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Serum Iron Concentration and Prostate Cancer in the United States

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2016

Abstract

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by

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M.B.A., American Intercontinental University, 2007

B.A., University of North Carolina at Chapel Hill, 2003

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Abstract

Over 2 million adult men in the United States have been diagnosed with prostate cancer, with nearly 200,000 new diagnoses each year. This type of cancer is the leading cause of mortality in U.S. men. One possible risk factor for prostate cancer is a high level of iron in the body, but the association has yet to be confirmed. This study was an investigation of the relationship between serum iron concentration and prostate cancer using data obtained from the 2009-2012 National Health and Nutrition Examination Surveys. This quantitative study involved 1,850 men in the U.S. aged 51 to 70 years. The framework for this research was based on the exposure-disease model. Participants' data were analyzed using chi-squared independence tests and hierarchical logistic regression, while controlling for demographic variables (body mass index, age, ethnicity, poverty-to-income ratio, educational attainment, and hours worked in the last week) to account for potential confounding effects. Serum iron concentration was not found to be significantly associated with prostate cancer diagnosis in this sample. Additional results indicated a significant association between age and prostate cancer, and between ethnicity and prostate cancer, confirming previous research findings. This study contributes to positive social change by confirming the importance of screening for prostate cancer among high-risk populations and by suggesting that it is premature to use serum iron concentration as a screening tool to detect prostate cancer.

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Dedication

I dedicate this research to my friends and family who supported me throughout this milestone.

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Table of Contents

List of Tables v

Chapter 1: Introduction to the Study 1

Background of the Study 2

Research Gap 3

Problem Statement 4

Purpose of the Study 5

Research Questions 6

Conceptual Framework 7

Nature of the Study 7

Definitions 9

Limitations 10

Assumptions 11

Scope of the Study and Delimitations 12

Significance of the Study 13

Summary and Transition 13

Chapter 2: Literature Review 15

Introduction 15

The Role of Iron in the Human Body 16

Iron Exposure 19

Iron Burden in Humans 20

Iron and Cancer Development 22

Oxidative Stress 25

Iron and Oxidative Stress 28
Oxidative Stress and Carcinogenesis 30
Prostate Cancer 32
Mechanisms of Prostate Cancer 33
Prostate Cancer and Oxidative Stress 34
The Role of Iron in Prostate Cancer 36
Age and Prostate Cancer 38
Ethnicity and Prostate Cancer 41
Body Mass Index and Prostate Cancer 42
Socioeconomic Status and Prostate Cancer 46
Employment Status and Prostate Cancer 47
The National Health and Nutrition Examination Survey and Iron 48
NHANES, Iron, and Cancer 49
NHANES and Prostate Cancer 51
Theoretical Framework 52
Summary 54
Chapter 3: Research Method 56
Introduction 56
Research Questions and Hypotheses 57
Research Design and Methodology 58
Population 59
Sample and Sampling Procedures 60
Variables 63

Data Collection 65
Statistical Analysis 66
Threats to Validity 68
Protection of Human Participants 69
Dissemination of Findings 69
Summary 70
Chapter 4: Results 71
Introduction 71
Data Collection and Screening 72
Descriptive Statistics 74
Sample Demographics 74
Total 76
Variable Descriptive Statistics 78
Hypothesis Testing 79
Research Question 1 80
Research Question 2 81
Research Question 3 81
Research Question 4 82
Research Question 5 83
Summary 84
Chapter 5: Discussion, Conclusions, and Recommendations 87
Interpretation of Findings 87
Serum Iron and Prostate Cancer 88

Prostate Cancer, Age, and Ethnicity 91
Recommendations for Future Research 93
Implications for Practice and Social Change 94
Limitations 95
Summary and Conclusion 96
References 98

List of Tables

Table 1. Distribution of Socio-Demographic Characteristics by Prostate Cancer Diagnosis 76

Table 2. Descriptive Statistics for Continuous Independent Variables by Prostrate Diagnosis, total n = 1,850 77

Table 3. Descriptive Statistics for Categorical Independent Variables by Prostate Diagnosis..... 79

Table 4. Logistic Regression Analysis for Prostate Cancer Diagnosis Regressed on Serum Iron, Age, and Ethnicity..... 80

Table 5. Logistic Regression Analysis for Serum Iron Predicting Prostrate Diagnosis* . 82

Table 6. Logistic Regression Analysis for Serum Iron Concentration Predicting Prostrate Diagnosis*..... 83

Table 7. Logistic Regression Analysis for Serum Iron Concentration Predicting Prostrate Diagnosis*..... 84

Chapter 1: Introduction to the Study

According to the American Cancer Society (2014), there are over 2 million adult males (1 in 6) in the United States diagnosed with prostate cancer, with a 1 in 35 mortality rate (American Cancer Society, 2014). This makes prostate cancer one of the main sources of mortality in adult males in the United States (Kuvibidila, Gauthier, & Rayford, 2004). Although there is a hereditary component to the diagnosis of prostate cancer (Choi et al., 2008; Helfland & Catalona, 2014), the disease has also been linked to a number of environmental and dietary factors, suggesting that the rate could be reduced through a clear comprehension of the practices that could increase the probability in developing prostate cancer.

Among these risk factors is a high level of iron in the body, which researchers have begun to link to prostate cancer and other cancers (Discacciati & Wolk, 2014; Divisi et al., 2006; Donaldson, 2004; Fernandez, Gallus, and La Vecchia, 2006; Grant, 2008; Gonzalez & Riboli, 2006; Kapiszewska, 2006). If an association between prostate cancer and excess iron in the body can be more securely established, it may become possible to target causes of excess iron, thereby reducing the danger of prostate cancer, diminishing the death rate, and improving male well-being. Therefore, this study was designed to determine, using broad epidemiological data from the United States, whether there is an association between the serum iron concentration and prostate cancer.

This chapter covers the background of the study, the problem statement, purpose of the study, and presents the research questions. Additionally, the conceptual framework is introduced; key terms are defined; delimitations, limitations, and assumptions are

discussed; and the significance of the study is described. A summary and transition section concludes the chapter.

Background of the Study

There is a high occurrence of prostate cancer among males between 51 and 70 years of age in the United States, approximately 8% of this population (National Cancer Institute, 2014). The consequences can be devastating as prostate cancer is the second major cause of cancer-related mortalities among American adult males (National Cancer Institute, 2014). Approximately 3% of adult males in the United States will die of prostate cancer (American Cancer Society, 2014). In the United States, the estimated annual cost of prostate cancer care was $9.86 billion in 2006, with a mean annual cost per patient of $10,612. The per-patient cost in the last year of life is, on average, $33,691 (Roehrborn & Black, 2011). As such, it is important to investigate potential risk factors related to prostate cancer development.

Serum iron is a measure of the amount of body iron bound to the protein transferrin. Serum iron concentration has been linked to forms of cancer such as colorectal, liver, and breast cancers (Huang, 2003; Liehr & Jones, 2001). Huang (2003) and Liehr and Jones (2001) concluded that serum iron concentration aggravates cancer occurrence and that the iron source is a main contribution to the occurrences. For example, Donaldson (2004), Gonzalez and Riboli (2006), Discacciati and Wolk (2014), and Tavani et al. (2000) concluded that diets high in iron-rich foods can increase the risk of cancer.

Researchers have focused on dietary levels of iron either through food items or cooking preparations and potential associations to cancer. Aune et al. (2009) reported that iron sources and cooking preparation indicate risk levels of cancer occurrence. Divisi et al. (2006), Donaldson (2004), Fernandez et al. (2006), Grant (2008), and Kapiszewska (2006) correlated iron level sources, proportions, and preparation, and prostate cancer cases and found that iron-rich diets with limited vegetable consumption can increase the risk factor of a prostate cancer diagnosis.

Researchers in the past have focused on attempts to identify possible mechanisms through which high serum iron concentration could lead to cancer. Grant (2008) reported on the potential mechanism for interaction between serum iron and cancers; iron can catalyze the production of free radicals, resulting in oxidation stress. Walter et al. (2002) concluded that serum iron concentrations have an optimal range, and with amounts may damage mitochondria and mitochondrial DNA, which can increase cancer risk. Chapter 2 contains a fuller discussion of these mechanisms.

Research Gap

This research contributes to a gap in the knowledge concerning the relationship between serum iron concentration and prostate cancer and the lack of research linking serum iron concentration to prostate cancer diagnoses in large samples. This study is important due to the high incidence and devastating consequences associated with prostate cancer among males between the ages of 51 and 70 in the United States (American Cancer Society, 2014). Likewise, no researchers have investigated the

relationship between serum iron concentration and prostate cancer among males between 51 and 70 years of age using large samples.

Problem Statement

The research problem addressed in this study is the association between serum iron concentration and prostate cancer diagnoses among males between 51 and 70 years of age remains unclear. There are over 2 million adult males in the United States with a prostate cancer diagnosis. One in every 6 men is diagnosed with prostate cancer, with a 1 in 35 mortality rate (American Cancer Society, 2014). Past researchers have indicated that serum iron concentration may be related to the development of cancer (Grant, 2008; Huang, 2003), but this relationship has not been explored in large samples. The high prevalence of prostate cancer diagnoses and mortality in the United States could be reduced with additional insights into the relationship between serum iron concentration and prostate cancer.

Although some researchers have found a relationship between serum iron concentration and cancers such as colorectal cancer and liver cancer, these studies have not focused on prostate cancer (Aune et al., 2009; Discacciati & Wolk, 2014; Donaldson, 2004; Gonzalez & Riboli, 2006; Huang, 2003; Liehr & Jones, 2001; Tavani et al., 2000). This is a critical distinction because risk factors differ between various forms of cancer. Additionally, some researchers have linked dietary iron to prostate cancer (Divisi et al., 2006; Donaldson, 2004; Fernandez et al., 2006; Grant, 2008; Kapiszewska, 2006), but these studies have not been based on an assessment of serum iron concentration. Thus,

the gap in the literature relates to the unknown link between serum iron concentration (rather than dietary iron) and prostate cancer (rather than other types of cancer).

Although there are some indications that serum iron concentration may be associated to cancer development (Grant, 2008; Huang, 2003), large samples have not been examined to date. In this study, the National Health and Nutrition Examination Survey (NHANES) data were analyzed to fill this disparity in the literature and determine whether serum iron concentration is correlated with prostate cancer. It is essential to study the relationship between serum iron concentration and prostate cancer due to the high rate of prostate cancer, the deaths which occur from prostate cancer, and preliminary indications that serum iron concentration may be related to cancer development.

Purpose of the Study

The purpose of this quantitative study was to determine whether there is an association between serum iron concentration and prostate cancer among a large sample of men aged 51 to 70 in the United States. An additional aim of the study was to determine whether such an association, if it exists, holds when controlling for age, ethnicity, body mass index (BMI), poverty-to-income ratio, educational attainment, and hours worked in the last week. The dependent variables were serum iron concentration, BMI, age, ethnicity, poverty-to-income ratio, educational attainment, and hours worked in the last week, and the independent variable was serum iron concentration (defined as µg of iron per dL of blood). To achieve these goals, analysis was conducted using secondary data gathered between 2009 and 2012 a component of the NHANES.

Research Questions

RQ1: Is there an association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer?

$H_0$1: There is no association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer.

H_a1: There is an association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer.

RQ2: Is there an association between age and prostate cancer in males?

$H_0$2: There is no association between age and prostate cancer.

H_a2: There is an association between age and prostate cancer.

RQ3: Is there an association between ethnicity and prostate cancer?

$H_0$3: There is no association between ethnicity and prostate cancer.

H_a3: There is an association between ethnicity and prostate cancer.

RQ4: Is there an association between serum iron concentration and prostate cancer when controlling for age and ethnicity?

$H_0$4: There is no association between serum iron concentration and prostate cancer when controlling for age and ethnicity.

H_a4: There is an association between serum iron concentration and prostate cancer when controlling for age and ethnicity.

RQ5: Is there an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week?

$H_0$5: There is no association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week.

H_a5: There is an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week.

Conceptual Framework

The conceptual framework for this study was the exposure-disease model (Sexton & Linder, 2011). In the exposure-disease model, exposure to risk factors in the environment increases the likelihood of disease development (Sexton & Linder, 2011). This model has been used in prior studies that have addressed exposure and prostate cancer risk (Nik-Zainal et al., 2012). For example, Huang (2003) and Liehr and Jones (2001) linked serum iron concentration to various forms of cancer. In addition, Donaldson (2004), Gonzalez and Riboli (2006), Discacciati and Wolk, (2014), and Tavani et al. (2000) concluded that diets high in iron-rich foods like red meat can escalate the risk of cancer. Aune et al. (2009) reported that iron sources and cooking preparation indicate risk levels of cancer occurrence. Each of these studies supports the exposure-disease model by linking environmental and dietary iron exposure to prostate and other cancers. More detailed analysis of the conceptual framework can be found in Chapter 2.

Nature of the Study

This study was undertaken using a quantitative method with an archival, associational design. Quantitative research is appropriate when the variables examined

are clearly defined and can be quantified or quantitatively coded according to clear criteria. This research method requires quantitative data related to the variables of interest because quantitative data can be analyzed to test research questions related to relationships between and among variables (Penelope & Pattison, 2012). By contrast, qualitative research is appropriate for open-ended exploration and description of phenomena, which may be more or less well defined (Stake, 2010).

This study was conducted using secondary data from the NHANES gathered from 2009 to 2012. The NHANES data are gathered using a multistage probability sampling design to obtain a sample representative of the entire noninstitutionalized U.S. population. For most variables studied by the NHANES, data are collected from one-third of the full sample.

Data from 2009 to 2012 were examined because these years represented the most current years available in the NHANES database that included all variables to be tested. The primary independent variable was serum iron concentration, defined as μg of iron per dL of blood and captured by the NHANES variable LBXIRN (this, like all NHANES codes introduced in this paragraph, is a variable code, not an abbreviation). This variable was dichotomized according to the 75th percentile. The dependent variable was prostate cancer diagnosis, which was coded as 0 or 1 depending on whether or not an individual has been diagnosed with prostate cancer. The corresponding NHANES variables were MCQ230a, MCQ230b, MCQ230c, and MCQ230d. Other independent variables were age (51-70), ethnicity (NHANES variable RIDRETH3), BMI (NHANES variable BMXBMI), poverty-to-income ratio (NHANES variable INDFMPIR), educational

attainment (NHANES variable DMDEDUC2), and hours worked in the last week (NHANES variable OCQ180).

Data analysis consisted of descriptive and inferential statistical analyses performed using SPSS software (Version 22.0). Initial data screening was performed to ensure that all values for all variables are within the allowable limits and valid. Chi-squared independence tests were used to test Hypotheses 1 to 3; hierarchical regression analysis was used to test Hypotheses 4 and 5.

Definitions

Blood serum: The component of blood that does not contain blood cells or clotting factors. It is also called plasma (Wang, Knovich, Coffman, Torti, & Torti, 2010).

Dietary iron: Intake of iron as a nutrient through consumption of iron-rich foods (including meat, vegetables like lentils and spinach, and enriched cereals) or through dietary supplementation (Domellöf, Thorsdottir, & Thorstenen, 2013).

Iron chelator: Any of a number of compounds that can bind to ferrous and ferric iron, preventing the iron molecules from engaging in potentially harmful reactions with reactive oxygen species (ROS; Valko, Morris, & Cronin, 2005).

Oxidative stress: A process of damage to cellular DNA caused by ROS (Bhagat et al., 2013).

Prostate-specific antigen: An enzyme produced in the prostate. Measuring prostate-specific antigen levels are the essential routine practice of diagnostic screening for prostate cancer (Hong et al., 2013).

Reactive oxygen species: A byproduct of ordinary aerobic energy metabolism in all aerobic organisms and play an important role in immune function and cell signaling (Smith, Latta, Denver, & Estes, 2014). Also known popularly as free radicals.

Serum iron concentration: The accumulation of body iron bound to transferrin in the blood serum (Huang et al., 2014).

