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Leptin Level Variance in Adults With and Without Cancer

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Walden University
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Abstract

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BS, University of Arkansas at Pine Bluff, 1996

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

In 2018, health statistics revealed that, despite the many preventive measures established, cancer was the second leading cause of death in the United States and the leading cause of death in 22 states, exceeded only by heart disease. With obesity/leptin levels reaching pandemic levels worldwide, and cancer having a well-known association with obesity, both chronic diseases represent a large proportion of public health challenges. Guided by the social ecological model, the purpose of this cross-sectional, quantitative study was to examine if a significant difference exists in leptin levels among adults with different types of obesity-associated and common cancers and those without cancer. Further, using secondary data from the third National Health and Nutrition Examination Survey, the correlation of cancer risk factors with leptin levels among a multiethnic sample of adults living in the United States was also examined. ANCOVA and multiple linear regression analysis revealed that a significant difference exists in leptin levels among individuals with different types of cancer. A correlation also exists between cancer risk factors and leptin levels in adults with different types of cancer. The results further revealed that those with cancer had higher leptin levels than those without cancer after adjusting for related covariates. Health professional and educators worldwide working together to increase awareness and health literacy to empower not only the current study population, but all populations in adopting healthier lifestyles that will hopefully aid in reducing the risk, incidence, and mortality rates of obesity and cancer at the individual, community, societal and national levels may ultimately lead to positive social change.

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Dedication

This dissertation is dedicated to the memory of my mother, Mrs. Helen J. Chatman-Stovall, who passed away at the tender age of 46 years due to colorectal cancer. This excruciatingly painful loss was the catalyst for my educational journey.

Acknowledgments

First and foremost, I would like to thank God Almighty, who is the head of my life, for without Him nothing would be possible. Thank you, Lord, for this supernatural blessing. The support, effort, and patience of many individuals have made this journey possible. I would like to thank Dr. Scott McDoniel, my dissertation chairperson. His leadership, support, and wisdom have been instrumental in this process, and I am sincerely grateful for the time and effort he put forth to help me reach my goal. I would also like to thank my methodologist, Dr. Zin Htway, who guided me through every step of the methodology process with expertise and patience. I am grateful that he demanded excellence and appreciate his guidance. His assistance was just what I needed to help get me over the threshold. I am thankful to have had such a gifted team.

Further, I would like to thank my biological family, church family, and friends for all their prayers and encouragement. I would particularly like to thank my friends and sorority sisters Terrilyn Ellis and Dana Woolfolk for encouraging and believing in me even when I did not believe in myself. Finally, I would like to thank my husband, Stephen L. Terry. There are not enough words to describe how much his unending support has meant to me. I thank him for his patience, the endless hours of discussions, lending a listening ear, and being there throughout this process. Thank you, honey. I love you.

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Chapter 1: Introduction of the Study

Introduction

Every year, cancer claims the lives of more than 500,000 Americans (Centers for Disease Control and Prevention [CDC], 2016k). Despite the many preventive and control measures established, cancer remains the second leading cause of death in the United States, exceeded only by heart disease (CDC, 2016k; Heron & Anderson, 2016). The number of new cancer cases is likely to rise in both men and women by 2020, to approximately 24% and 21%, respectively (CDC, 2016k). The largest increase expected is in melanoma (skin cancer), prostate, lung, female breast, and uterine cancers (CDC, 2016k). Researchers have shown the above-named cancers, as well as cancers of the ovaries and colon, have an association with obesity, whether inverse or direct (CDC, 2016k).

The prevalence of obesity in the past decade has more than doubled in the United States (Rodriguez, Mastronardi, & Paz-Filho, 2013). Biological, social, and environmental factors influence obesity (Sheesley, 2016; Trust for America's Health 2017). Obesity and leptin have become synonymous in recent times. Leptin is a peptide hormone produced mostly by adipose (fat) tissue (Rodriguez et al., 2013). Researchers have shown substantial interest in leptin, as leptin appears to serve as an indicator regarding why obesity has become a national epidemic in the United States (Rodriguez et al., 2013). The relationship between leptin/obesity and cancer has sparked the interest of researchers since the discovery of leptin in 1994. Existing epidemiologic studies in which researchers have examined the relationship between the level of leptin and cancer have

included a range of study designs and sample sizes and have produced conflicting results. Research studies on the leptin and cancer relationship have revealed that the lack of racial diversity indicates that external validity exists (Gupta et al., 2016). Conflicting results have again emerged among existing studies relating to the relationship between the level of leptin and cancer, thereby indicating the need for further research (Aleksandrova et al., 2012; Alshaker et al., 2015; Ollberding et al., 2013; Rodriguez et al., 2013; Romero-Figueroa et al., 2013; Vona-Davis & Rose, 2007; M. Wu et al., 2014; W. H. Wu et al., 2009). Researchers have conducted mostly retrospective studies to investigate leptin's relationship to cancer, indicating reverse causation that results from weight loss ultimately resulting from effects of cancer, which is influenced by leptin levels (Gupta et al., 2016).

The gap in literature addressed in this quantitative study concerns the lack of attention regarding whether a significant difference exists in mean leptin levels among a multiethnic sample of adults with different types of obesity-associated cancers (breast, colorectal, endometrial [uterine corpus], ovarian, prostate) and the most common cancers known to have an association with leptin/obesity (lung) in a single study. Researchers might use the results of the study to create innovative approaches for diagnosis, risk stratification, and prevention of cancer, particularly among those populations most negatively affected. A better understanding of leptin and the role it plays in the progression of adiposity in the human body and its correlation to cancer, particularly those associated with obesity/leptin, could potentially identify leptin as a true independent risk factor for cancer; aid health professionals and educators worldwide

through coordinated efforts to reduce the incidence and mortality rates of cancer through research, clinical practice, and policy changes; and possibly improve prevention efforts with lifestyle and behavior changes, ultimately promoting positive social change. Social change takes the form of contributing to the development of preventive measures and programs that target successful intervention and treatment.

I begin Chapter 1 with an introduction and outline of the background of the study, problem statement, purpose of the study, and nature of the study. The focus then moves to a detailed description of the research questions and hypotheses, theoretical framework, operational definitions, assumptions, limitations, scope, and delimitations. I conclude the chapter with a discussion of the significance of the study, followed by the chapter summary and a transition to the remainder of the study.

Background

Cancer prevalence should be a health concern for everyone. Analysts at the American Cancer Society (ACS) have projected that, by the end of 2019, there would be an estimated 1,762,450 new cancer cases since 2018 and 606,880 cancer deaths in the United States (ACS, 2019). That is 27,100 more cases than estimated in 2018. Statistically, the number of new cases and deaths equate to 146,870 new cases and 50,570 new deaths per month, 4,830 new cases and 1,660 new deaths per day, and three new cases and one death every minute (ACS, 2019). The direct medical costs for the treatment of cancer in United States were $74.8 billion in 2013 (Centers for Disease Control and Prevention [CDC], 2013). The prognosis of a cancer diagnosis has become much more favorable than it was in previous years. According to Healthy People 2020, among people

who develop cancer, more than half will be alive in 5 years (Office of Disease Prevention and Health Promotion, 2014). However, cancer remains the second leading cause of death in the United States (CDC, 2016a). The aforementioned statistics concerning projected cases indicates the need for continued research relevant to the risk factors that aid in causing the disease (i.e., tobacco use, obesity, ultraviolet radiation) and the preventive measures. Results of this type of research may aid in providing evidence to guide public health recommendations and regulations (ACS, 2017).

Various researchers have conducted studies to determine an association between leptin and obesity-associated cancers, such as breast, colon/colorectal, endometrial (uterine), ovarian, and prostate, and have provided contrary results in terms of a clear correlation in some of the human epidemiological studies conducted to support the relationship in both men and women (Aleksandrova et al., 2012; Frezza, Wachtel, & Chiriva-Internati, 2005; Ho et al., 2012; Rodriguez et al., 2013; Stattin et al., 2004). However, researchers have conducted very few studies to examine an association between increased leptin levels and an increased risk of developing certain types of obesity-associated cancers (Wang, He, Wang, Wang, & Wang, 2014; W. H. Wu et al., 2009). Even fewer researchers have conducted studies to determine leptin's relationship to the most commonly diagnosed cancers: skin (melanoma of the skin) and lung (Gogas et al., 2007; M. Song et al., 2014; Terzidis et al., 2009). In this study, I included an examination of both lung and skin (melanoma) cancers, although researchers neither commonly associate nor identify them as obesity-associated cancers. Although researchers have suggested that obesity increases the risk of developing melanoma in a

few epidemiological studies, no one has clearly established a direct cause and effect relationship (ACS, 2016a; Brandon et al., 2009). Obesity promotes leptin expression, which may contribute to neoplastic growth and ultimately lead to skin cancer (ACS, 2016a; Brandon et al., 2009). Researchers of epidemiological studies have revealed an association between elevated leptin levels and lung cancer, but the limited research on leptin, its receptors, and their relationship to lung cancer have produced conflicting results (Alemán et al., 2002; Gulen et al., 2012; Kerenidi et al., 2013; Terzidis et al., 2009).

The gap in the literature addressed in this study was the lack of attention in studies to examine if a noteworthy difference exists in leptin levels among a multiethnic sample (non-Hispanic White, non-Hispanic Black, and Mexican American/other) of adults with different types of cancers associated with obesity (breast, colorectal, endometrial [uterine corpus], ovarian, prostate) and common cancers (lung and skin) in a single study. Researchers might use the results of the study to create innovative approaches for the diagnosis, risks, and treatment of cancer, particularly among those populations most negatively affected. A better understanding of leptin and the role it plays in the progression of corpulence in the human body and its correlation to cancer (particularly those known to have an association with obesity/leptin) could potentially aid health professionals and educators worldwide through coordinated health literacy efforts to lessen the frequency and mortality rates of cancer through research, clinical practice, and policy changes and possibly improve prevention efforts with lifestyle and behavior changes, ultimately promoting positive social change.

Problem Statement

An association exists between high leptin levels and an increase in obesity incidence and obesity-associated cancers (CDC, 2017). Leptin is a well-established adipokine or hormone that influences appetite control, overindulgence, body weight, and the release of energy via its actions on the hypothalamus and other regions in the brain (Rodriguez et al., 2013). In recent years, both obesity and obesity-associated diseases (i.e., cancer, Type 2 diabetes, and cardiovascular disease) have been the subject of growing concern in the United States. Obesity refers to having a body mass index (BMI) > 30 kg/m^2, and with more than 78.6 million or 34.9% of adults classified as obese, it has reached epidemic proportions in the United States (CDC, 2017). An association also exists with regards to overweight and obesity and an increased risk of at least 13 types of cancer, and according to a recent vital signs report by the CDC, these cancers have accounted for approximately 40% of all cancers diagnosed in the United States in 2014 (CDC, 2017).

The problem is that individual/interpersonal factors such as poor diet or lack of physical activity yield incidence of becoming overweight, obese, or morbidly obese, which in turn leads to increased leptin hormone levels that can ultimately foster the development of obesity-associated cancers (breast, colorectal, endometrial, lung, ovarian, prostate, and skin). Researchers have shown an association between increased leptin levels and incidence of cancer. However, few researchers have examined if a significant difference exists in leptin levels among individuals diagnosed with different types of cancer. At the time of this study, there was no published research in which researchers

had investigated a difference in leptin levels to established cancer risks factors (age, gender, BMI, race/ethnicity, Type 2 diabetes mellitus [T2DM], occupation, education, income level [socioeconomic status; (SES)]) and individual/interpersonal factors (dietary intake and physical activity).

Purpose of the Study

The purpose of this quantitative study was to examine if a significant difference exists between leptin levels in individuals with different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, lung, and skin) and those without cancer after adjusting for established cancer risk factors among a multiethnic sample of adults living in the United States from a periodic survey: the third National Health and Nutrition Examination Survey (NHANES III; CDC, 2015). The researchers at the National Center for Health Statistics (NCHS) of the CDC who conducted NHANES III collected, analyzed, and disseminated data on the health status of residents residing in the United States (CDC, 2015). NHANES III was the seventh survey in a series based upon a complex plan with multiple stages conducted from 1988 to 1994 and created to provide national estimates of the health and nutritional status of residents in the United States (CDC, 2015). The independent variable for this study was the types of cancer reported. The covariates or risk factors examined were age, gender, BMI, race/ethnicity, T2DM, dietary intake, physical activity, education level, income level, and occupation. The dependent variable was leptin levels.

The results of this study may lead to an improved understanding of the possible correlation between leptin and cancer, particularly the cancers known to have an

association with obesity and observed in this study: colorectal, ovarian, prostate, breast, lung, endometrial (uterine corpus), lung, and skin (melanoma). Researchers could use the results to create innovative approaches for the diagnosis, risks, and treatment of cancer and obesity, particularly among those populations most negatively affected. Researchers at the National Center for Chronic Disease Prevention and Health Promotion lead efforts in the United States to prevent and control chronic illnesses (CDC, 2015). In terms of race and ethnicity, African Americans are more likely to die of cancer than are people of any other race or ethnicity (CDC, 2015). In 2011, the age-adjusted death rate per 100,000 people for all types of cancer combined was 199 for African Americans, 169 for European Americans, 112 for American Indians/Alaska Natives, 118 for Hispanics, and 106 for Asians/Pacific Islanders (CDC, 2015).

Cancer and diabetes are two of the most prevalent chronic diseases, and both have an association with obesity as a risk factor (CDC, 2015). Beginning in 2011–2012, the prevalence of obesity was highest among non-Hispanic Black adults (47.8%), with Hispanic adults (42.5%), non-Hispanic White adults (32.6%), and non-Hispanic Asian adults (10.8%) following (Ogden, Carroll, Kit, & Flegal, 2013). Understanding leptin and the role it plays in the progression of adiposity in the human body and its correlation to cancer, particularly those known to have an association with obesity/leptin, could aid health professionals and educators worldwide through coordinated efforts to reduce the incidence and mortality rates of cancer through research, clinical practice, and policy changes and could improve prevention efforts with lifestyle and behavior changes, ultimately promoting positive social change.

Research Questions and Hypotheses

The research questions and hypotheses used in the study were as follows:

Research Question (RQ) 1: Is there a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity)?

$H_0$1: There is not a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity).

H_a1: There is a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity).

Research Question (RQ)2: Is there a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, prostate, ovarian, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM)?

$H_0$2: There is not a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

H_a2: There is a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

Research Question (RQ) 3: Is there a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity)?

H_03: There is not a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity).

H_a3: There is a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity).

Research Question (RQ) 4: Is there a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, income (SES)] and two individual interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer?

H_04: There is not a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race-ethnicity, T2DM, occupational status, education, income (SES)] and the two individual/interpersonal factors [dietary intake and physical

activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer.

H_a4: There is a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race-ethnicity, T2DM, occupational status, education, income (SES)] and the two individual/interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer.

Theoretical Framework

The theoretical framework for this study was the ecological or social ecological model (SEM). Developed in the late 1970s, the SEM views health outcomes as if interwoven in the fabric of society (Bronfenbrenner, 1979; Stokols, 1996; Whittemore, Melkus, & Grey, 2004). The SEM aids in recognizing the relevant factors that influence behaviors and provides the necessary direction for developing successful programs through social environments (CDC, 2013). The public health community has used the SEM as the foundation of multilevel intervention design and implementation, encouraging researchers and practitioners to explore methods that promote internal and external changes via each of its five levels of influence: individual/intrapersonal, interpersonal, organizational, community, and policy levels (CDC, 2013; Moore, Buchanan, Fairley, & Smith, 2015).

The basic tenets of the SEM specify that ecological problems that occur from social issues deeply rooted within society influence human nature (CDC, 2013b). Social ecology recognizes the importance of social, institutional, and cultural components within

an individual and in the context of the relationship between individuals and their environment (Glanz, Rimer, & Viswanath, 2008). The environment is a vital component intertwined throughout an individual's personality and interacts with behavior to influence the individual's well-being (Stokols, 1996).

Various individual, social, and environmental factors influence cancer and obesity outcomes (Moore et al., 2015). The SEM factors are multifaceted and stem from a complex nature (Burke, Joseph, Pasick, & Barker, 2009). According to the ecological framework, using a multilevel approach that involves using interventions that mainly concentrate on health behaviors that involve interventions that focus on social, environmental, and policy as well as on the individual/intrapersonal level is most effective in reaching the intended goal (Glanz et al., 2008). The SEM further includes interpersonal, sociocultural, and other broader community or environmental factors (Glanz et al., 2008).

Several aspects of the social ecological perspective were relevant to this study. The first was that various factors within an environment can influence individuals and their patterns of behavior, as well as other characteristics (CDC, 2013). Personal factors and environmental change are examples of interventions that have not been successful in creating long-term behavioral change (Baranowski, Cullen, Nicklas, Thompson, & Baranowski, 2003). Thus, establishing interventions that help influence positive health outcomes that focus on several areas of change, including personal factors and broader environmental issues, may produce a more successful outcome (Baranowski et al., 2003).

Consequently, efforts to promote well-being should incorporate the individual as well as the environment (Baranowski et al., 2003). In this study, the individual/intrapersonal factors and community influences align with the SEM perspective of combining the individual and the environmental factors that influence health outcomes. Additionally, various levels of the environment that work together also influence the health of an individual, as was suggested by Baranowski et al. (2013). Efforts from family members, leaders in the community, and those who initiate health policies working together in the field of health promotion help influence the outcome of health. The following paragraphs include a detailed description of the components of the SEM related to this study.

Individual/intrapersonal level represents the characteristics of an individual's knowledge, attitudes, beliefs, genetics, risk factors, personality traits, and demographic characteristics (CDC, 2013; Moore et al., 2015). For this study, the individual/personal factors were age, gender, race/ethnicity, occupation, education, income level (SES), dietary intake, leptin levels, physical activity, BMI, and T2DM. The targeted cancers in this study were breast, colorectal, endometrial (uterine corpus), ovarian, prostate, and lung.

The *interpersonal level* of the SEM surrounds the individual and refers to formal and informal social networks and support systems that can influence individual behaviors, including family, friends, peers, coworkers, religious networks (i.e., churches), health care providers, community health workers, and patient navigators' customs or

traditions, and represent potential sources of support toward cancer and obesity prevention (CDC, 2013; Moore et al., 2015).

The *organizational level* of the SEM surrounds the interpersonal level. These activities serve to facilitate individual behavior change by influencing organizational systems and policies. Health care systems, employers or worksites, health care plans, local health departments, tribal or urban health clinics, and professional organizations represent potential sources of organizational messages and support (CDC, 2013; Moore et al., 2015).

Community level embodies the cancer and obesity prevention activities implemented at this level. The purpose of these activities is to promote individual behavior change by influencing resources and the involvement of community-level institutions, such as cancer control coalitions and health departments to expand cancer screening via public awareness and educational campaigns (CDC, 2013). This level also denotes relationships among entities within specific boundaries, which include organizations, institutions, community leaders, businesses, and transportation (CDC, 2013).

Policy level is the final level of the SEM. This level pertains to local, state, national, and global laws and policies regarding the allocation of resources and access to health care services regarding cancer and other prevention activities that promote healthy behaviors (CDC, 2013). Cancer and obesity prevention activities may involve working with organizations and partnerships to communicate policy decisions to the public or translating policies to members of communities.

