; Nead et al., 2016). However, limited and conflicting data exist regarding ADT's effects on cognitive function (Ahmadi & Daneshmand, 2013; Nead et al., 2016; Martins & Gandy, 2016). Studies investigating the association between ADT and neurocognitive disease are limited and disparate, suffering from small sample size and confounding factors, such as PCa risk groups. Only two known studies investigated the association between ADT and AD, both with short follow-up and small, convenience population sampling, which may have led to an overestimation or underestimation of AD outcomes, as results were conflicting (Chung et al., 2016; Lv et al., 2015; Nead et al., 2016). For example, Nead et al. (2016) had limited follow-up of 1 year, when AD may take several years for symptoms to manifest.

Given the significant patient, familial, and economic burden, and increased morbidity and mortality from AD, it is imperative to further investigate the association between ADT and AD and address these methodological flaws.

Purpose of the Study

The purpose of this study was to further explore the association between ADT and the development of AD through quantitative analysis of a large population database, the National Institute of Health (2016) Surveillance, Epidemiology, and End Results Program (SEER) Medicare-linked database, which contains long term, follow-up information of at least 5 years. Extended follow-up data are most useful for AD detection, because clinical symptoms of AD manifest after many years. While some studies suggest that ADT use may lead to cognitive impairment, more large-scale studies are needed, especially to

investigate the association between ADT and AD (Wu et al., 2013). Existing studies suffer from small sample sizes, such as the study by Wu et al. (2013) with $n = 11$, limited follow-up data of 5 years or less, low generalizability due to use of hospital data, potential bias from the use of convenience sampling, and failure to assess the effect that a particular stage of PCa has on the association between ADT and AD across PCa risk groups. In this study I sought to improve upon these methodological limitations and increase knowledge of the association between ADT and AD, leading to positive social change by reducing morbidity and mortality.

Research Questions and Hypotheses

RQ1: Is there an association between ADT (the independent variable) and AD (the dependent variable) after controlling for potential confounding factors, such as cardiovascular disease and Type 2 diabetes?

$H_0$1: There is no association between ADT and AD after controlling for potential confounding factors.

H_a1: ADT is significantly associated with AD, even after controlling for potential confounding factors?

RQ2: Does the association between ADT and AD risk vary by PCa risk groups (a possible moderator)?

$H_0$2: There are no differences in the association between ADT and AD by PCa risk groups.

H_a2: There is a stronger association between ADT and AD among men with advanced stage, high-risk PCa.

RQ3: Does the association between ADT and AD risk vary by race (a possible moderator)?

$H_0$3: Race does not influence the association between ADT and AD.

H_a3: Race modifies the association between ADT and AD with African-American men being less likely to develop AD than Caucasian men.

Conceptual Framework

Extensive research has resulted in better understanding of the neurophysiology of AD and neurodegeneration. The hallmarks of AD are extracellular accumulation of amyloid beta protein, resulting in neuritic, senile plaques and intracellular accumulation of tau protein, resulting in neurofibrillary tangles (Kandel & Schwartz, 1985; Vest & Pike, 2013). Amyloid beta protein oligomers act like ion channels allowing mass influx of calcium ions, which disrupts the cell membrane potential, resulting in neuronal cytotoxicity and cell death (Savelieff, Lee, Liu, & Lim, 2013). Amyloid beta protein activates several proinflammatory molecules, such as cytokines, nitric oxide, and chemokines (Rubio-Perez & Morillas-Ruiz, 2012). This results in synaptic dysfunction, cognitive decline, and neuronal cell death (Vest & Pike, 2013). This pathology is most prevalent in the hippocampus and cortex, areas of the brain responsible for memory and executive functioning, and most often implicated in AD. AD mainly arises from imbalance of amyloid beta protein production and its clearance in the brain (Selkoe, 2012). Most AD scientists agree that secondary prevention, or diagnosing and treating AD before overt clinical symptoms present, is more likely to slow pathological cognitive

decline (Selkoe, 2012). Thus, a better understanding of the association between risk factors and AD is imperative.

Testosterone is neuroprotective and exerts its effects in the hippocampus and cortex, areas of the brain responsible for memory and executive functioning, such as decision-making (Martins & Gandy, 2016). It also modulates production of amyloid beta protein by decreasing its accumulation and therefore preventing formation of senile plaques, pathological signs of AD (Nead et al., 2016). ADT, an effective treatment for high risk, locally advanced, or metastatic PCa, decreases testosterone levels to lower than normal physiologically low levels, and thus has recently been shown to have an association with AD development (Nead et al., 2016). However, more research is needed to understand the association between the potential side effects of ADT, dementia, and AD to prevent increased AD incidence and prevalence and possibly modify PCa treatment effects to prevent devastating side effects, such as cognitive impairment and AD.

Lastly, the Institute of Medicine defines health as complete physical, mental, and social well-being (Kohn et al., 2010). Health disparities remain a significant public health concern in the United States. A large portion of the population, mainly racial minorities, manifests poverty and low socioeconomic status (SES), which lead to poor health outcomes (Kohn et al., 2010). Previous research identified multiple factors associated with health disparities, which lead to poor health outcomes (Kohn et al., 2010). For instance, those with low SES, mainly racial and ethnic minorities, often do not receive adequate preventative medical care and treatment, such as PCa screening and ADT, and

thus suffer disproportionate rates of disease, such as advanced stage PCa and metastatic PCa (Kohn et al., 2010). Ultimately, this leads to increased morbidity in this population, which increases health care costs, and mortality often ensues (Ahluwalia et al., 2009).

In addition, cultural beliefs of racial minorities, such as African American men, often shape their health care decisions. The health belief model was developed as a means to explain and predict health behaviors. Its postulation is that people often do not seek health care prevention or treatment unless they perceive themselves as susceptible to disease, such as PCa, and believe that the benefits of treatment outweigh the risk. The elimination of health disparities is a major worldwide health objective. Research shows that low SES contributes significantly to poor health outcomes, increased morbidity, and premature mortality. Thus, one of the hypotheses for this study was that African American men may experience lower incidence of AD, because they often do not take ADT or take ADT but are already in advanced stage PCa and thus die earlier before AD incidence can develop.

Nature of the Study

This study is a retrospective, quantitative cohort study of subjects diagnosed with PCa using ADT and those not using ADT from a large population database, SEER Medicare-linked database, utilizing descriptive statistics along with correlation and multiple logistic regression analysis to evaluate the association between ADT use for PCa treatment and AD risk. I chose the quantitative study design not only because the variables in this study can be quantified, but also because it allows researchers to either refute or support study hypotheses via hypothesis testing and inferential statistics and is

best suited to answer the research questions. The independent variable was ADT use and the dependent variable was AD. The controls were PCa subjects, who did not receive ADT for PCa treatment.

This database contains follow-up information greater than 5 years as clinical symptoms of AD take years to present from inception. To address this issue, quantitative data such as demographics (age and race), PCa and AD diagnosis, medical history, clinical stage of PCa, treatment information such as ADT treatment, and comorbidities such as cardiovascular disease, diabetes, and stroke were collected and analyzed to respond to the research questions.

Definition of Terms

Alzheimer's disease: The most common, progressive form of dementia or loss of memory and intellectual functioning due to aging, loss of androgens, accumulation of amyloid beta in the form of neuritic plaques and tau protein as neurofibrillary tangles (CDC, 2015; Vest & Pike, 2013).

Androgen deprivation therapy (ADT): Use of gonadotropin-releasing hormone agonists or antagonists, such as Lupron, and/or anti-androgens, such as bicalutamide, to decrease the levels of androgens, or circulating testosterone in males, who are diagnosed with locally advanced, high-risk, or metastatic PCa (Martins & Gandy, 2016).

Prostate cancer: Male cancer of the prostate epithelium, which is the second leading cause of cancer death in men (National Cancer Institute, 2015a).

Racial health disparity: Differences in health outcomes due to ethnic/racial differences in socioeconomic status and/or access to healthcare (Tyson & Castle, 2014).

Age: One of the main risk factors for developing AD; several studies have suggested that androgen loss, as a result of aging, may promote cognitive decline in older men and increase risk of AD due to low levels of circulating testosterone (Ciocca et al., 2016; Martins & Gandy, 2016; Nead et al., 2016; Vest & Pike, 2013).

Cardiovascular disease: Cardiovascular disease, stroke, and cardiovascular disease risk factors such as hypertension and Type 2 diabetes may predispose a person to AD, because arteriosclerosis causes hardening of the arteries and the brain relies on blood and oxygen for its functioning. The brain receives approximately 15% of the cardiac output, 20% of oxygen consumption, and 25% of all glucose utilization (Singh, n.d.).

Other covariables: Hypothyroidism, reason for original Medicare entitlement, race/ethnicity, PCa stage, and risk group were covariates that were controlled for in this study.

Assumptions

The main assumptions of this study were that the data collected in the SEER database was reliable and accurate and were collected in a robust manner and that the medical coding of the medical history was accurate and precise. This assumption has been supported by information from the SEER Medicare-linked data website and is important for the integrity of the data and study. Moreover, it would not be feasible for me to audit the data, because I do not have access to patient identifiers/medical records but only limited datasets that are already coded. Another assumption was that all ADT exert effects on the androgen receptor, which lowers testosterone significantly leading to

low androgen levels, which is a main risk factor for cognitive dysfunction and that other hormonal pathways are less significant. This theory was a central tenet of this study.

Scope and Delimitations

This study was a retrospective, quantitative cohort study of subjects diagnosed with PCa using ADT and those who did not take ADT from a large ethnically diverse public database, the SEER Medicare-linked database. All PCa subjects diagnosed from 2004-2006, who were administered ADT, were included in the sample, except those with PCa diagnosis at time of death.

Limitations

One of the main limitations of this study was that it was a retrospective, observational study and may suffer from selection bias. However, because the SEER Medicare-linked database includes such a large sample size, these threats to internal validity may be more easily controlled for. Also it is possible to conduct some statistical adjustments to control for the nonrandom assignment of persons in the database. Another limitation was that the dependent variable, AD diagnosis, was confirmed via Medicare codes and not from a review of medical records or autopsies, where appropriate. However, this may not be a concern because healthcare visits are linked to medical coded information for reimbursement, and this is often very accurate.

Significance of the Study

The magnitude of the expected rise in AD is significant due to an aging population and will be an even more costly public health problem in the future (Mayeux & Stern, 2012). This research is important because AD incidence and prevalence are

increasing and there is no cure for this degenerative disease. With increasing healthcare costs and extensive burden on subjects and their caregivers, it is essential to learn more about risk factors of AD to prevent this neurodegenerative disease, slow its progression, and reduce national healthcare costs (Vest & Pike, 2013).

Given the ubiquitous and increasing use of ADT, it is imperative to understand the side effects of this treatment, such as cognitive dysfunction, to limit morbidity (Ahmadi & Daneshmand, 2013). Moreover, the results of this research may lead to ADT treatment adjustments to prevent or delay the onset of AD (see Ahmadi & Daneshmand, 2013; see Vest & Pike, 2013). For example, more information regarding cognitive dysfunction could lead clinicians to promote active surveillance for elderly subjects with close monitoring of disease progression to prevent AD (Ahmadi & Daneshmand, 2013). As current therapy for AD is palliative, and newer therapies are unproven, knowing who is at risk will make prevention and management of AD easier for society, subjects, and their family members (Mayeux & Stern, 2012).

Summary

AD is the most common progressive, neurodegenerative disease and form of dementia (CDC, 2015; Mayeux & Stern, 2012). As there is no cure for this debilitating disease, and current treatments do not halt its progression, it is important to understand the risk factors, especially modifiable risk factors that predict AD, for prevention (Lv et al., 2015; Nead et al., 2016). Scientists agree that secondary prevention, or diagnosing and treating the disease before symptoms manifest, as well as overall primary prevention, are essential to slow neuropathology and cognitive decline (Selkoe, 2012).

In addition, PCa remains a substantial public health challenge in the United States (Brawley, 2012; National Cancer Institute, 2015a). It is the most common malignancy and the second leading cause of cancer death in men in the United States, preceded only by lung cancer (Brawley, 2012; National Cancer Institute, 2015a). ADT, anti-androgen treatment for locally advanced, high-risk, or metastatic PCa, has become the mainstay of treatment. However, cognitive dysfunction and possibly AD incidence may be associated with its use.

In addition, racial health disparity is a growing challenge in that African American men often fail to receive ADT for treatment of advanced PCa, which may lead to increased morbidity and mortality (Tyson & Castle, 2014). Even after adjustment for treatment effects, African American men exhibit the lowest overall and PCa-specific survival among all racial groups (Tyson & Castle, 2014).

Moreover, African American men are less likely to be offered aggressive treatment options by physicians and less likely to desire treatments such as ADT that have side effects (Chornokur et al., 2011). This may result from African American men lacking adequate health insurance and being unmarried with less support for more aggressive treatment options (Chornokur et al., 2011). However, this racial health disparity may mean that African American men with PCa are less likely to develop AD.

Given the significant patient, familial, and economic burden, as well as increased mortality and morbidity from AD, it is important to further investigate the association between ADT and AD in order to prevent further morbidity and mortality and effect

positive social change. Chapter 2 provides additional background into AD, PCa, ADT, health disparity, and their association.

Chapter 2: Literature Review

Introduction

Globally, there are approximately 24 million people living with dementia and approximately 34 million with AD, and this number is expected to triple to over 100 million by 2050 due to an aging population (Lv et al., 2015; Mayeux & Stern, 2012; Selkoe, 2012). In the United States, there are approximately 5 million persons living with AD and this number is expected to triple to 13.8 million by 2050 (Mayeux & Stern, 2012; Moschetti, Cummings, Sorvillo, & Kuo, 2012; Tejada-Vera, 2013).