Limitations

There were four primary limitations to this study. The first limitation related to this study being a cross-sectional study. This means that causal inferences could not be deduced regarding the relationship between the independent and dependent variables (Black, 1999). Causal inferences are only justified in true experimental studies, and a true experimental research design was not feasible for this study because the independent variables (serum iron concentration, BMI, age, ethnicity, poverty-to-income ratio, educational attainment, and hours worked in the last week) could not be experimentally manipulated (Black, 1999). This study established an association between serum iron concentration and prostate cancer diagnoses, a causal link was not able to be made.

In cross-sectional studies, confounding variables can adversely affect the validity of the conclusions (Vogt, 2006). For example, if it had been shown in this study that there was a relationship between serum iron concentration and prostate cancer diagnoses, it could be the case that higher serum iron concentration caused prostate cancer or that some other (confounding) variable caused both high serum iron concentration and prostate cancer. In this study, two potentially confounding variables were included (age and race) because it was possible that these variables could affect the relationship

between serum iron concentration and prostate cancer, but other confounding variables could also have affected the results of this study.

A third limitation was there may have been errors in the NHANES database that affect the results from this study. Although this is a widely-used and tested database, it is nevertheless possible that errors in data collection or laboratory analysis could have existed that could have impacted the results of this study. However, this database has been used in a wide variety of research studies, and no reports of inaccurate or misleading data could be located. It was also assumed that the doctors who diagnosed the participants with prostate cancer (or not) accurately diagnosed the disease.

A fourth limitation was that the sample used may not have been a random sample from the population of males between the ages of 51 and 70 in the United States. Although the NHANES data collection procedures were carefully designed to create samples that were representative of the population (including the assessment of individuals from all 50 states, stratified in terms of gender, age, ethnicity, income, and other variables), perfect representativeness cannot be assumed. Sampling weights are available but are specific to each survey year, making it difficult to ensure generalizability when studying data from multiple survey years. Therefore, the outcome of the current study is not generalizable to the entire population and limited only to this sample.

Assumptions

The first assumption in this study was that the data used were accurate. Existing information from the NHANES surveys (2009-2012) was used in this study. This

database has been used in a wide variety of research studies, and no reports of inaccurate or misleading data could be located. However, it was assumed that the NHANES data were accurate and that the NHANES sample was illustrative of the population of the United States. It was also assumed that the doctors who diagnosed the participants with prostate cancer (or not) accurately diagnosed the disease and that the participants accurately reported whether or not they had been diagnosed with prostate cancer. Finally, it was assumed that the surveys were appropriately used, lab data were analyzed correctly and prostate cancer status was diagnosed accurately. An additional assumption was that serum iron concentration was appropriate for testing association with prostate cancer versus related variables. These assumptions were necessary to access and analyze the data collected as part of the NHANES.

Scope of the Study and Delimitations

The scope of this study was to examine the association between serum iron concentration and prostate cancer, while additionally researching the role of age and ethnicity with prostate cancer status and controlling for BMI, poverty-to-income ratio, educational attainment, and hours worked in the last week. The sample for this study was delimited to males between 51 and 70 years of age. Males younger than 51 or older than 70 were outside the scope of this study. The age group was selected for this study because it includes ages when the majority of prostate cancer diagnoses are made. This study did not include individuals with a prostate cancer diagnosis outside of this age range. This study also did not measure oxidative stress markers in order to determine if this is the pathway from iron to prostate cancer. Dose-response relationships were not studied. The

results of the current study are not generalizable to the entire population as no weights were used for the analysis.

Significance of the Study

This study was significant due to the high incidence of prostate cancer in the United States (American Cancer Society, 2014). Conducting a study that examines the relationship between serum iron concentration and prostate cancer among adult males in the United States advances knowledge in this realm of research. This study allowed an important step forward in understanding the as-yet-unclear relationship between iron and prostate cancer, raising crucial questions for future research that will contribute to the understanding of and ability to prevent one of the most deadly cancers in men. This study contributes to positive social change by confirming the importance of screening for prostate cancer among high risk populations and by suggesting that it is premature to use serum iron concentration as a screening tool to detect prostate cancer.

Summary and Transition

One in 6 adult males in the United States will be diagnosed with prostate cancer, which has with a 1 in 35 mortality rate (American Cancer Society, 2014). This makes prostate cancer a primary cause of mortality in adult males in the United States (Kuvibidila et al., 2004). Among the risk factors for prostate and other cancers is a high level of iron in the body (Discacciati & Wolk, 2014; Divisi et al., 2006; Donaldson, 2004; Fernandez et al., 2006; Grant, 2008; Gonzalez & Riboli, 2006; Kapiszewska, 2006). Iron can catalyze the production of free radicals, which can lead to oxidative stress and DNA damage, potentially causing cancer (Grant, 2008; Walter et al., 2002). However, there is a

gap in literature related to the link between serum iron concentration and prostate cancer. Therefore, the purpose of this quantitative study was to determine whether there is an association between serum iron concentration and prostate cancer among a large sample of men aged 51 to 70 in the United States. In Chapter 2, a literature review is presented that introduces the role of iron in the human body, prostate cancer, the relationship of ethnicity and age with prostate cancer, oxidative stress, and the NHANES. In Chapter 3, the research questions are presented as well as the research methodology.

Chapter 2: Literature Review

Introduction

Prostate cancer is the most diagnosed cancer among adult males in the United States and is one of the major causes of death (Kuvibidila et al., 2004). The sources of prostate cancer are complex and may include a hereditary component, but researchers have also begun to establish a link between dietary iron and prostate cancer (Divisi et al., 2006; Donaldson, 2004; Fernandez et al., 2006; Grant, 2008; Kapiszewska, 2006). Additionally, associations between serum iron concentration and various forms of cancer have been made, but studies in this area have typically not focused on prostate cancer (Aune et al., 2009; Discacciati & Wolk, 2014; Donaldson, 2004; Gonzalez & Riboli, 2006; Huang, 2003; Liehr & Jones, 2001; Tavani et al., 2000). Theoretically, serum iron concentration could assume a critical role in prostate cancer via raising levels of ROS in the human body. If an association is established between serum iron concentration and prostate cancer, it could be possible to advance serum iron concentration testing as an early screening tool to aid in the timely diagnosis of prostate cancer. Furthermore, iron may contribute to oxidative stress as an instrument to promote the development and progression of prostate cancer. Active monitoring of serum iron concentration in men could also facilitate both prevention and management of prostate cancer.

I researched the literature using the following search terms: *age*, *cancer*, *cancer development*, *carcinogenesis*, *ethnicity*, *exposure-disease model*, *iron*, *iron concentration*, *National Health and Nutrition Examination Survey*, *NHANES*, *oxidative stress*, *prostate cancer*, *reactive oxygen species*, and *serum iron*. Articles were selected based on

relevancy to the research hypotheses from databases including Academic Search Premiere, EBSCOHost, Google Scholar, Medline, ProQuest, and PubMed, as well as directly from research journal websites. Only articles in English were considered. Searches were limited to research published between 2009 and 2015, except in the case of seminal articles. Articles in peer-reviewed journals and government publications were considered for inclusion. Chapter 2 concluded with a summary that recaps the information and introduce Chapter 3.

The Role of Iron in the Human Body

Iron is a nonorganic substance that is instrumental in the upkeep of living cells. In humans, iron is present in its ionic forms, ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron, as distinguished from nonionic, metallic iron (Fe). Throughout the literature, it is conventional to refer to iron in the body generally as *iron* unless referring to a specific ionic form. I use this convention, unless otherwise noted.

The conversion of ferrous to ferric iron is an important part of the iron regulation systems, particularly those involving ferritin, an iron storage protein (Winter, Bazydlo, & Harris, 2014). Each ferritin molecule can contain approximately 4,500 ferric ions, and around 25% of all iron in the human body is stored as ferric iron in ferritin or ferritin-containing compounds (Winter et al., 2014). Transferrin is another important iron-binding protein and is important in the measurement of iron status (Winter et al., 2014). Although a very small proportion of total body iron is bound to transferrin, the protein is important because it is responsible for delivering iron to tissues throughout the body.

The majority (approximately 67%) of iron is complexed within hemoglobin, which is important for oxygen transport (Winter et al., 2014). Other functions of iron in the body include short-term oxygen storage (as myoglobin) and energy production (as cytochromes), and as a component of several important enzymes (Winter et al., 2014). Iron is unique among nutrients in that the human body cannot excrete iron excesses (Domellöf et al., 2013). Thus, the concentration of iron in the human body is dependent on, and related to, iron intake and absorption (Winter et al., 2014). Iron deficiency and excess iron can both lead to adverse consequences. In the case of iron deficiency, anemia and learning disorders can result. Excess iron in the body has a toxic effect on the heart, liver, skin, bones, and more (Winter et al., 2014). The role of iron in cancer development is discussed in detail later in this section.

The amount of iron in the bodies of healthy adults usually ranges from 3.5 to 5.0 grams (Winter et al., 2014). Ferritin, a protein that stores and releases iron, occurs throughout the body, including in the blood serum. Blood serum, or plasma, is the component of blood that does not contain blood cells or clotting factors. Because a small amount of ferritin is secreted into blood serum, the level of ferritin in the serum is a widely used proxy measure for the total level of iron in the body (Wang et al., 2010). However, multiple researchers (Ferraro, Mozzi, & Panteghini, 2012; Puliyel et al., 2011; Yin, Wuhan, Kulhalli, & Walker, 2014) have found that changes in serum ferritin levels do not satisfactorily anticipate changes in total body iron content. This finding calls into question the usage of serum ferritin as a mean of iron burden. Serum iron, which is used in this study, may be a more appropriate choice.

Serum iron is a measure of the amount of body iron bound to transferrin. It is measured by releasing iron from transferrin using acetic acid, then conforming all released iron to the ferrous state using hydroxylamine and thioglycolate (Centers for Disease Control [CDC] and Prevention, 2007). The ferrous iron is mixed with an iron reagent, and the change in absorbance is measured. From the change in absorbance, one can measure the total amount of iron in the original serum sample (CDC and Prevention, 2007). Huang et al. (2014) recently confirmed the use of serum iron as a proxy variable for total body iron in a study related to acute coronary syndrome. They sought a measure of iron deficiency and found that low serum iron levels predicted an increased risk of adverse coronary outcomes. This suggests that serum iron is a valid variable for the study of total iron level and its associations.

Serum iron is also an important variable for this study because it has been shown to have an association to increased oxidative related stress (Zhao et al., 2014). Serum iron concentration in this study is operationally defined as μg of iron per dL of blood. Researchers studying the connection between serum iron and prostate cancer have defined the normal range of iron in the serum as between 12 and 300 μg/L, equivalent to 1.2 to 30 μg/dL (Kuvibidila et al., 2004). These studies establish serum iron as a valid variable to study the association among iron and cancer. In this study, I examined if there was an association among serum iron concentration and prostate cancer. In addition, I explored the role of age and ethnicity with prostate cancer status while taking account for BMI, economic status, and occupational status. The following subsections address iron

exposure, iron burden in humans, and iron and cancer development in humans. Where possible, the specific iron-related variable under discussion is indicated.

Iron Exposure

The human body derives all of its iron from external sources, with diet as the primary source. In the United States, the Food and Drug Administration recommends healthy adults should consume an estimated amount between 8 mg and 18 mg of iron daily in order to meet basic health requirements (Institute of Medicine [IOM], 2010). Adult women require significantly more iron than men ([IOM, 2010), primarily owing to increased iron loss due to menstruation (Domellöf et al., 2013). Red meat is an excellent source of iron in the United States, as are breakfast cereals fortified with iron (National Institutes of Health [NIH], 2014). Several plant-based foods considered good sources of iron include white beans, dark chocolate, lentils, spinach, tofu, kidney beans, chickpeas, tomatoes, and potatoes (NIH, 2014). Plant-derived, nonheme iron has lower bioavailability than animal-based, heme iron sources (Ruxton, Derbyshire, & Pickard, 2012). There are two independent mechanisms for transporting heme and nonheme iron to the intestinal mucosal cells, and research has indicated that the heme-transporting mechanism is more efficient than the nonheme-transporting mechanism (Ruxton et al., 2012). In cases of iron deficiency, dietary iron supplementation is often considered (Bokhari, Derbyshire, Li, Brennan, & Stojceska, 2011).

Iron overload from dietary intake is uncommon. Instead, iron overload is often secondary to another condition, such as transplantation (Chong et al., 2014) or from inhalation (Nicolson, Doherty, Cooper, & Neilson, 2013). Genetic conditions such as

hereditary hemochromatosis may also cause overload. Hemochromatosis predisposes individuals to absorb excess iron from dietary sources, and such hereditary conditions have been strongly linked to certain cancers (Kew, 2014). This is significant to this study because the connection between genetic iron overload and cancer strengthens the rationale for examining a potential association between serum iron levels (whether due to genetic conditions or not) and prostate cancer.

Iron Burden in Humans

Iron burden has been associated with several disease conditions in humans. In general, iron burden may perform as a stimulant for the introduction of oxygen that damages cells (cytotoxic oxygen; Bartfay & Bartfay, 2014). High levels of oxidative stress have been associated to neurodegenerative disorders, type 2 diabetes, heart disease, and cancer development (Bartfay & Bartfay, 2014; Domellöf et al., 2013; Pelizzoni, Zacchetti, Campanella, Grohovaz, & Codazzi, 2013). Regular aerobic exercise can lower levels of iron burden as measured by serum iron (Bartfay & Bartfay, 2014). This suggests that iron burden could present a serious health risk and is therefore worthy of further study.

The prevalence of high iron burden in humans is difficult to estimate, particularly since the connection between serum ferritin, the most commonly measured variable, and total body iron is still controversial (Kolnagou et al., 2013). However, at least one major study attempted to address the existence of iron overload in diverse populations. Gordeuk et al. (2008) screened 101,168 primary care patients with and without hemochromatosis for elevated iron stores. Although iron overload is most commonly associated with

genetic disorders like hemochromatosis, Gordeuk et al. (2008) found that it can also exist in patients without these disorders and that it varies significantly with ethnicity. Based on their screening, the researchers estimated that the existence of higher levels of serum ferritin per 10,000 healthy people was 20 for African Americans, 13 for Hispanics, 38 for Asians and Pacific Islanders, and 7 for Caucasians (Gordeuk et al., 2008). They also found that females were significantly less likely than males to have elevated serum ferritin levels. Because men require less iron than women (IOM, 2010), men tend to have higher levels of iron stored in their bodies (Gordeuk et al., 2008; Winter et al., 2014), indicating that they may be at a higher risk for excess iron burden. Still, iron burden and male-only cancers such as prostate cancer rarely have been studied together.

The connection between high iron burden and decreased antioxidant defense capacity is an area of current research. Recent evidence points to an association. For example, Bhagat et al. (2013) studied patients with β thalassemia major, a genetic blood disorder that results in severe iron deficiency. Patients with this disorder receive regular blood transfusions, which puts them at risk for increased iron burden and associated oxidative stress (Bhagat et al., 2013). In the study, 140 patients received supplementary antioxidants to counteract the oxidation effects of iron burden. The results indicated that antioxidant supplementation was linked to an increase in the enzyme catalase, which protects cells from oxidative damage, as well as a decrease in serum ferritin (Bhagat et al., 2013). This finding suggests that potentially damaging oxidative stress may occur in patients with increased iron burden.

Iron and Cancer Development

Because excess iron may contribute to an increased ROS level, which associates to oxidative related stress and DNA damage (Bhagat et al., 2013), iron overload has been implicated in some cancers. Additionally, iron has a major part in cell proliferation, so it contributes to the growth of cancerous tumors (Pusatcioglu et al., 2014).

In 1988, Stevens, Jones, Micozzi, and Taylor published a study linking total body iron levels to colorectal cancer risk. This longitudinal study followed 14,000 adults from 1971 to 1984. As a measure of the total amount of iron in the body, the researchers used transferrin saturation (TSAT) level, another commonly used variable closely related to serum iron. TSAT is defined as the ratio between total iron-binding capacity and serum iron (i.e., amount of available transferrin), expressed as a percentage. Results indicated that among men who developed cancer, their TSAT level was higher compared with men who did not develop cancer (33.1% vs. 30.7%, respectively; $p = 0.002$). The relative risk of colorectal cancer for each TSAT-level quartile, relative to the bottom quartile, was 1.00, 1.01, 1.10, and 1.37 (Stevens et al., 1988). The link was not clear among women.