As previously mentioned, several individual, social, and environmental factors influence cancer outcomes. The foundations of the research questions posed in this study were theories based on the SEM that various individual factors (e.g., age, race, demographic characteristics, risk factors), social, and environmental factors influence cancer outcomes. Specifically, the research questions follow the concepts of individual, social, and environmental: RQ1 (social, environmental), RQ2 (individual, environmental), RQ3 (social, environmental), and RQ4 (individual, environmental). Thus, this study involved examining if specific individual level variables identified through the SEM would determine if a significant difference exists in leptin levels among a multiethnic sample of adults with different types of cancer. Leaders at the CDC have already adapted the SEM of health promotion to approach prevention for several cancers (CDC, 2013), which further supported using the SEM as a useful context for exploring the ways that leptin levels could influence cancer outcomes among adults living in the United States.

Nature of the Study

The nature of this study was a quantitative, cross-sectional approach based upon identifying individual/interpersonal factors from secondary data that may influence if significant differences in leptin levels exist in adults with and without cancer. The study involved performing secondary data analysis from the nationwide periodic survey NHANES III household adult data and leptin files. I used NHANES III to assess the relationship between leptin and cancer. The independent variable for this study was the type of cancer: breast, colorectal, endometrial (uterine corpus), ovarian, prostate, or lung.

The dependent variable was leptin levels. The variables examined were age, gender, BMI, race/ethnicity, T2DM, education level, dietary intake, physical activity, education level, income level and occupation (SES), and skin cancer.

The cross-sectional study design approach is one of the most frequently used designs in public health research (Aschengrau & Seage, 2008; Crosby, DiClemente, & Salazar, 2006). The low cost and capacity to generalize are major advantages of a cross-sectional study design (Aschengrau & Seage, 2008; Crosby et al., 2006). Descriptive analysis, analysis of covariance (ANCOVA), correlational quantitative methods, and multiple linear regressions were suitable for analyzing the data.

Operational Definitions

Operational definitions for terms and variables used in this study are as follows:

Body mass index (BMI): BMI is an adult's weight in kilograms divided by the square of stature in meters (CDC, 2015b). BMI does not gauge muscle to fat ratios specifically, but rather research has demonstrated that BMI has a reasonable association with more straightforward measures of muscle to fat attained from skinfold thickness estimations, bioelectrical impedance, densitometry (submerged underwater weighing), double vitality x-ray absorptiometry, and different techniques (CDC, 2015b).

The unit of measure for BMI is kilograms per square meter (kg/m^2; CDC, 2015b). BMI is categorized as 18.5 kg/m^2 to 24.9 kg/m^2, a normal weights status; 25.0 kg/m^2 to 29.9 kg/m^2, overweight; 30 kg/m^2 or higher, obese (CDC, 2015b). For this study, the categorization of BMI was as follows: normal $\leq$ 24.9 kg/m^2; overweight = 25.0 kg/m^2 to 29.9 kg/m^2; obese $\geq$ 30 kg/m^2 (CDC, 2015b). BMI is essentially a simple and

economical method of screening for various weight categories, such as underweight, normal/healthy weight, overweight, and obese (CDC, 2015b).

Additionally, researchers at the National Institutes of Health (NIH, n.d.) explained that obesity is further classified as Class I obese if BMI levels of men and women fall between 30 kg/m^2 and 34.9 kg/m^2. Adults in this category are at a high risk of developing associated diseases such as cancer, T2DM, hypertension, or cardiovascular disease (NIH, n.d.). A person is Class II obese if BMI level falls between 35.0 kg/m^2 and 39.9 kg/m^2; adults in this category are at a very high risk of developing associated diseases (NIH, n.d.). A person is Class III obese, also referred to as extreme or severe obesity, when BMI is above 40.0 kg/m^2; adults in this category are at an extremely high risk of developing associated diseases (NIH, n.d.).

Breast cancer: Cancer or malignancy begins when cells in the breast start to become wild and frame a tumor that may frequently be seen on an x-ray or felt as a hard knot (ACS, 2016d). Breast malignancy happens almost totally in women, although breast cancer does occur in men (ACS, 2016). Researchers at ACS (2018) predicted that by the end of 2018, approximately 266,120 new cases of invasive breast cancer would be diagnosed in women; about 63,960 new cases of carcinoma in situ, which is noninvasive and is the earliest form of breast cancer, would be detected; and an estimated 40,920 women would die from the disease.

Cancer: Cancer is a complex group of diseases with numerous possible causes (ACS, 2015). Cancer develops when the cells in the body start to grow uncontrollably and the cancer cells eventually evict normal cells from their environment (ACS, 2015).

Many types of cancer exist: it is not just one disease (ACS, 2015). Cancer can start in the lungs, breast, colon, ovary, prostate, skin, uterus, or blood (ACS, 2015). Successful treatment is an option for many people with cancer, and more people than ever before are leading normal lives after undergoing cancer treatment (ACS, 2015).

Colorectal/colon and rectal cancer: Colorectal cancer starts when cells in the colon or the rectum develop out of control, and, depending where it starts, it can also be referred to as colon or rectal cancer (ACS, 2018). Researchers often group the colon and rectal cancer together, as they have many common features (ACS, 2018). Researchers at ACS (2018) projected that an estimated 97,220 new cases of colon cancer, 43,030 new cases of rectal cancer, and 50,260 (colon and rectum cancer combined) deaths would occur by the end of 2018.

Education: Education provides future direction for occupational and income potential (Adler & Newman, 2002). Typical measures of education include number of completed years of education, highest level of education attained, and educational credential attained (Shavers, 2007).

Endometrial (uterine) cancer: Endometrial cancer starts when cells in the inner lining of the uterus (endometrium) begin to grow out of control (ACS, 2017a). Researchers at ACS (2018) estimated approximately 63,230 new cases of cancer of the body of the uterus (uterine body or corpus) would be diagnosed and about 11,350 women would die from cancers of the uterine body in 2018.

Established cancer risk factors: Established cancer risk factors identify some lifestyle risk factors for cancer: obesity, BMI, income level, and education (ACS, 2015).

Hyperleptinemia: Hyperleptinemia occurs when elevated leptin levels occur in the blood stream (Ren, 2004). Normal leptin levels are 1.2–9.5 ng/mL in adult males and 4.1–25.0 ng/mL in adult females with normal BMI levels (18–25 kg/m^2; Quest Diagnostics, n.d.). Analysts at Quest Diagnostics lab measure leptin levels using radioimmunoassay; however, analysts at other labs also use enzyme-linked immunosorbent assay to measure serum leptin (Quest Diagnostics, n.d.).

Individual socioeconomic status (SES): Individual SES is a dynamic set of economic and social variables that contribute to an individual's or a group's position in society (Buchanan, 2000; Shavers, 2007). Education and income are two the most common measures of individual SES (Buchanan, 2000).

Leptin: Discovered in 1994 and encoded by the obesity (ob) gene, leptin is a well-established adipokine that influences appetite control, overindulgence, body weight, and the release of energy via its actions on the hypothalamus and other regions in the brain (Rodriguez et al., 2013). Leptin is also the most important hormone when trying to understand why humans feel full or hungry (Gunnars, 2017; Rodriguez et al., 2013).

Leptin resistance: Leptin resistance occurs when the brain no longer recognizes the leptin signal sent from the adipocytes or fat cells, or it occurs when obese individuals are insensitive to their leptin production and continue to eat despite adequate amount energy stored in the body (Considine, 2011). Leptin resistance is the main obstacle for the successful treatment of obesity (Dagogo-Jack, 2015).

Lung cancer: Lung malignancy or cancer begins when cells of the lung start to become noticeably anomalous and begin to spread wildly (ACS, 2017a). As more

malignant cells develop, they can shape into a tumor and spread to different regions or areas of the body (ACS, 2017a). The most common type of primary lung cancer is non-small-cell lung cancer (NSCLC), which comprises approximately 80 to 85% of lung cancer diagnoses. The next most common type is small-cell lung cancer (SCLC), which comprises approximately 10 to 15% of all primary lung cancers (ACS, 2017a). According to researchers at the ACS, nearly 234,030 new cases of lung cancer (121,680 in men and 112,350 in women) and 154,050 deaths from lung cancer (83,550 in men and 70,500 in women) were expected to occur in 2018.

Obesity: Obesity is a common, costly, and serious chronic disease that has reached the status of pandemic in the United States (CDC, 2016a). Obesity means having a BMI $\geq$ 30 kg/m^2 (CDC, 2016a). In developed countries, such as the United States, a lifestyle that includes increased cigarette smoking, excessive alcohol consumption, poor diet, and overeating, coupled with low physical activity, leads to an increased prevalence of obesity (American Institute for Cancer Research [AICR], 2014).

Obesity-associated cancers: Cancers that develop as a result of being overweight or obese (ACS, 2015c). Twenty percent of all malignancies identified in the United States relate to preventable obesity, being physically sedentary, overabundant liquor intake, or poor nutrition and thus are preventable (ACS, 2015c; Obesity Society, 2015). Obesity-related cancers include postmenopausal breast, endometrial, ovarian, prostate, and colorectal cancer (ACS, 2015c; National Cancer Institute [NCI], 2012; Obesity Society, 2015).

Occupation status: Occupational status is an estimate of one's working conditions (Shavers, 2007). In this study, I categorized occupational status based on reported employment status.

Ovarian cancer: Ovarian cancer starts when cells in the ovaries begin to grow rapidly and uncontrollably (ACS, 2017a). Carcinomas are cancerous epithelial tumors. An estimated 85 to 90% of ovarian cancers are epithelial ovarian carcinomas. Approximately 22,240 women received a new diagnosis of ovarian cancer in 2018, and nearly 14,070 women were expected to die from ovarian cancer by the end of 2018 (ACS, 2018). Ovarian cancer mainly affects women 60 years and older (ACS, 2017a).

Prostate cancer: Prostate malignancy or cancer starts when cells in the prostate begin to develop wildly (ACS, 2017a). The prostate organ is in males and makes a portion of the seminal fluid (ACS, 2017a). Cancer of the prostate is almost always identified as adenocarcinomas created from prostate organ cells, which are the cells that make the prostate liquid that is added to semen (ACS, 2018). Around 164,690 new cases and about 29,430 deaths from prostate malignancy were likely in 2018 (ACS, 2018).

Skin cancer: Skin cancer begins when cells in the skin start to grow uncontrollably (ACS, 2016i). The three main types of skin cancer are basal cell, squamous cell, and melanoma (develop from melanocytes). Basal cell cancer is the most common type of skin cancer, and approximately eight out of 10 skin cancers fall in this category (ACS, 2016i). This type of cancer usually develops on sun-exposed areas, particularly the head and neck; if untreated, it can grow into nearby areas and invade the bone or other tissues beneath the skin (ACS, 2016i). Almost 100,000 (60,000 men and

40,000 women) new skin cancer cases and 13,500 (9,000 men and 4,500 women) deaths from skin cancer were likely in 2018 (ACS, 2018). Squamous cell carcinoma is the second most common "skin cancer," and approximately two out of 10 skin cancers are squamous cell carcinomas (ACS, 2016i). These cancers commonly appear on sun-exposed areas of the body such as the face, ears, neck, lips, and backs of the hands. They can also develop in scars or chronic skin sores elsewhere, and less often they form in the skin of the genital area (ACS, 2016i).

Melanoma skin cancer is cancer that starts in a certain type of skin cell (basal, squamous, or melanocytes) when these cells begin to grow uncontrollably (ACS, 2017a). Alternative names for melanoma cancer include *malignant melanoma* and *cutaneous melanoma*. Most melanoma cells still make melanin, so melanoma tumors are usually brown or black. But some melanomas do not make melanin and can appear pink, tan, or even white (ACS, 2017a). More than 91,000 new cases (55,000 men and 36,000 women) and 9,320 deaths (5,990 women and 3,330 women) were likely to occur in 2018 (ACS, 2018). Nonmelanoma skin cancer develops from skin cancer cells rather than melanocytes and tends to behave very differently from melanomas and often undergoes different methods of treatment (ACS, 2017a). This type of cancer usually responds to treatment and rarely spreads to other parts of the body (ACS, 2017a). Nonmelanoma skin cancers are most often found in areas exposed to the sun, such as the chest and back of men, the legs of women, and the face and neck. Soles of the feet, palms of the hands, and under the nails are additional areas on the body where melanomas occur, although more frequently in African Americans than in European Americans; however, having darker

pigmented skin lowers the risk of melanoma (ACS, 2016i). Melanoma is much less common than basal cell and squamous cell skin cancers, but far more dangerous because it is more likely to spread to other parts of the body if not discovered and treated early (ACS, 2016i).

Type 2 diabetes mellitus (T2DM): Diabetes mellitus (Type 1 and Type 2), the seventh leading cause of death in the United States, is a chronic disease that causes the pancreas not to produce enough insulin or is the inability to effectively use the amount of insulin the body produces (insulin resistance) as required for glucose homeostasis (CDC, 2015). Clinical diagnosis of diabetes occurs when an individual has a fasting blood glucose ≥ 126 mg/dL, or a 2-hour blood glucose ≥ 200 mg/dL (WHO, 2006). The most common type of diabetes is T2DM, which is distinguished by problems with insulin secretion and insulin reactivity (CDC, 2015).

Assumptions

This study included several assumptions. One assumption was that the sample of study participants of the NHANES III was an adequate representative of the multiethnic population in the United States. A second assumption was that participants of the NHANES III answered all questions regarding income level, T2DM, cancer incidence, occupational status, education, and age accurately and honestly. A third assumption was that bias resulting from using self-reported information in the NHANES III was minimal.

Assumptions are factors that could potentially affect the results of a study and over which the researcher has no control (Al-Habil, 2011). Although I took all measures to find more recent public data, an assumption of this study was that the study includes

the most recent public data. An additional assumption was that the data are accurate, and the instrument used to collect those data was a valid, reliable instrument. The final assumption was that the results of this study, which involved using specific groups of participants, would apply to similar groups of participants.

Scope and Delimitations

This study was limited to the multiethnic sample of adults in the United States who were part of the NHANES III. Data from the NHANES III included in this study were on cancer incidence, leptin levels, dietary intake, physical activity, income level, educational level, occupation, BMI, T2DM status, age, gender, and race/ethnicity data on non-Hispanic White, non-Hispanic Black, and Mexican American/other race adults aged 20 years old to over 90 years old. Additionally, the study was limited to individuals who reported having at least one of the seven cancers of focus for this study (breast, colorectal, endometrial, ovarian, prostate, lung, and skin). The study included peer-reviewed studies and gray literature as source documents. The study sample consisted of participants aged 20 years and older randomly assigned for an examination in the morning after an overnight fast to measure leptin levels (NCHS, 2002). The only data included were leptin levels and four known covariates/cancer risk factors: dietary intake, physical activity, BMI, and T2DM. The study did not include other known risk factors such as smoking. Data used came from a single source due to their availability and their vastness. The data are still valid and publicly available and arguably not yet saturated. Finally, the results of this study are generalizable to adults aged 20 years and older.

Limitations

Limitations, which are potential weaknesses of a study, exist within all research studies (USC Libraries, n.d.). A limitation of this study was the use of archival data collected from 1988 to 1994. However, because of the requirements to adhere to Health Insurance Portability and Accountability Act guidelines and honor the rights of all patients (U.S. Department of Health & Human Services, n.d.), a dissertation researcher is limited to data that are publicly available. If, at any time during this study, more recent data became available, the more current data would have been used for the study or at least introduced. The original data set was used as there were no current data available. Using data collected from a known source with a reputation for validity usually ensures the accuracy of the data collected, but not being able to cross-check these data for accuracy may lead to an increased likelihood of statistical error.

Significance of the Study

Cancer is still the second leading cause of death in the United States, despite the many preventive and control measures established, surpassed only by heart disease (CDC, 2016a). However, according to researchers at the CDC (2016c), cancer will soon become the leading cause of death. Researchers at the ACS (2018) projected that, by the end of 2018, there would be an estimated 1,735,350 new cancer cases and 609,640 cancer deaths in the United States, which totaled more than 9,000 more deaths than in 2017. Statistically, this equated to 144,610 new cases and 50,800 new deaths per month, 4,750 new cases and 1,670 new deaths per day, and three new cases and one death every minute (ACS, 2018). The financial costs of cancer are overwhelming. In 2013, researchers at the

Agency for Healthcare Research and Quality (AHRQ) estimated the direct medical costs (total of all health care expenditures) for cancer in the United States were $74.8 billion (AHRC, 2013). The estimated cost for direct cancer care in 2020 is $158 billion if cancer incidence, survival rates, population ages, and costs remain stable (NCI, 2011). The prevalence of cancer, despite the many established preventive measures, particularly among the populations most adversely affected (i.e., African Americans, low SES, lower educational attainment), suggests a better understanding of its etiology is necessary. Research has shown an association between leptin and the risk of cancer among various populations, and this study is unique because the focus is an area of cancer research that has received little attention. This study involved examining whether a significant difference exists in leptin levels among a national multiethnic sample of adults living in the United States and diagnosed with different types of cancer and those without cancer after adjusting for covariates or established risk factors for various obesity-associated cancers and reviewing each descriptively.

The findings of this study have possible significant implications for research, changes in policy, clinical practice or health organization efforts, and positive social change. The results of this study may contribute to the existing body of literature by opening new research areas in obesity-associated and common cancer regarding prevention and treatment. A better understanding of how leptin levels may influence the risk of certain cancers among a set of correlates may also result. By having an improved understanding of the leptin level and cancer risk/incidence relationship, preventive strategies such as new medicines, clinical practice/health organizational efforts, and

informed updates to existing policy may emerge to identify and thwart individual and environmental factors that contribute to increased leptin levels and obesity, thereby possibly reducing the risk of obesity-associated cancers among adults living both in the United States and around the world. The results of this study may bring about positive social change implications by determining if leptin levels may be a risk for obesity-associated cancers. In addition, health professionals and educators worldwide may use the results to make coordinated efforts to increase health literacy that may empower not only the study's population but all populations in adopting healthier lifestyles (i.e., diet and exercise) that may potentially aid in reducing the risk, incidence, and mortality rates of obesity and cancer at the individual, community, societal, and national levels.

Summary

Chapter 1 included a summary of the effects of obesity-associated cancers on the population of the United States. This chapter also included a brief discussion on the potential influence of leptin levels on the risk of developing cancer among adults living in the United States. In addition, this chapter included an outline of the purpose, nature, research questions, hypotheses, theoretical framework, limitations, delimitations, and significance of this study.

Chapter 2 provides a systematic evaluation of the existing body of literature to gain insight into the existing gap in knowledge regarding the relationship between leptin levels and obesity-associated cancer among adults living in the United States. Chapter 3 includes an in-depth characterization of the study methodology and design employed.

Chapter 4 includes the findings of this study, and an interpretation of the findings appears in Chapter 5.

Chapter 2: Literature Review

Introduction

An association exists between high leptin levels and an increase in obesity-associated cancers, as well as in the most frequently diagnosed or most common cancers. However, contrary results also exist in terms of a clear correlation in the human epidemiological studies conducted to support a relationship concerning leptin and cancer risk in both men and women (Aleksandrova et al., 2012; Alshaker et al., 2015; Frezza et al., 2005; Ho, 2012; Rodriguez et al., 2013; Romero-Figueroa et al., 2013; Stattin et al., 2004; Wang et al., 2014; Wu et al., 2009). However, few researchers have examined if a significant difference exists in the leptin levels of individuals with different types of cancer. Specifically, there is no evidence of any studies conducted where data are publicly available to determine if a significant difference exists in mean leptin levels among a sample of adults living in the United States after adjusting for established cancer risks (e.g., BMI [overweight/obesity], age, race, SES [low], and T2DM) and other covariates such as dietary intake and physical activity.