As heart disease incidence, prevalence, and mortality have declined over the last few decades, incidence, prevalence, and death from AD have increased by 39% from 18.1% to 25% of the population in the United States (Tejada-Vera, 2013). Moschetti et al. (2013) conducted a review of death certificates from men and women in the United States over a 10-year period from 1999-2008 and demonstrated that AD cases significantly increased from 45.3 per 100,000 persons in the United States to 50.0 per 100,000 persons. In this same period, they observed that deaths from heart disease and stroke decreased 15%-20%, while AD mortality increased 85%. The highest increase was observed in women, Caucasians, and those 75 years and older (Moschetti et al., 2012). As the population ages, more cases of AD are possible; however, unlike cancer and heart disease, despite research, treatment and cures remain elusive. In addition, the cost of healthcare for those with AD was approximately $200 billion in 2012 and will reach 1.1 trillion by 2050 as the population continues to age (Mayeux & Stern, 2012; Moschetti et al., 2012; Tejada-Vera, 2013). Since there is no cure for this degenerative and debilitating

disease, and current treatments do not halt its progression, it is imperative to understand the risk factors, especially modifiable risk factors that predict AD, for prevention (Lv et al., 2015; Nead et al., 2016).

The use of ADT has increased significantly over the last few decades due to its effectiveness as sole or adjunct therapy for PCa subjects (Martins & Gandy, 2016). Approximately 500,000 men currently use ADT in the United States for PCa and this number is increasing (Nead et al., 2016). While it is an effective treatment, ADT reduces androgens to extremely low levels and is likely associated with cognitive impairment (Martins & Gandy, 2016). With the number of PCa subjects expected to increase due to population growth and an aging population, and the burden that cancer places on subjects, family members, and healthcare, understanding treatment outcomes and side effects remains crucial (Ambs et al., 2008). However, limited, flawed, and contradictory studies have investigated the association between ADT and AD. The purpose of this study is to overcome some of the previous methodological flaws and further explore the association between ADT and the development of AD through quantitative analysis of a large population database, the SEER-Medicare linked database.

This chapter provides background information regarding the epidemiology of AD, the biology of AD, and its association with low testosterone levels due to aging and the use of ADT, a common therapy to treat PCa. I discuss the biology of PCa, its treatment, and its association with AD with regard to ADT use.

Literature Search Strategy

The information for this chapter was obtained from a thorough review of published peer-reviewed journal articles over the last 5 years from 2011-2017 using Medline, Google Scholar, Pub-Med, and CINAHL databases, as well as scientific books. These databases were queried using a combination of the following terms to locate articles: *ADT, type of ADT, PCa, health disparities, cognitive dysfunction, AD biology, PCa biology, ADT and AD, PCa and AD, PCa treatment, PCa epidemiology, AD epidemiology, AD, testosterone and PCa, testosterone and cognitive dysfunction,* and *testosterone and AD.* References of articles were reviewed to ensure all important primary articles were captured.

Alzheimer's Disease Epidemiology

AD is the most common progressive, neurodegenerative disease and form of dementia (CDC, 2015; Mayeux & Stern, 2012). It affects regions of the brain implicated in memory and cognitive function, such as the hippocampus and cortex, gradually destroying a person's ability to remember, learn, and ultimately carry out activities of daily living (Rubio-Perez & Morillas-Ruiz, 2012). It is the sixth leading cause of mortality in the United States, and the fifth leading cause of death in those aged 65 and older (CDC, 2015; Selkoe, 2012; Tejada-Vera, 2013). The etiology of AD is complex, with genetics and environmental factors playing a significant role (Nelson, Tanner, Van Den Eeden, & McGuire, 2004). For example, socioeconomic factors such as low income and low education predispose a person to AD/dementia (Nelson et al., 2004). Moreover, those with a family history of AD and predisposing socioeconomic factors often have a

32-times increased risk compared to those with no family history and high socioeconomic status (Nelson et al., 2004). Other risk factors associated with AD/dementia are cardiovascular disease, poor nutrition, cigarette smoking, diabetes mellitus, alcohol abuse, and head injury (Nelson et al., 2004).

Aging, family history, loss of androgens, and cardiovascular disease appear to be the main risk factors for AD; however, the exact cause is unknown (Nelson et al., 2004). Several studies suggested that androgen loss, as a result of aging, may promote cognitive decline in older men due to low levels of circulating testosterone (Ciocca et al., 2016; Martins & Gandy, 2015; Nead et al., 2016; Vest & Pike, 2013). Some studies have shown that low testosterone levels resulting from ADT are responsible for decreased cognitive functioning in men; however, results are equivocal (Ciocca et al., 2016; Lv et al., 2015). Moreover, physiologically low levels of testosterone have been associated with increased risk for AD; however, data are often conflicting (Martins & Gandy, 2015).

Aging is a well-known risk factor for AD, because it results in the body's inability to correct errors such as protein accumulation in the brains of AD subjects. Several studies have demonstrated a consistent increase in incidence of AD from approximately 0.5% per year from ages 65–70 to 6–8% per year for those over age 85 (Mayeux & Stern, 2012). Caucasians have a 26% increased mortality risk compared to African Americans (Mayeux & Stern, 2012). For men, the highest age-adjusted death rates are for non-Hispanic White men, followed by non-Hispanic Black men. Hispanic men and Hispanic women have the lowest death rates from AD (Tejada-Vera, 2013). Overall, persons with

AD have a 1.4- to 3-times greater risk of mortality than those without AD, due to neuronal cell death (Nelson et al., 2004).

AD is usually diagnosed by physical exam, medical history, mental status examination, and neurological exam (Nelson et al., 2004). Blood tests may be done to rule out deficiency states that mimic AD, such as hypothyroidism (Nelson et al., 2004). In addition, computerized tomography or magnetic resonance imaging (MRI) can rule out brain neoplasms and vascular dementia resulting from cardiovascular disease, both of which often mimic AD (Nelson et al., 2004). However, to date there are no reliable biomarkers for AD diagnosis.

The clinical course of AD can last from 3–20 years, with an average time of 7 years from AD onset (Nelson et al., 2004). Symptoms of AD include forgetfulness, confusion, restlessness alternating with lethargy, and errors of judgment (Kandel & Schwartz, 1985). AD manifests as cognitive or mental decline and loss of intellectual ability (CDC, 2015). As AD further progresses, it often leads to dysfunction in daily living, changes in mood and/or personality, and difficulty with executive functions such as making decisions (Mayeux & Stern, 2012). The disease may progress over a decade before the person loses interest in current events and is restricted to bed with loss of control of all bodily functioning (Kandel & Schwartz, 1985).

As there is no cure for this progressive and debilitating disease, and current treatments do not halt its progression, it is imperative to understand the risk factors, especially the modifiable risk factors, that can be changed as part of an AD prevention strategy (Lv et al., 2015; Nead et al., 2016). Scientists agree that secondary prevention, or

diagnosing and treating the disease before symptoms manifest, as well as overall prevention, are essential to slow neuropathology and cognitive decline (Selkoe, 2012).

Given the significant patient, familial, and economic burden, and increased mortality and morbidity from AD, it is imperative to further investigate the association between ADT and AD in order to prevent further morbidity and mortality and to effect positive social change.

The History of Alzheimer's Disease

Dr. Alois Alzheimer, a German neuropathologist and physician, first described this disease over 100 years ago after studying a patient who presented with a strange dementia syndrome (National Institute on Aging, 2014; Ramirez-Bermudez, 2012). He spent most of his career studying dementia and epilepsy, and characterizing the biology of AD. He worked closely with Franz Nissl, who developed the Nissl stain to observe and study neuronal cell bodies (Ramirez-Bermudez, 2012). Subsequent research throughout the decades has increased knowledge of the biology of AD.

Conceptual Framework

The Biology of Alzheimer's Disease

The main biological hallmark of AD is extracellular aggregation and accumulation of amyloid beta protein mainly in the hippocampus and prefrontal cortex, which forms extracellular neuritic plaques due to protein misfolding (Bettens, Sleegers, & Van Broeckhoven, 2013; Savelieff et al., 2013; Vest & Pike, 2013). In addition, AD subjects' brains also exhibit small volume, small size, and decreased glucose uptake, a sign of neuronal dysfunction (Savelieff et al., 2013). Amyloid beta protein forms from the

cleavage of amyloid precursor protein (APP), an intramembrane protein mainly involved in cellular differentiation and synapse formation (Rubio-Perez & Morillas-Ruiz, 2012; Savelieff et al., 2013). Its extracellular domain is likely involved in metal-ion homeostasis, mainly of iron and copper. Metals may become trapped in amyloid beta aggregates leading to metal ion dysregulation and thus higher accumulation of metal ions, which are cytotoxic to neurons and result in neuronal cell death (Savelieff et al., 2013).

Beta and gamma secretases cleave APP into amyloid beta 40 (95%) and amyloid beta 42 (5%) proteins (Cheng, Zhang, & Lian, 2015). Amyloid beta 42 is more likely to aggregate and accumulate based on several factors such as pH, the hydrophobic nature of the protein, temperature, concentration levels of the protein, and presence or absence of metals and other proteins, such as tau (Savelieff et al., 2013). Amyloid beta protein oligomers act like ion channels allowing mass influx of calcium ions, which disrupts the cell membrane potential, resulting in neuronal cytotoxicity and cell death (Savelieff et al., 2013). Irreversible neurodegeneration is the result of sustained calcium influx following activation of NMDA receptors and potentiation by the simultaneous depolarization of non-NMDA receptors. The presence of magnesium ions can convert a nontoxic concentration of NMDA into a toxic one resulting in cell death as a result of chromatin aggregation, mitochondrial swelling and dysfunction, activation of destructional enzymes such as phospholipases, resulting in membrane breakdown, and proteases, resulting in the destruction of the cytoskeleton.

Results of prospective cohort studies show that the deposition of amyloid beta protein is often a slow process over approximately two decades (Villemagne et al., 2013).

Villemagne et al. (2013) studied clinical and neuropsychological performance at baseline and at each follow-up visit, every 18 months, utilizing positron emission tomography (PET) and MRI of 200 participants (145 healthy controls, 36 with mild cognitive impairment, and 19 with AD). The results indicated that 82% of participants exhibited amyloid beta protein deposition over time. However, results from their PET imaging indicated that the rate of amyloid beta deposition slowed as AD progressed to late stages (Villemagne et al., 2013). This suggests that amyloid beta deposition and accumulation likely plays a role in cognitive impairment at the early stages of disease, where it precedes cognitive decline and cerebral atrophy (Villemagne et al., 2013).

While PET measures the rate of amyloid beta accumulation and deposition, functional MRI (fMRI) is a noninvasive technique that offers superior spatial resolution and can be repeated in longitudinal studies, since it is noninvasive (Yamasaki, Muranaka, Kaseda, Mimori, & Tobimatsu, 2012). When used together with electroencephalogram (EEG) recording, neuronal synaptic dysfunction can be assessed. For example, studies utilizing fMRI show aberrant activity in the parietal area of the brain, where the hippocampus resides, resulting in memory encoding difficulties in AD subjects (Yamasaki et al., 2012). Studies utilizing fMRI also show the distribution of amyloid beta plaques in visual association areas of the brain implicated in visuospatial memory, which is often affected in AD subjects (Yamasaki et al., 2012).

The neuritic plaques consist of a central core of amyloid protein surrounded by neural processes undergoing various degrees of degenerative changes, along with activated glial cells, particularly astrocytes and microglia, which is a sign of

neuroinflammation (Kandle & Schwartz, 1985). Amyloid beta protein activates several proinflammatory molecules, such as cytokines, NO, and chemokines (Rubio-Perez & Morillas-Ruiz, 2012). This results in synaptic dysfunction, cognitive decline, and neuronal cell death (Vest & Pike, 2013). AD ensues due to an imbalance between amyloid beta production and clearance in the brain, which precedes cognitive dysfunction. The cause of this imbalance is mainly unknown (Selkoe, 2012).

In AD, intracellular hyperphosphorylation of tau microtubule protein occurs, which leads to protein aggregation, dysfunction of microtubule assembly, and thus loss of neuronal cell trafficking leading to neuronal death (Iqbal, Liu, & Gong, 2016). Subsequently, AD is often known as a tauopathy (Cheng, Zhang, & Lian, 2015). Protein phosphatase 2A leads the active phosphorylation of tau. However, acetylation, truncation, and other post-translational modifications of tau protein can also result in its hyperphosphorylation (Iqbal, Liu, & Gong, 2016). Tau, a protein which composes the cytoskeleton of cells, normally functions in anterograde transport of neurotransmitters, organelles, and nutrients along nerve cell axons from cell body down the axon to the synapse, maintains neuronal shape, orchestrates signal transduction, and memory processing/formation (Savelieff et al., 2013). Hyperphosphorylation of tau forms neurofibrillary tangles and inhibits microtubule assembly for cytoskeletal function (Bettens et al., 2013; Iqbal, Liu, & Gong, 2016; Kandle & Schwartz, 1985). These degenerative lesions result in microglial activation (a sign of neuroinflammation) and neuronal dystrophy, loss of synapses, and neuronal death, which result in dementia (Sutherland, Chami, Youssef, & Witting, 2013; Vest & Pike, 2013). The amount of

synaptic loss correlates with the amount of neuritic plaques and neurofibrillary tangles and subsequently the severity of AD/dementia (Iqbal, Liu, & Gong, 2016; Nelson et al., 2004). Overall, there is approximately 60% loss of neurons, with a 50% reduction in hippocampal neurons and the rest in the neocortex, resulting in loss of memory, as well as of executive function (Nelson et al., 2004).