Since the Stevens et al. (1988) study, most of research has focused on linking iron levels to individual cancers. The best study of these has been liver cancer, where a link between iron overload and cancer development has been established (Fonseca-Nunes, Jakszyn, & Agudo, 2014). In a meta-analysis and methodical review of 59 epidemiologic studies, Fonseca-Nunes et al. (2014) determined that increased consumption of iron was positively associative with cancer risk. The researchers specifically analyzed the impact of an added 1 mg/day of heme iron on risk of colorectal, breast, lung, liver, and colon

cancers. They concluded that increased iron status resulting from iron consumption could be correlated with higher cancer risk. Interestingly, the researchers emphasized the potential unsuitability of serum ferritin as a biomarker for iron status and recommended further research using alternative biomarkers such as serum iron (Fonseca-Nunes et al., 2014).

Among men in particular, increased iron burden has also been related to risk of colorectal cancer. Pusatcioglu et al. (2014) compared systemic and tumor-specific iron levels in 20 adult males with colorectal cancer to 20 healthy control subjects. The median age for the cancer patients was 61.0, and the median age for the controls was 57.5. This age range was in conformity with the typical age at diagnosis of colorectal cancer. Participants' ethnicities were as follows: for cancer patients, 50% African American, 30% Caucasian, 5% Hispanic, and 15% Asian; and for controls, 75% African American, 5% Caucasian, 10% Hispanic, and 10% Asian (Pusatcioglu et al., 2014). Results of the study strongly indicated that cancer patients had lower iron status than controls, as measured by levels of serum transferrin receptor, a carrier protein for transferrin. Among cancer patients, 30% had accumulated iron in the colon, compared to only 5% of controls (Pusatcioglu et al., 2014). Because it focused on demographically diverse men, and because the population was largely over age 50, this study provides important support for the rationale of this study. If a similar link can be established between serum iron and prostate cancer, serum iron levels could be used as a particularly important early cancer screening tool for the demographic group in question.

Another review examining the relationship between iron and carcinogenesis included clinical data, epidemiological data, and animal models (Beguin, Aapro, Ludwig, Mizzen, & Österborg, 2014). Of the 19 epidemiological studies they reviewed, five used NHANES data, of which two used serum iron concentration for iron status measurement. In addition, one further study used serum iron concentration data from a 14-year longitudinal study. All of these studies yielded associations between elevated iron levels and cancer development or death. The study by Stevens et al. (1988) reviewed in detail above was one of the studies included. Beguin et al. (2014) also included studies by Wells, Mainous, Everett, and Gill (2005) and by Wu, Sempos, Freudenheim, Muti, and Smit (2004), both of which are reviewed in detail below in the section on NHANES, iron, and cancer.

In contrast to findings from the Fonseca-Nunes et al. (2014) review, Beguin et al. (2014) did not find any indication for a relationship between cancer risk and dietary iron, but they did find evidence of a link between cancer risk and iron biomarkers. According to the results, epidemiological evidence and some clinical evidence in humans suggests a link between elevated iron levels, whether through iron biomarkers or measured as dietary iron, and the risk of developing cancer. Supporting the Pusatcioglu et al. (2014) study, Beguin et al. found a particularly strong link for colorectal cancer. The authors emphasized the probability that iron overload can promote tumor growth, so in tumor-based cancers like prostate cancer, further investigation is especially warranted.

The studies and reviews discussed in this section support a potential link between iron overload and cancer development and underscore the need for further research in this

area. Iron's role in prostate cancer remains largely unknown. Increased iron could promote the growth of existing prostate tumors via oxidative stress, as Beguin et al. (2014) found that iron supplementation is linked to tumor growth. However, this contradicts one set of findings that decreased iron, particularly as measured by serum ferritin, is associated with tumor growth (Kuvibidila et al., 2004). Thus, the role of iron in tumor growth and tumor formation is not well understood, and further research is needed.

Oxidative Stress

Oxidative stress is a process of damage to cellular DNA caused by ROS, a term that covers several types of free radicals in the body (Bhagat et al., 2013). ROS are a byproduct of normal aerobic energy metabolism in all aerobic organisms and play an important role in immune function and cell signaling (Smith et al., 2014). Between 1% and 5% of all oxygen consumed in aerobic metabolism produces anionic superoxide (O^-_2) through a cellular process known as oxidative phosphorylation, which occurs at mitochondrial electron transport chains and produces ROS (Karihtala & Soini, 2007; Smith et al., 2014). In addition, ROS are produced at lower levels in a few other physical processes, most notably in inflammatory cells such as neutrophils and macrophages (Karihtala & Soini, 2007).

The superoxide anion is a relatively unreactive example of ROS, but it leads to the production of hydrogen peroxide (H_2O_2), which is an important precursor to more injurious types of ROS. Most relevantly in the context of iron in humans, the hydroxyl radical (•HO) is an unstable molecule that reacts quickly and can cause significant cellular damage (Karihtala & Soini, 2007). It is produced by a process called the Fenton

reaction, which is catalyzed by very small amounts of ferrous iron (see Equation 1below).

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot HO + OH^- \quad (1)$$

Thus, when the hydroxyl radical is developed via the Fenton reaction in the immediate vicinity of DNA, the hydroxyl radical reacts quickly, potentially damaging the deoxyribose structure of DNA, breaking DNA strands, modifying DNA bases, and, potentially damaging genes that suppress the growth of tumors (Karihtala & Soini, 2007). In addition to the hydroxyl radical, the Fenton reaction generates oxidized metal ions, which further react with the superoxide anion, to a potentially damaging effect (Karihtala & Soini, 2007).

The presence of ROS does not always result in lasting cell damage because a number of mechanisms have evolved to eliminate ROS and repair transient cell damage. Karihtala and Soini (2007) authored a comprehensive review summarizing these mechanisms. The most critical of these are antioxidant enzymes that include glutathione peroxidases, superoxide dismutases and catalases. Superoxide dismutases are present in cytoplasm, mitochondria, and outside of cells; their only known activity is converting oxygen anions into H_2O_2 and molecular oxygen (see Equation 2 below).

$$2O_2^{\cdot -} + 2H^+ \rightarrow H_2O_2 + O_2 \quad (2)$$

Catalase reduces H_2O_2 to water (H_2O) and oxygen, thus detoxifying it. The enzyme also detoxifies other various phenols and alcohols. Decreased catalase activity has been associated with breast, oral, and pancreatic cancers (Khiratili & Soini, 2007), but its production is not known to be induced by oxidative stress levels. Glutathione

peroxidases reduce the toxicity of hydroperoxides using glutathione (GSH) and results in glutathione disulfide (GSSG). (see Equation 3 below).

$$2H_2O_2 + 2GSH \rightarrow GSSG + 2H_2O \quad (3)$$

This is not an exhaustive list of antioxidant enzymes that detoxify ROS, but these are among the most important and well-studied. The exact processes by which these enzymes mediate oxidative stress are still largely undescribed (Karihtala & Soini, 2007). In addition to antioxidant enzymes, more generalized DNA repair enzymes can reduce the long-term burden of ROS-induced damage (Karihtala & Soini, 2007). There has also been recent attention to the antioxidative effects of certain nutritional compounds, especially fruit. Although a link has been demonstrated epidemiologically between fruit intake and cancer prevention, there is not much documentation to support that antioxidants are responsible for the effect, and some studies have reported that so-called dietary antioxidants may have a pro-oxidant effect (Karihtali & Soini, 2007).

Despite the natural protective mechanisms against oxidative damage caused by ROS, a number of factors can lead to an imbalance between ROS and the natural detoxification processes that may lead to oxidative damage (Smith et al., 2014). The accumulation of oxidative damage owing to ROS imbalance defines oxidative stress. Factors that lead to oxidative stress are numerous and can include elevated cortisol levels, often resulting from psychological stress (Aschbacher, O'Donovan, Wolkowitz, Dhabhar, Su, & Epel, 2013; Paschos, Pandya, Duivenvoorden, & Pinthus, 2013; Wolkowitz, Epel, Reus, & Mellon, 2010); environmental stressors, including exposure to harmful pollutants, excess heat, or ultraviolet light (Al-Gubory, 2014; Bandyopadhyay et al.,

2014; Paschos et al., 2013; Smith et al., 2014); endogenous health factors such as sickle cell disease (Chirico & Pialoux, 2012); and, potentially, elevated iron burden (Beguin et al., 2014; Bystrom, Guzman, & Rivella, 2014; Romeu et al., 2013).

Iron and Oxidative Stress

It has been inferred that iron could play a part in oxidative stress (Bhagat et al., 2013; Bystrom et al., 2014) via a number of different pathways. As described above, ferrous iron in the body plays an essential catalytic part in the Fenton reaction, which can result in cellular and DNA damage by creating highly reactive hydroxyl radicals (Karihtala & Soini, 2007). In addition to the hydroxyl radical, ferric iron is a byproduct of the Fenton reaction and can further react with superoxide anion to form free oxygen, which can catalyze chemical reactions that can alter DNA (Valko et al., 2005). Besides these reactions, researchers have described numerous other iron-related reactions that result in ROS formation both *in vivo* and *in vitro*.

Aerobic organisms have evolved mechanisms to reduce the damaging reactions that produce iron ions. Iron chelators are compounds that can bind to ferrous and ferric iron, preventing the iron molecules from reacting with ROS. There are many iron chelators, including desferrioxamine mesylate and ferrichrome. According to Valko et al. (2005), there is data to infer that, under common situations, these iron chelators reduce oxidative stress associated with body iron. A group of molecules known as siderophores can also shield iron from free-radical-forming reactions (Valko et al., 2005).

Research continues to largely support the conceptual link between iron and oxidative stress. A recent study conducted by Romeu et al. (2013) examined the

relationship between oxidative factors in the diet and biomarkers of lipoprotein oxidation among a randomly selected sample of 815 adults from the Mediterranean region of Europe. After assessing participants' diets over a three-day period, the researchers tested iron biomarkers (including serum iron) and TBARS, which is a measure of lipoprotein oxidation. The results indicated that consumption of heme iron from fish, saturated fatty acids and meat was related to elevated levels of oxidative stress, while consumption of non-heme iron from vegetables and other sources was not. This supports a link between heme iron and oxidative stress (Romeu et al., 2013). In a review, Koskenkorva-Frank, Weiss, Koppenol, and Burckhardt (2013) confirmed that there is empirical support for the role of non-chelated iron to induce cell damage and oxidative stress.

Another recent study supporting the link between iron and oxidative stress was conducted by Fukami, Yamagishi, Iida, Matsuoka, and Okuda (2014). The researchers tested associations between marondialdehyde and serum iron, an indicator of lipid oxidation, among 18 male participants aged 19 to 27. Using the formulation of one-way analysis of variance (ANOVA) and treating both variables as continuous, the researchers discovered a major relationship between marondialdehyde and serum iron. Furthermore, in patients treated with an iron chelator (deferoxamine), the researchers observed a marked decrease in both serum iron and oxidative stress (Fukami et al., 2014). Although no causal links can be drawn from the data, these results suggest that free iron in the body, which has the potential to react to form ROS, contributes to oxidative stress, but, consistent with the conceptual model, chelated (stable) iron does not.

Oxidative Stress and Carcinogenesis

The function of oxidative related stress in carcinogenesis is relatively well established. The hydroxyl radical is considered the most important ROS from the perspective of carcinogenesis because, as mentioned above, it has the potential to damage cellular DNA in a range of ways. Hydroxyl radicals can cause single-point mutations in DNA that activate cancer-causing genes, or they can damage or inactivate genes that normally suppress tumor growth (Karihtala & Soini, 2007). Not all ROS-induced DNA damage is carcinogenic, but high levels of ROS can, over time, contribute to accumulated DNA damage, which promotes tumor growth and metastasis (Karihtali & Soini, 2007). Finally, ROS can contribute to the proliferation of existing cancers by stimulating the production of cancer-promoting compounds. Because inflammation is characteristic of most cancers, increased ROS production is associated with these diseases, as well (Karihtala & Soini, 2007).

Sharma, Shirvastav, and Shirvastav (2014) conducted the most recent review of evidence associated to the function of oxidative related stress in carcinogenesis. Their review of 75 studies detailed the mechanisms by which oxidative stress contributes to carcinogenesis in oral, breast, cervical, lung, ovarian, prostate, gastric, and colon cancers, as well as in leukemia. In prostate cancer, which is of interest to this study, the authors noted that there is a research consensus regarding the imbalance between antioxidants and ROS in human, rat, and *in vitro* studies. The authors also emphasized evidence that genetic mutations leading to increased oxidative stress could be linked to prostate cancer progression and metastasis (Sharma et al., 2014).

In their review, Sharma et al. (2014) described research showing that ROS accumulation in the prostate can contribute to prostate-related issues, which can lead to elevated ROS production, resulting in a feedback loop of increased oxidative stress. Specifically, the antioxidant protein nuclear factor–like 2 (Nrf2) is downregulated in prostate cancer, as are several associated target genes. This status leads to continual increased oxidative stress production owing to decreased antioxidant production, which could result in progression of the cancer to a more advanced metastatic stage (Sharma et al., 2014).

Two studies have yielded evidence of decreased glutathione peroxidase levels in prostate cancer biopsy specimens, further indicating a role for oxidative stress in prostate cancer. Zachara et al. (2005) conducted the earlier of the two studies, measuring glutathione peroxidase levels in the red blood cells, serum, and prostate tissue of 30 healthy subjects, 32 subjects with prostate cancer, and 40 subjects with benign prostate hyperplasia. They found that glutathione peroxidase levels were considerably lower in prostate cancer subjects than in controls in both plasma and prostate tissue. The second of the two studies, conducted by Kotrikadze et al. (2008), yielded similar results. The researchers investigated the levels of glutathione peroxidase, as well as several other antioxidant enzymes (glutathione reductase, tripeptide glutathione, ceruloplasmin, catalase, and superoxide-dismutase) in the blood of 15 subjects with prostate cancer and 15 subjects with benign prostate hyperplasia. Their results indicated that glutathione peroxidase was sharply decreased in cancer patients. Other antioxidants that exhibited decreases in cancer patient included superoxide-dismutase and catalase (Kotrikadze et al.,

2008). This research indicates that damage caused by ROS-derived oxidative stress is an essential element of carcinogenesis and that oxidative stress contributes to many types of cancer, including prostate cancer.

The process of carcinogenesis is complex and involves multiple factors contributing to oxidative stress, as well as multiple effects of ROS themselves. Klaunig, Kamendulis, and Hocevar (2010) described a model in which both endogenous and exogenous factors contribute to ROS oxidative stress. This is mediated by antioxidant enzymes and, potentially, by dietary antioxidant sources. An imbalance in this model or damage to the body's ROS-mediating processes can lead to oxidative damage through three avenues: damage and mutation to DNA and other cell structures; accumulated mutations that lead to chromosomal instability; and altered expression of existing genes. These three effects of oxidative stress can lead to carcinogenesis (Klaunig et al., 2010). As such, researchers are exploring antioxidant therapy as a prevention and treatment for cancer, but this research area is still relatively new. More specific information is needed regarding the sources of oxidative stress, potentially including iron. The function of oxidative related stress in prostate cancer is outlined in detail in the following section on prostate cancer.

Prostate Cancer

Prostate cancer is the most frequently occurring non-skin cancer among American adult males (U.S. Cancer Statistics Working Group, 2013). Although prostate cancer spreads slowly and often does not cause symptoms before men die of other causes, it is nonetheless the second most frequent cause of mortality amongst Hispanic, American

Indian/Alaska Native, African American and Caucasian adult males. In the U.S., the estimated annual cost of prostate cancer care is $9.86 billion in 2006, with a mean annual cost per patient of $10,612. The per-patient cost in the last year of life is, on average, $33,691 (Roehrborn & Black, 2011). Understanding the causes and risk factors for prostate cancer could lead to improved prevention strategies, decreasing the economic and public health burden of this widespread cancer (Stokes, Black, Benedict, Roehrborn, & Albertsen, 2010).