The purpose of this quantitative study was to examine if a significant difference exists between leptin levels in individuals with different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) and those without cancer after adjusting for cancer risk factors or covariates among a multiethnic sample of adults living in the United States from a periodic survey: the NHANES III. Chapter 1 included the introduction, background of the study, problem statement, purpose of the study, nature of the study, and research questions and hypotheses. Chapter 1 also

included the theoretical framework, operational definitions, assumptions, limitations, scope and delimitations, significance of the study, summary, and transition. The literature includes research on various aspects of cancer. This literature review includes current and previous studies related to leptin levels and cancer.

Although researchers have associated increased leptin levels with certain cancers, they have not established the exact mechanism. Additionally, limited research is available on the differences in leptin levels in adults with different types of obesity-associated cancers and leptin's association with common cancers. Chapter 2 includes an outline of the literature search strategy and the theoretical basis of the study, as well as a systematic evaluation of the existing body of literature related to a difference in leptin levels and cancer, to determine what is known and unknown regarding the topic. Also discussed is the current body of literature related to the relationship between leptin level and cancer. The overarching purpose of Chapter 2 is to expand awareness of what the current research reveals about the differences in leptin levels and cancer among a multiethnic sample of adults living in the United States with different types of obesity-associated cancers. I begin the chapter with a focus on cancer's burden on the adult population living in the United States. The focus then moves to an overview of leptin. Additionally, the review includes an emphasis on the existing body of literature regarding obesity and the U.S. population, and finally the review of the existing studies on the relationship between leptin level and cancer proceeds.

Literature Search Strategy

Gathering literature relevant to the study involved consulting multiple general and specific databases related to the study topic, including online and university libraries and Google Scholar, as well as websites for the ACS, American Diabetes Association, CDC, and NCI. This literature review also involved using the CINAHL and MEDLINE databases from the Walden University library, EBSCOhost, ProQuest, PubMed, SAGE Publications, MedScape, MedLine, and ScienceDirect. Key terms and phrases used included *cancer, BMI and cancer, breast cancer, colorectal cancer, ovarian cancer, uterine cancer, endometrial cancer, prostate cancer, lung cancer, skin cancer, obesity-associated cancers, cancer risk factors, leptin and cancer, leptin levels and cancer, obesity and cancer, poverty income ratio/income and cancer, socioeconomic status and cancer, socioeconomic status and leptin, socioeconomic status and leptin levels, individual socioeconomic status and leptin, individual socioeconomic status and leptin levels, education and cancer, overweight,* and *morbid obesity*.

The searches for literature included these terms both individually and in various combinations to identify key articles. Literature older than 5 years was included due to its relevance and the limited availability of current research regarding this topic. The publication dates of resources in my literature review ranged from 1990 to 2018, with the majority published in 2011 or later. The review includes more than 170 relevant articles. As shown in Table 1, more than 90% of the references for this study were peer-reviewed sources. Table 1 also displays a summary of the types of sources used in the review.

Table 1

Summary of Sources Used in the Literature Review

Reference type	Total	Less than 5 years old	More than 5 years old
Peer-reviewed journals	176	126	50
Nonpeer-reviewed journals	3	3	0
Books	2	2	0
Websites	16	0	7
Total	195	131	57

Theoretical Foundation

The theoretical framework for this study was the ecological or social ecological perspective or model (U.S. Department of Health and Human Services [DHHS], 2003). Bronfenbrenner (1979) recommended an ecological model of human advancement and behavior in which behavior changes happen because of communication between individuals and their specific surroundings. Behavior is affected by and affects multiple levels of influence: micro level, meso level, and macro level (Applied Sociology, 2017; Neuman, 2000). The micro level is the smallest levels of society. These levels are more intimate societies which many humans will identify with first (Applied Sociology, 2017). Micro levels are families, church groups, schools, and so forth. The micro level involves daily actions and interactions of people in society (Applied Sociology, 2017). It also includes the social roles that adults take on within a society and ways to react to society and understand it. The micro level study of society includes the smallest elements that create an idea of what a society is and the norms and behaviors that make a society recognizable as a society. Ritual, socialization, segregation of activities, and sanctions are all indicators of how one should interact within a society.

The meso level is the least known of the society groupings, as this group does not deal with the huge societies of the macro level that affect many of the intriguing smaller micro levels that cope with day-to-day human interaction. The meso level involves organizations on a midlevel scale (i.e., communities or neighborhoods) compared to the macro level and entire cities (Applied Sociology, 2017). The macro level is the largest of the society groupings. Researchers who study the macro level examine how institutions within a large population affect the masses. The economy, government structure, religion, and so forth are their own smaller groups, but in conjunction they form the boundaries of the macro-level society. Many sociology professionals believe that, at the macro level of society, larger institutions are the catalyst of societal problems, which makes them a great concern (Applied Sociology, 2017). Problems at the larger level tend to trickle down into small-scale levels of societies, which means it is important to address problems immediately upon discovery (Applied Sociology, 2017). Lastly, at the macro level, societal groups can begin to rearrange the internal structure of a society to meet the needs of the growing and changing population (Applied Sociology, 2017).

At the very basis of any society, regardless of size, is the individual. Since the beginning of sociology as a science, researchers have continuously thought about how individuals and societies coexist (Applied Sociology, 2017). The individual level is important, and it is much more difficult to solve societal problems for this level due to actions or events at each of the other levels affecting individuals. The uniqueness of all humans and their widely differing circumstances in various societies increase the complexity further (Applied Sociology, 2017).

Building upon Bronfenbrenner's concept and explaining the first key concept of the ecological perspective of multiple levels of influence, McLeroy, Bibeau, Steckler, and Glanz (1988) identified the five levels of influence for health-related behaviors and conditions used to guide this particular study: the intrapersonal (individual characteristics), interpersonal (social networks and support), institutional (institutional and organizational features), community, and public policy. The natural viewpoint or SEM depends on the supposition that numerous features of physical and social situations affect well-being (Sallis & Owen, 2008; Stokols, 1996). These conditions are multidimensional (e.g., social or physical, real or supposed), human-condition connections can exist at different levels (e.g., singular, family, authoritative, or populace), and a reciprocal response can exist over various levels between groups of individuals (Sallis & Owen, 2008; Stokols, 1996).

Overcoming previous reactions to specialists who denounced well-being advancement and ailment anticipation advocates of faulting the casualty or victim while overlooking different impacts on health, the SEM or natural point of view has developed much more into a component that advances well-being (DHHS, 2003). In a description of SEM, researchers at DHHS (2003) mentioned that conduct is affected by cooperation and relationships among and between different levels of impact, additionally plotting intrapersonal or individual elements (hereditary qualities, socioeconomics, chance variables, etc.), relational or sociocultural elements (parts, social gatherings, religious gatherings, peers, etc.), and other more extensive behavioral and environmental components. The following serves to clarify how each level of impact may influence

well-being: An obese 46-year-old woman (BMI level above 30) delays having a suggested mammogram. At the individual level, her hesitation may be because of a dread of learning she has malignancy (DHHS, 2003).

At the interpersonal level, her doctor may neglect to educate her, even though it is crucial that she has the exam, or she may have companions who say they do not trust doctors (DHHS, 2003). At the organizational level, it might be difficult to arrange for services because personnel are available on a limited basis to provide services to benefit her (DHHS, 2003). At the policy level, due to a lack of adequate health coverage, she is unable to manage the cost for services rendered (DHHS, 2003). Subsequently, the woman's inability to get a mammogram may come about because of different elements that fall within the SEM (DHHS, 2003). Finally, a biological point of view demonstrates the benefits of multilevel mediations that consolidate behavioral and ecological segments (DHHS, 2003).

Obesity and obesity-related cancers are serious, contemporary, socioepidemiological, and worldwide health problems. More than one third (36.5%) of the U.S. population is obese, and the projected yearly therapeutic cost of being overweight in the United States was $147 billion in 2008 (CDC, 2016a). Additionally, 57% of the world's population live in a country where there are more people overweight and obese than underweight (WHO, 2017). There were an estimated 942,910 combined cases of cancer associated with my study (breast, colorectal, lung, endometrial [uterine corpus], ovarian, and prostate) that were expected to occur and 307,780 estimated combined deaths as a result of these cancers anticipated by the end of 2017 (ACS, 2017).

Researchers have hypothesized a possible link between both diseases by implicating high leptin levels (which have been associated with the incidence of obesity) in the link, but results have been unclear or contradictory, and more research is necessary. The ecological approach, or SEM, reflects the interrelationships among the factors that aid in understanding why adults who reside in various areas throughout the United States have high leptin levels and several obesity-associated cancers, as well as other chronic conditions related to this study (i.e., T2DM). The cancer burden on the adult population further indicates the necessity of the study.

Cancer's Burden on the Adult Population in the United States

Cancer affects everyone. Cancer is a burden on those diagnosed with the disease, their family, and their society (WHO, 2016). Cancer is one of the primary causes of death in developing countries (WHO, 2016). The mission of the ACS is to eradicate cancer as a chief public health dilemma in the United States, but since this disease knows no boundaries, the ACS's mission extends around the world (ACS, 2017). Cancer is an enormous health problem internationally and affects every region and socioeconomic group (ACS, 2017a). Cancer accounts for approximately 1 in every 7 deaths worldwide, which is more than HIV/AIDS, tuberculosis, and malaria combined (ACS, 2017a).

The worldwide strain from cancer is increasing at a disturbing rate, and researchers predict that by 2030, around 21.6 million new cases and 13.0 million casualties are likely, primarily due to the development and maturation of the global populace (ACS, 2017a). This future hardship may also be due to more people embracing undesirable practices and ways of life (e.g., smoking, undesirable eating routines, and a

lack of physical exercise) and due to changes in procreative patterns, such as having fewer children or conceiving later in life (ACS, 2017a).

Cancer is a complex group of diseases with numerous possible causes (ACS, 2015). The disease may start anywhere in the body and begins when cells grow uncontrollably, overcrowd normal cells, and eventually evict normal cells from their environment, which then impedes the body's normal function (ACS, 2015). There are many types of cancer, and cancer is not just one disease (ACS, 2015). Some of the most common places in the body that cancer may start are the breast, colon, lungs, ovary, prostate, skin, uterus, or blood (ACS, 2015). When cancer starts in one part of the body, such as the lung, and then metastasizes to the bone, doctors will still classify it as lung cancer because the cancer cells in the bones look like those from the lung (ACS, 2015).

Cancer has a major impact on societies across the world and remains the second most common cause of death in the United States, despite the many preventive and control measures established (CDC, 2016k; WHO, 2016). However, researchers at the CDC (2016c) predicted that cancer would soon become the primary cause of death, as the U.S. population is living much longer therefore fostering more cases. A report by researchers with the CDC (2016e) revealed that cancer had surpassed heart disease as the primary source of death for several racial populations in 22 states across the United States. Deaths resulting from cancer have risen consistently, as cancer was the leading cause of death in only two states in 2014 (CDC, 2016e). Accounting for 1 of every 4 deaths in the United States, the number of cancer deaths nearly tripled from 210,733 in 1950 to 576,691 in 2011, and deaths resulting from the disease increased by 2.6% from

576,691 to 591,699 during the same time frame, which ultimately surpassed the rates of heart disease (ACS, 2016k; CDC, 2016e).

As previously mentioned, researchers at ACS projected that by the end of 2019, there would be an estimated 1,762,450 new cancer cases since 2018 and 606,880 cancer deaths in the United States (ACS, 2019). That is 27,100 more cases that estimated in 2018. Statistically, the number of new cases and deaths equate to 146,870 new cases and 50,570 new deaths per month, 4,830 new cases and 1,660 new deaths per day, three new cases and one death every minute (ACS, 2019). Death resulting from cancer is much higher in men than women (207.9 per 100,000 men and 145.4 per 100,000 women) and is highest among African American men (261.5 per 100,000) and lowest in Asian/Pacific Islander women (91.2 per 100,000), based on 2008–2012 data (NCI, 2016).

Data gathered in 2010–2012 indicated that an estimated 39.6% of men and women would receive a diagnosis of cancer during their lifetimes (NCI, 2016). Total death rates due to cancer have decreased, and the number people who have survived bouts of cancer has increased (NCI, 2016). However, the population in the United States is aging, people are living longer, and cancer rates and risks increase with age. Though progress toward reducing the morbidity and mortality rates of cancer has increased, there is much more work to do (NCI, 2016). A cancer diagnosis comes with the worry of the economic burden that treatment may bring.

Economic Impact of Cancer

Costs of treating cancer have shown to be overwhelming for patients afflicted with the disease and for society. In 2013, researchers at the WHO projected that the direct

medical costs (total of all health care expenditures) for cancer in the United States were $74.8 billion. However, in 2014, researchers at the Agency for Healthcare Research and Quality estimated that the direct medical costs (total of all health care costs) for cancer in the United States were $87.8 billion (ACS, n.d.), with 58% of the cost being for hospital outpatient or physician office visits and 27% of the cost being for inpatient hospital stays (ACS, n.d.).

The inability to obtain adequate health insurance, as well as other obstacles, prevents many Americans from receiving ideal health care and impedes the ability to maintain optimal health (ACS, 2017a). More than 29 million Americans (9% of the population) were uninsured during the entire 2015 calendar year, but this was almost 13 million fewer uninsured than during 2013 because of the execution in January 2014 of several new provisions of the Patient Protection and Affordable Care Act (ACS, 2017a). African Americans and Hispanic Americans remain the most likely to be uninsured (11% and 16%, respectively) compared to 7% of non-Hispanic Whites (ACS, 2017a). The percentages of uninsured ranged from 3% in Massachusetts to 17% in Texas (ACS, 2017a). Malignancy is analyzed at a significantly later stage among the uninsured and among those that are classified as ethnic minorities. Additionally, malignancy is analyzed among these groups when treatment is all the more expensive across the board and least likely to be effective (ACS, 2017a). Cancer's prevalence, despite the many established preventive measures, and particularly among the populations most adversely affected, indicates the need for a better understanding of its etiology.

Obesity-Associated Cancers Associated With the Study

According to researchers at ACS (2015) and the NCI's "Obesity and Cancer Fact Sheet" (2012), the following are obesity-associated cancers: cancers of the breast (postmenopausal), colon and rectum, endometrium, ovary, and prostate. These cancers were included in this study. Breast cancer, as previously mentioned, is a malignancy that begins when cells in the breast start to become wild and frame a tumor that may be seen on an x-ray or felt as a hard knot (ACS, 2016d). There are different types of breast cancer, and the kind of breast cancer that develops depends on which cells in the breast turn into cancer (CDC, 2016e). The most widely recognized sorts of breast malignancy are invasive ductal carcinoma, where cells extend outside the conduits into different parts of the breast tissue, and invasive lobular carcinoma, where disease cells spread from the lobules to the breast tissues nearby (CDC, 2016e). In the United States, cancer of the breast is the most common and frequently diagnosed in women as well as the second leading cause of death among this gender (ACS, 2017a, 2017b, 2017c). Invasive breast cancer will develop in approximately 1 in 8 (12%) women in the United States at some point during their lifetime (ACS, 2017c).

The odds of a woman dying from breast cancer are about 1 in 37 (approximately 2.7%; ACS, 2017a, 2017c). Approximately 268,670 women and 2,550 men were likely to receive a diagnosis of invasive breast cancer in 2018 (ACS, 2017a, 2017b, 2017c, 2018). From 2004 to 2013, the most recent 10 years for which data are available, breast cancer incidence rates were steady in White women and increased marginally (by 0.5% per year) in Black women, which resulted in the merging of rates in African Americans and

European Americans (ACS, 2017a). Approximately 40,920 breast cancer deaths (40,440 women, 480 men) were expected by the end of 2017 (ACS, 2017a, 2017b, 2017c). Mortality trends showed that, from 2005 to 2014, breast cancer death rates decreased by 1.8% per year in both Black and White women (ACS, 2017a, 2017b, 2017c). Breast cancer rates of death declined by 38% from 1989 to 2014 due to enhancements in early recognition and treatment (ACS, 2017a).

Many risk factors exist and increase the chances of developing breast cancer; one risk factor is being overweight or obese (ACS, 2017a, 2017c). Women who are overweight or obese after menopause increase their risk of developing breast cancer, and researchers have shown an association between obesity and high leptin levels (ACS, 2017a, 2017c; NCI, 2012). Prior to entering menopause, ovaries make most of the estrogen, and adipose tissue makes only a small amount (ACS, 2017a). After menopause (when the ovaries stop making estrogen), most of a woman's estrogen comes from adipose (fat) tissue (ACS 2017a, 2017c; NCI, 2012). Having more fat tissue after menopause can help raise estrogen levels and increase the odds of a woman having a breast malignancy, however, the connection between weight and breast disease risk is significant (ACS, 2017a, 2017c). For example, women who have been overweight since childhood are at a lower risk for developing breast cancer than women who gained weight after menopause (ACS, 2017c; NCI, 2012). Research has shown that women who regularly gained weight from about age 18 to between the ages of 50 and 60 years have been steadily connected with a higher risk of breast cancer (ACS, 2017c; NCI, 2012). In addition, women who are overweight tend to have higher blood insulin levels, and

researchers have linked such levels to some cancers, including breast cancer (ACS, 2017c). Furthermore, excess fat stored in the waist area may be more likely to increase the risk of developing breast cancer than the same amount of fat located in the hips and thighs (NCI, 2012).

Colorectum/colorectal cancer occurs in the colon or rectum and is sometimes referred to as colon cancer (ACS, 2018). Regarding all cancers that affect both men and women, cancer of the colon is the second leading cause of cancer death in the United States (ACS, 2017a). Colorectal cancer (colon and rectal combined) is also the third most common cancer in men and women and second when men and women's cancer rates are combined (ACS, 2017a). The risk of developing CRC increases with age, and one of the most modifiable risk factors for CRC is obesity (ACS, 2017a).

An estimated 97,220 cases of colon cancer and 43,030 cases of rectal cancer were likely in the United States in 2018 (ACS, 2018). Incidence rates have been generally decreasing since the mid-1980s because of the increase in CRC screening among adults 50 years of age and older (ACS, 2017a). However, trends differ by age. According to the most recent data over 10 years (2004–2013), incidence rates declined by approximately 3% per year among adults 50 years of age and older but increased by approximately 2% per year among those younger than 50 years of age (ACS, 2017a). An estimated 50,630 deaths from CRC likely occurred in 2018, which represented an increase of 230 estimated cases compared to 2017 (ACS, 2018). Accurate statistics on deaths from colon and rectal cancers separately are not available because many deaths from rectal cancer are misclassified as colon cancer on death certificates (ACS, 2018). Death rates from 2010 to

2014 were 14.8 per 100,000, age adjusted to the 2000 U.S. standard population (ACS, 2017a, 2017b). Death rates due to CRC have been decreasing since 1980 in men and since 1947 in women, with an overall decrease of 49% from 1976 to 2012. This trend reveals improvements in early detection and treatment, as well as declines in incidence. From 2005 to 2014, death rates declined by 2.5% per year (ACS, 2017a). However, from 2006 to 2015, the death rate declined by 2.9% per year among individuals ages 55 and older but increased by 1% per year among adults younger than age 55.