The cause of hyperphosphorylation of tau is unclear, but likely due to the presence of amyloid beta protein and its aggregation, which is an early event, genetics, and possible environmental factors, which are yet to be definitively characterized. In addition, hyperphosphorylation of tau stimulates further aggregation and protein accumulation, since phosphorylated tau is less prone to enzyme protease degradation. This leads to neuronal swelling from the failure of the neuronal cell to destroy and recycle accumulating tau protein, which further results in neuroinflammation, dysfunction in axonal trafficking, and cell death (Savelieff et al., 2013). Dysfunction in axonal trafficking means that old organelles such as the mitochondria, which normally undergo autophagy more frequently, are not replaced. As a result, worn-out mitochondria cannot meet cells' energy demands resulting in increased production of free radicals or reactive oxygen species (ROS) and neuronal demise (Savelieff et al., 2013). Moreover, hyperphosphorylated tau is more likely to bind to cell membranes, disrupt normal membrane potentials, and lead to neuronal cell death (Savelieff et al., 2013).

Alzheimer's Disease and Neuroinflammation

Accumulation of amyloid beta and tau proteins results in activation of microglia and astroglia, signs of neuroinflammation (Rubio-Perez & Morillas-Ruiz, 2012). This

produces several pro-inflammatory molecules such as cytokines, growth factors, NO, chemokines, cell-adhesion molecules, ROS, and complement molecules. Disease progression is accelerated due to increased production of ROS, which ultimately results in neuronal cell demise (Holmes, 2012).

Inflammation is often an acute process incited by cell injury; however, in AD it is chronic and effectuates more neuronal cell damage and ultimately neuronal cell death (Rubio-Perez & Morillas-Ruiz, 2012). Moreover, the chronic presence of these inflammatory molecules in turn results in enhanced APP production and its processing to amyloid beta 42, which is more likely to aggregate (Rubio-Perez & Morillas-Ruiz, 2012). Astrocytes also induce amyloid beta protein aggregation in response to chronic inflammation (Rubio-Perez & Morillas-Ruiz, 2012).

Previously, research suggested that in normal individuals the blood-brain barrier (BBB) protected the brain during systemic inflammation caused by viral or bacterial pathogens (Holmes, 2012). Today, it is widely accepted that systemic inflammation links to central nervous system inflammation (Holmes, 2012). This results in a distinct behavioral syndrome with anorexia, somnolence, depression, and decreased activity, called “sickness behavior” (Holmes, 2012). This enables the body to adapt to the pathogen and fight infection (Holmes, 2012). This “sickness behavior” is often the result of pathogens activating pro-inflammatory cytokines, such as IL-1-beta, IL-6, and tumor necrosis factor (TNF), as well as other parallel processes, such as the production of chemokines (CCL2) and complement proteins (C3) (Holmes, 2012).

While there is a clear link between systemic and central nervous system inflammation, it usually does not lead to permanent damage in the brain (Holmes, 2012). There are anti-inflammatory mechanisms involved in systemic inflammatory response, such as the activation of IL-10, transforming growth factor (TGF)-beta, and prostaglandins (PGE2) to prevent permanent brain damage (Holmes, 2012). This is not true for AD, however. In AD, the insult is not acute but progressive. Thus, microglia involved in neuroinflammation are primed and further insults lead to more neuronal damage (Holmes, 2012).

Alzheimer's Disease and Oxidative Stress

Reactive oxygen species result in oxidative stress. Oxidative stress refers to the imbalance between the formation of free radicals and their destruction, primarily by endogenous antioxidants such as superoxide dismutase. Free radicals, which are natural by-products of cellular metabolism, contain unpaired electrons in their outer orbits, making them highly reactive molecules. The cell damage and pathology they induce are proportional to their quantitative accumulation, which may explain the progressive nature of AD (Sutherland et al., 2013).

The brain is highly susceptible to ROS. For one, the brain utilizes 20% of the body's oxygen consumption for its energy demands (Sutherland et al., 2013). While oxygen fulfills an important physiological function as the final electron acceptor in mitochondrial cellular respiration, this process also produces free radicals. When molecules such as glucose are oxidized, oxygen becomes reduced by receiving electrons and forms free-radical intermediates such as hydroxide radicals and superoxide radicals,

as well as hydrogen peroxide (Sutherland et al., 2013). These highly reactive molecules attack and destroy many biological molecules such as cell membranes and DNA, and cause mutations that contribute to neurodegeneration over time (Sun, Chen, & Wang, 2015). Since mitochondrial DNA exhibits a less efficient repair system than nuclear DNA, excessive oxidative damage devastates mitochondrial function and culminates in neuronal cell destruction. Neurons that are more likely to degenerate also experience more oxidative damage. The toxicity that results from the generation of free radicals overwhelms the brain's natural defense mechanisms. When the imbalance between ROS and endogenous antioxidants becomes pronounced, neurodegeneration from oxidative damage ensues (Sutherland et al., 2013).

NO is an endogenous molecule in the brain important in cell signaling and neuroprotection. During oxidative stress, NO can combine with superoxide free radicals to form peroxynitrite, a reactive nitrogen species (RNS) involved in oxidative stress and cellular dysfunction in the brain (Sutherland et al., 2013). An endogenous antioxidant, superoxide dismutase, which removes excess ROS, also yields the pro-oxidant, hydrogen peroxide. Hydrogen peroxide reacts with iron, which is abundant in the brain, and ultimately produces the destructive hydroxyl radical. The hydroxyl radical attacks almost every structure in the brain, especially DNA (Sutherland et al., 2013).

The brain also contains a high concentration of readily oxidized substrates, such as membrane polyunsaturated fatty acids. Abstraction of a hydrogen atom by ROS from membrane lipids leaves behind a carbon-centered radical, which reacts with oxygen to produce peroxyl radicals. These form membrane lipid hydroperoxides, which severely

disrupt membrane structure and fluidity and lead to the leakage of calcium ions across the membrane. Subsequent increases in cytosolic calcium induce cell death (Sutherland et al., 2013).

Aging leads to decreased function of cellular metabolism and subsequently enhanced accumulation of ROS. In addition, aging also results in decreased production of endogenous antioxidants and thus an accumulation of ROS that leads to lipid, cellular, and DNA damage (Sutherland et al., 2013). Programmed cell death or apoptosis often follows oxidative stress or cell damage, and is characterized by nuclear and DNA fragmentation, chromatin condensation, deficient DNA repair, and disassembly of cellular structures.

Genetic Factors

Less than 1% of AD cases arise as early onset, (before age 65) familial AD due to mutations in amyloid beta protein from APP , as well as mutations in intramembrane proteases, presenilin 1, and presenilin 2, which are components of gamma secretases that cleave APP into amyloid beta components (Bettens, Sleegers, & Van Broeckhoven, 2013; Selkoe, 2012). Mutations in APP, presenilin 1, and presenilin 2 impair the function of gamma secretase, which cleaves APP to amyloid beta protein. This results in a higher ratio of amyloid beta 42, the insoluable oligomer, compared to amyloid beta 40, the soluable oligomer. Thus, amyloid beta 42 is more likely to aggregate and form neuritic plaques that result in neuronal cell loss (Bettens et al., 2013; Cheng, Zhang, & Lian, 2015).

This autosomal, dominant pattern of disease results in accumulation and aggregation of amyloid beta protein, which is the hallmark of AD, often called the amyloid beta hypothesis (Cheng, Zhang, & Lian, 2015; Mayeux & Stern, 2012; Nelson et al., 2004). Nonetheless, mutations in these three genes only explain 13% of cases of early-onset AD, demonstrating that the interaction of genes with the environment plays a significant role in AD (Bettens et al., 2013).

Late-onset, sporadic AD after age 65 appears to be the most common (Bettens et al., 2013; Selkoe, 2012). Some cases may be associated with mutations in apolipoprotein E (APOE) (the epsilon 4 variant). Persons who are heterozygous for this allele have a three-times greater risk of developing AD, while those homozygous for this variant (compared to the normal variant APOE epsilon 3) have a 15-times increased risk of AD (Bettens et al., 2013). Genetic mutations in APOE result in a significant increase in the accumulation of amyloid plaque in the AD brain (Cheng, Zhang, & Lian, 2015).

Over the last few decades more candidate genes have been discovered which are associated with AD: Sortilin-related receptor 1 (SORL1), involved in APP recycling; clusterin (CLU), involved in lipid processing, immune system, and inflammation, as well as amyloid beta aggregation; ATP binding cassette subfamily A member 7 (ABCA7) in lipid processing, immune system, and inflammation; CD33 involving the immune system and inflammation; complement receptor (CR1), part of the complement system; phosphatidylinositol binding clathrin assembly protein (PICALM), involved in processing of APP; and bridging integrator 1 (BIN1), involved in synaptic cell functioning (Bettens et al., 2013; Mayeux & Stern, 2012). Identification of these novel

genes through genome-wide association studies illustrates that molecular mechanisms, such as lipid metabolism, the immune system, inflammation, and synaptic cell functioning underly AD, in addition to the widely accepted amyloid beta and tau pathways, which are key players implicated in AD (Bettens et al., 2013).

Overall, the main contributor of AD is amyoid beta protein aggregation and accumulation, along with genetics and environmental factors, which result in neurotoxicity and hyperphosphorylation of tau protein. This ultimately culminates in neuronal cell injury, dysfunction, and death, which leads to dementia and AD (Cheng, Zhang, & Lian, 2015).

Cancer Biology

Cancer is characterized by uncontrolled cell growth and proliferation, local tissue invasion, and metastasis or distant spread of cancerous cells. Cancers are classified according to the tissue and cell type from which they originate (LaFond, 2012). Carcinoma remains the most common cancer type, which derives from epithelial cells. Approximately 90% of cancer formation occurs in cells that line internal and/or external body surfaces (LaFond, 2012). Cancer is often called a genetic disease in which hereditary and/or epigenetic mutations lead to unabated cellular proliferation, local tissue invasion, and metastasis over several or more years (LaFond, 2012). This subsequently results in genetic instability and the gradual accumulation of additional mutations, which is the hallmark of most cancers (LaFond, 2012).

The Prostate and Prostate Cancer Biology

The prostate gland secretes an alkaline substance, which provides a liquid medium that nourishes sperm, and facilitates their motility during ejaculation (National Cancer Institute, n.d.; Turner & Drudge-Coates, 2010). It is a chestnut- shaped, walnut-sized, male reproductive organ, found in the pelvic cavity. The prostate gland lies in front of the rectum, directly below the urinary bladder, surrounding the urethra, and behind the pelvic symphysis (National Cancer Institute, n.d.; Turner & Drudge-Coates, 2010). It is held in place by the anterior ligaments of the bladder, levator ani muscles, and the triangular ligament.

The prostate gland is part glandular and part muscular and contains ducts that connect to and empty into the urethra. Its base points upward, directly below the bladder, while its apex faces downward in close proximity to the triangular ligament. The posterior surface of the prostate gland remains flattened and rests on part of the rectum. The anterior surface, however, appears convex and separated by a plexus of veins and adipose tissue. The lateral sections are covered by anterior portions of the levator ani muscles.

The prostate also contains several lobes: anterior lobe, median lobe, left and right lateral lobes, and posterior lobe (National Cancer Institute, n.d.). The anterior lobe lies in front of the prostatic urethra; it lacks glandular tissue and is composed primarily of fibromusclar tissue (Fine & Reuter, 2012; National Cancer Institute, n.d.).The median lobe lies between two ejaculatory ducts and the urethra (Fine & Reuter, 2012; National Cancer Institute, n.d.). The lateral lobes, however, comprise most of the mass of the

prostate gland and are separated by the prostatic urethra (National Cancer Institute, n.d.). The posterior lobe is part of the lateral lobes, lying near the rectum, and can be palpated via digital rectal exam (DRE) (National Cancer Institute, n.d.). In addition, the prostate contains three glandular zones and one nonglandular zone, which are fused and enclosed within a fibromuscular sheath, called the "capsule". The capsule consists of an inner layer of smooth muscle and an outer membrane (Fine & Reuter, 2012).

The three glandular zones are termed: central, peripheral, and transitional (Fine & Reuter, 2012; Turner & Drudge-Coates, 2010). PCa mainly arises in the peripheral zone (Fine & Reuter, 2012). Physicians can easily palpate peripheral zone tumors during DRE, due to their proximity to the rectum (Fine & Reuter, 2012). Up to 30% of cancers are found outside the peripheral zone (Das & Crawford, 1993; Turner & Drudge-Coates, 2010). For example, physicians detect more low volume, localized, PCa in the transitional zone, which is often not palpable and thus more difficult to evaluate during a DRE (Fine & Reuter, 2012). Central zone tumors, while less common, are more aggressive and exhibit higher Gleason scores and PSA values, as well as increased extracapsular extension and seminal vesicle invasion (Vargas et al., 2012). They are more difficult to distinguish than tumors in other zones (Vargas et al., 2012).

In a retrospective study of 211 PCa subjects, Vargas et al. (2012) utilized magnetic resonance (MR) images and reported high localization of central tumors, even though rare, as well as high tumor aggressiveness (Vargas et al., 2012).