Mechanisms of Prostate Cancer

Like other cancers, prostate cancer is a disease that forms when defective cells develop genetic mutations that lead to the growth of tumors (Choi et al., 2008). The specific genetic mechanisms of prostate cancer are complex, potentially involving many gene mutations and genetic risk factors (Helfland & Catalona, 2014). Prostate cancer can metastasize to other organs in the body. In people among whom prostate cancer is the cause of death, 70% have bone metastasis at autopsy (Josson et al., 2013). Among patients whose prostate cancer has metastasized, the median 5-year survival rate is 31% (Josson et al., 2013).

Several studies have specifically linked prostate cancer to ROS in cells. The presence of ROS causes oxidative stress, which can damage DNA in the prostate (Choi et al., 2008). Because iron overload is a source of oxidative stress (Bhagat et al., 2013), it could play a major factor in prostate cancer advancement. This role is described in detail in the following subsection.

Prostate Cancer and Oxidative Stress

Over the past several years, there has been ample research attention on the relationship between oxidative stress and prostate cancer. A review written by Paschos et al. (2013) summarized the current state of related research. The authors indicated that oxidative stress is one of the key hallmarks of aggressive forms of prostate cancer, suggesting that excess ROS levels play an important role in disease prognosis. In contrast to healthy cells where oxidative stress is prevented or managed by the processes described at the beginning of this section, prostate cancer cells are characterized by innate oxidative stress (Paschos et al., 2013). This oxidative stress is due to several factors including inflammation, damaged DNA, and genetic androgen receptor activation (Schultz et al., 2014). Another recent study conducted by Pande et al. (2013) demonstrated association between oxidative stress, prostate cancer cell proliferation, and clinical stage of prostate cancer. Understanding the function of oxidative related stress in prostate cancer, including its association with iron and other sources, is essential to proper management and potential disease prevention.

An important study uncovered an explicit link between pre-cancer oxidative stress and the development of cancerous tumors in the prostate. Yang et al. (2014) examined a process known as loss of imprinting, whereby inherited genetic traits are lost as an organism ages. They examined the *IGF2* gene that encodes the insulin-like growth factor 2 (IGF2) hormone. IGF2 is similar in structure to insulin and is one of only three protein hormones that exhibit that trait. Loss of imprinting at *IGF2* has been linked to cancer in men. Using *in vivo* mouse models and *in vitro* models, researchers found that oxidative

related stress cause loss of imprinting in both non-cancerous and cancerous prostate cells. This is a significant finding because it demonstrates a direct association between oxidative stress in healthy prostates and the subsequent development of prostate cancer via loss of *IGF2* imprinting (Yang et al., 2014).

Oxidative stress could also be associated with prostate cancer via impairments in the production of antioxidant enzymes, particularly glutathione peroxidase. In a study implementing regression analysis of retrospective data from 7,532 cases of prostate cancer, Blein et al. (2014) observed a negative association between prostate cancer and genetic mutations responsible for altered glutathione peroxidase production. The researchers noted that more studies would be necessary to confirm the link, but there is a significant step toward comprehending the function of oxidative related stress in prostate cancer.

Irrespective of the specific pathways by which oxidative stress leads to prostate cancer, there is a strong connection between physical exercise and a reduced risk of prostate cancer. In a comprehensive review of related literature, Rebillard, Lefeuvre-Orfila, Gueritat, and Cillard (2013) hypothesized that, since physical exercise is known to enhance the human body's natural antioxidant systems, exercise could play a role in reducing oxidative stress that might otherwise lead to diseases like prostate cancer. Although the authors did not specifically mention the role of iron or other compounds in oxidative stress, they strengthened the argument that oxidative stress is linked to prostate cancer. All sources of oxidative stress therefore warrant investigation in order to improve prostate cancer prevention and treatment approaches.

The Role of Iron in Prostate Cancer

The role of iron in prostate cancer is an understudied topic. Choi et al. (2008) studied the association between iron consumption and prostate cancer risk among 661 adult males with confirmed prostate cancer diagnosis and 1,360 control subjects. The researchers also conducted data on age, as a continuous variable, and ethnicity (Caucasian, African American, and others). Dietary iron intake data were gathered through a self-report food consumption questionnaire, the results of which were then translated to a number of milligrams per day using a national database of nutrition guidelines (Choi et al., 2008). Resultant data on iron intake were modeled as continuous and then in control-based tertiles.

Although the results indicated no association between prostate cancer and dietary iron in general, there was a major association between elevated iron consumption and the aggressive prostate cancer risk, which the researchers defined as "that which was diagnosed with extraprostatic extension or metastasis (stage III or IV) or with Gleason sum of ≥7" (Choi et al., 2008, p. 364). This is consistent with the findings related to oxidative stress and cancer progression, reviewed in the above section: Oxidative Stress and Carcinogenesis. In the Choi et al. (2008) study, the association was strongest among men with below-average intake of fruits and vegetables. Genetic predisposition to antioxidant activity also played a role; variations in the genes encoding the antioxidants manganese superoxide dismutase and myeloperoxidase were related with elevated risk in certain groups (Choi et al., 2008). Because clinically aggressive prostate cancer is more likely to be lethal than less aggressive forms (Choi et al., 2008), this study suggests that

excess iron intake could elevate the risk of fatal forms of prostate cancer. Additionally, the study used archival data, indicating that this type of data is appropriate to study the association between prostate cancer and iron.

In a study of 59 patients with hereditary hemochromatosis, a disorder that predisposes individuals to absorb excess iron from dietary sources, Geier, Hebert, and Potti (2002) found that 22% developed cancer, including three patients who developed prostate cancer. The median age of participants was 46 (range: 10-68 years). This led the researchers to conclude that hereditary iron overload is related with the elevated risk of malignancies, to include prostate cancer. This early evidence warranted further examination in studies of prostate cancer specifically, yet the area remains understudied.

One of the only studies that examined serum iron in relation to prostate cancer was conducted by Kuvibidila et al. (2004). The researchers measured serum iron, serum ferritin, and iron-binding capacity total, all as continuous variables, among 34 men with newly diagnosed prostate cancer (31 of whom were African American) and 84 healthy men (52 of whom were African American). The men ranged in age from 49 to 78 years; age was operationalized using the following intervals: <51, 51-55, 56-60, 61-70, and 71 and above. In contrast to the researchers' expectations, patients with prostate cancer had vastly lower mean concentrations of serum ferritin than men without prostate cancer (156 µg/L and 245 µg/L, respectively, $p = 0.043$), along with higher total iron-binding capacity (69.87 µmol/L and 60.43 µmol/L, respectively, $p = 0.0178$). The researchers did not find a difference in serum iron levels between prostate cancer cases and controls (Kuvibidila et al., 2004). The large majority of the prostate cancer cases were African

Americans, suggesting a need to consider race as a potential confounding variable, which the Kuvibidila et al. (2004) study failed to do. This study had a sample size of only 117 participants, which is a limitation underscoring the need for further examination of the connection between prostate cancer and serum iron.

Some studies have shown a decreased risk of prostate cancer in adult males that reported higher dietary intake of tomato products (Matos et al., 2006), an effect that could be a result of the presence of lycopene and beta-carotene, two constituents that block oxidative DNA damage. To study this effect, Matos et al. (2006) injected rats with an iron compound and measured the effect on prostate damage with and without lycopene and beta-carotene supplementation. In the prostates of rats injected with iron, the researchers observed 78% higher levels of oxidative stress markers compared with control rats. Of the rats injected with iron, those treated with lycopene and beta-carotene had 70% less oxidative damage (Matos et al., 2006). This finding is quite suggestive of the damaging effect of iron overload on prostate tissue via increased oxidative stress. However, the lack of comprehensive study indicates the need to elucidate the complexities of the relationship between prostate cancer, cancer treatment, and iron levels. Because the existing studies, as well as this study, have sought to establish associations rather than causation, it is appropriate to include potentially confounding variables such as age and race.

Age and Prostate Cancer

The association between prostate cancer and age is well studied. Age is an important factor in prostate cancer because it is directly related to screening policies.

Early detection of aggressive forms of prostate cancer is essential to effective treatment (Shafique & Morrison, 2013), so the age at which regular prostate cancer screenings begin is important to reduce the social impact of the disease. Measuring prostate-specific antigen (PSA) levels is the most prevalent screening process. However, this presents a problem because men are more likely to have high PSA levels not associated with prostate cancer as they age (Hong et al., 2013).

Leal, Hamdy, and Wolstenholme (2014) recently sought to determine the prevalence of prostate cancer by age. They analyzed 25 autopsy studies of adult males who had not been diagnosed with prostate cancer in order to determine the age at which detection and diagnosis could be improved through screening. Based on their analysis, they estimated that the prognosis of prostate cancer elevates with age, with the following histological prevalence rates for each age group: age 20-29, 2%; age 30-39, 7%; age 40-49, 11%; age 50-59, 15%; age 60-69, 26%; age 70-79, 35%; age 80-89, 49%; and age 90-99, 67% (Leal et al., 2014). In another study, Hong et al. (2013) analyzed retrospective data from adult males diagnosed with high-risk prostate cancer between the years of 2004 and 2008 to find age associations. Age was treated as a continuous variable, and they used 50 as the baseline age, although men in their retrospective cohort had been diagnosed with prostate cancer as early as age 37. Although they treated age as a continuous variable in their analyses, the researchers grouped age in the following intervals in their report: <50, 50-64, 65-74, and >74. The researchers did not justify the choice of 50 years as baseline, nor did they justify their choice of grouping intervals for the report. They observed an association between older age and increased likelihood of

high-risk prostate cancer (Hong et al., 2013). This study strongly justifies the inclusion of age as a variable in this study and others studies related to prostate cancer epidemiology.

Due to the relatively lethargic growth of most forms of prostate cancer, age is also taken into account by practitioners to decide when cancer screening should continue or cease. For patients with co-morbid conditions after a certain age, prostate cancer screening could be associated with more harm than benefit (Lansdorp-Vogelaar et al., 2014). As men age, there is an increased risk of false positive screening prognosis and over-diagnosis. In simulation models based on nationwide average data, Lansdorp-Vogelaar et al. (2014) concluded that regular prostate cancer screening should cease at between 66 and 76 years, depending on the number and severity of comorbid conditions.

Daskivich et al. (2013) investigated the effect of age, along with several other factors, on death from prostate cancer in men with early-stage disease. Their study was conducted among 3,183 men from a nationally representative, population-based sample. Age was categorized into the following intervals: ≤55, 56-65, 66-75, and ≥76; this decision was not justified in the report. Participants were followed for 14 years. The results indicated that men who are diagnosed with prostate cancer at older ages were more unlikely to endure prostate-cancer-specific mortality than those diagnosed at younger ages, particularly when co-morbid conditions are involved. This finding confirmed previous research (Russo, Chen, Aizer, Hattangadi, & D'Amico, 2012) that reached similar conclusions.

Taken together, the existing body of research related to age and prostate cancer underscores the need to understand potential risk factors. These risk factors particularly

include oxidative stress in this context, since ROS have the potential to contribute to carcinogenesis and cancer development via genetic mutations (Karihtala & Soini, 2007), and mitochondrial genetic damage can accumulate with age (Kennedy, Salk, Schmitt, & Loeb, 2013). Minimizing risk and taking preventive measures may be more effective and less harmful for men as they age. However, since older adult males are more likely to develop high-risk prostate cancer, further understanding age-related associations is important.

Ethnicity and Prostate Cancer

Along with age, ethnicity is an important factor in prostate cancer screening policies. So far, available evidence suggests clear associations between ethnicity and prostate cancer risk. Hong et al. (2013), in a study of over 70,345 adult males with prostate cancer, observed an extremely higher aggressive prostate cancer risk among African American men than among Caucasian men at the baseline age of 50 years (odds ratio [OR] = 3.31, 95% CI 2.85-3.84). Similarly, Zhou, Bigler, and Pound (2012) observed that, based on 3,000 retrospectively analyzed pathology reports, African American men tended to have earlier prostate cancer onset by 1 and a half years and earlier and vigorous onset of prostate cancer by 9 years, versus with their Caucasian counterparts.

Leal et al. (2014) also sought to examine the relationship between prostate cancer and ethnicity, particularly among men with undiagnosed prostate cancer cases detected at autopsy. In their review of 25 studies, they confirmed that ethnicity was a potential predictor of prostate cancer prevalence. Specifically, they found the highest prevalence of

undiagnosed prostate cancer among Blacks (operationalized as African Americans in the Leal et al. 2014 study) and the lowest prevalence among Asians (operationalized as Chinese/Japanese in the study).

In addition to ethnicity-related discrepancies in cancer risk, differences have also been observed in the risk of mortality from prostate cancer. Evidence shows that members of minority ethnicities have lower survival after diagnosis than Caucasians, ranging in one study from 2% lower relative survival for pancreatic cancer to 16.4% lower relative survival for non-Hodgkin's lymphoma (Pulte, Redaniel, Brenner, & Jeffreys, 2012). According to Pulte et al. (2012), this disparity may be lessening as a result of attempts to remedy social inequalities in the healthcare system. A causal link cannot be asserted with certainty, however, since similar disparities for other forms of cancer have not changed (Pulte et al., 2012).

Body Mass Index and Prostate Cancer

BMI is a weight measurement status derived by dividing an individual's body mass in kilograms by the square of body height in meters. The measure is used by international health organizations to define overweight and obesity thresholds (Masuda et al., 2012). Currently, individuals with a BMI greater than 25 kg/m^2 are overweight, and individuals with a BMI greater than 30 kg/m^2 are characterized as obese, according to the World Health Organization (WHO; 2015). These numbers correspond to risk thresholds for mortality and for a range of chronic diseases including colon cancer, breast cancer, endometrial cancer, osteoarthritis, diabetes, and cardiovascular diseases (Masuda et al., 2012; WHO, 2015).

In recent years, researchers have begun to examine possible associations between prostate cancer and BMI, although the link has not yet been firmly established. According to results of a study among 3,258 men who underwent biopsy, BMI was significantly associated with high-risk prostate cancer (OR = 2.31, p = .03). However, BMI was only associated with overall prostate cancer risk among adult males with an ancestral history of the disease (OR = 3.73, p = .02). The researchers concluded that BMI should be included in prostate cancer screenings (Liang, Ketchum, Goodman, Klein, & Thompson, 2014). Similarly, Haque et al. (2014) found in their case-control study of 571 men that increased BMI was significantly associated with incidence of death from prostate cancer; for patients with Gleason scores ≥ 8, the odds ratio for mortality was 2.37 (95% CI 1.11-5.09). Additionally, the Haque et al. study indicated overall elevated risk of mortality and prostate cancer diagnosis with increased BMI, regardless of disease severity.

Not all researchers have supported the same conclusion. Giovannucci et al. (2003) noted that the relationship between BMI and prostate cancer may be complicated by issues related to hormones, which are in part modulated by body weight. Using archival data from the Health Professionals Follow-Up Study from 1986 to 2000, the researchers found that, in a sample of 2,896 prostate cancer cases, higher BMI was associated with lower risk of prostate cancer in males younger than 60 and males with a family history of prostate cancer (Giovannucci et al., 2003). The researchers supposed that the lower testosterone concentration associated with high BMI might explain this effect, but no similar effect was found for older men with non-hereditary cancer. In another report of

the same study, Platz, Leitzmann, Michaud, Willett, and Giovannucci (2003) revealed that increased self-reported energy intake was associated with increased risk of fatal or metastatic prostate cancer (relative risk = 1.38, 95% CI = 0.96-1.98). This risk was moderated by BMI; men with lower BMI had a more pronounced risk from higher energy intake. This might suggest a positive BMI association when controlling for physical activity and other factors, since high energy intake might be associated with high BMI. Again, the researchers hypothesized that the energy intake and BMI effect was attributable to hormone and growth factor production.

In an attempt to replicate the Giovannucci et al. (2003) finding, Bradbury, Wilk, and Kaye (2005) conducted a matched case-control study of 730 prostate cancer cases and 2,740 controls. They found that BMI at obesity levels (≥ 30) was indeed associated with lower risk of developing prostate cancer compared with men of normal weight (adjusted odds ratio = .78, 95% CI = 0.56-1.09). The researchers concluded that their data supported an association between BMI and prostate cancer.