Ovarian cancer is cancer that starts in the ovaries (CDC, 2014c). All women are at risk for developing ovarian cancer, but postmenopausal women are much more likely to develop the disease than are younger women (CDC, 2014c). Approximately 90% of women who get ovarian cancer are older than 40 years, with the greatest number of cases occurring in women aged 60 years or older (CDC, 2014c). In 2018, approximately 22,240 new cases of ovarian cancer were diagnosed, and approximately 14,070 ovarian cancer deaths occurred in the United States (ACS, 2018). These numbers represented a decrease of 200 estimated cases and a decrease of 10 estimated deaths from 2017 (ACS, 2018).

Since the mid-1980s and accelerating in the early 2000s, incidence rates for ovarian cancer have decreased by approximately 1% per year in White women and by 0.4% per year in Black women (ACS, 2017a). Ovarian cancer is responsible for only 5% of cancer deaths among women but causes more deaths than any other gynecologic cancer (ACS, 2017a, 2018). Death rates have been declining since 1975, and from 2005 to 2014, the rate decreased by approximately 2% per year among White women and 1% per year among Black women (ACS, 2017a). The most important risk factor is a strong

family history of breast or ovarian cancer (ACS, 2016a). Researchers have also revealed that obese women with a BMI of at least 30 mg/dL have a higher risk of developing ovarian cancer than other women do (ACS, 2016f).

Prostate cancer begins when cells in the prostate gland start to grow out of control (ACS, 2016h). Aside from skin cancer, cancer of the prostate is the most common or frequently diagnosed cancer in American men (ACS, 201h). Approximately one in seven men will receive a diagnosis of prostate cancer during his lifetime (ACS, 2016h). Prostate cancer develops mainly in older men. About six in ten men aged 65 or older are diagnosed with prostate cancer. Prostate cancer is rare before age 40 (ACS, 2016h).

An estimated 164,690 new cases of prostate cancer were likely diagnosed in the United States in 2018. The risk of prostate cancer is 74% higher in African Americans than in European Americans for reasons that remain unclear (ACS, 2018). The risk of prostate cancer is 74% higher in Blacks than in non-Hispanic Whites, also for unclear reasons (ACS, 2017a, 2017b). Incidence rates for prostate cancer spiked dramatically in the late 1980s and early 1990s, in large part because of widespread screening with the prostate-specific antigen blood test. However, from 2009 to 2013, rates decreased by 8% per year (ACS, 2017a).

With an estimated 29,340 deaths likely to have occurred in 2018, which was 2,610 more than the number of deaths expected in 2017, prostate cancer is the third-leading cause of cancer death in men, just behind lung and colorectal cancers, respectively (ACS, 2016h, 2017). Prostate cancer has the potential to be a serious disease, but most men diagnosed with prostate cancer survive. More than 2.9 million men in the

United States diagnosed with prostate cancer at some point in their lifetime were still alive in 2016 (ACS, 2016h). Prostate cancer death rates have been decreasing since the early 1990s in men of all races and ethnicities, although they remain more than twice as high in Blacks than in any other group (ACS, 2017a, 2017b, 2018).

The only well-established risk factors for prostate cancer are increasing age, African ancestry, family history of the disease, and certain inherited genetic conditions (ACS, 2017a, 2017b, 2018). Beyond age, race, and family history, there are few established risk factors for prostate cancer (Allott et al., 2012). However, researchers have found that obesity also has an association with prostate cancer (Allott et al., 2012). The epidemiologic association of obesity and aggressive prostate cancer is particularly relevant because of the prevalent nature of both diseases and the large numbers of men affected. The identification of obesity as an additional risk factor for prostate cancer is of significant public health interest because of its modifiable nature (Allott et al., 2012). Epidemiologic evidence linking obesity and aggressive prostate cancer underlines the importance of taking body size into account when screening, treating, and monitoring prostate patients, as well as when counseling obese patients about healthier lifestyle choices and weight loss. Black men in the United States and Caribbean men of African descent have the highest documented prostate cancer incidence rates in the world (ACS, 2017a). Some researchers have found that obese men may be at greater risk for having more advanced prostate cancer and dying from the disease (ACS, 2016, 2017a, 2017b).

Endometrial (uterine corpus) cancer starts when cells in the inner lining of the uterus (endometrium) begin to grow out of control (ACS, 2016f). Cancer of the

endometrium is the most common cancer of the female reproductive organs in the United States (ACS, 2016f, 2017a, 2017b). An estimated 63,230 cases of cancer of the uterine corpus (body of the uterus) were diagnosed in the United States in 2018. Cancer of the uterine corpus is often referred to as endometrial cancer because most cases (92%) occur in the endometrium (lining of the uterus; ACS, 2017a, 2018). From 2004 to 2013, the incidence rate increased by 1% per year among White women and 3% per year among Black women (ACS, 2017a). Endometrial cancer affects mainly postmenopausal women (ACS, 2017a). The average age of women diagnosed with endometrial cancer is 60, and the cancer is uncommon in women under the age of 45 (ACS, 2016f). Although endometrial cancer is more common among White women, Black women are more likely to die from the disease (ACS, 2017a). An estimated 11,350 deaths from uterine corpus cancer (UCC) occurred in 2018. From 2005 to 2014, death rate for cancer of the uterine corpus increased by 1% per year among White women and 2% per year among Black women (ACS, 2017a). Obesity and abdominal fatness increase the risk of uterine cancer, most likely by increasing the amount of circulating estrogen, which is a strong risk factor for contracting endometrial cancer (ACS, 2017a).

Most Commonly Diagnosed Cancers in the United States Showing a Link to Leptin

Lung cancer starts when cells of the lung become abnormal and begin to grow out of control (ACS, 2016g). As more cancer cells develop, they can form into a tumor and spread to other areas of the body (CDC, 2014d). The two main types of lung cancer are NSCLC, which occurs in about 80–85% of diagnosed cases, and SCLC, which occurs in approximately 10–15% of diagnosed cases (ACS, 2016g). Lung cancer (both SCLC and

NSCLC) is the second most common cancer in both men and women, not including cancer of the skin. Prostate cancer is most common among men (after skin cancer), and breast cancer is most common among women (after skin cancer; ACS, 2016g).

Epidemiological studies have revealed that elevated leptin levels are associated with lung cancer, but researchers have conducted limited research regarding the hormone, its receptors, and its relationship to lung cancer, and results have been conflicting (Alemán et al., 2002; Boucher, Boudreau, Ahmed, & Atlas, 2015; Gulen et al., 2012; Kerenidi et al., 2013; Terzidis et al., 2009). In addition, skin (melanoma/basal/squamous) cancer is the most common cancer in the world, with more than 5 million people affected yearly, and results of epidemiological studies indicate that obesity (linked to increased leptin levels) increases the risk of developing melanoma (ACS, 2017a). According to researchers at ACS (2017e), lung cancer (SCLC and NSCLC) is the deadliest of all cancers, although results conflict among the few studies conducted to determine why elevated leptin levels have a surprising association with the disease independent of obesity, even though it is not a common risk factor lung cancer.

Researchers at ACS estimated that 234,030 (121,680 in men and 112,350 in women) new cases of lung cancer would be diagnosed and about 154,050 deaths (83,550 men and 70,500 women) would occur as a result of the disease in 2018 (ACS, 2018; see also ACS, 2017a, 2017e). An estimated 1 in 4 cancer deaths are a result of lung cancer (ACS, 2017a, 2017e). Each year, more people die of lung cancer than those diagnosed with cancers of the colon, breast, and prostate collectively (ACS, 2017e). About 2 of 3 individuals diagnosed with lung cancer are at least 65 years of age (ACS, 2017e).

In 2013, the most recent year for which numbers were available, Black men had the highest incidence of lung cancer, followed by White, American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic men (CDC, 2016i). Among women, White women had the highest rate of lung cancer, followed by Black, American Indian/Alaska Native, Asian/Pacific Islander, and Hispanic women. Overall, the chance that a man will develop lung cancer in his lifetime is about 1 in 14, and the risk is approximately 1 in 17 for a woman (ACS, 2017e; CDC, 2016h). Cigarette smoking is by far the most important risk factor for lung cancer; smoking is the cause of 80% of lung cancer deaths in the United States (ACS, 2017e). In addition, M. Song et al. (2014) showed an association exists between lung cancer and elevated leptin levels.

Skin cancer is the most common form of cancer in the United States (ACS, 2017a, 2018; CDC, 2016i). Of this cancer, basal and squamous cell carcinomas (nonmelanoma) are the two most common types. Although both types of cancers are highly curable, they can be costly and disfiguring (ACS, 2017a; CDC, 2016i). Melanoma is the third most common skin cancer and by far the most dangerous of the three because it causes the most deaths among the three (ACS, 2017a; CDC, 2016i). Melanoma is cancer that starts in a certain type of skin cell when cells in the body begin to grow out of control (ACS, 2017a). Nonmelanoma skin cancer usually responds to treatment and rarely spreads to other parts of the body. The majority of basal and squamous cell and these three types of skin cancer are caused by exposure to ultraviolet light (ACS, 2017a; CDC, 2016i).

Although difficult to estimate because these cases (basal and squamous cell) are not required to be reported, the most recent study of skin cancer occurrence indicated

that, in 2012, 5.4 million cases were diagnosed among 3.3 million people (more than one case diagnosed in many people; ACS, 2017a). Deaths from basal and squamous cell cancer are uncommon, and estimates indicate that approximately 2,000 people in the United States die each year from these cancers (ACS, 2017a, 2017b). Most people who die from these cancers are elderly and may not have seen a doctor until the cancer had already grown quite large, and other people more likely to die of these cancers are those with suppressed immune systems, such as those who have had organ transplants (ACS, 2017a, 2017b).

According to researchers at the ACS, an estimated 99,550 (about 60,350 in men and 39,200 in women) new cases of melanoma would be diagnosed in 2018. Melanoma accounts for only 1% of all skin cancer cases but a large majority of skin cancer deaths (ACS, 2017a, 2017b, 2018). Some people are at higher risk of skin cancer than others, but anyone can get a diagnosis of skin cancer (CDC, 2016i). Skin cancer is most commonly diagnosed in non-Hispanic Whites; the annual incidence rate is 1 (per 100,000) in Blacks, 4 (per 100,000) in Hispanics, and 25 (per 100,000) in non-Hispanic Whites (ACS, 2018). Incidence rates are higher in women than in men before age 50, but by age 65, rates in men are double those in women, and by age 80 they are triple (ACS, 2017a). The incidence of cutaneous melanoma has risen rapidly since 1986. However, 2011 data indicated that rates are declining or plateauing among those younger than 50. For example, from 2003 to 2013, incidence rates increased by 2% to 3% per year among men and women ages 50 and older but stabilized among men and women younger than 50 years of age (ACS, 2017a).

The risk factors for melanoma include a personal family history of melanoma and the presence of atypical, large, or numerous moles (typically more than 50 moles; ACS, 2017a). People at highest risk include those with sun sensitivity, which includes those who sunburn easily; have difficulty tanning; have natural blond or red hair; have a history of excessive sun exposure, including sunburns; have diseases or treatments that suppress the immune system; and have a history of skin cancer. Epidemiological studies indicate obesity increases the risk of developing melanoma (ACS, 2017a). Although researchers have not established a direct cause and effect relationship yet, obesity also increases the expression of leptin that may contribute to tumor growth leading to this type of cancer (Brandon et al., 2009). Finally, data indicated, by the end of 2018, approximately 13,640 (about 9,320 men and 5,990 women) deaths from melanoma and 3,520 deaths from other types of skin cancer would occur (ACS, 2018).

Overview of Leptin

Since its discovery, both leptin and its association with obesity and obesity-associated diseases have received a substantial amount of interest. As previously mentioned, leptin is a peptide hormone produced mostly by adipose (fat) tissue and has become synonymous with the term obesity, as leptin appears to indicate why obesity has become a national epidemic in the United States (Rodriguez et al., 2013). Discovered in 1994 and encoded by the obesity gene, leptin is a well-established adipokine that influences appetite control, overindulgence, body weight, and the release of energy via its actions on the hypothalamus and other parts of the brain (Caro et al., 1996; Jung & Choi, 2014; Rodriguez et al., 2013; Wasim, 2015). Long before leptin was cloned in 1994, its

presence had been demonstrated in leptin-deficient ob/ob and leptin receptor-deficient db/db mice. It was understood that ob/ob mice were missing a circulating factor that could cure obesity in ob/ob mice, while db/db mice were unresponsive to it. Researchers initially hoped that the ability to clone the hormone leptin would resolve the ongoing increase in the prevalence of human obesity. The hereditability of obesity is between 0.7 and 0.8, which is higher than the heritability for most other traits. All of the obesity genes identified thus far are in the brain.

The physiological factors that influence circulating human leptin levels include the amount of body fat, gender, age, puberty, fasting, feeding, and exercise (Dagogo-Jack, 2015). Leptin levels also show a daytime pattern, with peak values occurring at night and trough values in the late afternoon. Additional studies indicated the daytime pattern in plasma leptin levels is directed to meals rather than the true circadian clock. Hyperleptinemia in obese persons suggests that human obesity may be a leptin-resistant state; however, the mechanism of leptin resistance is unclear. In rodent models and rare human examples, the cause of leptin-resistant obesity is leptin receptor mutations (Dagogo-Jack, 2015). Leptin resistance is the main obstacle for successfully treating obesity (Dagogo-Jack, 2015).

Researchers associated a mutation in this gene with severe obesity and type II diabetes in mice; thus, researchers initially viewed leptin as a way to cure obesity, and this view received a lot of attention from both the scientific community and the media (Alexe & Petridou, 2009). Human obesity, however, is a much more complex condition that does not occur due to a deficit in leptin. The fact that most people who suffer from

obesity not related to the very rare condition of a defect in the *ob gene* actually have hyperleptinemia has led researchers to determine what makes the hypothalamus of these individuals resistant to leptin (Alexe & Petridou, 2009).

Leptin receptors are extensively distributed and are predominantly found in the hypothalamus, islet cells, liver, kidney, lung, skeletal muscle, and bone marrow. Insulin, glucocorticoids, and catecholamines are the main regulators of leptin secretion from adipocytes and its circulatory levels (Dutta, Ghosh, Pandit, Mukhopadhyay, & Chowdhury, 2012). Leptin is a hormone, and the word comes from the Greek word meaning *thin* and is also known as the *Ob gene* located on chromosome 7q31.3 in humans, whereas in mice it is on chromosome 6' (Wasim, 2015). Leptin is the most important hormone when trying to understand why humans feel full or hungry (Rodriguez et al., 2013).

A 16-kilodalton protein, leptin is secreted by adipocytes and has a major role in body weight regulation by maintaining a balance between food intake and expenditure of energy (Wasim, 2015). As fat is stored in cells, leptin is secreted into the bloodstream and gives off signals that make humans eat more or less (Wasim, 2015). It is also produced in the stomach and other tissues in small amounts and has been studied intensively in relation to obesity-associated cancers, because as leptin levels increase, body fat mass increases (Boguszewski, Paz-Filho, & Velloso, 2010). Leptin has several other endocrine functions, and the most important are regulating immune and inflammatory responses as well as angiogenesis and wound healing (Wasim, 2015). Leptin also plays major role in

the development of hypertension in obesity (Bravo, Morse, Borne, Aguilar, & Reisin, 2006).

Researchers have revealed that obese people have unusually high levels of leptin (Society for Endocrinology, 2014). In some obese people, the brain does not respond to leptin, so they keep eating despite sufficient (or excessive) fat stores, which is a theory known as leptin resistance (Society for Endocrinology, 2014). Leptin resistance causes fat cells to produce even more leptin. This is similar to the way people with type 2 diabetes have unusually high levels of insulin, as their body is resistant to the effects of insulin. The cause of leptin resistance is still unclear. However, leptin resistance is the main obstacle in obesity treatment (Society for Endocrinology, 2014).

Leptin is synthesized mainly by adipose tissue, but it is also produced by a variety of cells, including placental cells and secretory cells of the mammary epithelium. Digestive epithelia and gastric mucosa have also received attention as sources of leptin (Alexe & Petridou, 2009). Once synthesized, leptin is not stored in large pools in the adipose cell but is secreted through a consecutive pathway that acts through a receptor from the class I cytokine receptor family, which has at least six isoforms (Ob-Ra to Ob-Rf). However, the specific actions of all isoforms of Ob receptors remain unknown. Leptin signaling is mediated mainly through the long form of Ob-Rb, but involvement of the short form Ob-Rb has also been indicated.

Leptin is intended to function in the body in a relatively simple manner. As previously discussed, it is produced by fat cells; the more fat a person carries, the more leptin that person produces. Leptin is transported via the bloodstream to the brain where a

signal is sent to the hypothalamus, which is the area that controls the time and the quantity of food eaten. Fat cells use leptin to tell the brain the amount of fat carried. High levels of leptin signal the brain that a sufficient amount of fat is stored, and low levels of leptin, according to researchers, tell the brain that the amount of fat stored is less than sufficient and the risk of starvation is probable (Ogunwobi, 2015).

Serum leptin levels are determined via blood tests (Ogunwobi, 2015). Since the discovery of leptin, numerous research investigations have provided a group of reference ranges for normal, high, and low leptin results (Ogunwobi, 2015). The results of these studies indicate that leptin is indeed a regulated human hormone that interacts with a vast array of physiological, hormonal, immunological, and inflammatory mediators and targets (Dagogo-Jack, 2015). In addition, concentrations of leptin are higher in women than in men, with levels decreasing as age progresses. Furthermore, this occurs even after the adjusting for total body fat mass (Havel, Kasim-Karakas, Dubuc, Mueller, & Phinney, 1996; Rosenbaum et al., 1996). One explanation for this tendency is differential regulation of leptin expression by sex hormones, with estrogens reported to upregulate leptin levels and testosterone observed to decrease leptin levels (Hardwick, Van den Brink, Offerhaus, Van Deventer, & Peppelenbosch, 2001; Jaffe & Schwartz, 2008; Koda, Sulkowska, Kanczuga-Koda, Surmacz, & Sulkowski, 2007). Researchers of subsequent studies documented that, in addition to its primary function as a regulator of food intake, leptin can also affect fetal development, sex maturation, lactation, and hematopoiesis (Bonnet et al., 2002; Brann, Wade, Dhandapani, Mahesh, & Buchanan, 2002; Goumenou, Matalliotakis, Koumantakis, & Panidis, 2003; Neville et al., 2002; Wauters, Considine, &

Van Gaal, 2000). Hematopoiesis is the production of all blood cell types, including the formation, development, and differentiation of blood cells and immune responses (Medicine Net, 2016).

Aleke and Petridou (2009) noted that insulin may enhance leptin release and elevate circulating leptin levels. Given the knowledge gained regarding the biological actions of leptin, it seems as if obese individuals develop resistance to leptin, as high levels of leptin occur in these cases (Aleke and Petridou, 2009). Because obesity is an established risk factor in various cancers, and leptin plays a significant role in the physiopathology of obesity, exploring leptin's link to cancer risk is of considerable importance. Researchers have intensively studied the role of leptin in the pathogenesis of different forms of cancer, particularly breast, endometrial, ovarian, prostate, and colon. Various epidemiological, prospective, case-control studies concerning the relationship between leptin and various obesity-associated cancers have produced inconclusive and contradictory findings that resulted in the need for further research.