Similar risk factors ensue for both AD and PCa. One similar pathway is inflammation due to aging (Hodgson, Bowden, & Agoulnik, 2012). Inflammatory

cytokines, such as IL-6, are observed in both disease states (Hodgson et al., 2012). In fact, two major hallmarks of aging in men are decreased testosterone and systemic inflammation (Hodgson et al., 2012). In turn systemic inflammation decreases testosterone levels. Subsequently, IL-6 and other inflammatory cytokines, such as NF-KB, activate the androgen receptor (AR) found in prostate epithelium, endothelium, and stromal cells in a ligand-independent manner resulting in prostate cellular proliferation that leads to tumorigenesis (Hodgson et al., 2012).

Local and systemic inflammation are often hallmarks of cancer initiation, progression, and metastasis, as well as neurodegenerative disease or AD (Holmes, 2012). Macrophages, cytokines, and chemokines promote neoplasia, angiogenesis, tumor progression, and often increased mortality due to metastasis, and are also implicated in amyloid beta accumulation which leads to neuronal cell death and AD (Holmes, 2012). Moreover, chronic inflammation is a key player in the development of all solid cancers, such as PCa (Ruhland, Coussens, & Stewart, 2016). However, the definitive association between PCa development, inflammation, and neurodegenerative disease is not yet conclusive (Ruhland et al., 2016). In fact, some data suggest an inverse association between cancer and AD (Driver, 2014). Driver (2014) provided a review of several meta-analyses and longitudinal studies and showed that those with AD have a lower incidence of cancer, compared to a reference group without AD, and those with cancer have a lower risk of AD, compared to a reference group without cancer. These results were consistent between pre and post diagnoses as well as those who survived and those who did not. Nonetheless, limited data exist to support these claims and thus more research is needed.

Five types of proteins that include growth factors, growth factor receptors, transducers, transcription factors, and cell cycle control proteins, participate in cell growth and cancer (LaFond, 2012). Proto-oncogenes encode proteins that are essential to cell growth, proliferation, differentiation, migration, and survival (Bologna, Vicentini, Muzi, Pace, & Angelucci, 2011; LaFond, 2012). Mutations in these proto-oncogenes often activate oncogenes, which result in uncontrolled cell growth (LaFond, 2012).

The unabated cell proliferation in tumorigenesis leads to hypoxia, low blood flow, and nutrient delivery to tumor cells (Ackerman & Simon, 2014). Tumors, thus, induce angiogenesis, or growth of new blood vessels, via chemical signals in order to survive and metastasize (LaFond, 2012). Vascular endothelial growth factor (VEGF) promotes new blood vessel formation. It is implicated in PCa in that if blocked by anti-angiogenic molecules, cancer progression would be inhibited (Bilusic & Wong, 2014). Angiogenesis provides nutrients and oxygen to organisms (Carmeliet & Jain, 2011). Since cancer cells depend on oxygen and nutrients, such as glucose and preferably lipids, such as unsaturated fatty acids for survival, angiogenesis is critical for tumor survival and cancer progression (Bilusic & Wong, 2014). Unsaturated fatty acids may be derived externally through diet, but more likely via adipocyte lipolysis. This is illustrated in cancer subjects with cachexia in advanced cancer stages, who undergo atrophy of adipose tissue, and in those with obesity, who may be more at risk for tumorigenesis and cancer progression (Ackerman & Simon, 2014).

The epithelial growth factor receptor (EGFR), a tyrosine kinase receptor, is also implicated in PCa. It activates downstream src and leads to tumorigenesis through

cellular proliferation, invasion, and angiogenesis (Bologna et al., 2011). For example, the receptor tyrosine kinase, Axl, contributes to prostate tumorigenesis, tumor cell survival, and metastasis (Paccez et al., 2013). Axl exhibits its mitogenic effect through activation of the NF-kB/Akt pathway (Paccez et al., 2013). Thus, Axl remains an essential player in PCa development and progression.

Moreover, subjects with advanced PCa harbor protein tyrosine phosphatase (PTEN) mutations (Barbieri, Demichelis, & Rubin, 2012). This tumor suppressor gene, PTEN, normally acts as a protein tyrosine phosphatase, which counteracts the PI3K/Akt cell proliferation pathway. Mutations in PTEN, therefore, lead to uncontrolled cellular proliferation through increased cellular growth signaling via the PI3K/Akt pathway, as well as tumor invasion and metastasis (Barbieri, Demichelis, & Rubin, 2012).

Other genetic alterations include activation of the mitogen-activated protein kinase (MAPK) signaling pathways and amplification of the AR, which induce cellular proliferative (Barbieri, Demichelis, & Rubin, 2012). In addition, it is well known that PCa is characterized by mutations in genes involved in cell cycle control, such as P53 tumor suppressor, signal transduction, transcription such as signal transducer and activator of transcription STAT-3 and STAT-5 and its interaction with AR, cell migration, and mitosis (Singh et al., 2012).

Tumor suppressor genes inhibit cellular growth and proliferation via inhibition of cell cycle processes when DNA repair is necessary due to mismatch bases, and induce apoptosis when DNA repair is futile (LaFond, 2012). Thus, mutations in cell cycle

control proteins, such as p53 or tumor suppressors, release cells from this inhibitory control or checkpoint and lead to tumorigenesis (LaFond, 2012).

Pathology

Pathologists classify most PCa as adenocarcinoma, which is a malignancy that originates in the prostate glandular epithelium or cells that make and release mucus and other body fluids (National Cancer Institute, n.d.). Some subjects, however, manifest ductal or mucinous carcinomas, which are rare (Das & Crawford, 1993). Ductal carcinomas arise along the ducts, which connect to the urethra; mucinous carcinomas produce mucin, similar to ovarian and gastrointestinal cancers (Das & Crawford, 1993). In addition, some rare forms of PCa arise from tissue surrounding the prostate gland, such as rhabdomyosarcoma, which originates from immature muscle cells (National Cancer Institute, n.d.).

PCa should not be confused with benign prostatic hyperplasia (BPH), which is enlargement of the prostate gland that causes frequent urination in men over 45 years old. While BPH is not usually a precursor for malignancy, PCa is found in approximately 38% of men, many of whom have surgery to relieve symptoms of BPH (National Cancer Institute, n.d.).

Evidence shows that prostatic intraepithelial neoplasia (PIN) may be a precursor to PCa (Adami et al., 2002; Das & Crawford, 1993; National Cancer Institute, n.d.; Ro, Shen, Zhai, & Ayala, 2012). Clinicians characterize premalignant changes, known as dysplasia, as level 1 (low-grade PIN), and levels 2 and 3 (high-grade PIN) (Das & Crawford, 1993; Ro et al., 2012). Those with multifocal, high-grade PIN harbor PCa in

the majority of cases (Ro et al., 2012). High-grade PIN exhibits characteristic cytology such as nuclear and nucleolar enlargement. Low-grade PIN, however, manifests less distinct morphology (Das & Crawford, 1993). Prostatic intraepithelial neoplasia occurs predominantly in the peripheral zone of the prostate, with less prevalence in the transitional zone and central zone. This parallels the zonal predilection of PCa (Ro et al., 2012).

Prior to the development of Gleason grading system by Dr. Gleason, tumor histological grading as a prognostic indicator remained poorly defined. The Gleason system identifies the aggressiveness and severity of PCa tumors (Srigley, Delahunt, Egevad, Samaratunga, Yaxley, & Evans, 2016). Cancer cells that resemble normal prostate gland cells are considered well-differentiated and least aggressive, and those that appear disorganized and do not resemble normal PCa cells are poorly differentiated and most aggressive (Turner & Drudge-Coates, 2010).

During the last 10 years the Gleason scoring system underwent revision. Specifically, Grade 1 denotes well-differentiated cells and encompasses Gleason scores 2-6 (Srigley et al. 2016). Grade 2 manifests well-differentiated cells, but more variable single glands with tumor that is less well circumscribed and Gleason scores 3+4 = 7 (Srigley et al., 2016). Grade 3 indicates moderately differentiated cells, which are more dispersed and Gleason score 4+3 = 7. Grade 4 tumors are more infiltrating with Gleason scores 4+4 = 8, 3+5 = 8, and 5+3 = 8. Last grade 5 tumors exhibit very disordered and least-differentiated cells, Gleason 9-10, and poor prognosis (Delahunt et al., 2012).

The pathologist assigns a primary grade of 1-5 for the area with the most cancer cells, and a secondary grade of 1-5 where cancer cells appear least. Pathologists report the Gleason grade as the sum of the two most predominant patterns found in a given specimen, with grades higher than 7 being high-grade tumors (Turner & Drudge-Coates, 2010). Moreover, some tumors also exhibit a tertiary pattern: A high grade tertiary pattern, which is uncommon, is often associated with more aggressive disease (Delahunt et al., 2012).

High Gleason scores are often associated with prostate capsular extension, seminal vesicle involvement, lymph node metastases, and distant metastases (Das & Crawford, 1993). However, grading is still a subjective prognostic indicator and varies with pathologist expertise (Das & Crawford, 1993). Those with Gleason grades 8-10 post-prostatectomy are more likely to exhibit regional lymph node metastases with subsequent biochemical failure and death, although this is relatively rare (Kryvenko et al., 2013). Those with a Gleason grade of 7, however, manifest a more variable prognosis.

Clinicians also utilize the common tumor, nodes, metastases (TNM) classification to stage prostate tumors (Turner & Drudge-Coates, 2010). PCa staging is divided into three categories: localized (T1-2, N0, M0), which is confined to the prostate and does not invade the capsule or seminal vesicles; locally advanced (T3, N0-1), which is cancer that has invaded the prostate capsule, seminal vesicles, or regional lymph nodes, such as the pelvic, inguinal, and obturator lymph nodes; and metastatic (T4, M1), which is cancer

that has spread to distant sites, such as pelvic bones, spine, liver, lungs, or distant lymph nodes (National Cancer Institute, n.d.; Turner & Drudge-Coates, 2010).

Clinicians compile this information into risk categories: low risk, which is unlikely to grow or metastasize and exhibits a pre-treatment PSA below 10ng/ml, Gleason score of 6 or less, and tumor stage T1 or T2a; medium risk, which is unlikely to grow or spread for several years with PSA 10-20 ng/ml, Gleason score of 7, and tumor stage T2b; and high risk, which is likely to grow and disseminate in a few years with PSA greater than 20 ng/ml, Gleason of 8 and up, and tumor stage T2c and higher (National Cancer Institute, n.d.).

Clinical Characterization

Subjects with early stage PCa are usually asymptomatic until the tumor evades the capsule (National Cancer Institute, n.d.). They then often manifest clinical symptoms such as nocturia, urinary frequency, urinary urgency, painful urination, painful ejaculation, and sometimes pain from bone metastases in more advanced stages (Adami et al., 2002; National Cancer Institute, n.d.; Turner & Drudge-Coates, 2010). In addition, hematuria, hematospermia, erectile dysfunction, unexplained anemia, and skeletal pain may be present (Turner & Drudge-Coates, 2010).

Research demonstrates that prostate biopsy tumor volume often correlates with actual tumor volume and degree of differentiation, capsular penetration, seminal vesicle invasion, metastases, and death (Das & Crawford, 1993; Knoedler, Karnes, Thompson, Rangel, Bergstralh, & Boorjian, 2014; Zavaski et al., 2014). For example, tumors less than 1 cc rarely metastasize, while those greater than 5 cc more likely metastasize and are

not likely cured by definitive treatment (Das & Crawford, 1993; Knoedler et al., 2014; Zavaski et al., 2014). Research demonstrates that the most likely sites of lymph node metastases are the obturator lymph nodes, iliac lymph nodes, and para-aortic lymph nodes. Moreover, the most likely sites of distant metastases are bones, such as the vertebral column, ribs, pelvic bones, followed by soft tissue, and lungs (Das & Crawford, 1993).

Diagnosis often occurs via general physical examination, DRE, biopsy, and Gleason score/staging, as well as PSA blood levels (Adami et al., 2002). The age-related PSA cutoffs which prompt further investigation and/or biopsy are: 50-59 >3.0 ng/ml; 60-69 > 4.0 ng/ml; 70-79 > 5.0 ng/ml (Turner & Drudge-Coates, 2010).

Due to advances in prostate screening techniques, there has been an increase in the number of subjects diagnosed with localized PCa (Keyes, Crook, Morton, Vigneault, Usmani, & Morris, 2013). Validated screening techniques, such as PSA assay, have resulted in increased PCa detection and thus incidence over the past 20 years (Das & Crawford, 1993). Screening techniques have allowed men to be treated at an early stage of PCa, before metastasis occurs (Namiki & Arai, 2010). This decreases morbidity and mortality, since metastasis is ultimately incurable (Das & Crawford, 1993). However, since the natural history of PCa is variable, positive screening results may lead to unnecessary treatment of indolent disease (Das & Crawford, 1993).

Higher screening rates often produce higher detection and thus incidence rates, but no effect on mortality, since the prevalence of early-stage, indolent disease is high and some 15- to 30% of men over age 50 will have PCa with a low potential for growth

and metastasis (Adami et al., 2002). Overall, the presence of indolent disease is greater than that of clinically relevant disease, and PSA screening increases the detection and thus incidence rate for these localized lesions (National Cancer Institute, 2015a). Thus, the 5-year survival rates for PCa have increased due to an increased number of men with clinically localized disease (Brawley, 2012). However, less than 33% of men diagnosed with metastatic disease live 5 years (Brawley, 2012).