However, these findings are by no means uncontroversial, especially when considering the hypothesized mechanism of hormone production. In a review of 124 topical publications, Regis et al. (2015) concluded that testosterone levels cannot yet be conclusively linked to prostate cancer diagnosis or aggression. Additionally, San Francisco, Rojas, DeWolf, and Morgentaler (2014) found low testosterone levels to be positively associated with prostate cancer progression. These findings complicate the connection.

According to some researchers, elevated BMI is associated with increased cancer risk primarily by way of inflammation, which has often been measured using high-sensitivity C-reactive protein (hs-CRP) as a proxy variable (Swede et al., 2014; Voils & Cooper-DeHoff, 2014). Because oxidative stress can be a byproduct of both inflammation and inherited androgen receptor activation (Schultz et al., 2014), the findings of the present study are able to suggest directions for future research on these topics, even without including hs-CRP as a variable. It is possible that lower testosterone levels and increased oxidative stress have competing effects on prostate cancer in high-BMI individuals, and there may be a hereditary component as well. Because the present study is concerned primarily with the relationship between serum iron concentration and prostate cancer diagnosis, it is beyond the current scope to attempt to untangle the complex effect of BMI, but its examination herein should contribute another piece of evidence to the debate.

Weight gain after diagnosis has also been linked to elevated occurrence of prostate-cancer-related mortality (HR = 1.93, 95% CI 1.18-3.16), according to research by Bonn et al. (2014). These studies suggest a relationship between BMI and prostate cancer. Although the exact nature of the relationship is not yet understood, there is compelling evidence that increased BMI impacts the diagnosis and disease-related risk factors for mortality. Therefore, BMI may have a confounding effect on the relationships between other factors and prostate cancer. Other researchers studying iron and prostate cancer have included BMI as a control variable or a case matching criterion (e.g., Antognelli et al., 2013; Pusatcioglu et al., 2014).

Socioeconomic Status and Prostate Cancer

In addition to BMI, employment status and socioeconomic status (SES) have potentially confounding effects on a number of health outcomes. Socioeconomic status refers to an individual's position in society relative to others, and can include many components (Drewnowski & Rehm, 2015). The two most important components of SES are income level and educational attainment. Individuals with higher incomes and higher educational attainment levels are considered to have higher SES (Drewnowski & Rehm, 2015). SES is an important factor in a variety of health-related outcomes, through various mechanisms.

Lower SES has been strongly linked to cell aging, which is related to oxidative stress and genetic mutations that can lead to cancer (Wolkowitz et al., 2010). With regard to prostate cancer specifically, results related to the association with SES have been mixed. Garcia-Gil et al. (2014) found that prostate cancer was more common in affluent regions of Southern Europe (incidence rate ratio = 0.92, 95% CI 0.80-1.00). They measured SES using a continuous deprivation index calculated from census data related to unemployment rate, manual labor, temporary labor, illiteracy rate, and school dropout rate. Similar results were obtained among 98,484 men in California; compared to the lowest quintile of SES based on neighborhood-level census data, the highest quintile had significantly elevated risk of prostate cancer diagnosis (relative risk = 1.28; 95% CI 1.25–1.30) (Cheng et al., 2009).Outcomes, however, seem to exhibit the opposite association.

According to research conducted by Shafique and Morrison (2013), adult males diagnosed with prostate cancer had a significantly increased risk of death if they also had

lower SES (RER 1.48, 95% CI 1.31–1.68, $p < 0.001$).The effect was independent of age. SES was measured utilizing the Scottish Index of Multiple Deprivation, which includes data related to housing, education, health, employment and income (Shafique & Morrison, 2013). The researchers suggested that, in addition to later diagnoses, low-SES men may have increased comorbidities or may receive differential treatment, accounting for the result.

Associations between SES and cancer can vary by ethnic group and type of cancer (Valverde, 2015), and multiple authors have pointed out that the associations are neither clear nor well understood (Cyrus-David, 2010; Rundle et al., 2013). The existence of an association between prostate cancer and SES indicates a potential confounding effect on the relationships between other factors and prostate cancer.

Employment Status and Prostate Cancer

Although this literature review uncovered no associations between employment status and prostate cancer diagnosis, researchers have examined the effect of prostate cancer survivor status on employment status, with results revealing that some associations may exist. For example, Bradley Neumark, Luo, and Schenk (2007) studied employment status among a sample of individuals diagnosed with breast and prostate cancer. Their results indicated that, for prostate cancer, the greatest change in employment status was observed at six months following diagnosis, when the 294 diagnosed men were 10% ($p < .05$) less likely to be working than the non-diagnosed control group (Bradley et al., 2007). By 18 months after the diagnosis, several participants went back to work. The researchers measured employment status in terms of

whether or not participants were employed and the number of hours worked weekly (Bradley et al., 2007). This indicates that employment status may shift with prostate cancer diagnosis.

In a similar study, Gunnarsdottir et al. (2013) compared employment participation rates of cancer survivors with those of non-cancer controls. Compared to the controls, survivors of prostate cancer were more unlikely to be employed (OR = 0.50; CI 0.35-0.73); survivors of other types of cancer exhibited different employment rates. Again, these results suggest that employment status may be linked to prostate cancer, although the mechanism of this link is not understood (Gunnarsdottir et al., 2013). Therefore, the present study includes employment status as a confounding variable.

The National Health and Nutrition Examination Survey and Iron

The National Health and Nutrition Examination Survey (NHANES) contains nutritional intake information from a diverse, nationally representative sample a free-willed population (Sacco, Dodd, Kirkpatrick, & Tarasuk, 2013). Data for the NHANES are collected primarily via interview, physical examination, and laboratory testing (Zalawadiya, Veeranna, Panaich, & Afonso, 2012). The first NHANES was conducted in 1971. Between 1971 and 1999, there were three NHANES surveys, and, the survey has been conducted every two years since 1999 (Archer, Hand, & Blair, 2013). Some researchers have drawn attention to the limited reliability of NHANES data, but the survey is still widely used for population-based health and nutrition studies (Archer et al., 2013).

NHANES, Iron, and Cancer

Several studies have examined iron-related variables using NHANES data. Commonly, this research has examined dietary iron intake. For example, Sacco et al. (2013) investigated the probability of consuming excess iron and other nutrients as a result of voluntary food fortification. Iron was among the nutrients they found to be associated with an elevated possibility of exuberant intake among adults, with the strongest effect occurring among men aged 19 to 30 years. In this group, 4.3% of individuals in the upper quintile of iron intake had iron intake levels above the tolerable upper limit for adults (Sacco et al., 2013).

Serum iron is measured as a part of the NHANES (variable code LBXSIR) by spectrometric analysis of the reaction between FerroZine® (a commercial iron reagent) and ferrous iron (Wells et al., 2005), and participants are followed up for mortality after the survey (Kim, Son, Hong, & Lee, 2012). It should be noted that the NHANES includes measures of both serum iron and serum ferritin (variable code SSFER); serum iron was used for the purpose of this study owing to mixed evidence in the literature regarding whether or not serum ferritin is an appropriate proxy for total body iron (Ferraro et al., 2012; Puliyel et al., 2011; Yin et al., 2014). From NHANES data, Wu et al. (2004) sought potential associations between serum iron as a measure of iron status and mortality from cancer. The researchers observed a significant association between excess serum iron and cancer mortality. Additionally, they categorized serum iron concentration into four quartile cutoffs and found that the association became stronger as total serum iron

increased. They concluded that adult males and females with high serum iron concentrations had an elevated risk of mortality from cancer (Wu et al., 2004).

It should be noted that the Wu et al. (2004) study is one of the only studies to use intervals to measure serum iron. The majority of research treats serum iron as a continuous variable (e.g., Fukami et al., 2014). Choi et al. (2008) treated serum iron as continuous and then used tertiles based on the distribution among a control group. None of these researchers justified their treatment of the variable. The study conducted by Wells et al. (2005) has been perhaps the most rigorous to date, since they used population weights and analyzed data over an 18-year period to arrive at longitudinal, nationally representative results. The researchers dichotomized serum iron according to the 75th percentile. Therefore, the 75th percentile method was used in this study following the Wells et al. (2005) research protocol.

Wells et al. (2005) used NHANES data to evaluate the relationship between development of cancer and serum iron (LBXSIR). The researchers noted that it is unclear what level of serum iron might be associated with cancer risk. Therefore, they dichotomized serum iron (high, low) according to the 75th percentile of the population (122.44 μg/dL); at or above the 75th percentile, participants were considered to have a high level of serum iron. Wells et al. (2005) has been one of the only research teams to provide justification for their treatment of the serum iron variable. The researchers found a strong association between the development of all types of cancer and serum iron. This association was strengthened when high serum iron levels were considered in combination with high cholesterol (Wells et al., 2005) suggesting a potential dietary

source impact. The study did not specifically examine oxidative stress or other mechanisms by which serum iron could be related to cancer development. However, the link between serum iron (as measured by the NHANES) and cancer development, taken together with the relationships among iron, oxidative stress, and cancer suggested elsewhere in this review, supports the rationale for this study, in which hypothesized an association between prostate cancer and serum iron on the basis of oxidative stress mechanisms.

NHANES and Prostate Cancer

Prostate cancer has been examined extensively using NHANES data. Many researchers have sought associations between prostate cancer and biomarkers found in blood serum. McDonald et al. (2014) and Walser-Domjan et al. (2013) studied the association between PSAs and other biomarkers. McDonald et al. (2014) found an association between PSAs and markers of systemic inflammation (plasma fibrogen, OR = 1.88; 95% CI, 1.09–3.25; neutrophil-lymphocyte ratio, OR = 1.14; 95% CI, 1.03–1.26) in men without prostate cancer and concluded that inflammation could identify a high-risk population. Walser-Domjan et al. (2013) found that serum PSA level was not associated with urinary isoflavone and lignan concentrations.

Han, Song, and Talbott (2013) and Rycyna, Bacich, and O'Keefe (2013) investigated links between prostate cancer and serum folate. Han et al. (2013) found that non-diagnosed men with higher serum folate had a lower risk of elevated PSA (OR = 0.71, 95% CI = 0.52–0.95); they concluded that higher folate status could protect against

prostate cancer. Rycyna et al. (2013), by contrast, found that higher folate status could contribute to prostate cancer progression.

Schwartz and Skinner (2012) studied the relationship between fatal prostate cancer and serum calcium using NHANES data. According to their findings, men with higher serum calcium were at higher risk for fatal prostate cancer (Relative Hazard = 1.50 per 0.1 mmol/L total serum calcium, 95% CI = 1.04–2.17). This elevated risk did not persist beyond 96 months of follow up.

Despite the body of evidence using serum variables to study prostate cancer, the literature search for this review yielded no studies addressing the relationship between serum iron and prostate cancer using NHANES data. Dietary intakes of various nutrients have also been explored for possible associations with mortality and prostate cancer diagnosis. Among the nutrients that have been examined are flavonoids and proanthocyanidins (Wang et al., 2014). However, the literature search for this review yielded no research related to dietary intake of iron and prostate cancer. Due to the lack of existing research related to prostate cancer and iron status measured by serum iron, this study fills a gap by contributing to the understanding the role of iron in prostate cancer development.

Theoretical Framework

The theoretical framework for this study was the exposure-disease model (Sexton & Linder, 2011). In this model, developed by Gee and Payne-Sturges (2004), exposure to risk factors in the environment increases the likelihood of disease development. This model, which proposes that stress and stressors are mediating risk factors, organizes these

factors into two dimensions: community vulnerability and individual vulnerability. Like concepts are then clustered in both dimensions and causally ordered (as indicated by arrows), and their relationships are unidirectional (Sexton & Linder, 2011). Concepts in the community vulnerability dimension include race and ethnicity, environmental hazards and pollutants, and exposure. Concepts in the individual vulnerability dimension include individual stressors and coping and the resultant health effect (Sexton & Linder, 2011). The notion of vulnerability has been widely applied to non-biological and biological factors, including social conditions (potentially including diet), pre-existing health conditions (such as hemochromatosis) and genetic predisposition. Thus, the notion of vulnerability allows researchers to predict damage to health in a variable way that is responsive to previous exposures and takes into account ability to resist, cope, or adapt (Sexton & Linder, 2011).

The exposure-disease model has been used in prior studies in which researchers have examined prostate cancer risk and exposure. For instance, the purpose of Charles et al.'s (2003) nested case-control study was to examine if there was a relationship between polychlorinated biphenyls (PCBs) or occupational exposures to electromagnetic fields (EMFs) and increased risk of death from prostate cancer among U.S. electric utility workers. The study consisted of five controls and 387 cases that contained prostate cancer as the cause of death. After adjusting for polychlorinated biphenyls exposure, race, and employment status, workers classified in the top 10% of electromagnetic field exposure were more likely to die from prostate cancer than individuals exposed to electromagnetic fields at lower levels. Non-Caucasian racial background showed a strong association with

risk of death from prostate cancer (Charles et al., 2003). This indicates that using the exposure-disease model to examine prostate cancer and potential associated risk factors can yield important results.

Because NHANES data do not specify genetic predispositions to iron overload or secondary overload caused by transfusion, the serum iron data gathered in the study relates to primary iron status as a result of dietary and other exposure. For this reason, the exposure-disease model is relevant to this study. The exposure-disease model allows for statistical analysis of potential association between serum iron levels and prostate cancer. Further, study is warranted to better understand how the risk factors identified in the model apply to serum iron concentration and prostate cancer.

Summary

This literature review revealed a major gap in existing research related to the relationship between serum iron as a measure of iron status and the development of prostate cancer. Although iron has been implicated in a number of other cancers, including colorectal and liver cancers (Fonseca-Nunes et al., 2014; Pusatcioglu et al., 2014), recent research is inconclusive regarding the association between high serum iron and prostate cancer (Kuvibidila et al., 2004). Additionally, existing studies have often had very small sample sizes. The relationship between iron and prostate cancer has not been studied using data from the NHANES. This survey is an important source of information and allows for studies with large sample sizes.

There is a theoretical and biological framework to support the idea that iron may impact prostate cancer, since excess iron has long been thought to increase levels of ROS

and oxidative stress, which can lead to prostate cancer (Bhagat et al., 2013; Bystrom et al., 2014; Paschos et al., 2013). However, the link remains to be investigated in detail. If such a link is established, serum iron might be used as an early screening tool to aid in the timely diagnosis of prostate cancer. This study examined the relationship between prostate cancer, serum iron concentration, age, ethnicity, poverty-to-income ratio, educational attainment, and hours worked in the last week. The study used data from the NHANES in order to fill the gap in existing research and contribute to the understanding of the complex interaction between iron status and cancer development. In Chapter 3, the design of the study is described, including the research design and methodology, the population and sampling procedure, a detailed description of variables and NHANES data collection process, the data analysis process, threats to validity, protection of human participants, and dissemination of findings.

Chapter 3: Research Method

Introduction

This study consisted of an examination of the relationships between serum iron concentration, age, ethnicity, poverty-to-income ratio, educational attainment, and hours worked in the last week, and prostate cancer. There is a significant occurrence of prostate cancer among males between the ages 51 and 70 years in the United States. With regard to men aged 50, 2.26% will develop prostate cancer over the next decade, with 7.98% developing prostate cancer over the next 2 decades, and 13.47% over the next 3 decades (National Cancer Institute, 2014). Among men aged 60, 6.29% will develop prostate cancer over the next decade, with 12.34% developing prostate cancer over the next2 decades, and 14.57% over the next 3 decades. Additionally, 7.52% of men aged 70 will develop prostate cancer over the next decade, with 10.30% over the next 2 decades (National Cancer Institute, 2014). The consequences can be devastating, with prostate cancer being the second main cause of cancer death among American adult males (National Cancer Institute, 2014). In total, 1 in 36 men will suffer death from prostate cancer (American Cancer Society, 2014). There is a significant gap in the literature concerning the role of serum iron concentration and prostate cancer. Specifically, no prior researcher has explored the relationship between prostate cancer and serum iron concentration among males between 51 and 70 years of age using a large sample.