Global Impact of Obesity

Obesity has reached epidemic proportions globally, with at least 2.8 million people dying each year as a result of being overweight or obese (WHO, 2017). More than one third (34.9% or 78.6 million) of adults in the United States are obese (CDC, 2016a). Nearly 8% are extremely obese (State of Obesity, 2017). This preventable condition is one of the most common, serious, and costly of all chronic diseases (State of Obesity, 2017). According to researchers at the WHO, more than 1.9 billion adults (39%) worldwide aged 18 years and older in 2014 were overweight (38% of men and 40% of

women). Of these, more than 640 million adults were classified as obese (WHO, 2017). In 2014, about 13% of the world's adult population (11% of men and 15% of women) was obese. The worldwide prevalence of obesity more than doubled between 1980 and 2014; thus, developing preventive measures is imperative (WHO, 2017). Governments, international partners, civil societies, nongovernmental organizations, and the private sector all have vital roles in contributing to obesity prevention (WHO, 2017).

Overweight and obesity are abnormal or excessive fat accumulation that presents a risk to health (WHO, n.d.). Obesity is associated with increased cancer risk, and leptin may be a potential mediator of this association (Renehan, Tyson, Egger, Heller, & Zwahlen, 2008). A crude population measure of obesity is BMI. A person with a BMI of 30 or more is generally considered obese, and an individual with a BMI equal to or more than 25 is considered overweight (WHO, n.d.). Morbid obesity is the extreme form of obesity and is associated with significant medical and psychological morbidity and mortality. Morbid obesity is generally defined as BMI > 40 kg/m^2 or BMI > 35 kg/m^2 with associated medical problems (Papageorgiou, Papakonstatinou, Mamplekou, Terzis, & Melissas, 2002). BMI is calculated using a person's height and weight. The calculation is a person's weight in pounds divided by height in inches squared. This number is then multiplied by 703 (CDC, 2015). The typical categories of BMI are as follows: below 18.5 = underweight; 18.5–24.9 = normal; 25.0–29.9 = overweight; 30.0–39.9 = obese; 40 and above = morbidly obese (CDC, 2015). The various categories indicate that while obesity is a diagnosis unto itself, it can range in severity.

Overweight and obesity are major risk factors for a number of chronic diseases, including cardiovascular diseases, cancer, and diabetes (University of Michigan, 2016; WHO, n.d.). Obesity was once considered a problem only in high-income countries, but the incidence of overweight and obesity is now dramatically increasing in low- and middle-income countries, particularly in urban settings (WHO, 2017). Obesity has become a common, costly, and serious, but preventable, problem in the United States and throughout the world (Jackson, Yeh, Szklo, Hu, Wang, Dray-Spira, et al., 2014; CDC, 2016a). The estimated annual medical cost of obesity in the United States was $147 billion in 2008 U.S. dollars (CDC, 2016a). Annual medical costs for people who are obese were $1,429 higher than for people of normal weight (CDC, 2016a). Although obesity can affect anyone, it affects some groups more than others (CDC, 2016a). Obesity is higher among middle age adults age 40–59 years (40.2%) and older adults age 60 and over (37.0%) than among younger adults age 20–39 (32.3%; CDC, 2016a). U.S. military service members and members of their families who are obese cost the military approximately $1 billion every year in health care costs and lost productivity (State of Obesity, 2017). Furthermore, 70% of young adults who attempt to join the military are ineligible due to fitness or overweight concerns, which greatly impedes the overall readiness of the military as well as national security (State of Obesity, 2017).

More than 33% of adults who earn less than $15,000 per year are obese, compared with 24.6% of those who earned at least $50,000 per year (State of Obesity, 2017). However, non-Hispanic Black and Mexican American men with higher incomes are more likely to be obese than those with low to lower income levels (CDC, 2016a). In

women, those with higher income levels are less likely to be obese than those with low to lower income levels (CDC, 2016a). Obesity rates are higher among Blacks (48.4%) and Latinos (42.6%) than among Whites (34.6%) and Asians (12.6%; State of Obesity, 2017). Black women (16.8%) are more likely to be extremely obese than White women (9.7%; State of Obesity, 2017). Further, researchers have revealed that a significant relationship does not exist between obesity and education among men. However, women with college degrees are less like to be obese than less educated women are (CDC, 2016a).

The impact of obesity goes beyond the impact on the body. Finkelstein, Trogdon, Cohen, and Deitz (2009) noted that a strong link exists between the rising rate of obesity and the rising rates of medical costs. When compared to nonobese individuals, obese men take about six more sick days per year and obese women take about nine more sick days per year (Begley, 2012). Even when obese individuals are at work, shortness of breath and pain can negatively affect productivity. Approximately $190 billion, or 21% of medical costs, is attributed to obesity (Begley, 2012). To reduce the effects of obesity on health and finances, and to live a healthier and longer life, losing weight through diet and exercise is imperative.

Regardless of the many measures established to prevent obesity, it is still a pandemic in the United States (CDC, 2016a). In developed countries, such as the United States, a lifestyle that includes frequent cigarette smoking, excessive alcohol consumption, poor diet, and overeating, coupled with low physical activity, leads to an increased prevalence of obesity (AICR, 2014). As of 2013, according to researchers at the CDC (2013), not one state in the United States had an obesity prevalence of less than

20%, which exceeded the nation's goal of 15%. The lowest rates (20–25%) were in California, Colorado, Hawaii, Massachusetts, Montana, Utah, Vermont, and Washington, DC. The highest rates (35% or higher) were in Mississippi and West Virginia. Regionally, the South had the highest prevalence (30.2%), and the West had the lowest rate of obesity (24.9%; Gonzalez-Campoy, 2016). Approximately 122,200 cases of cancer in the United States every year exist because of excess body fat (AICR, 2014). This figure has steadily increased from 100,000 preventable cases of cancer in 2009 to almost 117,000 in 2013, which indicates the need for more effective preventive measures (AICR, 2014).

Studies on the Relationship Between Leptin (Level) and Cancer

Since the discovery of leptin in 1994, interest on the polypeptide hormone and its association with obesity and obesity-related or associated diseases has been high. The focus of initial interest in leptin was on its role in obesity. Researchers associated leptin with the inflammatory response, insulin signaling, and carcinogenesis (Pais, Silaghi, Silaghi, Rusu, & Dumitrascu, 2009). Researchers have detected the leptin receptor in both normal and malignant tissue in humans (Gupta et al., 2016; Renehan et al., 2008). Existing epidemiologic studies examining the relationship between leptin (level) and cancer have included a range of study designs, sample sizes, and results. Existing studies reporting the association between leptin and cancer have lacked external validity due in part to a relative lack of racial diversity (Gupta et al., 2016). Researchers have also produced conflicting results in existing studies relating to the relationship between leptin (level) and cancer, which indicates the need for further research (Aleksandrova et al.,

2012; Alshaker et al., 2015; Baillargeion et al., 2006; Harris et al., 2011; Ollberding et al., 2013; Rodriguez et al., 2013; Romero-Figueroa et al., 2013; Vona-Davis & Rose, 2007; Wu et al., 2009, 2014). Studies on the association between leptin and cancer have largely been retrospective and may contain bias resulting from reverse causation due to the effect of cancer-associated weight loss on leptin levels.

A gap in the literature existed regarding the lack of research on whether a significant difference exists in leptin levels among adults with different types of obesity-associated cancers (breast, colorectal, endometrial [uterine corpus], ovarian, prostate) and commonly diagnosed cancers (lung and skin) that have an association with leptin in a single study. The focus was on relevant studies in which researchers investigated the relationship between leptin (level) and cancer. Researchers have found contradictory results in previous case control and prospective studies relating to the relationship between leptin (level) and breast cancer, which indicated a need for further research (Chen et al., 2006a; Coskun et al., 2003; Han et al., 2005; Miyoshi et al., 2006; Ozet et al., 2001; Sauter et al., 2004; Stattin et al., 2004; Tessitore et al., 2000; Vona-Davis & Rose, 2007). Romero-Figueroa et al. (2013) conducted one related cross-sectional study to examine if a difference existed between serum leptin levels and insulin in obese patients with and without breast cancer. Romero-Figueroa et al. examined 156 women: 78 obese women with BMI > 30, newly diagnosed breast cancer, and no current diagnosis of type II diabetes and 78 obese women with BMI > 30, without breast cancer, and no current diagnosis of type II diabetes. The women received an invitation to participate in the study at Instituto Mexicano del Seguro Social in Toluca, Mexico (Romero-Figueroa

et al., 2013). The study involved measuring variables such as glucose, triglycerides, high-density and low-density lipoproteins, cholesterol, insulin, and leptin and calculating a homeostasis model assessment (Romero-Figueroa et al., 2013).

Romero-Figueroa et al. (2013) found serum leptin levels in obese women were higher in patients with newly diagnosed breast cancer. However, the possible cause and effect and the implication in prognosis was not well established, which revealed a need for further research (Khan, Shukla, Sinha, & Meeran, 2013; Romero-Figueroa et al., 2013). The role of leptin in breast cancer research has many potential implications, not only as a possible risk factor, but also as a possible therapeutic target (Romero-Figueroa et al., 2013). Descriptive statistics were presented as mean values and standard deviations. Variables were tested for normality using the Kolmogorov-Smirnov test. Student's *t* test or the Mann-Whitney i/-test was used to compare the two groups, as appropriate (Romero-Figueroa et al., 2013). Romero-Figueroa et al. used analysis of variance (ANOVA) to compare more than three groups, Spearman's correlation coefficients to examine the correlation between homeostasis model assessment and leptin, and statistical analysis using SPSS software Version 17. The strength of the study was the evaluation of the serum leptin concentration in an obese population with newly diagnosed breast cancer (Laird Statistics, 2013; Romero-Figueroa et al., 2013). The limitations were the cross-sectional design so cause and effect could not be demonstrated, and the relatively small number of subjects analyzed (Romero-Figueroa et al., 2013). The majority of breast cancers require the action of estrogens for their growth and progression (Romero-Figueroa et al., 2013). Leptin may also increase breast cancer risk in

postmenopausal women, specifically when the only source of estrogens is adipose tissue (Maccio et al., 2010; Rose, Komninou, & Stephenson, 2004). However, further research is necessary.

Most breast cancers require the action of estrogens for growth and progression, and leptin in excess may also contribute to the pathogenesis of breast cancer (Paz-Filho, Lim, Wong, & Licinio, 2011). Paz-Filho et al. (2011) discussed whether leptin induces breast cancer to induce the growth of breast cancer cells through extracellular signal-regulated kinases ½ and/or phospoinositide 3-kinase pathways. Leptin can facilitate angiogenesis by inducing the expression of vascular endothelial growth factor receptor 2 and interacts with insulin like growth factor 1 in triple negative breast cancer cells transactivating the epidermal growth factor receptor and promoting invasion and migration (Paz-Filho et al., 2011). Finally, leptin and its receptor are significantly overexpressed in human primary and metastatic breast cancer and most abundant in less differentiated tumors (Paz-Filho et al., 2011).

Gupta et al. (2016) conducted and published another leptin (level) and cancer-related epidemiologic study. Gupta et al. explained that leptin dysregulation (resistance) had been suggested to affect cancer risk through its effects on obesity and inflammation. Epidemiological data evaluating this relationship are conflicting, and studies with non-White participants were lacking. This motivated Gupta et al. to examine the relationship between prediagnostic plasma leptin levels and the risk of obesity-associated cancer incidence (to include postmenopausal breast and endometrial cancers in women, along with esophageal, pancreatic, gall bladder, colorectal, kidney and thyroid cancer in men

and women) among a group of multiethnic adults (aged 18–65 years) with oversampling of non-Hispanic Black participants in the Dallas Heart Study (DHS). The study participants enrolled in the DHS without established cancer and with baseline leptin measurements, and incident cancer cases were identified through a systematic linkage of the DHS and the Texas Cancer Registry (Gupta et al., 2016). Leptin was evaluated both as a continuous variable and in sex-specific quartiles. The study involved performing multivariable Cox proportional hazards modeling to examine the association between leptin levels and obesity-associated incident cancer after adjusting for age, sex, race, smoking status, alcohol use, family history of malignancy, BMI, diabetes mellitus, and C-reactive protein (Gupta et al., 2016).

Gupta et al.'s (2016) results revealed that among the 2,919 predominantly minority participants (median age 44 years; 54% women; 70% nonwhite; median BMI 29.4 kg/m^2), 190 (6.5%) developed cancer after median follow-up of 12 years. Median leptin levels were 12.9 (interquartile range [IQR]: 5.8–29.5) ng/ml in the incident cancer group vs. 12.3 (IQR: 5.4–26.4) ng/ml among those without an incident cancer (p = .34; Gupta et al., 2016). Leptin was not associated with cancer incidence in multivariable analysis (unit standard deviation increase in log-transformed leptin, hazard ratio 0.95; 95% confidence interval [0.77–1.16]; p = .60; Gupta et al., 2016). In cases with more than one known cancer, only the first cancer was included. Carcinoma in situ and skin cancers were not included. No association was observed in analyses stratified by sex, race/ethnicity, diabetes, or obesity status (Gupta et al., 2016). Furthermore, there was no association between premorbid leptin levels and cancer, even though preclinical basis and

positive outcomes were identified in previous studies (Gupta et al., 2016). The younger age of the study's cohort compared to other cohorts may have contributed to the observed lack of association in some cancers (prostate; Gupta et al., 2016). Furthermore, the relatively young age of the participants was likely responsible for a lower cancer incidence rate than some other databases, which also precluded the ability of the researchers to perform individual analyses for each cancer site (Gupta et al., 2016).

Elevated estrogen levels associated with obesity and higher leptin levels contribute to breast and uterine carcinogenesis and account for a more linear relationship in women, as demonstrated by the positive association of leptin with endometrial and breast cancer (Gong, Wu, Wang, & Ma, 2015; Niu et al., 2013). Given the fact that leptin levels are higher in women than in men, it is practical to consider that leptin could have a positive association in women where leptin levels are higher, but not in men (Gupta et al., 2016). Both breast and endometrial cancer are also obesity-associated cancers, which raises the possibility that leptin increases the risk of obesity-associated cancers (Gupta et al., 2016).

Gupta et al. (2016) noted that the strength of their study included a large, multiethnic population cohort with accurate leptin measurement with close follow-up for the development of cancer. The intentional oversampling of the Black population in the DHS cohort provided a unique opportunity to evaluate this relationship in less well represented racial/ethnic groups (Gupta et al., 2016). Limitations of Gupta et al.'s study included an observational design that prevented an ability to determine causation. Those

DHS participants diagnosed with cancer outside the State of Texas may not have been captured, so a degree of ascertainment bias may have been present (Gupta et al., 2016).

In direct contrast to the previous investigation, Yeung et al. (2013) conducted a single study in Hong Kong, China, where a lower prevalence of obesity and different body fat distribution was evident when compared with European American counterparts. Yeung et al. evaluated premorbid leptin levels and the risk of all-incident cancer and found no difference in leptin levels between participants who developed cancer and those who did not in a population-based cohort. Yeung et al.'s longitudinal community-based cohort included participants from the Hong Kong Cardiovascular Risk Factors Prevalence Study (CRISPS) study that ran from 1995 to 1996 (CRISP-1) with baseline assessments that included evidence of obesity. Participants were reassessed in Interleukin 6 (IL-6), soluble tumor necrosis factor receptor 2 (sTNFR2; as a surrogate marker of tumor necrosis factor-α activity), leptin, lipocalin 2 and encodes a protein that belongs to the lipocalin family (Yeung et al., 2013). Members of this family transport small hydrophobic molecules such as lipids, steroid hormones, and retinoids. The protein encoded by this gene is a neutrophil gelatinase-associated lipocalin and plays a role in innate immunity by limiting bacterial growth as a result of sequestering iron-containing siderophores. This protein is thought to be involved in multiple cellular processes, including maintenance of skin homeostasis and suppression of invasiveness and metastasis (National Center for Biotechnology Information, 2016) adiponectin and adipocyte-fatty acid binding protein. Yeung et al. identified incident cancer cases up to December 31, 2011.

Yeung et al. (2013) found that 205 of 2,893 participants recruited at CRISPS-1 had developed incident cancers at a rate of 4.62 per 1,000 person-years. More of the subjects who developed cancers were obese (22.1 vs. 16.1%) or had central obesity (36.6 vs 24.5%) according to Asian cut-offs after a median follow-up of 16.0 years (IRQ: 15.6–16.5 years). Of the most commonly diagnosed cancers, 44 participants were diagnosed with lung cancer, 36 participants were diagnosed with CRC, 20 participants were diagnosed with breast cancer, 18 participants were diagnosed with prostate cancer, and 14 participants were diagnosed with cancers of the female reproductive tract (Yeung et al., 2013). Results also demonstrated that those who developed cancer were most likely to be male, older, or current or ex-smoker; had higher BMI, had higher waist circumference; had been diagnosed with hypertension or type 2 diabetes; and had dyslipidemia at baseline. Waist circumference (adjusted hazard ratio (HR) 1.02 [1.00–1.03] per cm; p = .013), but not BMI (adjusted HR 1.04 [1.00–1.08] per kg/m^2; p = .063), was a significant independent predictor for incident cancers after adjustment for age, sex, and smoking status. In all, 99 of 1,899 participants reassessed at CRISPS-2 had developed cancers. Participants who developed cancers had a significantly higher level of C- Reactive Protein, IL-6, sTNFR2, and lipocalin 2. After adjustment for conventional risk factors, only IL-6 predicted cancer development (Yeung et al., 2013). No difference existed between participants diagnosed with cancer and those without cancer regarding their level of adiponectin, leptin, and adipocyte-fatty acid binding protein (Yeung et al., 2013).

Some limitations of Yeung et al.'s (2013) study included the relatively small number of incident cancer cases. Researchers should validate the findings in studies

involving larger sample sizes. The baseline assessments were performed in 2006, and because the list of adipokines is growing, not all adipokines were measured in this study. As a result of the limitation of an observational study design, the findings could merely imply association but not a causal relationship, although multiple molecular mechanisms had been identified to link cancer development with elevated cytokines in chronic inflammatory states (Yeung et al., 2013). Variables were tested for normality using the Kolmogorov-Smirnov test, and skewed variables were natural-logarithmically transformed before analysis (Yeung et al., 2013). Biologically relevant variables were entered into Cox proportional hazard regression analyses by forced entry to identify the independent predictors for incident cancers (Yeung et al., 2013).

Several of the studies in which researchers conducted epidemiological studies on the relationship between leptin level and cancer examined the association between prostate cancer and leptin level showed an unclear association, no statistical significance, or a null association (Allot, Masko, & Freedland, 2013; Hsing et al., 2001; Lai et al., 2011; Li et al., 2010; Stattin, Kaaks, et al., 2003). According to Stattin, Kaaks, et al. (2003), a potentially nonlinear relationship between leptin levels and prostate cancer was also demonstrated, and the results indicated an association existed between very elevated leptin levels and reduced cancer incidence. In studies where there has been an association, leptin values were more closely associated with prostate cancer risk in older patients (65 years and older) compared to younger patients (under 65 years), which raised the assumption that the contribution of leptin to cancer or carcinogenesis may be age-dependent (Bologna, Patrizia, Vicentini, & Angelucci, 2013). Stattin, Kaaks, et al. (2003)

also did not point out the race or ethnicity of their participants, which indicated the need for further research on various racial backgrounds. Regardless of these contradictory data, leptin may be associated with more advanced, hormone-refractory prostate cancer, which is referred to as prostate cancer that is no longer helped by any type of hormone therapy (ACS, 2016j; Freedland & Platz, 2007).