Thus, while the United States Preventative Services Task Force does not recommend PSA screening for the population, since the risks outweigh the benefits, oncologists and urologists often disagree given that there are limited, adequate, screening options and PCa treatment is curative if PCa is detected early (United States Preventative Services Task Force, 2012; Witte, Lindaman, & Rosinsky, 2015). Therefore, the United States Preventative Services Task Force recommend that PSA screening should be preceded by a discussion between physician and patient and subjects should be educated to make informed decisions with their physicians (United States Preventative Services Task Force, 2012).

Those with early stage disease may often undergo active surveillance rather than aggressive treatment or ADT, which is often provided for those with more advanced PCa. However, a subset of PCa subjects, particularly the elderly who are not candidates for more aggressive treatment, such as surgery or radiation therapy, are often given ADT as primary therapy (Lu-Yao et al., 2014). There is limited data on the use of ADT in early-stage PCa and current data show no significant results in overall survival and/or PCa-specific survival (Lu-Yao et al., 2014).

The Androgen Receptor Pathway

The prostate depends on AR activity and testosterone, its primary ligand, for development, regulation of prostate epithelial growth, and suppression of apoptosis (Hodgon et al., 2012; Miyamoto et al., 2012). Testosterone is produced in the Leydig cells of the testes and when secreted, it is normally found bound to sex hormone-binding globulin (SHBG) (Michaud, Billups, & Partin, 2015). Testosterone is then converted to its primary metabolite, dihydrotestosterone (DHT), in prostate epithelial cells and peripheral tissue by the enzyme 5-α reductase (Morgentaler, 2013). Dihydrotestosterone more specifically binds to AR than testosterone. Since PCa is hormone dependent, endogenous hormones such as testosterone and its active metabolite, dihydrotestosterone, have been implicated in PCa risk (Adjakly et al., 2015; Morgentaler, 2013; National Cancer Institute, 2015a).

The AR pathway is implicated in over half of all PCa cases and 100% of all metastatic PCa (Hodgson et al., 2012). Androgens promote proliferation through signals that modulate critical regulators of the cell cycle (Hodgson et al., 2012). Androgens induce signals, such as cyclin-dependent kinases that regulate the G1-S phase in the cell cycle, as well as the transcription and turnover of cell cycle regulators such as p21 (Hodgson et al., 2012).

The AR is a well-known target for PCa treatment. It is implicated in PCa progression and metastasis (Hodgson et al., 2012). Men diagnosed with AR positive PCa develop advanced cancer, metastatic disease, and mortality (Pascoe & Sundar, 2012). However, many respond well to ADT (Pascoe & Sundar, 2012). ADT, treatment for

locally advanced, high-risk, and/or metastatic PCa decreases testosterone levels to well below normal physiologically low levels, which is below 350 ng/dL total testosterone (Ciocca et al., 2016; Martins & Gandy, 2016). Its use has increased significantly over the last few decades, due to its effectiveness as sole or adjunct therapy for PCa subjects (Martins & Gandy, 2016). Approximately 500,000 men currently utilize ADT in the US for PCa and this number is increasing (Nead et al., 2016). However, while ADT is effective early in treatment administration a large subset of subjects treated with ADT develop castrate-resistant prostate cancer (CRPC) in which first line ADT becomes ineffective, PCa progresses, and mortality ensues (Miyamoto et al., 2012). This may occur due to reactivation of AR despite low circulating level of testosterone (Miyamoto et al., 2012). Biomarker analysis by measuring circulating tumor cells (CTCs) in advanced PCa subjects demonstrate that AR activity varies, indicating a role for other mitogenic, cancer progression pathways, such as ras (Miyamoto et al., 2012). Several second line treatments, such as abiraterone acetate, may be effective in CRPC once first line ADT therapy fails; however, more research is needed (Miyamoto et al., 2012).

Prostate Cancer Risk Factors

Age is the most common risk factor for PCa, with an exponential increase beginning at age 50-55 (Brawley, 2012; National Cancer Institute, 2015a; Park et al., 2015). PCa is rarely seen in men younger than age 40 (National Cancer Institute, 2015a). The incidence of PCa in men ages 50-59 is 1 in 44, but increases to 1 in 9 in men age 70 and older (National Cancer Institute, 2015a). This pattern is more evident in Western countries such as the United States, where Caucasian males ages 75-79 have

approximately 130 times the risk of PCa of men ages 45-49 (National Cancer Institute, 2015a).

As with breast and colon cancer, family history is also an important risk factor for PCa. 5%-10% of PCa cases are primarily attributed to high-risk inherited genetic factors (National Cancer Institute, 2015a). Family history remains a primary risk factor for PCa as seen from several large case-control and cohort studies with diverse populations (Adami, Hunter, & Trichopoulos, 2002; Brawley, 2012; National Cancer Institute, 2015a). For example, the Massachusetts Male Aging population study found a > 3-fold higher risk of PCa among men with a family history of the disease, compared to those without a family history of PCa (National Cancer Institute, 2015a). Some studies show higher risk with higher number of first degree relatives with PCa and increased risk with first degree relatives diagnosed before age 65 (Brawley, 2012; National Cancer Institute, 2015a).

A large Swedish population-based study, Family Cancer Database of 26,657 diagnosed PCa cases, showed a 2.12 hazard ratio (HR) for a family history with father only, 2.96 with affected brother only (indicative of an X-linked inheritance) and 8.51 with an affected father and two brothers (National Cancer Institute, 2015a). Risks were higher, when the affected father was diagnosed before age 70 (National Cancer Institute, 2015a). Family history has also been demonstrated to be a risk factor in different racial and ethnic groups (National Cancer Institute, 2015a; Park et al., 2015).

In a population-based case control study of PCa among African Americans, Caucasians, and Asian Americans in the United States and Canada, 5% control and 13%

of all cases reported a father, brother, or son with PCa. There was, however, a lower prevalence of PCa among Asian Americans (National Cancer Institute, 2015a). A positive family history was associated with a two to threefold higher risk in each of the three ethnic groups. Overall, odds ratio associated with a family history of PCa was 2.5 after adjusting for age, race, and ethnicity (National Cancer Institute, 2015a). However, there is some indication that men with a family history of PCa are more likely to obtain PSA screening and this may inflate incident rates among men with a family history (Adami, Hunter, & Trichopoulos, 2002; Brawley, 2012).

Several epidemiologic studies strongly suggest that PCa susceptibility genes exist in the population, such as circadian cycle genes (Markt et al., 2015). However, analysis demonstrated that circadian cycle genes, such as CLOCK, are not strongly or consistently associated with fatal PCa (Markt et al., 2015). An analysis of monozygotic and dizygotic twin pairs in Scandinavia concluded that 42% of PCa risk may be accounted for by heritable factors (Adami, Hunter, & Trichopoulos, 2002; National Cancer Institute, 2015a). This is in agreement with a previous U.S. study that showed a concordance of 7.1% between dizygotic twin pairs and a 27% concordance between monozygotic twin pairs (National Cancer Institute, 2015a).

Moreover, familial clustering of disease among men with early-onset PCa was best explained by the presence of a rare (frequency of 0.003) autosomal dominant, highly penetrant allele(s) (National Cancer Institute, 2015a). Hereditary PCa susceptibility genes were predicted to account for almost half of early-onset disease (age 55 years or younger). A study of 4,288 men who underwent radical prostatectomy (RP) between

1966 and 1995 found that the best fitting genetic model of inheritance was the presence of a rare, autosomal dominant susceptibility gene (frequency of 0.06). In this study, the lifetime risk in carriers was estimated to be 89% by age 85 years and 3.9% for noncarriers (National Cancer Institute, 2015a). This study also suggested the presence of genetic heterogeneity, as the model did not reliably predict PCa risk in first degree relatives of those diagnosed at age 70 years or older. More recent segregation analyses have concluded that there are multiple genes associated with PCa in a pattern similar to other adult-onset hereditary cancer syndromes, such as those involving the breast, ovary, colorectum, kidney, and melanoma (National Cancer Institute, 2015a). In addition, a segregation analysis of 1,546 families from Finland found evidence for Mendelian recessive inheritance. Results showed that individuals carrying the risk allele were diagnosed with PCa at younger ages (<66 years) than noncarriers. This is the first segregation analysis to show a recessive mode of inheritance (National Cancer Institute, 2015a).

The first PCa susceptibility gene, HPCI, on chromosome 1 was established in 1996, but may only be associated with 10% of hereditary PCa cases (Adami, Hunter, & Trichopoulos, 2002). Also, the AR genes for which small nucleotide polymorphisms (SNPs) have been associated with PCa risk are on the X chromosome (Adami, Hunter, & Trichopoulos, 2002). One particular polymorphism, a CAG repeat on exon 1, has been implicated in PCa (Adami, Hunter, & Trichopoulos, 2002).

Moreover, researchers identified numerous SNPs that contribute minimally to the increased PCa risk in African American men, such as genes on cytochrome P450 3A4

(CYP3A4) and the AR. These genes influence androgen metabolism causing prostate tumor growth and progression. However, major influential genes have yet to be identified (Chornokur et al., 2011).

In addition, dietary factors, such as high red meat consumption, high fat diets, low fruit and vegetable intake, and increased dairy consumption may also lead to PCa, although results are not consistent (Brawley, 2012). Dairy intake contributes to high fat intake and increased calcium levels that may be risk factors for PCa (Adami, Hunter, & Trichopoulos, 2002; Adjakly, 2015; Brawely, 2012). On the contrary, high intake of fruits and vegetables, as well as isoflavonoids, such as phytoestrogens in soy, may be protective against PCa (National Cancer Institute, 2015a). For example, Asian men, who consume large amounts of plant-based foods and soy, have the lowest risk of PCa (National Cancer Institute, 2015a). Phytoestrogens may be estrogenic, inhibit angiogenesis, stimulate apoptosis, inhibit cell proliferation, and exhibit antioxidant properties (Adjakly et al., 2015). Soy phytoestrogens exhibit these properties by binding to the estrogen receptor β (ERβ) and mimicking estrogen, which is protective against PCa, and by activating cell signaling pathways (Adjakly et al., 2015). However, some studies, such as a large, multiethnic, population-based study showed no association (Parker et al., 2015).

Some nutrients have been studied for their potential influence on PCa risk. The effect of selenium and vitamin E in preventing PCa was studied in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). This randomized placebo-controlled trial of selenium and vitamin E among 35,533 healthy men found no evidence of a reduction

in PCa risk, although a statistically significant increase HR, 1.17, in PCa with vitamin E supplementation alone was observed (National Cancer Institute, 2015a).

Lycopene, a carotenoid found in tomato sauce, tomatoes, watermelon, and pink grapefruit, may prevent PCa; however, data have been discordant (Zu et al., 2014). Zu et al. (2014) conducted a prospective study of ~ 50,000 male professionals utilizing questionnaires, nutrient intake measurement, histology/pathology for PCa diagnoses, and immunohistochemistry to measure biomarkes of angiogensis and other cancer progression factors. Results demonstrated an inverse association between lycogene intake, mainly from tomato sauce and tomato based foods, and PCa incidence and risk of lethal PCa. Intake of lyocepene was measured at several timepoints to prevent bias from a cross-sectional measurement (Zu et al., 2014). While these results support lycopene as a dietary prevention for PCa more studies are needed to support these results.

Other risks, such as increased alcohol consumption and tobacco, have been controversial (National Cancer Institute, 2015a). For example, in large U.S. cohort studies, men who consumed more than five alcoholic drinks per day after adjusting for age, smoking, race, and education, had the same risk as men, who consumed less than one drink per day (Adami, Hunter, & Trichopoulos, 2002; Parker et al., 2015). On the other hand, several studies demonstrate a relationship between smoking and PCa mortality. For example, cigarette smokers are two times more likely to die from PCa than nonsmokers (Adami, Hunter, Trichopoulos, 2002). However, some studies demonstrated an inverse association between smoking and PCa, particularly for early stage disease (Parker et al., 2015).

Insulin-like growth factor 1 (IGF-1), a major growth-regulating molecule, known to be a potent mitogen and inhibitor of apotosis, may play a role in PCa risk (Adami, Hunter, & Trichopoulos, 2002; Brawely, 2012). Studies show that an increase of 60 to 100 ng/ml may double the risk of PCa (Adami, Hunter, & Trichopoulos, 2002). This effect has been supported by several case-control and prospective cohort studies.

The World Health Organization (WHO) defines obesity as a body mass index (BMI) (weight in kg over height in m2) of greater or equal to 30 kg/m2 (Buschemeyer & Freedland, 2007). Obesity has been shown to increase risk of PCa (National Cancer Institute, 2015a). It has been particularly associated with progression of disease, metastasis, and PCa-specific death (National Cancer Institute, 2015a). Weight gain as an adult and high BMI may also predispose one to PCa (Brawely, 2012; Turner & Drudge-Coates, 2010). Identification of obesity as an additional risk factor for PCa is of public health significance, due to its modifiable nature. However, the association between obesity and cancer is equivocal (Caan & Kroenke, 2017). Caan & Kroenke (2017) show that mild obesity may benefit those with cancer as it provides nutritional stores and energy, lower likelihood of cancer treatment toxicities, and better prognosis. While a sudden and significant weight loss after cancer diagnosis often signals poorer prognosis (Caan & Kroenke, 2017). In addition Greenlee, Unger, LeBlanc, Ramsey & Hershman (2017) pooled data across 22 cancer trials, 14 different cancers, and over 11, 000 subjects and showed that the correlation between obesity and cancer survival varied by cancer type and sex. For example, men compared to women benefited from obesity. In addition

no association was observed between BMI and breast cancer survival (Greenlee et al., 2017).