The specific problem addressed in this research was that the relationship between prostate cancer diagnoses and serum iron concentration among males of differing ethnicities between 51 and 70 years of age remains unclear. Although there are some

indications that serum iron concentration may be related to the development of some cancers (Grant, 2008; Huang, 2003), large samples have not been examined to date. The purposes of this quantitative study was to examine whether there was an association between prostate cancer and serum iron concentration and determine if age or ethnicity were correlated with prostate cancer in males aged 51 to 70.

This chapter consists of a narrative of the research methodology and design to be used, including a description of the population, sample, and sampling procedures. Then, the procedures for recruitment, participation, and data collection are described with an emphasis on the use of archival data. Threats to validity are addressed including threats to internal validity and external validity. Lastly, it explains how subjects were protected and how this information will be dispersed.

Research Questions and Hypotheses

The following are the research questions and related hypotheses for this study:

RQ1: Is there an association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer?

$H_0$1: There is no association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer.

H_a1: There is an association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer.

RQ2: Is there an association between age and prostate cancer in males?

$H_0$2: There is no association between age and prostate cancer.

H_a2: There is an association between age and prostate cancer.

RQ3: Is there an association between ethnicity and prostate cancer?

$H_0$3: There is no association between ethnicity and prostate cancer.

H_a3: There is an association between ethnicity and prostate cancer.

RQ4: Is there an association between serum iron concentration and prostate cancer when controlling for age and ethnicity?

$H_0$4: There is no association between serum iron concentration and prostate cancer when controlling for age and ethnicity.

H_a4: There is an association between serum iron concentration and prostate cancer when controlling for age and ethnicity.

RQ5: Is there an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week?

$H_0$5: There is no association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week.

H_a5: There is an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week.

Research Design and Methodology

This was a secondary data examination from information gathered from the NHANES from 2009 to 2012. Data from 2009 to 2012 were examined because these

years represent the most current years available in the NHANES database that included all variables to be tested.

Population

The NHANES program includes the collection of health-related data on approximately 5,000 adults each year (CDC and Prevention, 2014a), and the information is released in 2-year increments. Four years' worth of data were used in this study (between 2009 and 2012). For this study, the relevant data files are for the 2009-2010 (*N* = 10,537) and the 2011-2012 (*N* = 9,756) releases, for a total *N* of 20,293.

Outcome definition. Prostate cancer diagnosis was the outcome variable in this study and was operationally defined as whether an individual has (coded as 1) or has not (coded as 0) been diagnosed with prostate cancer. Four NHANES items were used to assess the presence of prostate cancer: MCQ230a, MCQ230b, MCQ230c, and MCQ230d. The subjects were questioned about if they had ever been given a cancer diagnosis and if so, which type, with the four variables representing up to four types of cancer. Prostate cancer was coded as 30, meaning that if any of these four variables has a value of 30, the individual was in the positive prostate cancer diagnosis group.

Exposure definition. Exposure is defined as serum iron concentration, which was the primary independent variable in this study. It is operationally defined as μg of iron per dL of blood. Serum iron concentrations were assessed in the NHANES data using the variable LBXIRN, which consists of the test results from the laboratory from the reference method. This measure is recommended by the CDC for use over the LBXSIR measure (which is derived from the biochemistry profile rather than directly from the

laboratory rest results; CDC, 2014d). This variable was dichotomized into two groups. The first group was the low serum iron concentration group and was those with scores below the 75th percentile on the µg of iron per dL of blood scale. The second group was the high serum iron concentration group and was those with scores at the 75th percentile or higher on the µg of iron per dL of blood scale. This process was used successfully by Wells et al. (2005) in a study similar to this study.

Sample and Sampling Procedures

Of the 20,293 individuals in the combined 2009 to 2012 database, 10,212 were female and were removed from the database, leaving 10,081 males. Those under 51 years of age were removed (N = 7,350) as were those over 70 years of age (N = 881), leaving 1,850 as the final sample. Individual research questions had different sample sizes, since not all data were available for all subjects. All subjects were included after exclusions. A power study was administered to examine the required sample size for this study. In regard to the age variable, an analysis of research showed that it is not uniformly operationalized across studies. Some researchers treated it as continuous, while others have preferred to use intervals. Few researchers have justified their choices. In this study, I treated age as a continuous variable on a scale between 51 and 70 rather than dichotomizing into two groups at some arbitrary point. The lower age (51) was used in this study because prior researchers have regarded men up to 50 years of age as a baseline and those over 50 years of age (i.e., 51 and older) as the comparison group (Daskivich et al., 2013; Hong et al., 2013). The higher age (70) was used as the upper limit because researchers have shown that it may be harmful, rather than beneficial, to screen for

prostate cancer after the age of 70 (Calonage et al., 2008; Lansdorp-Vogelaar et al., 2014; Moyer, 2012). The study examined data from men aged 51 to 70 years. The G*Power computer program was used for this analysis (Faul, Erdfelder, Lang, & Buchner, 2007). The analyses for this study consisted of one 2 x 2 crosstabulation, one bivariate logistic regression analysis, one 6 x 2 crosstabulation, and one hierarchical logistic regression analysis with three control variables.

For the logistic regression analysis for the first research question, the following parameters were specified: two tails, odds ratio of 2.33 (based on Pr(Y = 1|X = 1) H_a2 = .50, Pr(Y = 1|X = 1) $H_0 2$ = .30), alpha of .05, desired power of .95, R^2 for other controls = 0, normal distribution, X parm $\mu = 0$, and X parm $\sigma = 1$. With these specifications, G*Power indicated that 104 participants would be required.

For the second research question, a bivariate logistic regression analysis was performed and the following specifications were entered into G*Power: two tails, odds ratio of 2.33 (based on Pr(Y = 1|X = 1) H_a2 = .50, Pr(Y = 1|X = 1) $H_0 2$ = .30), alpha of .05, desired power of .95, R^2 for other controls = 0, normal distribution, X parm $\mu = 0$, and X parm $\sigma = 1$. With these specifications, G*Power indicated that 104 participants would be required.

For the third research question, the following parameters were specified: 1 degree of freedom (based on the 6 x 2 crosstabulation), effect size of w = .30, alpha of .05, and desired power of .95. Entering those specifications into G*Power indicated that 220 participants would be required for the crosstabulation performed for the third research question.

For the fourth research question, the following specifications were entered in G*Power for the hierarchical logistic regression analysis: two tails, odds ratio of 2.33 (based on Pr(Y = 1|X = 1) H_a4 = .50, Pr(Y = 1|X = 1) $H_0 4$ = .30), alpha of .05, desired power of .95, R^2 for other controls = .10, normal distribution, X parm μ = 0, and X parm σ = 1. With these specifications, G*Power indicated that 115 participants would be required.

For the fifth research question, the following specifications were entered in G*Power for the hierarchical logistic regression analysis: two tails, an expected odds ratio of 2.33 (based on Pr(Y = 1|X = 1) H_a4 = .50, Pr(Y = 1|X = 1) $H_0 4$ = .30), alpha of .05, desired power of .95, R^2 for other controls = .20, normal distribution, X parm μ = 0, and X parm σ = 1. With these specifications, G*Power determined that 130 subjects would be needed. Thus, the highest needed sample size for any of the statistical tests was 220. Given that the sample size for this study was N = 1,850, the statistical power to reject all null hypotheses was adequate.

Of these 1,850 individuals, 65 (3.5%) had received a diagnosis confirming the presence of prostate cancer. Based on the definition of exposure (serum iron concentration) as low (serum iron concentration scores below the 75th percentile on the μg of iron per dL of blood scale) versus high (serum iron concentration scores at the 75th percentile or higher on the μg of iron per dL of blood scale), 75% of the participants were in the low group and 25% were in the high group.

Variables

Serum iron concentration. Serum iron concentration was the primary independent variable in this study and was operationally defined as µg of iron per dL of blood. Serum iron concentrations were assessed in the NHANES data using the variable LBXIRN, which consists of the laboratory test result from the reference method. This measure is recommended by the CDC for use over the LBXSIR measure (which is derived from the biochemistry profile rather than directly from the laboratory rest results; CDC, 2014d). This variable was dichotomized into two groups. The first group was the low serum iron concentration group and was those with scores below the 75th percentile on the µg of iron per dL of blood scale. The second group was the high serum iron concentration group and was those with scores at the 75th percentile or higher on the µg of iron per dL of blood scale. This process was used successfully by Wells et al. (2005) in a similar study to this one.

Prostate cancer diagnosis. Prostate cancer diagnosis was the dependent variable in this study and was operationally defined as whether an individual has (coded as 1) or has not (coded as 0) been diagnosed with prostate cancer. Four NHANES items are used to assess the presence of prostate cancer: MCQ230a, MCQ230b, MCQ230c, and MCQ230d. The participating individuals were questioned whether they had ever received a cancer diagnosis and if so, which type, with the four variables representing up to four types of cancer. Prostate cancer was coded as 30, meaning that if any of these four variables had a value of 30, the individual was in the positive prostate cancer diagnosis group.

Age. Age was assessed in the NHANES survey using a continuous scale. Within the age range analyzed in this study (51-70), age was retained as a continuous variable in the analyses conducted. Age was assessed with the NHANES variable RIDAGEYR. A number of previous studies have treated age or time since onset as continuous measures rather than dichotomizing age at some arbitrary point (Armitage, 1953; Gyde et al., 1988).

Ethnicity. Ethnicity was operationalized as a nominal variable with six possible values: non-Hispanic Asian (4), non-Hispanic Black (3), non-Hispanic White (2), other Hispanic (1), Mexican American (0), and other including multiracial (all other code numbers). Ethnicity was assessed with the NHANES variable RIDRETH3.

Body mass index. BMI was assessed in the NHANES as a continuous variable (BMXBMI). For the purpose of the present study, BMI was retained as a continuous variable for the present study, conforming to the treatment of the variable in the majority of existing research (Haque et al., 2014; Liang et al., 2014).

Poverty-to-income ratio and educational attainment. Poverty-to-income ratio was operationalized as a continuous variable (INDFMPIR). Educational attainment (DMDEDUC2) was coded following the structure of the NHANES data. In the NHANES, educational attainment levels are coded according to the following five possible responses: less than 9th grade (1), 9th to 11th grade, including 12th grade with no diploma (2), high school graduate/GED or equivalent (3), some college or associate's degree (4), college graduate or above (5).

Hours worked in the last week. Following the NHANES, hours worked in the last week was operationalized as a continuous variable indicating the number of hours each individual worked in the week previous to data collection (variable OCQ180).

Statistical analyses. Descriptive statistical analyses consisted of the demographic and background variables of age, race, education, income, and marital status. Frequency tables were constructed for all categorical measures, which report the sample sizes and percentages associated with each category of response. Additionally, measures of central tendency and variability were used for all continuous measures analyzed, with the mean, median, and standard deviation reported along with minimum and maximum scores. Measures of skewness and kurtosis were also reported as measures of normality. Inferential analyses were conducted to test the null hypotheses of the study.

Data Collection

The participants for NHANES were selected through a multistage probability sampling design to select a sample that was representative of the noninstitutionalized civilian population in the United States (CDC, 2014c). The data for the NHANES project were collected from a variety of sources including examinations, interviews, and the collection of laboratory data based on urine, blood, and DNA tests (CDC, 2014c). The quality of the NHANES interview data was addressed by training the interviewers in principles of quality control and quality assurance (CDC, 2014c). The quality of the physical samples taken from each person was tested by randomly selecting specimens for blind duplication quality control.

With regard to the lab procedures used, the measures taken for iron content consisted of a portion of the standard biochemistry profile, with evaluations conducted utilizing a Hitachi Model 704 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) (CDC, 2014d). With regard to the measures of iron, Fe3+ was isolated from transferrin through the use of guanidium chloride in the low acidic pH range and diminished to Fe2+ with ascorbic acid, with Fe2+ forming a colored complex with ferrozine (CDC, 2014d).

The data for this study is publically available on the NHANES website in .XPT files. The relevant data were included for the demographic data (for the assessment of age and ethnicity), the laboratory data (for serum iron concentration), the examination and body measurements data (for the prostate cancer diagnosis and BMI information), and the occupation questionnaire (for information about employment). For each of these three areas, there are separate .XPT files for the 2009-2010 and the 2011-2012 periods for a total of six data files. These six databases were merged based on the unique respondent sequence number which is present in all data files.

Statistical Analysis

Both descriptive and inferential statistical analyses were performed using SPSS software (Version 23.0). Initial data screening was performed to ensure that all values for all variables were within the allowable limits and valid. The dependent variable for all the aims of this study was prostate cancer diagnosis which was a dichotomous variable coded as 0 = no prostate cancer diagnosis and 1 = prostate cancer diagnosis. On the basis of the

data screening, number of hours worked per week was changed to a categorical variable. This is described further in Chapter 4.

The first research question asked the following: *Is there an association between serum iron concentration and prostate cancer?* Both of the variables were dichotomous, and therefore a chi-squared independence test was performed to compare serum iron concentration (high versus low) and prostate cancer diagnosis (yes or no).

The second research question asked the following: *Is there an association between age and prostate cancer?* A chi-squared independence test was performed with age (a continuous variable) as the independent variable and prostate cancer diagnosis (yes or no) as the dependent variable.

The third research question asked the following: *Is there an association between ethnicity and prostate cancer?* For this research question, both variables were categorical and therefore a (6 x 2) chi-squared independence test was performed.

The fourth research question asked the following: *Is there an association between serum iron concentration and prostate cancer when controlling for age and ethnicity?* There were two control variables (age and ethnicity) and one independent variable (serum iron concentration group). A hierarchical logistic regression analysis was performed to answer this research question.

The fifth research question asked the following*: Is there an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week?* A hierarchical logistic regression analysis was performed to determine if serum iron

concentration was associated with prostate cancer diagnosis when the other variables were included in the statistical model.

Threats to Validity

Because this study was conducted using archival data from the NHANES, there were few threats to external or internal validity. No experiment was conducted for the purpose of this study, so all validity threats pertain to the original data collection. National surveillance data have been criticized for lacking strong validity, and NHANES data in particular are thought to suffer from significant underreporting (Archer et al., 2013). Additionally, certain NHANES variables may suffer from self-reporting errors, particularly with respect to weight and height (Archer et al., 2013). However, the NHANES is still widely used to test population-wide associations among variables, and at present it remains the most complete source of data available for such purposes (Archer et al., 2013). Because the present study does not seek to examine relationships involving variables like weight and height, which might suffer from self-report bias, this is not a major threat. The NHANES data are gathered using a multi-stage probability sampling design to obtain a sample representative of the entire non-institutionalized U.S. population. This study did not use sample weights in order to generalize the results to the entire population of the U.S.

The NHANES provides strict methodological instructions for testing for serum iron concentration (CDC, 2014d). However, there is no guarantee that all NHANES data were collected using the same methods. This is a threat to internal validity because there could be variations in data caused by differing methods, and it is not possible to capture

these differences using NHANES data. Therefore, it was extremely important to verify any positive results from this study using novel, controlled research methods, preferably with large sample sizes. Validity of all statistical conclusions was safeguarded to the extent possible using the methods described above.

Protection of Human Participants

Due to the fact that this study was a secondary data analysis of NHANES data, no original data were collected and therefore no informed consent procedures are required beyond those already implemented in the original NHANES data collection. NHANES participants are protected under NCHS Research Ethics Review Board (ERB) Approval Protocol #98-12. The CDC and Prevention and the Office for Protection from Research Risks (OPRR) are responsible for the protection of human subjects in the NHANES study. Rigorous steps were taken to ensure protection of human participants (CDC, 1997). In the NHANES data available to the public that were used in this study, no personal identifiers are present. This study was approved and protected by the Walden Institutional Review Board.

Dissemination of Findings

Findings will be disseminated in several ways. The data and findings from this study will be submitted for potential publication in peer-reviewed research journals. Additionally, the findings will be presented at professional meetings and conferences.

Summary

In this chapter, the data collection and analysis methods are described for this study. This quantitative study used archival data obtained from the NHANES from 2009–2012, which are freely available to the public. These data were used to analyze relationships among the independent variables, serum iron concentration, BMI, age, ethnicity, poverty-to-income ratio, educational attainment, and hours worked in the last week, and the dependent variable, prostate cancer diagnosis. All data were screened for acceptability before proceeding with statistical analysis. Along with descriptive statistics, regression analyses and chi-squared independence test were performed to test the five research hypotheses. The results and discussion of findings are presented in Chapters 4 and 5, respectively.