Studies on the relationship between leptin level and CRC had contradictory results (Aleksandrova et al., 2012; Nakajima et al., 2010; Stattin et al., 2004; Stattin, Palmkqvist, et al., 2003; Tamakoshi et al., 2005; Tessitore et al., 2000; Xu et al., 2011). Some researchers found a positive association between leptin levels and CRC (Ho et al., 2012; Stattin et al., 2004; Stattin, et al., 2003; Tamakoshi et al., 2005; Touvier et al., 2012). The findings indicated that obesity-associated abnormalities cooperatively increase the risk of CRC in obese individuals. The researchers of several epidemiological studies have also demonstrated the chemo-preventive effects of statins on various malignant diseases, including CRC (Shirakami, Ohnishi, Sakai, Tanaka, & Shimizu, 2017). Shirakami et al. (2017) discussed the strategies for preventing CRC by targeting obesity-related disorders such as high leptin levels through nutraceutical and pharmaceutical approaches. The use of statins possesses anticancer properties by inducing apoptosis in CRC cells, attenuating colonic inflammation, and suppressing inflammation-related colorectal carcinogenesis in mice (Shirakami et al., 2017). Further, the use of pitavastatin has helped decrease leptin levels, which indicates that the pharmaceutical approach appears to be one of the potential strategies for preventing obesity-related CRC because these drugs are in clinical use and have known

pharmacological effects against the obesity-related metabolic disorders, in addition to their cancer chemo-preventive effects (Shirakami et al., 2017).

However, researchers in other prospective studies observed a null association (Aleksandrova et al., 2012; Nakajima et al., 2010; Tessitore et al., 2000). As a result, it is questionable whether leptin is a predictor of CRC or a bystander because leptin does not have as strong an association with CRC in women as it has in men, although leptin levels in women are much higher than the levels in men (Paz-Filho et al., 2011). Further, two meta-analyses published in 2013 and 2014 did not indicate a significant association exists between leptin and CRC risk (a well-known obesity associated cancer), which indicated a need for further research that includes large-scale prospective studies to improve the understanding of these associations (Gialamas et al., 2013; Joshi & Lee, 2014). A significant association was not observed in the two studies between leptin and CRC after stratifying by the design of the study, which coincided with the results from Gialamas et al. (2013; (see also Joshi & Lee, 2014). Although significant heterogeneity existed between the studies (Q test $p < .000$ for overall, Q test $p < .001$ for prospective, and $p = .035$ for retrospective studies), the heterogeneity could not be greatly explored by meta-regression, as the meta-analysis did not include many studies (Joshi & Lee, 2014). The results of the aforementioned study further indicated the need for properly designed studies for predicting an overall association of leptin's influence on CRC risk. Other studies revealed that expressively low serum leptin levels in patients with colorectal tumors were present independent of BMI and weight loss (Arpaci et al., 2002; Kumor, Daniel, Pietruczuk, & Małecka-Panas, 2009).

Wang, Gao, Chai, and Wang (2017) conducted a cross-sectional, prospective study to compare the serum leptin levels between overweight colon cancer Chinese patients and colonoscopy-negative controls, as well as in preoperative and postoperative cancer patients. Sixty-three patients (29 men and 34 women) with ages ranging from 27 to 78 years (*Mdn* = 61 years; *M* = 58.4 years) were involved in the study (Wang et al., 2017). Based on histology grading, 13 of the patients had Grade 1, 22 had Grade 2, and 28 had Grade 3 tumors. Based on the TNM staging system, 2 had stage I, 14 had stage II, 46 had stage III, and 1 had stage IV disease. The mean BMI was 27.32 ± 2.3 kg/m^2 in the control group, and 27.24 ± 2.0 and 27.31 ± 2.1 kg/m^2 before and after colectomy, respectively, in the patient group (Wang et al., 2017). A significant difference in BMI was not observed between the patients and the controls or between patients before and after colectomy (Wang et al., 2017). The results of the study revealed that colon cancer patients had significantly higher serum leptin levels compared with those in the cancer-free controls (22.67 ± 12.56 vs. 12.68 ± 7.8 ng/ml, respectively, $p < .05$; Wang et al., 2017). The serum leptin levels significantly decreased after the operations (18.67 ± 8.54 vs. 22.67 ± 12.56 ng/ml, respectively, $p < .05$; Wang et al., 2017). There was a significant correlation of the leptin, p-Akt, p-mTOR, and P-70S6K status with the serum leptin levels ($p < .05$) in the colon cancer group (Wang et al., 2017). Akt/mTOR/70S6K is a critical pathway for tumor growth and progression (Wang et al., 2017). P-Akt activates mTOR, which subsequently phosphorylates 70S6K, inducing translation of mRNA and finally cell growth (Wang et al., 2017). However, there was no significant association of the serum leptin level with age, gender, or lymph node involvement ($p > .05$; Wang et al.,

2017). The findings indicated that leptin may be associated with colon carcinogenesis, and the serum leptin level may be used for early diagnosis and monitoring of the response to the treatment of colon cancer in overweight Chinese patients (Wang et al., 2017).

Obesity is a well-recognized risk factor for developing endometrial cancer (Gong et al., 2015). Researchers previously considered adipose tissue to be an energy-storage site (Gong et al., 2015). However, researchers found this tissue to be an endocrine organ producing and secreting several bioactive peptides, including adipokines such as adiponectin and leptin (Gong et al., 2015). In contrast, the biological functions of leptin are involved in cell proliferation, angiogenesis, and metastasis in several cell lines (Gong et al., 2015). Wang, He, Wang, Wang, and Wang (2014) suggested that high leptin levels may increase the risk of endometrial cancer, but available data were conflicting, and whether high leptin level was an independent risk factor of endometrial cancer is unclear. Although I specifically examined the difference in leptin levels and obesity associated cancers, as well as common cancers among adults in the United States, my study is relevant because there are no studies I am aware of in which researchers observed this relationship. Researchers associated leptin levels with the presence of endometrial cancer in a small number of previous studies. This association, however, disappeared when adjusted for BMI, which indicates that leptin may just be a bystander and not a predictor of endometrial cancer (Cymbaluk, Chudecka-Glaz, & Gorska, 2008; Petridou et al., 2002; Yuan et al., 2004).

Wang et al. (2014) completed a meta-analytic study to determine if leptin levels were an independent risk factor of endometrial cancer, as previous results were unclear.

The following six studies were included the meta-analysis: Ashizawa et al. (2010), Dallal et al. (2013), Friedenreich et al. (2012), Luhn et al. (2013), Ma, Liu, Zhang and Lu (2013), and Petridou et al. (2002). Wang et al. (2014) revealed that elevated leptin levels were associated with an increased risk of endometrial cancer (RR = 2.55, 35% confidence interval [CI] [1.91–3.41], p < .001; Wang et al., 2014). After adjusting for BMI and other aspects, elevated leptin levels were still associated with an increased risk of endometrial cancer (RR =1.67, 95% CI [1.28–2.17], p < .001; Wang et al., 2014). Moreover, after adjusting for confounding factors, high leptin levels were also associated with an increased risk of endometrial cancer (RR =1.59, 95% CI [1.27–1.98], $p < .001$; Wang et al., 2014). The subgroup analysis by study design found similar findings ($p < .01$; Wang et al., 2014). Thus, the findings suggested that high leptin levels are an independent risk factor of endometrial cancer, and leptin does indeed play an important role in the carcinogenesis of endometrial cancer (Wang et al., 2014). More prospective studies are necessary for further confirmation of this association in the future (Wang et al., 2014).

Wang et al. (2014) noted that researchers have demonstrated high leptin levels and low adiponectin levels in clinical and case-control in various populations (Ashizawa et al., 2010; Cust et al., 2007; Cymbaluk et al., 2008; Luhn et al., 2013; Petridou et al., 2003; Rzepka-Gorska, Bedner, Cymbaluk-Ploska & Chudecka-Glaz, 2008). However, Wang et al. performed a meta-analysis to evaluate the relationship between adipokines-related biomarkers and endometrial cancer risk both comprehensively and quantitatively. The results indicated that increased circulating adiponectin or decreased leptin concentrations have a significant association with a reduced risk of endometrial cancer

(Gong et al., 2015). Further prospective studies are necessary to confirm the finding in this meta-analytic study.

Ovarian cancer is the most lethal gynecological cancer in developed countries (Chen, Chang, Lan, & Breslin, 2013). Ovarian cancer is an obesity-associated cancer (NCI, 2012). With obesity being a risk factor in the development of ovarian cancer, Jin et al. (2016) conducted a study to explore differences in plasma adiponectin and leptin concentrations between patients with and without ovarian cancer with the same BMI to determine whether adiponectin and leptin are related with ovarian carcinogenesis. Plasma adiponectin and leptin levels are the two most abundant adipokines associated with obesity (Jin et al., 2016). An adipokine is a hormone secreted from adipose tissue and is an obesity-related hormone (Jin et al., 2016). Adiponectin is an adipokine that can suppress cancer cell growth and invasiveness and can inhibit angiogenesis by suppressing estrogen receptor α and vascular endothelial growth factor (Jin et al., 2016). Plasma leptin levels are higher in overweight and obese individuals than they are in normal-weight individuals (Kimura, Matsumoto, Samori, Kato, & Kawahara, 2000; Ma, Liu, Zhang, & Lu, 2013). Between September 2006 and October 2014l, 52 patients were histologically diagnosed with ovarian cancer at the Gynecology and Oncology Center of Ewha Woman's University Mokdong Hospital and were recruited as subjects (Jin et al., 2016). Due to the difficulty in collecting absolute healthy female blood samples, 50 patients clinically diagnosed with benign disease during the same period were selected for the control group (Jin et al., 2016). Clinical data were reviewed from medical records, including body weight and height, for the calculation of the patients' BMI. The study also

included age and cancer history (Jin et al., 2016). The patients' BMI was categorized as underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), and obese (>30; Jin et al., 2016).

Jin et al. (2016) noted that the mean plasma adiponectin concentrations were significantly lower in the ovarian cancer group (8.25 ± 0.97 μg/mL) than those of the control group (11.44 ± 1.13 μg/mL; $p = .026$). The mean plasma leptin concentrations were significantly lower in the ovarian cancer group (7.09 ± 1.46 ng/mL) than the control group (15.4 ± 2.04 ng/mL; $p < .001$; Jin et al., 2016). However, no significant difference existed in adiponectin and leptin levels between early-stage (I/II) and advanced-stage (III/IV) disease ($p = .078$, $p = .675$; Jin et al., 2016). The leptin concentration was higher in nonserous type (7.17 ± 2.75 ng/mL) than in serous type (6.94 ± 1.67 ng/mL) cancer, but there was no statistical significance ($p = .941$; Jin et al., 2016). Compared with the other gynecological cancers, the level of adiponectin and leptin was decreased in ovarian cancer (Jin et al., 2016). Likewise, the median age of the patients with ovarian cancer in the study was 47.9 years (range 31–78 years), while the median age of individuals in the control group ($n = 50$) was 52.3 years (range 13–77 years); no significant difference was found between the two groups ($p = .126$; Jin et al., 2016). The mean BMI levels for patients with ovarian cancer and the control group were 23.34 kg/m^2 (range: 17.71–33.59 kg/m^2) and 23.77 kg/m^2 (range 17.36–29.15 kg/m^2), respectively; no significant difference was found between the two groups ($p = .659$; Jin et al., 2016).

An additional ovarian-cancer-related study revealed similar results as previous studies. As mentioned, available data regarding serum leptin levels in ovarian cancer

have produced contradictory results. Grabowski, Markowska, and Markowska (2014) reported lower leptin levels in patients with ovarian cancer than in healthy individuals. Grabowski et al. conducted a prospective study that involved evaluating serum leptin levels in ovarian cancer patients before and after primary surgery, as well as after first-line chemotherapy, and the researchers compared this population's leptin levels with a control group consisting of patients with benign ovarian findings. Fifty-three patients with primary epithelial ovarian cancer were treated at the Department of Oncology, Division of Gynecology, Poznan University of Medical Science, between 2006 and 2007; the average in the control group was 42.5 years (range 29–68), and the average age of the patients in the study group was 53.9 years (range 44–71; Grabowski et al., 2014). Significantly lower mean leptin levels in ovarian cancer patients versus the control group were revealed (9.26 ± 4.04 ng/ml and 15.25 ± 2.82 ng/ml ($p < .0001$), respectively (Grabowski et al., 2014). Patients with advanced ovarian cancer FIGO III/IV had lower mean serum leptin levels in comparison to women with FIGO I/II stage, 7.08 ± 1.87 ng/ml and 14.73 ± 1.87 ng/ml, respectively ($p < .0001$; Grabowski et al., 2014). There were no significant differences in mean serum leptin concentrations observed between patients with early ovarian cancer and the control group (Grabowski et al., 2014).

Moreover, Grabowski et al. (2014) did not observe significant differences between pre- and postoperative mean serum leptin levels in the study and control group, 11.04 ± 4.03 ng/ml ($p = .052$) and 14.9 ± 3.1 ng/ml ($p = .064$), respectively (Grabowski et al., 2014). The subgroup analysis showed no significant change of postoperative mean serum leptin concentration in stage FIGO I/II ovarian cancer patients ($p = .057$)

(Grabowski et al., 2014). Significant elevation to 13.71 ng/ml ($p < .001$) of mean postoperative serum leptin concentrations in patients who underwent complete tumor resection were identified. In contrast, mean postoperative serum leptin levels did not significantly change in patients who underwent suboptimal surgery ($p = .059$; Grabowski et al., 2014).

Moreover, Grabowski et al. (2014) noted the mean BMI level of patients in the study group was 24 kg/m^2 (range 18.2–32.8) and 22 kg/m^2 (range 17.2–30.3) in the control group ($p > .05$). Mean BMI in patients with early ovarian cancer was 23.7 kg/m^2 (range 18.2–31.9) and in the advanced group 24.4 kg/m^2 (range 19.0–32.8; $p > .05$). No statistical difference in initial BMI between early or advanced ovarian cancer and the control group was found ($p > .05$; Grabowski et al., 2014). Positive correlations between serum leptin concentrations and BMI in the control group, as well as in early and advanced ovarian cancer patients ($p < .05$), were observed (Grabowski et al., 2014). However, mean serum leptin concentrations in women with benign ovarian tumors and early ovarian cancer patients (FIGO I/II) were significantly higher in comparison to advanced ovarian cancer patients (FIGO III/IV) by similar BMI values in those groups ($p < .05$; Grabowski et al., 2014).

Grabowski et al. (2014) showed statistically significant elevated serum leptin concentrations after complete cytoreduction (reduction in the number of cancer cells) in advanced ovarian cancer patients but did not observe statistically significant elevated leptin concentrations in patients who underwent suboptimal surgery or those with early ovarian cancer. Grabowski et al. did not observe BMI differences among advanced, early

ovarian cancer, and the control group. Concomitant (naturally occurring or associated) cancer progression, inflammation, and catabolic processes led to a decrease of serum leptin concentration (Grabowski et al., 2014).

In a similar gynecologic study, Wu et al. (2014) aimed to identify the risk factors for the development of UCC and ovarian cancer by following up a large community-based women cohort in Taiwan. Wu et al. examined the associations of leptin and adiponectin with the development of UCC and ovarian cancer. The focus was on lifestyle exposure (cigarette smoking and alcohol intake), reproductive factors (age when first began menstruating, number of childbirths, use of contraceptive pills, and age at menopause) and adiposity factors (Wu et al., 2014). Wu et al. recruited 11,258 women aged 30–65 during 1991–1993 and followed them for UCC and ovarian cancer cases until December 31, 2011. For the adipokine (leptin and adiponectin) portion of the study, Wu et al. conducted a nested case control study within the cohort and assayed a baseline plasma sample of 40 incident gynecological cancer cases and 240 age–menopause matched controls for adipokine levels.

Wu et al.'s (2014) nested case-control study revealed that case subjects with incident gynecological cancer had a significantly higher level of leptin and a significantly lower level of adiponectin in plasma at enrollment compared with the control subjects (Wu et al., 2014). Leptin was median 22.53 ng/ml (IQR: 19.47–29.05 ng/ml) in UCC cases versus 9.81 (6.16–14.56) in the age- and menopause-matched controls and 23.58 (14.92–42.61) in ovarian cancer cases versus 9.79 (6.50–14.74) in their matched controls. The corresponding adiponectin levels were 4.71 μg/ml (3.95–6.62 μg/ml) versus 8.92

(6.66–11.28 µg/ml) for UCC and 7.98 (5.21–9.60 µg/ml) versus 9.08 (6.37–12.61) for ovarian cancer (Wu et al., 2014). After adjusting for age and risk covariates, patients with leptin in the highest tertile 3 had an increased risk of incident gynecological cancer as compared with those in the lowest tertile 1 (odds ratio *OR* = 10.68, 95% CI[2.09–54.67], p =.005, and *OR* = 11.83, 95% CI[1.40–1.11], p = .023) for UCC and ovarian cancer, respectively (Wu et al., 2014). Patients with baseline adiponectin in tertile 3 had a decreased risk of subsequent gynecological cancer as compared with those in tertile 1 for UCC and ovarian cancer, respectively (Wu et al., 2014). Obesity is the dominant predictor for ovarian cancer risk among the study cohort and in addition to estrogen exposure; other risk factors such as alcohol intake and serum triglycerides may also be involved in UCC carcinogenesis (Wu et al., 2014). The data indicated that circulating leptin and adiponectin may mediate the link of triglycerides and obesity, respectively, to UCC and ovarian cancer risk (Wu et al., 2014).

Skin is the largest human organ. Skin conditions combined rank as the fourth leading cause of all human diseases, affecting almost one third of the world's population (Li, Cho, Weinstock, Mashfiq, & Qureshi, 2016). With the rates of skin cancer (basal/squamous/melanoma) rising steadily since 1986, it is by far the most common of all cancers (ACS, 2016c). Although melanoma accounts for approximately only 1% of skin cancer, it causes the large majority of skin cancer deaths (ACS, 2016c). Melanoma has an association with obesity (Gogas et al., 2007). Leptin is a melanoma growth factor, and the leptin autocrine loop may contribute to the uncontrolled proliferation of these cells (Ellerhorst et al., 2010). An association exists between elevated leptin levels and

increased risk for developing melanoma, but the elevated levels were not attributed to obesity, although leptin tracks closely with BMI, and most individuals with high leptin have elevated BMI and thus tend to be obese (Ellerhorst et al., 2010; Gupta et al., 2016). The high BMI and obesity relationship could be due to the fact those people who are genetically predisposed to higher circulating leptin levels, regardless of body mass, are at a greater risk for developing leptin responsive tumors (Ellerhorst et al., 2010).