Several large prospective studies indicate that adult obesity is associated with a higher incidence of advanced/metastatic PCa, death, and a lower incidence of early stage localized PCa (Buschemeyer & Freedland, 2007; Vidal et al., 2016). This may occur since obesity may lower PSA levels and thus PCa may only be detected at a more advanced stage (Buschemeyer & Freedland, 2007). In addition DRE may be more difficult in obese men and thus PCa diagnosis is missed at an early stage (Buschemeyer & Freedland, 2007). Moreover, obesity has been associated with more aggressive features, such as higher grade tumors, a higher rate of positive surgical margins, and a greater risk of biochemical failure and death after RP (Buschemeyer & Freedland, 2007; Vidal et al., 2016).

Obesity is difficult to study because it is not only associated with excess body fat, but with changes in serum concentrations of a multitude of hormones, such as leptin, insulin, IGF-1, testosterone, and estrogen (Buschemeyer & Freedland, 2007). In addition, obese men consume more calories and high fat content, which has also been linked to prostate and other cancers (Buschemeyer & Freedland, 2007). Moreover, obesity is also associated with inflammation and inflammatory factors, which may also be linked to PCa (Buschemeyer & Freedland, 2007).

Studies of obesity and PCa have used disparate or less precise measures of obesity, which make it hard to analysis data. For example, researchers, who utilize BMI as a measurement of obesity, incur potential study bias, since BMI does not consider lean

body mass, which often contributes to high BMI measures (Caan & Kroenke, 2017; Buschemeyer & Freedland, 2007). Some studies report alternative measures of obesity, such as waist/hip ratio and waist circumference, which makes extrapolation of data difficult (Buschemeyer & Freedland, 2007). Currently, several studies demonstrate that obesity measurements utilizing body composition (muscle and adiposity) may be more precise (Caan & Kroenke, 2017). Nonetheless, BMI is still the most commonly used measurement for obesity and is mostly accurate (Buschemeyer & Freedland, 2007).

Prostate Cancer Treatment

Treatment options for PCa are based on age, clinical stage, initial PSA level, and Gleason score, together with comorbidities, and baseline urinary and sexual function (Keyes et al., 2013; Turner & Drudge-Coates, 2010). Definitive, aggressive treatments for early stage, localized PCa are: brachytherapy, external beam radiation therapy (EBRT) with or without ADT for intermediate or advanced disease, and RP (Holmboe & Concato, 2000; Keyes et al., 2013). RP is the preferred treatment for those younger than 70 with early stage, localized disease, greater than 10 years life expectancy, and few comorbidities (Cross, Ritter, & Reding, 2012; Keyes et al., 2013). These younger men have less aggressive disease and lower pathological grade than men age 70 and older and are more likely to receive aggressive treatment than older men (Graefen & Schlomm, 2012).

RP entails complete removal of the prostate, seminal vesicles, and pelvic lymph nodes (Turner & Drudge-Coates, 2010). In this younger age group, RP can increase survival and decrease risk of metastasis (Graefen & Schlomm, 2012). Surgeons perform

either laproscopic, perineal, retropubic, or robotic surgery. Complications may include postoperative hemorrhage, infection, erectile dysfunction, and/or urinary incontinence, which is similar with all surgical techniques (Keyes et al, 2013; Turner & Drudge-Coates, 2010). These postsurgical complications are affected more by comorbidities than age (Graefen & Scholomm, 2012). Thus, in men with no comorbidities, surgery offers a greater survival advantage (Graefen & Schlomm, 2012). However, older men with multiple comorbidities and more advanced disease are often referred for radiation therapy plus ADT, as they are often not candidates for surgery (Cross, Ritter, & Reding, 2012; Graefen & Scholomm, 2012).

External beam radiation therapy is another treatment option for subjects with localized or locally advanced disease (Keyes et al., 2013; Turner & Drudge-Coates, 2010). For locally advanced disease, it is often preceded by ADT two months before and up to two years postradiation treatment for more advanced disease (Turner & Drudge-Coates, 2010). While surgery and radiation therapy are common treatments for PCa, they are not without significant side effects, such as urinary incontinence, rectal damage, and erectile dysfunction (Holmboe & Concato, 2000).

For select subjects, brachytherapy may be administered. Brachytherapy entails temporary or permanent implantation of radioactive seeds directly into the prostate or surrounding tissue (Keyes et al., 2013). Side effects are often urinary, bowel, and sexual symptoms (Keyes et al., 2013; Turner & Drudge-Coates, 2010). Radiation therapy can also remain palliative for relief of pain from bone metastases (Turner & Drudge-Coates,

2010). Radiation therapy, however, may produce gastrointestinal bleeding, sexual dysfunction, and urinary incontinence (Turner & Drudge-Coates, 2010).

Another treatment option is active surveillance, which is reserved for early stage, localized disease (Keyes et al., 2013). Those eligible for active surveillance will need repeat prostate biopsies every 6-12 month in order to diagnosis malignant transformation that will require immediate and more aggressive treatment (Keyes et al., 2013).

Another investigational treatment for PCa is Cyberknife, which is a linear accelerator that delivers conformal, hypofractionated, radiation therapy to the prostate via a robotic arm with image guidance (Seisen et al., 2013). Clinicians utilize a standard dose of 5 fractions of 7.5 Gy each (Seisen et al., 2013). Cyberknife results in urinary toxicities and often erectile dysfunction (Seisen et al., 2013). While there are several Phase I/II trials illustrating positive treatment outcomes with Cyberknife, Phase III randomized controlled trials are lacking (Seisen et al., 2013). Thus, at this time with the high cost and maintenance of this technology, it is not yet considered equal or superior to other standard treatments and definitive therapy (Seisen et al., 2013).

While RP and EBRT are widely utilized therapies, there is no gold standard for treatment, as treatment outcomes do not vary across techniques (Cross, Ritter, & Reding, 2012). Thus, despite several different therapeutic options, no definitive evidence exists that one particular treatment modality reduces mortality from PCa (Holmboe & Concato, 2000). Men with advanced PCa, therefore, often succumb to their disease even after definitive treatment and ADT (Berger et al., 2011).

Tyson and Castle (2014) report a retrospective study using SEER data of 294, 160 men diagnosed with localized PCa between January 1,1995 and December 31, 2003. The purpose of the study was to compare overall survival and PCa specific survival, after accounting for clinical variables and treatment effects of RP and radiation therapy, among several racial groups, such as Caucasian, Hispanic, African American, Asian, and Other men (Tyson & Castle, 2014).

Results demonstrated that Asians had significantly higher rates of overall and PCa specific survival among all ethnic groups, while African American men had the lowest rates (Tyson & Castle, 2014). The largest disparity occurred in those who did not undergo treatment, many of which were African American men (Tyson & Castle, 2014). Even after adjustment for treatment effects, African American men exhibited the lowest overall and PCa specific survival among all racial groups (Tyson & Castle, 2014). While this study was informative, one major limitation is that researchers did not include other factors, such as comorbidities, which may have influenced treatment choices.

Powell et al. (1997) studied 369 men (120 African American and 249 Caucasian), who had undergone RP. The effects of age at RP, clinical stage, preoperative Gleason score, preoperative PSA level, and race upon positive surgical margins were assessed using multiple logistic regression models. Results demonstrated that African American men were significantly older than Caucasian men in the study and had a higher preoperative PSA level (Powell et al., 1997). However, the two racial groups were comparable with regards to clinical stage and Gleason scores.

In addition, results showed that African American men exhibited more positive surgical margins than Caucasian men. Race was an independent predictive factor of positive surgical margins among subjects with clinically localized PCa. Positive surgical margins significantly influenced time to progression independently of other prognostic factors, such as Gleason score, stage, and preoperative PSA levels (Powell et al., 1997). Men with localized PCa and a life expectancy of less than 10 years are often not provided aggressive treatment (Turner & Drudge-Coates, 2010). However, men with more advanced PCa may benefit from definitive treatment (Turner & Drudge-Coates, 2010).

Overall, selection of treatment for localized PCa can be daunting (Chornokur et al., 2011; Zeliadt et al., 2006). Thus, without a gold standard it remains imperative to understand what factors drive subjects to select one treatment over another for better therapeutic outcomes (Zeliadt et al., 2006). Treatment decisions play an important part in enhancing PCa survival and reducing PCa mortality (Akpuaka, Clarke-Tasker, Nichols-English, Daniel, & Akpuaka, 2013). Holmboe and Concato (2000) conducted a qualitative study to assess patient preferences for treatment. They investigated how these subjects chose their treatment to understand why subjects often rejected watchful waiting or active surveillance. The researchers recruited 102 participants and utilized semi-structured interviews to obtain information on what treatment these subjects chose, why they chose it, and why they rejected watchful waiting as a treatment option (Holmboe & Concato, 2000). Results showed that the majority of participants chose brachytherapy, rather than standard therapy, such as RP and EBRT (Holmboe & Concato, 2000). Side effects, external, and intrinsic factors of therapy were the most cited reasons that subjects

chose brachytherapy (Holmboe & Concato, 2000). For example, subjects cited the positive attributes of brachytherapy, such as short treatment duration, less invasive treatment, and more focused treatment directed to the prostate as major reasons that influenced their treatment choices (Holmboe & Concato, 2000).

In addition, subjects cited external factors or information regarding therapy and intrinsic factors of therapy as the most prominent reasons for treatment decisions, rather than being influenced by their primary physicians (Holmboe & Concato, 2000). Since the primary care physician often sees PCa subjects first, this information can help them best understand the subjects' beliefs, value systems, and motives for treatment decisions, so that they can help them make more informed decisions (Holmboe & Concato, 2000). The most frequent reason that subjects did not chose watchful waiting is fear of dying and need to do something about their cancer (Holmboe & Concato, 2000). Interestingly, many men in this study with a life expectance of less than 10 years still chose aggressive treatment, such as RP (Holmboe & Concato, 2000).

While this study provided useful information, minorities were underrepresented and thus this information may not be generalizable (Holmboe & Concato, 2000). However, several studies show that African American men often chose less aggressive therapies. In addition the fact that most subjects in this study chose brachytherapy may not reflect the current state of treatment in most of the United States, in which RP and EBRT are more prevalent (Holmboe & Concato, 2000). In addition while only 37% of subjects cited that their physicians influenced their treatment decisions, this information may not be representative of the true percentage, since physicians were not interviewed in

this study and thus there may likely be response bias (Holmboe & Concato, 2000). Nonetheless, the results of this study strongly suggest that factors other than physician advice are affecting men's decisions about treatment (Holmboe & Concato, 2000).

Zeliadt et al. (2006) also showed through retrospective review that there are varied factors, which contribute to men's treatment decisions. However, cancer control and eradication remain the most influential factors in treatment decision making (Zeliadt et al., 2006). In their study cost was a small but nonetheless additional cited factor. Moreover, Shavers et al. (2004) reported that several factors are associated with the receipt of watchful waiting among PCa subjects. These include race/ethnicity, stage, grade, life expectancy, age, comorbidities, marital status, income, and education. Racial differences in the receipt of watchful waiting were not completely explained by differences in clinical characteristics, comorbidities, or life expectancy at the time of diagnosis. After controlling for stage, grade, life expectancy, age, comorbidities, marital status, income, and education in a multivariate model, race/ethnicity was independently associated with the receipt of watchful waiting (Shavers et al., 2004).

African American men are less likely to be offered aggressive treatment options by physicians and less likely to desire treatments, which have side effects, such as RP (Chornokur et al., 2011). This may result from African American men lacking adequate health insurance and being unmarried with less support for more aggressive treatment options (Chornokur et al., 2011). On the other hand, Caucasian men were more likely to choose RP (Chornokur et al., 2011). In addition, Caucasian men were less likely to receive ADT than RP for localized, low risk PCa than African Amercian men (Chornokur

et al., 2011). Caucasian men were also less likely to receive radiation therapy than RP for localized, low risk disease than African American men (Chornokur et al., 2011). African American men were also less likely to receive ADT for advanced disease, compared to Caucasian men (Chornokur et al., 2011). One potential reason is African American men's distain for treatment side effects (Chen et al., 2016). This often leads to higher mortality rates and decreased quality of life among African American men, compared to Caucasian men (Chornokur et al., 2011).

To summarize, PCa treatment options vary by disease stage, PCa-risk group, age, and patient/physician preferences.

Prostate Cancer Epidemiology and Racial Disparity

PCa remains a substantial public health challenge in the United States (Brawley, 2012; National Cancer Institute, 2015a). Aside from skin cancer, PCa is the most common malignancy and the second leading cause of cancer death in men in the United States, preceded only by lung cancer (American Cancer Society, 2017; Brawley, 2012; National Cancer Institute, 2015a). The National Cancer Institute (2015a) indicated that approximately 220,800 new cases of PCa and 27,540 deaths occurred in 2015. The American Cancer Society (2017) indicates that there will be approximately 161, 360 new PCa cases in 2017. Moreover, a United States male has a 1-in-7 lifetime risk of developing PCa (American Cancer Society, 2017). Worldwide, PCa remains the third leading cause of cancer death in men (Buschemeyer, & Freedland, 2007; World Health Organization, 2017).

PCa incidence rates vary around the world. For example, Asian countries exhibit the lowest age-adjusted incidence rates of 2-10 per 100,000 and Western countries such as the United States and northern Europe exhibit the highest. Moreover, African American men have the highest PCa incidence and mortality rates in the world with a 1.4 times greater risk of PCa diagnosis than Caucasian men and a 2.5 times greater risk of death (Brawley, 2012; Chornokur et al., 2011; National Cancer Institute, 2015a). Overall, African American men have a significantly higher PCa incidence and mortality than any other racial or ethnic group (Khani et al., 2014).