Chapter 4: Results

Introduction

The purpose of this quantitative study was to determine whether there is an association between serum iron concentration and prostate cancer among a sample of men aged 51 to 70 in the United States. An additional aim of the study was to determine whether such an association holds when controlling for age, ethnicity, BMI, poverty-to-income ratio, educational attainment, and hours worked in the last week. The research questions and associated hypotheses were as follows:

RQ1: Is there an association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer?

$H_0$1: There is no association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer.

H_a1: There is an association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer.

RQ2: Is there an association between age and prostate cancer in males?

$H_0$2: There is no association between age and prostate cancer.

H_a2: There is an association between age and prostate cancer.

RQ3: Is there an association between ethnicity and prostate cancer?

$H_0$3: There is no association between ethnicity and prostate cancer.

H_a3: There is an association between ethnicity and prostate cancer.

RQ4: Is there an association between serum iron concentration and prostate cancer when controlling for age and ethnicity?

$H_0$4: There is no association between serum iron concentration and prostate cancer when controlling for age and ethnicity.

H_a4: There is an association between serum iron concentration and prostate cancer when controlling for age and ethnicity.

RQ5: Is there an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week?

$H_0$5: There is no association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week.

H_a5: There is an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week.

In this chapter, I present the results of the study. First is a description of the data and data collection as it actually took place, including data screening details. This is followed by a presentation of descriptive statistics pertaining to the sample. Next, the results are presented, with a separate section pertaining to each research question. A summary, including the answers to the research questions, concludes the chapter.

Data Collection and Screening

The NHANES data were gathered using a multistage probability sampling design to obtain a sample representative of the entire noninstitutionalized U.S. population. For most variables studied by the NHANES, data were collected from one-third of the full

sample. Data were downloaded from the NHANES databases in March, 2016. The actual sample size was 1,850. However, since not all data were available for all cases, the sample sizes for individual tests ranged from 1,502 to 1,850. Sample sizes for each test are presented in the tables in this chapter. Data were screened to ensure all cases met the inclusion criteria. All cases were within the 50-71 age range, and all were male. Next, continuous variables were examined to determine whether they met the assumptions for statistical analysis. To test for normality, the skewness statistic was computed for serum iron, hours worked per week, and BMI. For serum iron, the skewness value was 1.03. Because this value was slightly outside the range for normality, histograms were examined to further assess normality. This visual inspection indicated that the distribution of serum iron values was approximately normal, meeting the assumption for analysis.

For hours worked per week, the skewness statistic was 0.762, suggesting normality. However, a visual inspection of the histogram revealed that a large number of participants worked 0 hours per week, resulting in an extreme positive skew. Therefore, the data were transformed to make hours worked per week a categorical variable. The categories were in 10-hour increments: 0 to 10 hours, 11 to 20 hours, 21 to 30 hours, 31 to 40 hours, and more than 40 hours. After transforming the variable, the hours worked per week data met the assumption of normality for multivariate analysis. All other variables were normally distributed.

Descriptive Statistics

The section was divided into subsections on the demographic variables describing the sample and the independent variables of interest for the study. There were 1,850 participants in the sample. Of these, 65 (3.51%) had prostate cancer.

Sample Demographics

With respect to ethnicity, the plurality of participants with no prostate cancer diagnosis was non-Hispanic White (38.5%), followed by Mexican American and other Hispanic (35.6%), then non-Hispanic Black (26.3%). This suggested a fairly even ethnic distribution among those without diagnoses. For those with diagnoses, the distribution was more unequal, with 46.2% of diagnoses occurring among non-Hispanic Blacks, followed by non-Hispanic Whites (29.2%) and Mexican Americans and other Hispanics (16.9%). The odds ratio of Black patients with prostate cancer to White patients with prostate cancer was 2.31 (95% CI = 1.28–4.15), indicating that the odds of being diagnosed with prostate cancer is 2.31 times higher for Blacks than Whites. The confidence intervals for the other ethnicities span 1.00, indicating that the odds of prostrate diagnosis did not reach statistical significance for the other ethnicities compared with Whites.

With respect to marital status, the majority were married in both the nondiagnosed (63.1%) and diagnosed (67.7%) group. In the nondiagnosed group, 22.6% were widowed, divorced, or separated, compared with 15.4% in the diagnosed group. All confidence intervals for marital status span 1.00, indicating that the odds of prostate cancer diagnosis

did not reach statistical significance for the widowed, divorced, and separated categories compared with married patients.

Nearly half of both the nondiagnosed (47.4%) and diagnosed (47.7%) groups listed high school/GED or some college as their education level. For the nondiagnosed group, 30.6% did not graduate high school, and 21.9% had a college degree. The diagnosed group was more highly educated: 35.4% had a college degree, and only 16.9% did not graduate high school. The confidence interval for less than ninth grade ranged from .03 to .54, indicating lower odds of prostate cancer for patients who had less than ninth grade education compared with college graduates. The confidence intervals for the other education levels spanned 1.00, indicating that the odds of prostate diagnosis did not reach statistical significance for the other education levels compared with college graduates. These results are summarized in Table 1.

Table 1

Distribution of Socio-Demographic Characteristics by Prostate Cancer Diagnosis

	Total		Prostate Cancer		Crude OR*	95% CI**
Variable	n	%[a]	n	%[b]		
Ethnicity, *n* = 1,850						
Mexican American	275	14.9%	3	4.6%	0.40	0.12, 1.36
Other Hispanic	194	10.5%	8	12.3%	1.56	0.67, 3.61
Non-Hispanic Black	500	27.0%	30	46.2%	2.31	1.28, 4.15
Other	175	9.5%	5	7.7%	1.06	0.39, 2.89
Non-Hispanic White	706	38.1%	19	29.2%	Reference	Reference
Marital Status, *n* = 1,848						
Widowed	79	98.8%	1	1.2%	0.32	0.04, 2.38
Divorced	263	97.4%	7	2.6%	0.68	0.30, 1.53
Separated	62	96.9%	2	3.1%	0.83	0.20, 3.49
Never married	164	97.6%	4	2.4%	0.63	0.22, 1.76
Living with partner	89	93.7%	6	6.3%	1.73	0.72, 4.16
Married	1,127	96.2%	44	3.8%	Reference	Reference
Education, *n* = 1,848						
Less than 9th grade	272	99.3%	2	0.7%	0.13	0.03, 0.54
9-11 grade	275	96.8%	9	3.2%	0.56	0.25, 1.22
HS/GED	403	96.9%	13	3.1%	0.55	0.27, 1.10
Some college/AA	442	96.1%	18	3.9%	0.69	0.37, 1.30
College graduate	391	94.4%	23	5.6%	Reference	Reference

Note. [a]Percents represent percent of respective variable levels for the total sample
[b]Percents represent percent of respective variable levels for prostate diagnosis
*OR = odds ratio; **CI = 95% confidence interval

The mean age for both groups was about 60 years (nondiagnosed: mean = 60.00 years and standard deviation = 2.68 years; diagnosed: mean = 62.20 years and standard deviation = 4.80 years). The mean of income-to-poverty ratio for both groups was similar, with the diagnosed group having a slightly higher ratio (nondiagnosed: mean = 2.68 and standard deviation = 1.69; diagnosed: mean = 3.25 and standard deviation =1.75). With respect to BMI, the mean of both groups was about 29 kg/m^2 (nondiagnosed: mean = 28.96 kg/m^2 and standard deviation = 5.82 kg/m^2; diagnosed

mean = 29.08 kg/m^2 and standard deviation = 6.68 kg/m^2). Both groups worked about 15 to 20 hours during the week prior to data collection (nondiagnosed mean = 18.52 hours and standard deviation = 22.01 hours; diagnosed mean = 15.18 hours and standard deviation = 19.70 hours). These results are summarized in Table 2.

Table 2

Descriptive Statistics for Continuous Independent Variables by Prostrate Diagnosis, total n = 1,850

	n	%	Mean	Std. Dev.
		No Prostate Cancer Diagnosis		
Age	1,785	96.5%	60.00	2.68
Income ratio	1,611	96.5%	2.68	1.69
Iron (ugl/dl)	1,621	96.7%	92.20	34.60
BMI	1,709	96.5%	28.96	5.82
Hours worked	1,785	96.5%	18.52	22.01
		Prostate Cancer Diagnosis		
Age	65	3.5%	62.20	4.80
Income ratio	58	3.5%	3.25	1.75
Iron (ugl/dl)	55	3.3%	95.55	41.25
BMI	62	3.5%	29.08	6.68
Hours worked	65	3.5%	15.18	19.70

In summary, these results suggested the sample was reasonably evenly distributed with respect to most demographic variables, suggesting the appropriateness of comparing the sample in terms of the independent variables of interest. Because the data were not weighted, the findings can only describe the study population, not the U.S. population as a whole.

Variable Descriptive Statistics

The dependent variable was prostate cancer diagnosis (yes, no). The independent variables in this study were serum iron concentration (low, high), BMI, age (in years), ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, Other), poverty-to-income ratio, educational attainment, and hours worked in the last week. Serum iron was dichotomized into low (below 75th percentile [110 µgl/dl and lower]) and high (75th percentile [111 µgl/dl and higher]). Before dichotomizing, the mean among the nondiagnosed group was 92.2 µgl/dl and standard deviation = 34.6 µgl/dl, and the mean for the diagnosed group was slightly higher, at 95.6 µgl/dl and standard deviation = 41.2 µgl/dl.

With respect to serum iron concentration, the majority of both groups were in the low (less than 75th percentile) category. However, 74.6% of the nondiagnosed group had low serum iron, compared with only 69.1% of the diagnosed group. In the high serum iron group, 30.9% were diagnosed with prostate cancer. The number of hours worked in the last week was also similar between groups. Among the nondiagnosed group, 54.3% worked 0 to 10 hours in the last week, compared with 56.9% of the diagnosed group. Those who worked 31 hours or more in the last week accounted for 35.9% of the nondiagnosed group and 52.7% of the diagnosed group. These results are summarized in Table 3.

Table 3

Descriptive Statistics for Categorical Independent Variables by Prostate Diagnosis

	Total		Yes		Crude OR*	95% CI**
Variable	*n*	%	*n*	%		
Hours Worked Last Week, *n* = 1,850						
0-10	1,006	54.3%	37	56.9%	1.27	0.58, 2.75
11-20	80	4.3%	6	9.2%	2.69	0.90, 7.98
21-30	105	5.7%	4	6.2%	1.31	0.39, 4.45
31-40	386	20.9%	10	15.4%	0.88	0.34, 2.26
More than 40	273	14.8%	8	12.3%		Reference
Serum Iron – Low = less than 75th Percentile, high = above 75th Percentile, , *n* = 1676						
Low	1,247	74.4%	38	69.1%	0.76	0.43, 1.36
High	429	25.6%	17	30.9%		Reference

Note. *OR = odds ratio; **CI = 95% confidence interval

Hypothesis Testing

This section contains the results related to each research question and set of hypotheses. Table 4 summarizes the results of logistic regression analyses conducted to answer the first three research questions.

Table 4

Logistic Regression Analysis for Prostate Cancer Diagnosis Regressed on Serum Iron, Age, and Ethnicity

Variable	*p*	Crude OR*	CI 95% (OR)**
Iron, Omnibus χ^2 (1, n = 1,676) = .81, p = .368			
Low[a]	.360	.76	0.34, 1.12
High		Reference	Reference
Age, Omnibus χ^2 (1, n = 1,676) = 9.65, p = .002			
Age (years)	.002	1.07	1.03,1.12
Ethnicity, Omnibus χ^2 (1, n = 1,850) = 16.01, p = .003			
Mexican American	0.14	0.40	0.12, 1.36
Other Hispanic	0.30	1.56	0.67, 3.61
Non-Hispanic Black	0.01	2.31	1.28, 4.15
Other	0.90	1.06	0.39, 2.89
Non-Hispanic White		Reference	Reference

Note. [a]Serum iron = 0 = less than 75th percentile, 1 = 75th percentile or higher
*OR = odds ratios; **CI = 95% confidence intervals

Research Question 1

The first research question asked the following: Is there an association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer? The variables were serum iron concentration (low, high) and prostate cancer diagnosis (yes, no). Because both variables were categorical, a chi-squared independence test was used to address this question. The results indicated a nonsignificant difference (p = .36). See Table 4. Based on this result, the null hypothesis is retained.

Additionally, because researchers differ widely with respect to how serum iron concentration is operationalized (continuous, tertiles, quartiles), the tests of RQ1 were followed by reclassifying the serum iron concentration variable into tertiles and quartiles,

and by treating it as a continuous variable. In all cases, there was no statistically significant association between serum iron concentration and prostate cancer diagnosis.

Research Question 2

The second research question asked the following: Is there an association between age and prostate cancer in males? The independent variable was age (continuous), and the dependent variable was prostate cancer diagnosis (yes, no). Therefore, logistic regression analysis was used to test the hypothesis. The results indicated a significant, positive association ($p = .002$) between age and cancer prostate diagnosis. See Table 4. Therefore, the null hypothesis was rejected. Additionally, Wald statistic was significant for age (Wald = 9.32, $p = .002$), and the odds ratio ($OR = 1.07$) indicates that, as age increases by 1 year, the predicted odds log for a prostate diagnosis increases. As age increases, the likelihood of having prostate cancer increases.

Research Question 3

The third research question asked the following: Is there an association between ethnicity and prostate cancer? The variables were ethnicity (categorical) and prostate cancer diagnosis (yes, no). Therefore, a chi-squared independence test was used to test the hypothesis. The results indicated a significant association ($p = .003$). See Table 4. Therefore, the null hypothesis was rejected. There is a significant relationship between ethnicity and prostate diagnosis. Non-Hispanic Blacks were more likely to be diagnosed with prostate cancer (6.0%). Other Hispanics were the second most at-risk ethnic group, with a 4.1% diagnosis rate ($OR = 1.56$, 95% CI = 0.67–3.61), followed by non-Hispanic Whites (2.7%; reference for *OR*). Mexican Americans had the lowest diagnosis rate

(1.1%; *OR* = 0.40, 95% CI = 0.12–1.36). The odds ratio (*OR* = 2.31) for Black men indicates that the odds of being diagnosed with prostate cancer is 2.31 times higher than that of White men.

Research Question 4

The fourth research question asked the following: Is there an association between serum iron concentration and prostate cancer when controlling for age and ethnicity? The independent variables were age, ethnicity, and serum iron concentration, and the dependent variable was prostate cancer diagnosis. Hierarchical logistic regression analysis was used to test the hypothesis. The first step of the regression included the control variables. In step two, serum iron concentration was added. The results are summarized in Table 5.

Table 5

*Logistic Regression Analysis for Serum Iron Predicting Prostrate Diagnosis**

Variable	Crude OR**	CI*** 95%	p	Adjusted OR	CI 95%
Low[a]	0.76	0.43, 1.36	0.11	0.62	0.34, 1.12
High	Reference	Reference		Reference	Reference

Note. [a]Serum iron = 0 = less than 75th percentile, 1 = 75th percentile or higher
*Adjusted for age and ethnicity; *OR = odds ratios; **CI = 95% confidence intervals

The results indicate that there is not a significant relationship between the variables when serum iron is added to the model for predicting prostate diagnosis (p = .11). The null hypothesis was retained, and it cannot be concluded that there is an association between serum iron concentration and prostate cancer diagnosis when controlling for age and ethnicity.

Research Question 5

The fifth research question asked the following: Is there an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week? The independent variables were poverty-to-income ratio (PIR), educational attainment, BMI, hours worked in the last week ("work"), and serum iron concentration. The dependent variable was prostate cancer diagnosis. Hierarchical logistic regression analysis was used to test the hypothesis. The first step of the regression included the control variables. In step two, serum iron concentration was added. The results are summarized in Tables 6 and 7.