Ellerhorst et al. (2010) noted that leptin was expressed in normal skin cells as well as in both squamous cell and basal cell carcinomas. However, Ellerhorst et al. also noted that, because all 19 squamous cell carcinoma cases examined (100%) and only two of the 14 basal cell carcinoma cases (15.4%) revealed leptin expression in tumor cells, nuclear expression was in favor of squamous cell carcinoma. As a result of Ellerhorst et al.'s findings, Faraq et al. (2016) indicated leptin could have a more important role in the pathogenesis of cutaneous squamous cell carcinoma, but not basal cell.

In 2007, in the first and possibly only study conducted to explore the role of leptin and the way its levels increase with obesity in melanoma development, 55 patients with incident melanomas and their age and gender matched healthy controls participated in an interview (Gogas et al., 2007). The age range among the cohort cases was 23–88 years, with a mean of 52.7 years, and the average age among controls was 23–87 years with a mean value of 53.2 years (Gogas et al., 2007). Gogas et al. observed a high melanoma risk for sun-sensitive individuals and those with high circulating levels of leptin, odds ratio (*OR*) 1.56, 95% CI [1.07–2.28], $p < .02$, after controlling for age, smoking, diabetes mellitus, and education (Gogas et al., 2007). Increased physical exercise, lower alcohol

consumption, and plant food consumption seemed to play a protective role against melanoma development (Gogas et al., 2007). Finally, a positive association existed between melanoma risk and serum leptin levels, and an inverse relationship existed with health lifestyle factors; however, further prospective studies are necessary to confirm the underlying pathophysiologic mechanisms and the role of the risk factors in predicting future risk of melanoma in humans (Gogas et al., 2007).

The results when examining the association between obesity and the risk of melanoma and nonmelanoma skin cancers, when compared to participants (adult men and women) with a normal BMI indicated those classified as obese (according to their BMI) had a 32% lower risk of developing squamous cell cancer, and those with a BMI in the morbidly obese category had a 37% lower risk of developing squamous cell cancer in women only (Pothiawala, Qureshi, Yunhui, & Han, 2012). When compared to participants who fell in the normal BMI category, those classified as obese had a 19% lower risk for developing basal cell carcinoma, and those with a BMI in the morbidly obese category had a 29% lower risk of developing basal cell carcinoma. The risk of developing melanoma did not statistically differ according to BMI (Pothiawala et al., 2012). Obesity is a potential surrogate marker of chronic sun exposure, and further studies of potential mechanisms underlying different associations between obesity and various skin cancers are necessary to bring skin cancer carcinogenesis to the forefront (Farag, Elnaidany, & El-Dien, 2016; Pothiawala et al., 2012).

After increasing for decades, lung cancer rates began to decrease nationally, as fewer people are smoking cigarettes (CDC, 2014d). However, lung cancer is still the

leading cause of cancer death and the second most diagnosed cancer in both men and women in the United States (CDC, 2014d). Leptin and leptin receptors are involved in the development, progression, and prognosis of different types of cancer (Artac & Altundag, 2012; Garofalo & Surmacz, 2006). However, the few studies conducted regarding leptin and its receptors and their relationship to lung cancer have produced conflicting results (Alemán et al., 2002; Gulen et al., 2012; Kerenidi et al., 2013; Terzidis et al., 2009). In one study, an association existed between lung cancer and elevated leptin levels (M. Song et al., 2014). However, Gulen et al. (2012) conducted a study to investigate the relationship between adipokines and systemic inflammation in weight-losing advanced stage NSCLC patients and found dissimilar results. The study participants had lower serum adiponectin levels compared to the control group, but leptin levels among the lung cancer patients and the healthy controls showed very few if any differences. However, a positive association existed between leptin and BMI in the study's NSCLC patients (Gulen et al., 2012). A decrease in leptin concentration should increase the appetite and decrease energy use, resulting in increased fat storage, which was not the case in cancer patients and may suggest a block in the hypothalamic response to low-circulating leptin concentrations (Gulen et al., 2012). In contrast, a previously conducted related study indicated that elevated serum leptin levels were indicative of an independent risk factor for NSCLC (Terzidis et al., 2009).

In the most recent publicly available study found concerning leptin levels and lung cancer, the researchers evaluated the expression and clinical significance of leptin in lung cancer (M Song et al., 2014). The study included 126 patients with lung cancer

whose ages ranged from 30 to 83 years, with the median age being 59.1 years, along with 60 controls. After adjusting for age, gender, histology, surgical treatment, and nodal stage, the results revealed that the median leptin level of the patient group was significantly higher compared to the control group (median ± IQR: 9.66 ± 7.73 vs. 4.75 ± 4.02, $p < .001$) (M Song et al., 2014). The results also revealed that a strong association existed between leptin and gender, but there were no correlations with other related factors (M Song et al., 2014). Tissue samples also revealed significantly higher leptin levels than in those of the control group, which indicated that leptin may be a tumor marker for screening and predicting lung carcinogenesis (M Song et al., 2014).

Risk Factors Associated With the Relationship Between Leptin (Level) and Cancer

A risk factor is anything that affects a person's chance of getting a disease such as cancer. Different cancers have different risk factors, and some risk factors, like smoking, can change. A person's age or family history cannot change (ACS, 2016e). However, having a risk factor, or even several, does not mean that a person will get the disease, and some people who get the disease may not have any known risk factors.

Previous leptin and cancer research have presented a wide range of covariates in analyzing the relationship. Because very few studies exist with a focus on the differences in leptin levels between adults with and without obesity-associated and common cancers, I reviewed relevant studies. Overweight/obesity (Amos et al., 2013; Assiri, Kamel, & Hassanien, 2015; Babaei et al., 2015; Chen et al., 2013; Dallal et al., 2013; De Pergola & Sivestri, 2013; Gupta et al., 2016; Ho et al., 2012; Iles et al., 2013; Johnson et al., 2013; Laiyemo, 2014; Lee, Meyerhardt, Giovannucci, & Jeon, 2015; Lee et al., 2015; Mercola,

2015; Murphy et al., 2016; NIH, 2012; Paz-Filho et al., 2011; Pothiawala, Qureshi, Li, & Han, 2012; Praestegaard et al., 2015; Riondino et al., 2014; Romero-Figueroa et al., 2013; Tewari et al., 2013; Tilg & Moschen, 2014; Yang et al., 2012), SES (Rametta et al., 2013), and T2DM (Cohen et al., 2012) are major contributors or disparities that may increase the risk of cancer development in obesity-related cancers, and therefore significant attention has been placed on the prevention and control of these factors and ultimately this chronic disease (ACS, 2016; CDC, 2016; NCI, 2016a). These factors are modifiable risk factors, which include health behaviors and lifestyle factors (Ohio Department of Health and Human Services, 2015). Researchers have associated many other risk factors with the aforementioned relationship, such as smoking, but the focus of this study was obesity/BMI, T2DM, dietary intake, physical activity, and SES.

Obesity and Cancer

Obesity has reached pandemic levels worldwide (CDC, 2016a). As a result, obesity-associated diseases account for a large portion of public health challenges, with cancer being one of the most prevalent (CDC, 2016a; Riondino et al., 2014). The effects of obesity have become so profound that experts expect obesity will overtake smoking as the leading cause of at least 10 different types of cancer by 2025 (Donnelly, 2015; Mercola, 2015). Excess body fat may be a cause of approximately 130,600 U.S. cancer cases every year (AICR, 2016). Only 52% of Americans now realize that obesity is a cause of cancer (AICR, 2016). Several prospective epidemiological studies have demonstrated an association, whether direct or inverse, between being overweight and cancer, even though obesity alone does not increase the risk of cancer in all related body

tissues equally (Azvolinksy, 2016; Brandon et al., 2009; Calle & Kaaks, 2004; Calle, Rodriguez, Walker-Thurmond, & Thun, 2003; Drew, 2012; International Agency for Research on Cancer, 2002; Laiyemo, 2014; Renehan et al., 2008; Reeves, Pirie, Beral, Green, & Spencer, 2007; Taubes, 2012; Wolin, Carson, & Colditz, 2010).

Studies have also indicated that excess body fat is a cause of the following cancer types: endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal; less common, inverse, and conflicting inversely positive associations are leukemia, non-Hodgkin's lymphoma, multiple myeloma, malignant melanoma, and thyroid tumors (AICR, 2016; De Pergola & Silvestris, 2013; Kitahara et al., 2013; Martinez-Useros & Garcia-Foncillas, 2016; Paz-Filho et al., 2011; Pothiawala et al., 2012; Praestegaard et al., 2015). However, the results of several studies supported an inverse association between BMI and lung cancer incidence in both men and women (Praestegaard et al., 2015; Smith et al., 2012; Yang et al., 2012).

Researchers at NCI noted several potential mechanisms can explain the correlation of obesity with increased risk of certain cancers such as colon and rectum, breast (after menopause), and endometrium (lining of the uterus). Fat cells produce hormones, known as adipokines, including leptin, which is more abundant in obese individuals and appears to promote cell proliferation and production (NIH, 2012). NIH researchers also noted that fat tissue produces excess amounts of estrogen, high levels of which have an association with the risk of breast, endometrial, and other cancers (Hopkins, Goncalves, & Cantley, 2016; NIH, 2012). Additionally, obese individuals frequently have increased levels of insulin and insulin-like growth factor-1 (IGF-1),

which is a condition known as hyperinsulinemia or insulin resistance, in their blood (Hopkins et al., 2016; NIH, 2012). Obese individuals are prone to having chronic low-level, or subacute, inflammation, which researchers have associated with increased cancer risk (Hopkins et al., 2016; NIH, 2012).

Moreover, according to NIH researchers, overweight and obesity are associated with a modest increase in risk of postmenopausal breast cancer, with a higher risk evident in women who have never used menopausal hormone therapy and for tumors that express both estrogen and progesterone receptors. Researchers have consistently associated increased levels of estrogen in obese women and weight gain during adult life between the ages of 18 and 60 years with breast cancer after menopause (NIH, 2012). The risk is higher because, after menopause, ovaries stop producing hormones, and fat tissue are the primary source of estrogen (NIH, 2012). Thus, the more obese a woman is, the more fat tissue is present; therefore, her estrogen levels are higher than women of normal weight (NIH, 2012). This also leads to more rapid growth of estrogen-responsive breast tumors (NIH, 2012). Finally, the relationship between obesity and breast cancer risk may vary by race and ethnicity (NIH, 2012).

In a case-cohort study nested within the Women's Health Initiative cohort of women, Ho et al. (2012) investigated whether seven adipokines, along with fasting insulin, are risk factors for CRC and whether they may mediate its association with obesity. Ho et al. assayed 457 CRC cases and 841 subcohort subjects for leptin and other adipokines. After adjusting for age, race, colonoscopy history, and estrogen level, an association existed between leptin and an increased risk of CRC (Ho et al., 2012). Leptin

also remained significant after further adjustment for insulin when comparing extreme hazard ratio (HR) quartiles (HRQ4–Q1), 1.84; 95% CI [1.17-–2.90] (Ho et al., 2012). The findings show that an association exists between adipokines involved in inflammation and CRC risk, and insulin may be the main mediator of their effects, with leptin bearing an independent effect (Ho et al., 2012).

Endometrial cancer has been consistently associated with being overweight or obese (Dallal et al., 2013; NIH, 2012). Obese women have a two- to four-times higher risk of developing breast cancer than women of normal weight, regardless of their menopausal status (ACS, 2016g; CDC, 2014a; NIH, 2012). Researchers have not yet fully determined why obesity is a risk factor for endometrial cancer, but diabetes, combined with low levels of physical activity and high levels of estrogen produced by fat tissue, may play an important role (NIH, 2012).

Once more, a strong influence exists between endometrial cancer risk and obesity, but the exact mechanism is unclear (Dallal et al., 2013). Leptin is an obesity-related hormone secreted from adipose tissue and is playing a significant role in carcinogenic processes such as cell proliferation, angiogenesis, and insulin regulation (Dallal et al., 2013). As a result, Dallal et al. (2013) conducted a case-control study to assess prediagnostic serum leptin and other obesity-related hormones in relation endometrial cancer among a group (n = 15,595) of postmenopausal women. The results of the study revealed a significant association existed between endometrial cancer and higher leptin and BMI levels (Dallal et al., 2013). The findings indicated that the leptin–BMI

relationship may increase endometrial cancer through mechanisms other than estrogen-driven proliferation (Dallal et al., 2013).

High BMI among men has a strong association with an increased risk of developing CRC (Attner, Landin-Olsson, Lithman, Noreen, & Olsson, 2012; Johnson et al., 2013; Kitahara et al., 2013; Laiyemo, 2014; NIH, 2012; Riondino et al., 2014). Abdominal obesity has shown a strong correlation with colon cancer among men. There is also an association between BMI and waist circumference in colon cancer risk among women, but it is much weaker, and using menopausal hormone therapy may alter this association in postmenopausal women (Johnson et al., 2013; NIH, 2012). Insulin or IGF may also promote cancer development in obese people (NIH, 2012).

Some researchers have reported conflicting results on the association between BMI and prognosis of CRC. As a result, Lee et al. (2015) conducted a meta-analysis of prospective studies, which involved examining the association of pre- and post-diagnostic BMI with CRC-specific mortality and all-cause mortality in patients with CRC. Lee et al. found, after analyzing 58,917 patients who were followed up over a period ranging from 4.9 to 20 years (median: 9.9 years), that being underweight before cancer diagnosis was associated with increased all-cause mortality relative ratio (RR) 1.63, 95% CI [1.18–2.23], $p < .01$. Being classified as obese (BMI ≥ 30 kg/m^2) before cancer diagnosis was associated with increased CRC-specific mortality, RR 1.22, 95% CI [1.003–1.35], $p < .01$, and all-cause mortality, RR 1.25, 95% CI [1.14–1.36], $p < .01$ (Lee et al., 2015). In contrast, being underweight, RR 1.33, 95% CI [1.20–1.47], $p < .01$; obese, RR 1.08, 95% CI [1.03–1.3], $p < .01$; and class II/III obese BMI ≥ 35 kg/m^2, RR 1.13, 95% CI [1.04–

1.23], $p < .01$, after diagnosis had an association with significantly increased all-cause mortality (Lee et al., 2015). Lee et al. summarized that being obese prior to a diagnosis of CRC was associated with increased CRC-specific mortality and all-cause mortality, whereas being obese after diagnosis was associated with increased all-cause mortality. The associations with being underweight may reflect reverse causation (Lee et al., 2015).

Researchers have positively linked obesity to CRC through various studies (Drew, 2012; Ho et al., 2012; Laiyemo, 2014; Murphy et al., 2016). One such study was a 2016 case-control study nested within the european prospective investigation into cancer and nutrition (EPIC) study (Murphy et al., 2016). The results revealed that in multivariable-adjusted conditional logistic regression models with BMI used to define adiposity, compared with metabolically healthy/normal weight individuals, a higher CRC risk was observed among metabolically unhealthy/normal weight (*OR* = 1.59, 95% CI [1.10–2.28]) and metabolically unhealthy/overweight (*OR* = 1.40, 95% CI [1.01, 1.94]) participants, but not among metabolically healthy/overweight individuals (*OR* = 0.96, 95% CI [0.65–1.42]; Murphy et al., 2016). Among overweight individuals, the researchers observed lower CRC risk for metabolically healthy/overweight individuals compared with metabolically unhealthy/overweight individuals (*OR* = 0.69, 95% CI [0.49–0.96]) (Murphy et al., 2016). Murphy et al. (2016) also revealed that adipokines involved in inflammation, such as leptin, are associated with CRC risk, but insulin might mostly mediate their effects, with leptin exerting an independent effect. Hyperinsulinemia and hyperleptinemia may partially explain the adiposity association with CRC in postmenopausal women (Ho et al., 2012).

According to Laiyemos (2014), although the ideal measurement of the degree of body fatness that correlates well with CRC risk is uncertain, the BMI is the most widely studied metric. The increased risk of colon cancer is fairly consistent across studies, irrespective of the measure of obesity used (Laiyemos, 2014). In research conducted in Asia, which sometimes has lower cut-off points (e.g. overweight = BMI 25.0–27.9 kg/m^2 and obese = BMI > 28.0 kg/m^2), an increased burden of colon cancer was still prominent in both overweight and obese categories (Laiyemos, 2014). Surgery is the most definitive treatment for CRC with a potential for a cure, but obesity has been associated with poor surgical outcomes due to complications (Laiyemos, 2014). Laiyemos also associated obesity with inferior results after a CRC diagnosis in patients with stage II and III disease in some cohorts, possibly due to challenges in determining appropriate doses of chemotherapy to administer to obese patients as clinicians struggle to achieve the same maximum intensity in obese patients by balancing the risk of underdosing with the risk of toxicity (Laiyemos, 2014). Weight loss is a pertinent strategy to reduce risk of CRC (ACS, 2017a). However, it is uncertain if such risk reduction is possible and how long individuals must maintain the new weight to accomplish the risk reduction (Laiyemos, 2014). Laiyemos pointed out that neither BMI nor weight loss or gain between chemotherapy and after 6 months after completion of therapy was associated with an increased risk of cancer recurrence or death. In contrast, BMI and moderate weight gain was associated with increased risk of colon cancer, but weight loss had no effect on colon or rectal cancer (Laiyemos, 2014).

Researchers have also linked obesity to other cancers, such as prostate cancer. Researchers have reported a potentially nonlinear relationship between leptin levels and prostate cancer, with very elevated leptin levels associated with reduced cancer incidence, in previous studies (Gupta et al., 2016; Stattin et al., 2003). Results of individual studies, according to researchers NIH (2012), do not indicate a consistent association between obesity and prostate cancer. However, when pooling data from several studies, analyses show that an association may exist between obesity and a very slight increase in the risk of prostate cancer (NIH, 2012). In contrast, obese men have a higher risk of aggressive prostate cancer than men of normal weight, with the risk of prostate cancer being associated with specific hormones and IGF-1 (NIH, 2012). For example, Barrington et al. (2015) conducted a prospective study to determine whether the association of obesity with prostate cancer risk differs between African American and non-Hispanic White men and whether obesity modifies the excess risk associated with the African American race. The results of the study revealed at follow-up that no association existed between BMI and an increase risk among White men, and a positive association existed between BMI and an increased risk among African American men (BMI < 25 vs. ≥ 35: HR 1.49, 95% CI [0.95–2.34], p =.003 (Barrington et al., 2015). The risk among African American men increased from 28% among men with BMI less than 25 to 103% among African American men with BMI of at least 35 (Barrington et al., 2015).

Consequently, an inverse relationship existed between BMI and low-grade prostate cancer within non-Hispanic White men, but a positive association existed

between BMI and risk within African American men (Barrington et al., 2015). A positive association existed between BMI and risk of high-grade prostate cancer in both non-Hispanic White men (BMI < 25 vs. ≥ 35: HR 1.33, 95% CI [0.90–1.97], $p < .01$) and African American men; the increase may be larger within African American men, though not statistically significant among racial interaction, BMI < 25 versus ≥ 35: HR 1.81, 95% CI [0.79–4.11], p = .02 (Barrington et al., 2015).