African American men are diagnosed at earlier ages, with higher PSA values, higher Gleason scores (grade 8 and up) and more advanced disease than Caucasian men (Chornokur et al., 2011; Khani et al., 2014; National Cancer Institute, n.d). African American men also exhibit higher rates of invasive cancer compared to Caucasian men (Ro, Shen, Zhai, & Ayala, 2012). Moreover, African American men with localized PCa are often found to have more aggressive disease post biopsy and treatment. In addition, African American men exhibit more disease recurrence after treatment, which is often difficult to resolve (Barocas & Penson, 2010). African American men also receive less primary therapy and are diagnosed and often treated later than Caucasian men, which is often due to their lower socioeconomic status, as measured by income (Ziehr et al., 2015).

Nonetheless, these differences are not solely due to social factors such as access to quality healthcare and socioeconomic status, but genetic factors may also contribute to this health disparity (Brawley, 2012; National Cancer Institute, 2015a). Khani et al.

(2014) demonstrated that there are molecular differences between African American men and Caucasian men that may explain the PCa health disparities between the two groups. Khani et al. (2014) showed via immunohistochemistry that African American men exhibit overexpression of SPINK1, which is often associated with more aggressive tumors and higher rates of mortality. Other factors that influence treatment and mortality also need to be assessed as health disparities remain a significant public health concern in the United States (Barocas & Penson, 2010).

Previous research identifies multiple factors associated with health disparities, which lead to poor health outcomes (Kohn et al., 2010). For instance, those with low socioeconomic status, mainly racial and ethnic minorities, often have minimal or no health insurance, which prevents them from receiving adequate preventative medical care and treatment (Adler & Newman, 2002; Kohn et al., 2010). Ultimately, this leads to increased morbidity in this population, which increases health care costs, and mortality often ensues (Ahluwalia et al., 2009). Lack of health insurance remains a persistent and major barrier to eliminating health disparities (Kohn et al., 2010). Racial and ethnic differences are not the only factors attributable to health inequality; other factors, such as education and environment, also play a role. For instance, large numbers of minorities in the U.S. lack adequate education, which is associated with poor health outcomes. Due to low education, many fail to enroll in Medicaid or Medicare services, which are available to the poor (Adler & Newman, 2002).

One of the main goals of the federal initiative, Healthy People 2010, is to combat significant health disparities (Orsi, Margellos-Anast, & Whitman, 2010). Health

disparities could be eliminated through community education outreach, broad access to health care for U.S. citizens, and increased community involvement in preventative intervention programs. For the uninsured, the responsibility of population-based care and treatment falls on local public health facilities, which rely on data to implement and evaluate effective outreach programs (Ahluwalia et al., 2009).

Validated screening techniques such as PSA assay have resulted in increased PCa detection over the past 20 years (Das & Crawford, 1993). Subsequently, clinicians diagnose men at earlier stages of cancer with more localized disease (Namiki & Arai, 2010). However, higher screening rates often produce higher detection and thus incidence rates, but no effect on mortality, since the prevalence of indolent PCa is high: around 15 to 30% of men over age 50 will have PCa with a low potential for growth and metastasis (Adami, Hunter, & Trichopoulos, 2002). Overall, the presence of indolent disease is greater than that of clinically relevant disease, and PSA screening increases the detection of these localized lesions (National Cancer Institute, 2015a). Thus, the 5-year survival rates have increased due to an increased number of men with clinically localized disease (Brawley, 2012). However, less than 33% of men diagnosed with metastatic disease live 5 years (Brawley, 2012). In addition, African American men tend to lack or have reduced health insurance, which limits screening availability and may lead to racial disparity in PCa diagnosis, treatment, and survival (Chornokur et al., 2011).

There are 1.4 million African immigrants living in the United States of which 13% are Nigerian immigrants. However, there are limited studies focusing on PCa in the Nigerian population (Akpuaka, Clarke-Tasker, Nichols-English, Daniel, & Akpuaka,

2013). Like African Americans, Nigerian men are at a disproportionately high risk of developing PCa; it is actually the number one cancer killer in Nigerian males in the U.S and Africa. (Akpuaka et al., 2013). The majority of Nigerian males who are diagnosed with PCa succumb to the disease (Akpuaka et al., 2013). The poor health education of Nigerian males may account for the late presentation of PCa with increased mortality, unlike PCa that is detected early and treated definitively (Akpuaka et al., 2013). Akpuaka et al. (2013) conducted a study that explored Nigerian male immigrant's knowledge, attitudes, health practices, and beliefs towards PCa and PCa screening. This study was conducted because there is limited research. Moreover, due to the growing number of Nigerian male immigrants currently residing in the United States, there is need for more PCa education and screening, using a survey instrument that is culturally appropriate, sensitive, reliable, and valid, which was a major objective in this study (Akpuaka et al., 2013).

The researchers based the theoretical framework for this study on the health belief model (HBM), which is a psychological model that attempts to explain and predict individuals' health behaviors (Kleier, 2004). The four tenets of the HBM that predict health behavior and decision making are perceived susceptibility, perceived severity, perceived benefits, and perceived barriers (Kleier, 2004). Motivation is a primary tenet of the HBM that stimulates health behaviors and actions.

In this study, the researchers utilized a validated survey questionnaire that measured several concepts, such as knowledge about PCa, health practices and beliefs about PCa, and demographic information (Akpuaka et al., 2013). While the sample size

was small—22 Nigerian males—27% of these males believed that PCa screening was not necessary since they did not have prostate problems (Akpuaka et al., 2013). While many were knowledgeable regarding early detection of PCa for cure, 36% of these sampled, Nigerian males would not want to know if they had PCa, and 45% believed that PCa screening would be painful (Akpuaka et al., 2013).

Moreover, 68% of these Nigerian males did not believe that PCa was more prevalent in Nigerian or African Americans than Caucasian men. In addition, many in this culture would or did refuse DRE as they will not have a man touch their genitals due to their cultural upbringing (Akpuaka et al., 2013). The results of this study, aside from the cultural beliefs regarding DRE, were similar to other studies of African American men (Akpuaka et al., 2013).

Others studies support the high incidence of PCa in African American males compared to Caucasians. Anderson and Marshall-Lucette (2016) indicate that African-Caribbean men have the highest rate of PCa compared with Caucasians and compared to other African males. This result is steady whether these men migrate to the U.S or reside in the Caribbean. While definitive reasons for increased incidence of PCa among those of African descendent compared to Caucasians are uncertain, some risk factors may be genetics and socioeconomic factors (Anderson & Marshall-Lucette, 2016). In addition African males and African American males are more reluctant to undergo DRE and other PCa cancer screening and treatment due to cultural beliefs of enhanced masculinity (Anderson & Marshall-Lucette, 2016).

Another study that supports evidence of increased PCa incidence among African American men compared to Caucasian men is the study of African American men in Georgia, which has the highest incidence rate of PCa in the nation (Wagner, Bauer, Bayakly, & Vena, 2013). This study also supported disparities in tumor grade between African American men and Caucasian men in which African American men in Georgia were diagnosed with high-grade and stage tumors compared to their Caucasian counterparts (Wagner, Bauer, Bayakly, & Vena, 2013). This trend persistent throughout the 10 year study and resulted in increased mortality in these African American men (Wagner, Bauer, Bayakly, & Vena, 2013).

Similar to other studies, genetics, socioeconomic factors, and lack of adequate access to healthcare in rural areas were discussed as potential reasons for this health disparity (Wagner, Bauer, Bayakly, & Vena, 2013). Health disparities, particularly in the uninsured, minority populations, lead to increased morbidity and mortality (Kohn et al., 2010). If researchers understand and address factors that lead to health inequity at the local level, the goal of improving health outcomes may be more easily attainable

Androgens and Alzheimer's Disease

Age is one of the main risk factors for AD, and several studies have suggested that androgen loss, as a result of aging, may promote cognitive decline in older men and increase risk of AD due to low levels of circulating testosterone (Ciocca et al., 2016; Martins & Gandy, 2016; Nead et al., 2016; Vest & Pike, 2013). Physiologically low levels of testosterone due to aging have been associated with increased risk for AD by both in vitro and in vivo studies; however, data are often conflicting (Martins & Gandy,

2016; Verdile et al., 2014). Testosterone is neuroprotective, helping to mitigate oxidative stress, and prevent amyloid beta accumulation and neurotoxicity (Verdile et al., 2014). In vitro studies indicate that androgens prevent amyloid beta protein accumulation and toxicity via neprilysin, an amyloid beta protein degrading enzyme (Vest & Pike, 2014). This prevents the formation of senile plaques (Nead et al., 2016). Androgens directly increase neprilysin expression via genomic pathways (Vest & Pike, 2014). Since androgen receptors reside in the hippocampus and prefrontal cortex, low levels of testosterone (the primary male androgen) result in a decline in cognition, memory, and visuospatial ability leading to dementia and often AD (Verdile et al., 2014).

Androgens have a significant effect on hippocampal structure and function, synaptic plasticity, and long-term potentiation, which solidifies memories (Atwi, McMahon, Scharfman, & MacLusky, 2016). Testosterone has been shown to induce spines and synapses on CA1 pyramidal neurons in the hippocampus, potentially through its interaction with brain-derived neurotrophic factor (BDNT) (Atwi et al., 2016). Testosterone is found to be excitatory on the dendrites of hippocampal pyramidal neurons, but inhibitory in the mossy fiber system of the hippocampus (Atwi et al., 2016). Thus, testosterone's effect in the hippocampus is both significant and complex.

Decreased testosterone due to aging has been implicated in cognitive decline in men and the aggregation of amyloid beta protein (Verdile et al., 2014). Hormonal decrease due to aging occurs from the dysreguation of the hypothalamic-pituitary-gonadal axis, which is associated with cognitive decline and impairment (Verdile et al., 2014). In normal physiology, testosterone is converted in the brain to estrogen via the

enzyme aromatase, which also has been implicated in neuroprotection. However, estrogen intermediates are often not required for androgen to exert effects in the brain (Verdile et al., 2014).

Androgen receptors reside in the hippocampus and prefrontal cortex mainly. Activation of these androgen receptors results in CA1 pyramidal spine formation, which sends excitatory impulses to the entorhinal limbic area via the release of glutamate and acetylcholine, the excitatory neurotransmitters released from NMDA and acetylcholinergic receptors (Atwi et al., 2016). This leads to an influx of calcium ions into these neurons when they are depolarized, and promotes longer term memory formation or long-term potentiation (LTP).

On the contrary, a decrease in testosterone will increase BDNF, which increases mossy fiber activation and thus inhibitory GABAergic synapses, which inhibit hippocampal spine and synapse formation (Atwi et al., 2016). Since memory is a combination of encoding and retrieving in which the left hemisphere or hippocampal region functions in encoding or long-term potentiation and the right hemisphere or prefrontal cortex is involved in retrieving memory, low levels of testosterone result in cognitive decline, since these brain areas are implicated in memory formation, memory retrieval, and visuospatial ability (Yamasaki et al., 2012). Moreover, testosterone also protects against neuroinflammation and oxidative stress (Verdile et al., 2014).

Several in vitro and in vivo studies have demonstrated the age-related increase in gonadotrophins, such as leutinizing hormone (LH), due to loss of negative hormonal feedback from decreased androgens as a result of aging, which leads to cognitive decline

and increased risk for AD (Verdile et al., 2014). In addition, reduction in testosterone has been implicated in increased amyloid beta protein levels. In the first in vivo study, Verdile et al. (2014) enrolled 427 male subjects: 151 controls, 150 with subjective memory complaints (SMC), 50 with mild cognitive impairment, and 76 with AD. In the study, PET imaging was used to measure amyloid beta protein. Plasma levels of amyloid beta 40 and amyloid beta 42 were also available (Verdile et al., 2014). Factors, such as age, LH, and the presence of APOE-epsilon 4 allele, known risk factors for AD, showed significant impact on brain amyloid beta burden (Verdile et al., 2014).

Several studies have also shown that men with AD/dementia have lower total serum testosterone levels than normal controls (Verdile et al., 2014). Verdile et al. (2014) conducted a study that examined whether the levels of testosterone are lower in male subjects with AD compared to controls, as well as the impact of testosterone levels on neuropsychological functioning among subjects with AD and normal elderly men. Results show that AD subjects had significantly low levels of testosterone compared to normal controls.

In addition, Lv et al. (2015) conducted a systematic meta-analysis of seven prospective cohort studies to explore and confirm the association between low testosterone levels and risk of AD. There were 240 participants across all seven prospective cohort studies. Results showed that low plasma testosterone in elderly men was significantly associated with increased risk of AD. For all studies, follow-up data spanned at least 1 year. After controlling for a moderate degree of heterogeneity among the studies, low testosterone levels were still significantly associated with an increased

risk of AD in elderly men (Lv et al., 2015). Therefore, elderly men with lower serum testosterone levels may require more intervention to reduce risk of cognitive impairment and AD.

Martins and Gandy (2016) discussed that ADT decreases levels of testosterone to well below physiologically low levels and its use has increased significantly over the last few decades. While ADT has enhanced PCa treatment and increased survival, it exhibits a myriad of side effects, such as cognitive impairment. However, the association between ADT and cognitive impairment, especially AD, has been less well studied and results are conflicting: some studies have demonstrated an association between cognitive impairment and ADT, and some have not.