Table 6

*Logistic Regression Analysis for Serum Iron Concentration Predicting Prostrate Diagnosis**

Variable	**Crude OR****	**CI*** 95%**	***p***	**Adjusted OR**	**CI 95%**
Low[a]	0.76	0.43, 1.36	0.96	0.99	0.51, 1.89
High	Reference	Reference		Reference	Reference

Note. [a]Serum iron = 0 = less than 75 percentile, 1 = 75 percentile or higher
*Adjusted for PIR, educational level, and hours worked; **OR = odds ratio; ***CI = 95% confidence interval

Table 7

*Logistic Regression Analysis for Serum Iron Concentration Predicting Prostrate Diagnosis**

Variable	Crude OR**	CI*** 95%	*p*	Adjusted OR	CI 95%
Low[a]	0.76	0.43, 1.36	0.32	0.74	0.41, 1.34
High	Reference	Reference		Reference	Reference

Note. [a]Serum iron= 0 = less than 75 percentile, 1 = 75 percentile or higher
*Adjusted for BMI; **OR = odds ratio; ***CI = 95% confidence interval

The results indicated that there is no significant relationship between the variables when serum iron is added to the model for predicting prostate diagnosis, either when controlling for poverty-to-income ratio, educational attainment, and hours worked in the last week ($p = .96$) or when controlling for BMI ($p = .32$). When testing BMI in categories conforming to the CDC's low, normal, and high BMI cutoffs, the BMI result was still non-significant. Thus, the null hypothesis was retained. It cannot be concluded that there is an association between serum iron concentration and prostate cancer when controlling for poverty-to-income ratio, educational attainment, BMI, and hours worked in the last week.

Summary

In summary, the answers to the research questions are as follows:

RQ1: "Is there an association between serum iron concentration, measured as µg of iron per dL of blood, and prostate cancer?" This study failed to support an association between serum iron concentration and prostate cancer diagnosis. The alternative

hypothesis H_a1, "There is an association between serum iron concentration, measured as μg of iron per dL of blood, and prostate cancer," is rejected.

RQ2: "Is there an association between age and prostate cancer in males?" This study supported a positive association between age and prostate cancer diagnosis. The alternative hypothesis *H*a2, "There is an association between age and prostate cancer," is accepted.

RQ3: "Is there an association between ethnicity and prostate cancer?" This study supported an association between ethnicity and prostate cancer diagnosis. The alternative hypothesis *H*a3, "There is an association between ethnicity and prostate cancer," is accepted.

RQ4: "Is there an association between serum iron concentration and prostate cancer when controlling for age and ethnicity?" This study did not supported such an association. The alternative hypothesis *H*a4, "There is an association between serum iron concentration and prostate cancer when controlling for age and ethnicity," is rejected.

RQ5: "Is there an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week?" This study failed to support such an association. The alternative hypothesis *H*a4, "There is an association between serum iron concentration and prostate cancer after controlling for body mass index, poverty-to-income ratio, educational attainment, and hours worked in the last week," is rejected.

The following chapter contains a detailed discussion of these results. In Chapter 5, the results are considered in light of previous research and in light of the theoretical

framework of this study. Chapter 5 also contains implications of these findings for practice, recommendations for future research, and a consideration of the limitations of this study.

Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of this quantitative study was to determine whether there is an association between serum iron concentration and prostate cancer, generally, and when controlling for age, ethnicity, BMI, poverty-to-income ratio, educational attainment, and hours worked in the last week, among a sample of men aged 51 to 70 in the United States. This was a secondary data examination using data gathered from the NHANES from 2009 to 2012. Chi-squared independence tests and logistic regression analyses were used to test five sets of hypotheses. Results indicated there was no significant association between serum iron concentration and prostate cancer diagnoses in the research sample. However, a significant association was observed between prostate cancer diagnosis and age, as well as a significant association between prostate cancer diagnosis and ethnicity.

This chapter contains a discussion and interpretation of the results in light of existing literature on the research topic and in light of the theoretical framework of this study. Following this interpretation of findings, the limitations and generalizability are described in the study. Next are recommendations for future research and implications for social change and for practice. Finally, summaries and conclusions are presented for the study.

Interpretation of Findings

In this section, I present an interpretation of the findings. First, findings related to the primary association of interest, between serum iron concentration and prostate cancer, are discussed. Next, findings related to the control variables, especially age and ethnicity,

are interpreted, since these associations were of secondary importance to the research aim.

Serum Iron and Prostate Cancer

This study failed to demonstrate an association between serum iron concentration and prostate cancer diagnosis in this sample population. The study findings are not in agreement with other studies, who report and association between serum iron and the risk of prostate cancer (Grant, 2008; Huang, 2003). Conflicting findings are reported in literature. At least one study has directly examined the relationship between serum iron concentration and prostate cancer and, like this study, also failed to find an association (Kuvibidila et al., 2004). However, the Kuvibidila et al. (2004) study had a small sample size of 117. In that study, the sample was largely African American, which suggests a need to consider ethnicity as a potentially confounding variable. In the present study, the study has diverse representation of all races. Therefore, this study supported the finding of Kuvibidila et al. (2004) that high serum iron concentration does not increase the probability of prostate cancer diagnosis. While the sample size was 1,850 males, sampling variability cannot not be ruled out. Therefore, these findings should be interpreted with caution. The results show an association based on the study population, but were not conclusive. More studies are imperative in this area.

This research calls into question some findings that have suggested an association between iron and prostate cancer. Matos et al. (2006) observed significant prostate damage in rats injected with iron compound, strongly suggesting a link between increased iron and prostate risk. Similarly, Geier et al. (2002) found a higher risk of

malignancies, including prostate cancer, in a sample of individuals with hereditary iron overload. These findings suggested a need for further research into the relationship between iron and prostate cancer risk. This study demonstrated that any link between serum iron and prostate cancer diagnosis was not statistically significant for this research sample, thereby lending considerable weight to the supposition that no link exists. In a muddled research area with ambivalent findings, the clear result of this research is an important step forward. However, since the data were not weighted, the result holds definitively only for the population of this study and cannot be generalized to other populations.

The theoretical framework upon which this research was based suggested that serum iron concentration could be associated with prostate cancer diagnosis through oxidative stress pathways. Large bodies of research link excess iron to oxidative stress (Bhagat et al., 2013; Bystrom et al., 2014; Karihtala & Soini, 2007; Koskenkorva-Frank et al., 2013; Romeu et al., 2013; Valko et al., 2005) and oxidative stress to carcinogenesis (Klaunig et al., 2010; Kotrikadze et al., 2008; Sharma et al., 2014; Zachara et al., 2005). Therefore, based on the exposure–disease model, increased iron exposure is hypothesized, leading to increased serum iron concentration, could be associated with risk of prostate cancer diagnosis. However, this study failed to support the hypothesized pathway, calling the theoretical framework into question. There are several possible explanations for the result, each of which suggests a modification of the theory that grounded this study.

First, it is possible that oxidative stress does not influence prostate cancer development, but leads to more aggressive forms of prostate cancer and thereby to increased risk of mortality and morbidity from prostate cancer. This possibility is strongly supported by the findings of Paschos et al. (2013), whose research indicated a link between oxidative stress and aggressive prostate cancers. Research conducted by Choi et al. (2008) supports the iron connection. The researchers found no connection between prostate dancer and dietary iron, but there was a major association between elevated iron consumption and the risk of aggressive prostate cancer risk (Choi et al., 2008). In this present study, there was no data collected on the aggressiveness or metastatic status of participants' prostate cancer diagnoses and may, therefore, have failed to uncover a link between serum iron concentration and aggressiveness of prostate cancer. This issue is mentioned further in the Recommendations section of this chapter.

Another possible explanation for the contradiction between these research findings and the theoretical framework is that serum iron concentration is not an adequate proxy for primary iron status. Although recent research has been conducted using serum iron concentration as a proxy for total body iron (Huang et al., 2014), not enough research exists to confirm the utility of this variable. Although serum ferritin is a more commonly used proxy, a growing body of evidence suggests that it does not adequately reflect total body iron (Ferraro et al., 2012; Puliyel et al., 2011; Yin et al., 2014). Therefore, the use of serum iron concentration as an alternative is in the emerging stages, and it cannot be concluded with certainty that it yields accurate results for hypotheses about total body iron and overall iron exposure. Compared with other explanations,

however, this seems less likely, because serum iron concentration has been found to have a positive association with oxidative stress (Zhao et al., 2014), which supports its use as a proxy variable for total body iron and supports the empirically established connection between iron and oxidative stress. Nevertheless, more research will be required to establish the adequacy of serum iron concentration in studies like this one.

Finally, when directly comparing serum iron concentration to prostate cancer diagnosis with no control variables included (RQ1), I did not find a significant correlation. This is important because it strongly suggests the absence of a link in this sample, independently of other factors. However, if there are confounding factors that would tend to dampen a statistical correlation between serum iron and prostate cancer diagnosis, failure to control for these could have obscured a more significant result. For example, there may be hereditary factors that give certain men predisposition to or resiliency against prostate cancer, regardless of their iron exposure. It is known that men can be genetically predisposed to developing hereditary prostate cancer (Lynch et al., 2016). Since it is unknown with what type of prostate cancer the men in this study were diagnosed with, it is possible that the sample contained a large number of patients with genetic predispositions toward or against prostate cancer, regardless of iron exposure. Such a sample would tend to obscure a link that might hold in the absence of genetic factors.

Prostate Cancer, Age, and Ethnicity

This study supported previous findings indicating positive relationships between prostate cancer and age, and prostate cancer and ethnicity. Recent research has

established a higher prevalence of prostate cancer diagnosis with increasing age (Daskivich et al., 2013; Hong et al., 2013; Leal et al., 2014). Confirming these findings, in the present study demonstrated that, as age increases, the probability of having a prostate cancer diagnosis increases. Because this sample excluded men over 70 years of age, the finding is particularly important because it emphasizes the utility of age-related prostate cancer screenings before this advanced stage of life. However, compared with prior studies, the odds ratio for age in this study (*OR* = 1.07) was relatively low. As mentioned previously, this could suggest the presence of other factors in the sample that overcame the influence of age.

Similarly, existing research related to ethnicity and prostate cancer diagnosis was confirmed. Previous researchers have found that prostate cancer risk is uniformly higher among African Americans (Hong et al., 2013; Leal et al., 2014; Zhao et al., 2012) compared with other ethnicities. This study also clearly indicated that Non-Hispanic Blacks had the highest risk of prostate cancer. Among this research sample 6.0% of non-Hispanic Blacks had a diagnosis, compared with only 2.7% of non-Hispanic Whites (*OR* = 2.31). There was no evidence found of an association between prostate cancer and BMI or between prostate cancer, poverty-to-income ratio, hours worked per week, and educational attainment, the findings provide some support for a genetic predisposition to prostate cancer among non-Hispanic Blacks, or for a link to social determinants other than economics. This is important because it suggests that the ethnicity difference is not simply an artefact of socioeconomic and health disparities between Blacks and other ethnic groups but other factors as well.

This study contributes new evidence of lower prostate cancer risk among Mexican Americans, who had the lowest diagnosis rate (1.1%) in this sample. This supports the early finding of Martin and Suarez (1987), who found that Mexican Americans had lower rates of common cancers, including prostate cancers, than other Whites. However, limited research exists addressing prostate cancer risk among Mexican Americans. One study focusing on prostate cancer risk in this ethnic group found that increased agrochemical exposure and decreased occupation-related physical activity contributed to prostate cancer risk among Mexican Americans in Texas (Strom, Yamura, Flores-Sandoval, Pettaway, & Lopez, 2008). However, these researchers did not compare Mexican Americans to other ethnic groups. Other Hispanics were, in the present study, the second most at-risk ethnic group, with a 4.1% diagnosis rate. This suggests statistically significant differences, whether genetic or lifestyle related, between Mexican Americans another Hispanics in the United States. These differences deserve to be investigated further.

Recommendations for Future Research

The findings of this study reveal several important avenues for future researchers. First, these findings lend focus to the area of research on prostate cancer and iron exposure. Most notably, the next phase of this research should address the relationship between serum iron concentration and aggressive forms of prostate cancer. Although this study failed to reveal a connection between serum iron and prostate cancer within the sample population, it did not take type or metastatic status into account. On the basis of prior research findings, it is possible that a connection exists between iron and aggressive

forms of prostate cancer, even if the relationship does not hold for prostate cancer overall. Therefore, it is recommended that researchers explore the possible correlation between serum iron concentration and aggressive prostate cancer risk in a large sample such as the one used in this study.

Second, this study calls into question the appropriateness of using serum iron concentration as a proxy variable for total body iron, especially in comparison with other possible proxy variables. Researchers should continue to conduct investigations to determine the adequacy of this proxy. Finally, to more robustly confirm the lack of association between serum iron concentration and prostate cancer diagnosis, researchers should repeat this study with other control variables that could obscure or contribute to an association.

Implications for Practice and Social Change

This study has some implications for healthcare practice and social change, particularly with respect to public health. Most importantly, it confirmed the importance of screening for prostate cancer based on demographic characteristics such as age and ethnicity. Given the dangers of undetected prostate cancer and the body of empirical evidence suggesting associations between age and ethnicity, regular screenings for those in high-risk categories could reduce the overall prostate cancer disease burden in the United States.

Furthermore, this study suggested that it is premature to use serum iron concentration as a screening tool to detect prostate cancer risk. Practitioners are encouraged to continue use of more established screenings, such as PSAs, and to await

further research before considering iron intake and exposure as a factor in prostate cancer. This does not, however, contradict previous findings related to hereditary iron overload and cancer risk, since hereditary conditions were not considered as a factor.

Finally, this study contributes to social change and public health improvement by providing a renewed focus for research on iron, oxidative stress, and prostate cancer. In the future, researchers may use these findings as a point of departure for studies that will contribute to our overall understanding of prostate cancer in the United States.

Limitations

This study is subject to certain limitations that readers should carefully bear in mind when interpreting the results. First, the study consisted of secondary data collected as part of the NHANES. The NHANES data were gathered using a multistage probability sampling design to obtain a sample representative of the entire noninstitutionalized U.S. population. For most variables studied by the NHANES, data were collected from one-third of the full sample. The study was unable to consider factors not contained in the NHANES dataset. Any inaccuracies in measurement, reporting, and data entry to which the NHANES data were subjected to were limitations to this study. For example, if laboratory technicians failed to accurately measure serum iron, the data for this study could be inaccurate. However, the NHANES dataset is robust and has been used by numerous other researchers to study a wide range of topics. Therefore, possible data inaccuracies do not present a great risk to the study. Additionally, there are no claims to the generalizability of results beyond the study.

Because the NHANES data were drawn from a nationally representative sample, the sample of this study may be nationally representative. However, because no sample weights were used, the study cannot be generalized beyond the specific sample of the study. The results may not be generalizable to other countries or to men of other ages. Additionally, the results cannot be generalized to other forms of cancer or other measures of primary iron status.

Summary and Conclusion

According to the American Cancer Society (2014), there are over 2 million adult males in the United States diagnosed with cancer of the prostate, which has a 1 in 35 mortality rate. As such, prostate cancer is one of the main causes of mortality in adult males in the United States (Kuvibidila et al., 2004). There is an urgent need to understand risk factors, including dietary and exposure factors, in order to improve prostate cancer prevention and reduce the disease burden, and thereby improving public health disease outcomes. The present study accomplished the goal of investigating the link between iron and prostate cancer.

This study failed to find an association between serum iron concentration and prostate cancer diagnosis among a sample of men aged 51 to 70 but there was a contribution to the body of knowledge. First, it contributed to what had been an ambiguous research area by lending significant weight to the claim that there is no broad association between iron and prostate cancer risk; second, it provided several new and important research directions, notably, there is a need to investigate a potential connection between serum iron concentration and aggressive forms of prostate cancer;

and finally, it represented a methodological model for investigating prostate cancer risk factors using NHANES data.

Although the study did not find the hypothesized relationship to serum iron concentration, the study did confirm that age and ethnicity are significant risk factors in predicting prostate cancer diagnosis. Additionally, the quest to understand the relationship between iron and prostate cancer is not over. Other factors, including hereditary factors, may play a confounding role. Further, oxidative stress is complex and multifaceted, and exposure risks play only one small part. Further research is needed to reduce prostate cancer risk to men in the United States. It is hoped that this present study will serve as a source of direction and inspiration to other researchers, and that, working together, the research community can reduce the significant burden of prostate cancer.

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