Wu et al. (2013) presented the results of a small, qualitative study that supports an association between ADT and cognitive impairment. Eight out of 11 participants reported impairments in concentration, information processing, visuospatial processing, memory, and executive functioning. The results of this study may help clinicians become more aware of how subjects verbalize cognitive dysfunction.

Nead et al. (2016) presented the first large, retrospective cohort study of 2,397 hospital-based subjects diagnosed with PCa, who received ADT for less than, equal to, or greater than 12 months. The results support an association between the use of ADT for the treatment of PCa and increased risk of AD, especially when treatment duration was 12 months or longer.

The results from a large, retrospective, cohort study indicates that ADT may be associated with AD (Martins & Gandy, 2016; Nead et al., 2016). However, limited and

conflicting data exist regarding ADT's effects on cognitive function (Ahmadi & Daneshmand, 2013; Nead et al., 2016; Martins & Gandy, 2016). Studies investigating the association between ADT and neurocognitive disease are limited and disparate (Lv et al., 2015; Nead et al., 2016).

Nonetheless, although some studies show an association between low testosterone and increased risk of developing AD, there are conflicting data about the role of testosterone in cognitive functioning. There is a lack of robust prospective studies, as well as limited numbers of relevant studies on the relationship between low testosterone levels and AD (Lv et al., 2015).

The androgen receptor is a well-known target for PCa treatment. It is implicated in PCa progression, castration-resistant PCa, and metastasis (Hodgson et al., 2012). However, the biology of castrate-resistant PCa is not well understood. Many with this diagnosis develop advanced cancer, metastatic disease, and mortality (Pascoe & Sundar, 2012). However, many respond well to ADT (Pascoe & Sundar, 2012).

Since androgen receptors reside in the hippocampus and prefrontal cortex, low levels of testosterone, the primary male androgen, result in a decline in cognition, memory, and visuospatial ability leading to dementia and often AD (Verdile et al., 2014). Moreover, some studies show that low testosterone levels resulting from ADT are responsible for decreased cognitive functioning in men; however, results are equivocal (Ciocca et al., 2016; Lv et al., 2015).

Summary

Some studies show that low testosterone levels resulting from ADT are responsible for decreased cognitive functioning in men; however, results are equivocal (Ciocca et al., 2016; Lv et al., 2015). ADT, treatment for locally advanced, high-risk, and/or metastatic PCa decreases testosterone levels to well below normal physiologically low levels, which is below 350 ng/dL total testosterone (Ciocca et al., 2016; Martins & Gandy, 2016). Its use has increased significantly over the last few decades, due to its effectiveness as sole or adjunct therapy for PCa subjects (Martins & Gandy, 2016). Approximately 500,000 men currently utilize ADT in the US for PCa and this number is increasing (Nead et al., 2016). While it is an effective treatment, ADT reduces androgens to extremely low levels and is likely associated with cognitive impairment and possibly AD (Martins & Gandy, 2016; Nead et al., 2016).

While some studies suggest that ADT use may lead to cognitive impairment, more large-scale studies are needed, especially to investigate the association between ADT and AD (Wu et al., 2013). Since existing studies suffer from small sample sizes (such as the study by Wu et al., (2013) in which $n = 11$), limited follow-up data of 5 years or less, low generalizability due to use of hospital data, and lack of discernment of the association between ADT and AD by PCa stage and risk groups, this study seeks to improve upon these methodological limitations and increase knowledge of the association between ADT and AD to produce positive social change.

Given the significant patient, familial, and economic burden, and the increased mortality and morbidity from AD, it is imperative to further investigate the association

between ADT and AD in order to prevent further morbidity and mortality. Given the ubiquitous and increasing use of ADT, it is imperative to understand all of the side effects of this treatment, such as cognitive dysfunction, to limit morbidity (Ahmadi & Daneshmand, 2013). Moreover, the results of this research may lead to ADT treatment adjustments to prevent or delay the onset of AD (Ahmadi & Daneshmand, 2013; Vest & Pike, 2013). For example, more information regarding cognitive dysfunction could lead clinicians to promote active surveillance for elderly subjects with close monitoring of disease progression to prevent AD (Ahmadi & Daneshmand, 2013). Since current therapy for AD is palliative and newer therapies are unproven, knowing who is at risk will make prevention and management of this devastating disease easier for society, subjects, and their family members (Mayeux & Stern, 2012).

Moreover, racial health disparity remains a public health dilemma. For example, African American men are less likely to be offered aggressive treatment options for PCa and less likely to desire treatments, which have side effects (Chornokur et al., 2011). Moreover, African American men are also less likely to receive ADT for advanced disease, compared to Caucasian men (Chornokur et al., 2011). This often leads to higher mortality rates and decreased quality of life among African American men compared to Caucasian men (Chornokur et al., 2011).

The largest health disparities occur in those men who do not undergo treatment, many of whom were African American (Tyson & Castle, 2014). Even after adjustment for treatment effects, African American men exhibit the lowest overall and PCa specific survival among all racial groups (Tyson & Castle, 2014). While higher mortality rates

occur among African American men, compared to Caucasian men, reduced use of ADT in the African American population may prevent development of AD (Chornokur et al., 2011).

The magnitude of the expected rise in AD is significant due to an aging population, and AD will be an even more costly public health problem in the years to come (Mayeux & Stern, 2012). This research is important since AD incidence and prevalence are increasing and there is no cure for this progressive disease. With increasing healthcare costs and extensive burden on subjects and their caregivers, it is essential to learn more about risk factors of AD to prevent this devastating, neurodegenerative disease or to slow its progression (Vest & Pike, 2013).

Chapter 3: Research Method

Introduction

The purpose of this study is to explore the association between ADT and the development of AD through quantitative analysis of a large population database, the SEER-Medicare linked database, which contains long-term, follow-up information of PCa subjects selected for this study. Extended follow-up data will be most useful for AD detection, because clinical symptoms of AD manifest after many years (Nead et al., 2016). While some studies suggest that ADT use may lead to cognitive impairment, more large-scale studies are needed, especially to investigate the association between ADT and AD (Wu et al., 2013). Because existing studies suffer from small sample sizes, limited follow-up data of 5 years or less, low generalizability, due to use of hospital data, and lack of information regarding the association between ADT and AD by stage of PCa and across PCa risk groups, in this study I sought to improve on these methodological limitations and increase knowledge of the association between ADT and AD (Wu et al., 2013).

This chapter includes a description of the study's research design and rationale, the methodology, population, sampling procedures, inclusion/exclusion criteria, and sample size determination. This chapter also includes the data analysis plan and procedures involved in the study. This includes justification of the descriptive and inferential statistics used. Finally, information regarding internal/external study validity and ethical practices are also included.

Research Design and Rationale

In this section I describe the research design and rationale for this study including the study variables and covariates, research questions, and time and resource constraints.

Research Design

Some types of quantitative research involve measurement of empirical, objective data via an experimental design (Crosby, DiClemente, & Salazar, 2006; Frankfort-Nachmias & Nachmias, 2008; Creswell, 2009). Researchers utilize an experimental design to study cause and effect relationships. However, experimental designs are often time consuming and costly and thus often inappropriate for diseases that require a long follow-up such as AD.

Quantitative researchers try to control biases and focus on objectivity, rather than subjective matters (Creswell, 2009; Crosby et al., 2006). They endeavor to uphold internal validity by using peer review to ensure that their methodology aligns with their hypotheses and study purpose. Quantitative research is more effective when outcomes are desired. For example, a researcher should use a quantitative design to study the effects of treatment on cancer subjects. Because this study analyzes relationships between variables—the independent variable of interest is ADT use and the dependent variable is AD—a quantitative research method was best because hypothesis testing is used to examine the relationship between the independent and dependent variables.

This study was a retrospective, longitudinal, observational, quantitative cohort study of subjects diagnosed with PCa from a large population database, the National Cancer Institute's (2015b) SEER-Medicare linked database, utilizing descriptive

statistics, chi squared, correlational, and multiple logistic regression statistics to evaluate the association between ADT use for PCa treatment and AD risk.

The SEER Medicare-linked dataset is a large population database, which contains matched medical claims and demographic information for Medicare beneficiaries diagnosed with cancer (National Cancer Institute, 2015b). The SEER program consists of regional and state-based tumor registries located throughout the country, representing approximately 26% of the U.S. population after 2001.The SEER database is a cross-sectional database with Medicare linked information in a longitudinal design with long term follow-up data collected annually. This is important because clinical symptoms of AD take years to present from inception (Nead et al., 2016).

Rationale

The quantitative study design was chosen not only because the variables in this study can be quantified, but also because it allowed me to either refute or support the hypotheses of this study via hypothesis testing and inferential statistics and was best suited to answer the research questions, which were as follows:

RQ1: Is there an association between ADT and AD after controlling for confounding factors, such as age and cardiovascular disease?

RQ2: Does the association between ADT and AD risk vary by PCa risk groups?

RQ3: Does the association between ADT and AD risk vary by race?

Theory elucidates relationships between variables implicated in cause and effect relationships and helps researchers identify gaps in current knowledge (Creswell, 2009). For example, the main framework and theoretical basis for this study were as follows.

Extensive research has resulted in better understanding of the neurophysiology of AD and neurodegeneration. The hallmarks of AD are extracellular accumulation of amyloid beta protein, resulting in neuritic, senile plaques and intracellular accumulation of tau protein, resulting in neurofibrillary tangles (Kandel & Schwartz, 1985; Vest & Pike, 2013). This pathology is most prevalent in the hippocampus and cortex, areas of the brain responsible for memory and executive functioning. AD mainly arises from imbalance of amyloid beta protein production and its clearance in the brain (Selkoe, 2012). Most AD scientists agree that secondary prevention, or diagnosing and treating AD before overt clinical symptoms present, is more likely to slow pathological cognitive decline (Selkoe, 2012).

Testosterone has been known to be neuroprotective and to exert its effects in the hippocampus and cortex (Martins & Gandy, 2016). It has also been shown to modulate production of amyloid beta protein by decreasing its accumulation and therefore thwarting formation of senile plaques (Nead et al., 2016). ADT, an effective treatment for high risk, locally advanced, or metastatic PCa, decreases testosterone levels to lower than normal physiologically low levels, and thus has recently been shown to have an association with AD (Nead et al., 2016). However, more research is needed. The aim of this study was to understand the relationship between ADT use for PCa treatment and outcome of AD after controlling for several confounding variables, such as cardiovascular disease and age.

Study Variables

I describe the independent, dependent, and control variables used in this study below. I obtained data containing these variables from the SEER-Medicare-linked

database composed of 11 data sources. The SEER Patient Entitlement and Diagnosis Summary File (PEDSF; 2004-2013) contains the PCa subjects (ICD-9 diagnosis codes 183, 790.93, and C61) with data on the following variables used in this study: age, race/ethnic group, Medicare eligibility and reason for eligibility, primary cancer site, cancer risk category, year of diagnosis, tumor grade, and clinical stage (Stage 1 = cancer is localized to the prostate; Stage 2 = tumor has grown inside the prostate but has not extended outside the prostate; Stage 3= cancer has spread outside the prostate but no spread to lymph nodes nor metastatis; Stage 4 = cancer has spread to other tissues, such as lymph nodes, bones, liver, or lungs).Medicare outpatient claims data files, such as durable medical equipment (DME) file (2004-2014), physician/supplier (NCH; 2004-2014), outpatient (2004-2014), home health agency (HHA; 2004-2014), and hospice (2004-2014) contain information regarding diagnoses, treatment, and services. Other Medicare carrier claims files used in this study were the chronic conditions flags (2004-2014) used for diagnoses information, and MEDPAR (2004-2014) for inpatient treatment and diagnosis information.

Independent variable. ADT is the use of androgen agonists or antagonists to treat locally advanced and/or metastatic PCa. Approximately 500,000 men in the United States currently use ADT for PCa, and this number is increasing (Nead et al., 2016). While it is an effective treatment, ADT reduces androgens, testosterone, to extremely low levels and is likely associated with cognitive impairment (Martins & Gandy, 2016).

For this study there were three research questions with one independent variable of interest—ADT, a dichotomous variable (1 = ADT, 0 = no ADT). Information

regarding the independent variable, ADT, is available in the Medicare Claims, NCH, Outpatient, DME, HHA, and Hospice files utilizing the following J codes, which are related to procedural CPT codes of common ADT therapy: J9202 (goserelin, which is a GnRH antagonist), J9217 and J9218 (leuprolide [Lupron], which is another GnRH antagonist), J91555 (degarelix or Firmagon, which is a GnRH antagonist), and J3315 (triptorelin acetate, which is an LHRH analog).

Dependent variable. AD is the most common progressive, neurodegenerative disease and form of dementia (CDC, 2015; Mayeux & Stern, 2012). It affects regions of the brain implicated in memory and cognitive function, such as the hippocampus and cortex, gradually destroying a person's ability to remember, learn, and ultimately carry out activities of daily living (Rubio-Perez & Morillas-Ruiz, 2012). Information regarding the dependent or outcome variable, AD, which is dichotomous, is found within the following Medicare claims files with ICD-9 code 331.0: MEDPAR, NCH, Outpatient, DME, and HHA

Covariates. Multiple covariates were included to limit confounding and bias. These variables included the following

Age. This is one of the main risk factors for developing AD. Several studies have suggested that androgen loss as a result of aging may promote cognitive decline in older men and increase risk of AD due to low levels of circulating testosterone (Ciocca et al., 2016; Martins & Gandy, 2016; Nead et al., 2016; Vest & Pike, 2013). This continuous variable is obtained from the PEDSF file.