Skin cancer (melanoma and nonmelanoma/basal/squamous) is the most common cancer diagnosed in the United States (ACS, 2016c, 2017a; CDC, 2016i). Cancer research scientists in the United Kingdom at the University of Leeds showed that people with particular variations in a stretch of DNA within the FTO gene, called intron 8, the gene most strongly linked to obesity and overeating according to Iles et al. (2013), could be at greater risk of developing malignant melanoma, which is the deadliest form of skin cancer. Variations in a different part of the FTO gene called intron 1 are linked to BMI, but Iles et al. were the first to reveal that FTO intron 8 affects a disease (skin cancer) which is not known to be linked to obesity and BMI. This revealed an association between several single nucleotide polymorphisms (SNPs) in intron 8 of the FTO gene, including rs16953002, which replicated using 12,313 cases and 55,667 controls of European ancestry from Europe, the United States, and Australia (combined $p = 3.6 \times 10^{-12}$, per-allele OR for $A = 1.16$; Iles et al., 2013). This was the first study to identify and replicate an association with SNPs in FTO not related to BMI. These SNPs are not in intron 1 (the BMI-related region) and show no association with BMI (Iles et al., 2013).

Iles et al.'s research was the catalyst for future research into both obesity-related diseases and skin cancer.

In contrast, Tang et al. (2013) conducted a large, geographically diverse, longitudinal, prospective Women's Health Initiative Observational Study to study the indefinite relationship of obesity to incident melanoma and nonmelanoma skin cancer risks. The study took place over a mean 9.4 years of follow-up. The study involved comparing risks of melanoma and nonmelanoma skin cancer in normal-weight women to risks in overweight (BMI = 25–29 kg/m^2) and obese (BMI $\geq$ 30 kg/m^2) women using Cox proportional hazards models for melanoma and logistic regression for nonmelanoma skin cancer (Tang et al., 2013). Among the 386 melanoma and 9,870 nonmelanoma skin cancer cases, risk of melanoma did not vary across weight categories (p = .086); however, in fully adjusted models, NMSC risk was lower in overweight, OR 0.93, 95% CI [0.89–0.99], and obese, OR 0.85, 95% CI [0.80–0.91], women, p < .001 (Tang et al., 2013). Excess body weight was not associated with melanoma risk in postmenopausal women but was inversely associated with nonmelanoma skin cancer risk, possibly due to lower sun exposure in overweight and obese women (Tang et al., 2013). The above findings support previous studies demonstrating the relationship between excess body weight and skin cancer risk (Tang et al., 2013).

Moreover, Paz-Filho et al. (2011) and Yang et al. (2013) reported being lean had a stronger association with lung cancer risk among current and former smokers. As previously mentioned, obesity also leads to several comorbidities, such as diabetes, dyslipidemia, hypertension, sleep apnea, osteoarthritis, menstrual disorders, infertility,

gout, stroke, ischemic heart disease, congestive heart failure, deep vein thrombosis, and pulmonary embolism (Paz-Filho et al., 2011; Weir et al., 2016). Twenty percent of all malignancies are due to obesity and based upon gender and site (De Pergola & Silvestris, 2013). BMI, weight increase, and body fat, particularly visceral, guide the association between obesity and a higher risk of developing cancer (De Pegola & Sivestris, 2013). DePergola and Selvistris (2013) concluded that hyperinsulinemia and insulin resistance, the activities of sex hormones, general and adipose tissue, low-grade inflammation, changes in adipose tissue production of adipokine and vascular growth factors, oxidative stress, endocrine disruptors, and alterations in immune function are the most important biological mechanisms mediating the unfavorable influence of the above factors. Further studies are necessary regarding the reduction of cancer risk related to weight.

Wang and Beydoun (2007) noted that, since the mid-1970s, the United States had experienced a considerable rise in the prevalence of obesity, which had contributed to a public health crisis. Wang and Beydoun also explained that the body of evidence that has reported tremendous disparities among population groups and ongoing changes associated with patterns that include the epidemic of obesity in the United States has increased. In their quantitative meta-analytical study, Wang and Beydoun found that obesity was related to gender, age, socioeconomic, racial/ethnic, and geographical characteristics. Wang and Beydoun also indicated that individuals who had less than a high school education had a prevalence of obesity that was higher than their counterparts, except African American women. African American women with less than a high school education had the lowest prevalence of obesity as compared to those who had a higher

level of education (CDC, 2016a; Wang & Beydoun, 2007). Furthermore, among non-Hispanic Black and Mexican American men, those with higher incomes levels are much more likely to be obese than are those with lower income (CDC, 2016a).

In a 2012 article concerning the unraveling of the obesity and cancer connection, Taubes noted that German biochemist Otto Warburg observed that tumor cells can survive without oxygen and generate energy by a relatively inefficient process known as aerobic glycolysis. This conversion of cancer cell metabolism to aerobic glycolysis has come to be known as the Warburg effect (Taubes, 2012). Warburg hypothesized that the high-glucose metabolism drives cancer (Taubes, 2012). However, it is still unclear why cancer cells use glucose (Taubes, 2012). Most researchers studying the Warburg effect have indicated that the signaling pathways driving it are the insulin and insulin-like growth factor pathways (Taubes, 2012). Additionally, insulin and insulin-like growth factors tend to be the most appealing mechanisms to explain the link between obesity and cancer, but cell-suicide suppression is their primary role, which leads to the requirement of more research to determine a direct connection between obesity and cancer (Taubes, 2012).

In a 2016 article from the *Journal of the National Cancer Institute*, Azvolinsky outlined various studies that discussed how obesity fueled cancer. Azvolinsky noted that maintaining a healthy weight is a likely way to avoid metabolic imbalances such as insulin resistance and high circulating levels of hormones such as leptin, which could decrease risk of T2DM, heart disease, and obesity-related cancers. However, reducing the risk of obesity-related cancer resulting from weight loss is actually difficult to identify

due to confounding factors. Additionally, a basal like breast cancer study in mice who were obese, normal weight and formerly obese was conducted in the quest to understand how some obesity-associated markers are evident even after significant weight loss and its effect on cancer development (Azvolinsky 2016). Despite a 10% reduction in weight and the stabilization of insulin and leptin levels, both the formerly obese mice and the obese mice had similar tumor growth as well as related circulating inflammatory markers in the mammary tissue (Azvolinsky, 2016). DNA methylation in the mammary tissue of both groups of mice was similar and higher than the normal-weight control animals, which suggested an epigenetic memory of the obese state in the mice that were obese but lost weight (Azvolinksky, 2016). The finding indicated that weight loss alone may not be enough to overcome some of the negative effects of obesity (Azvolinksky, 2016). The same study is taking place in humans to determine if it holds true for humans (Azvolinksky, 2016). Researchers believe epigenetic reprogramming occurs with chronic obesity, and researchers are trying to determine which metabolic factors actually explain the obesity–cancer link (Azvolinsky, 2016). Furthermore, an association between ovarian cancer and obesity may reflect increased levels of estrogen (Azvolinsky, 2016). Some researchers have shown a weak association between increasing BMI and risk of ovarian cancer, especially in premenopausal women, whereas other researchers have not found an association (NIH, 2012).

Although hormones play a significant role, alone they are not likely enough to explain the connection (Azvolinksy, 2016). Researchers measured the metabolite changes of 68 women at high risk for obesity-related cancer who had bariatric surgery that led to a

weight reduction that was an average of 45 kg (99 pounds), which equaled about 34.5% of their weight (Azvolinsky, 2016). After surgery, the women had improved glucose, insulin, and free fatty acid levels, as well as decreased inflammation (Azvolinsky, 2016). The results revealed that after women lost weight, their insulin and glucose homeostasis improved; larger studies are necessary to determine if these results will make a difference in developing cancer versus not developing cancer for these participants in the future (Azvolinsky, 2016).

In addition to the amount of fat, its location in the human body is pertinent to the obesity cancer link (Azvolinksy, 2016; Lee et al., 2014). Visceral fat is a risk factor for heart disease, T2DM, and some types of cancer, and researchers believe it secretes more hormones that affect glucose metabolism and tend to have higher levels of inflammation (Azvolinsky, 2016; Lee et al., 2014). Researchers conducted a study to examine pathways that linked particular fat depots and metabolic deregulation; metabolites in the blood of participants in relation to subcutaneous, visceral fat; and overall BMI to try to identify causal metabolic factors (Azvolinsky, 2016). Lee et al. (2014) also positively associated visceral fat with CRC in postmenopausal women, although they could not determine causality. White adipose tissue of the breast, a fat depot that occurs in most obese women, is associated with increased levels of aromatase, which is the rate-limiting enzyme for estrogen biosynthesis (Azvolinksky, 2016). The local effect of inflammation and aromatase expression in fat tissue promotes cancer progression in women with breast cancer and may be a marker of breast cancer risk (Azvolinksky, 2016). Women at high

risk of breast cancer who take an aromatase inhibitor have as much as a 50% reduction in risk, as evidenced in large trials (Azovlinsky, 2016).

Researchers have also linked systemic metabolic syndrome to increased breast cancer risk, but more research is still warranted. One hundred women with early-stage breast cancer who had white adipose inflammation in the breast also had elevated insulin, glucose, triglycerides, and other markers of metabolic syndrome (Assiri, Kamel, & Hassanien, 2015; Azvolinsky, 2016). Assiri et al. (2015) noted in their cross-sectional study that, in addition to metabolic factors having a possible association with increased breast cancer risk in Saudi women, adipokine levels such as leptin were higher in postmenopausal women, but not premenopausal women after adjusting for certain factors. Additionally, researchers noted that, in a second cohort of 127 women, inflammation was associated with a worse course of disease for women who went on to develop metastatic breast cancer (Azvolinsky, 2016; Babaei et al., 2015). The results bolstered a belief that inflammation may be critical for understanding the established link between metabolic syndrome and breast cancer risk. Finally, if inflammation has multiple effects, including contributing to insulin resistance, then anti-inflammatory strategies to reduce risk may be more effective than simply targeting insulin (Azvolinsky, 2016).

Tilg and Moschen (2014) noted that obesity and obesity-related disorders such as type 2 diabetes demonstrate an increased risk of developing various gastrointestinal cancers such as CRC, although the underlying mechanisms remain unclear. Chronic inflammation coupled with obesity has become a major contributor (Tilg et al., 2014). Tilg and Moschen also showed that leptin contributes to the development of

gastrointestinal cancer as a tumor promoter. The exact molecular pathways that dominate in the promotion of obesity-related cancers in humans remain unclear (Tilg et al., 2014). The translational science challenge is to determine how researchers may dissect several pathways activated in conjunction to understand future dominant pathways that may potentially develop better treatment other than weight loss in cancer patients (Tilg et al., 2014).

Obesity and Leptin Levels

Studies have shown that an association exists between leptin and a major public health challenge: obesity. Martins, Lima, and Francesa (2012) examined the relationship between leptin and obesity (expressed in BMI) and several components of the metabolic syndrome in a sample of adults. The results revealed BMI as an index of overall adiposity had a strong correlation with serum leptin and BMI levels, which increased as serum leptin levels increased in the first to the third tertiles. Martins et al. observed a strong correlation between leptin and BMI, $r = 0.524$ in men, $r = 0.0603$ in women, with high statistical significance ($p < .001$). The association between leptin and obesity defined as BMI ≥ 30 kg/m^2 demonstrated high odds ratios in both men and women, 10:11 and 6:0, respectively, on univariate regression analysis and 30.09 in men and 21.08 in women on multivariate regression analysis (Martins et al., 2012). The components of MS results revealed increased serum levels of the study variables were observed as leptin concentrations rose from the first to the third tertiles (excluding high-density lipoprotein, cholesterol, which actually decreased; Martins et al., 2012).

Al Maskari et al. (2006) studied the relationship between serum leptin levels and related variables (weight, BMI, and fat percentage). Although the study is out of date, it warrants mentioning due to its relevance to my study. The study included a group of 35 obese Omani women and 10 obese Omani men and a group of 20 nonobese healthy subjects. The results of the study revealed that a significant difference ($p < .001$) existed in serum leptin between the obese group (34.78 + 13.96 ng/ml) and the nonobese control group (10.6 ± 4.2 ng/ml; Al Maskari et al., 2006). Leptin levels were higher in females compared to males, possibly due to body composition (Al Maskari et al., 2006). A significantly positive correlation existed between leptin levels in obese subjects with weight ($p = .002$), body fat percentage ($p < .001$), and BMI ($p < .001$; Al Maskari et al., 2006). Although the study population was relatively small, the results revealed that circulating leptin levels were high and positively associated with body weight, body fat percentage, and BMI (Al Maskari et al., 2006). The pattern of the increase could reflect lifestyle, diet, physical activity, or cultural and economic differences tailored to the Middle East (Al Maskari et al., 2006).

Leptin is emerging as a common predictor that links obesity to various conditions such as cardiovascular disease, T2DM, and cancers, particularly those deemed obesity-related cancers. Researchers have performed multiple epidemiological studies over the past few years to examine serum leptin levels in women with breast cancer. However, conflicting results have indicated a complex relationship exists (Niu et al., 2013; Saxena & Sharma, 2013). Some researchers have indicated a clear positive relationship between high serum leptin levels and increased breast cancer risk, while the results of a few other

studies found no change or even reduced levels of leptin associated with breast cancer (Saxena & Sharma, 2013). Niu et al. (2013) performed a meta-analysis to investigate contradictory results regarding the association between leptin level and breast cancer (Niu et al., 2013). The results revealed that the mean serum leptin level of case groups was significantly higher than that of the control groups, which indicated that leptin may play a role in the formation and development of breast cancer, as well as its diagnosis (Niu et al., 2013). However, the principal mechanisms remain unclear and further studies are necessary (Niu et al, 2013).

Obesity is one of the most prevalent and preventable public health challenges (Obesity Society, 2015). As previously mentioned, leptin may contribute to the pathogenesis of breast, endometrial, colorectal, and potentially other obesity-related cancers (Cohen et al., 2012; Paz-Filho et al., 2011). Many of these cancers have marked differences in the incidence and mortality patterns between Black and White women (Cohen et al., 2012). Research has established that non-Hispanic Black women have the highest prevalence of obesity (39% with BMI > 30) and non-Hispanic White women have the lowest (22%). Classification of leptin levels across racial groups is essential in helping to determine possible mechanisms, and leptin may add to racial disparities in obesity-related cancers in addition to both cardiovascular disease and type 2 diabetes (Cohen et al., 2012).

Cohen et al. (2012) conducted a cross-sectional study of 915 White and 892 Black women (ages 40–79 years) enrolled in the prospective epidemiologic Southern Community Cohort Study, half of which were postmenopausal. The purpose of this study

was to compare leptin levels between Black and White women, assess a potential correlation of serum leptin levels separately for Black and White women, and evaluate any racial differences in leptin levels across a significant range of BMI levels while controlling for demographic and lifestyle factors between the two groups (Cohen et al., 2012).

The results of the study revealed that leptin mostly increased as BMI, age, income, education, and previous diagnosis of diabetes, cardiovascular disease, hypertension and high cholesterol increased, although there were some pattern differences between both groups (Cohen et al., 2012). Dissimilarly, leptin levels mostly decreased as physical activity, total energy and fiber intake, alcohol consumption, and cigarette smoking increased (Cohen et al., 2012). Serum leptin levels were higher in Black women than in White women (geometric mean 22.4 vs. 19.0 ng/ml, $p < .0001$), despite making necessary adjustments (Cohen et al., 2012). Similar racial differences also occurred in a subset of 802 women with fasting blood samples (geometric mean 23.6 ng/ml in Blacks vs. 18.3 ng/ml in Whites; $p < .0001$; Cohen et al., 2012).

Mutschler et al. (2013) conducted a population-based case control study to examine if a certain functional genetic variant (single-nucleotide polymorphisms of neuropeptide-Y (NP-Y) promoter gene is associated with serum leptin levels and body fat distribution. The NP-Y gene is a strong candidate gene in the pathophysiology of obesity-linked behavior, and SNP of NP-Y have already been linked to body weight and appetite, but results were inconclusive (Mutschler et al., 2013). Mutschler et al. genotyped and measured the serum leptin levels of the NP-Y rs16147 polymorphism in 1,097 European

American participants in the multicenter study. Measurements calculated were weight, height, waist circumference, BMI, and waist-to-hip ratio. The results of the study revealed the CT genotype of the SNP rs16147 significantly associated with lower waist-to-hip ratios and higher serum leptin levels was found in women only when compared with homozygote gene carriers (Mutschler et al., 2013). The results provide evidence that the SNP in the NP-Y promoter gene affects body fat distribution and serum leptin levels in women, which indicates possible behavioral effects of NPY in obesity (Mutschler et al., 2013).

Monalisa (2015) conducted a review to highlight the role of leptin in obesity. As previously discussed, leptin is a 16-kilodalton adipocyte-derived hormone that circulates in the free and bound form and is made by fat cells that regulates the amount fat stored in the body (Monalisa, 2015). Leptin acts by binding to specific receptors in the hypothalamus to alter the expression of several neuropeptides that regulate neuroendocrine function and energy intake and expenditure (Monalisa, 2015). Maintenance of body weight depends on the balance between energy intake and energy expenditure (Monalisa, 2015). Energy intake relates to food intake, and energy expenditure is derived from complex thermogenesis (Monalisa, 2015). According to Monalisa (2015), leptin signaling is the best model of body weight control. Serum leptin levels are associated with the amount of body fat and the regulation of energy consumption and expenditure. This process happens as a result of interacting with hypothalamic leptin receptors (Monalisa, 2015).

Leptin promotes hematopoiesis, which is the process of blood cell production, multiplication and specialization in the bone marrow (Monalisa, 2015). Leptin influences pubescent development and fetal growth, but the mechanism of leptin's action in these processes is not clear (Monalisa, 2015). Future studies are still necessary to determine the significance of leptin's influence in the pathogenesis of obesity, insulin resistance, and other related conditions (Monalisa, 2015).

T2DM and Cancer

T2DM and cancer are two of the most frequently diagnosed, debilitating, and in some cases preventable conditions. T2DM increases the risk for the development of cancers, particularly those associated with obesity, such as colorectal and female breast cancers (ACS, 2016i). The T2DM and cancer codiagnosis is becoming more prevalent, due in part to both obesity-associated cancers and T2DM sharing some of the same risk factors. Some of those risk factors include age, gender, race/ethnicity, overweight status, physical inactivity, smoking, and alcohol consumption (American Diabetes Association, 2017). Although researchers have conducted studies to have a better understanding of the link between cancer and T2DM, it remains unclear. Additionally, researchers have revealed that men and women diagnosed with diabetes have an increased risk of developing cancer overall. Diabetes was shown to be responsible for a 39% increased risk in men developing cancer, specifically colorectal and prostate, and a 17% increase in the development of breast cancer in women when compared to those women without diabetes (Gallagher & LeRoith, 2015).

Researchers have conducted a vast amount of research regarding these two major chronic diseases to determine their correlation, and yet more is necessary. The relative risks associated with T2DM and cancers of the pancreas, liver, and endometrium are greater than twofold, and the relative risk is 1.2- to 1.5-fold for colorectal, breast, and bladder cancers (Szablewski, 2014). The relative risk for lung cancer is even lower, with a value of less than 1, and prostate cancer occurs less frequently in male patients diagnosed with diabetes (Szablewski, 2014). The potential biologic link between T2DM and cancer is not completely clear (Szablewski, 2014). Results from observational studies reveal that some medications identified to treat conditions such as hyperglycemia are associated with either increased or reduced risk of cancer, but antidiabetic drugs have very little influence on cancer risk (Szablewski, 2014). However, drugs used to treat cancer may either cause diabetes or complicate preexisting diabetes.

If hyperinsulinemia acts as a critical link between the observed increased cancer risk and T2DM, patients with type 1 diabetes would be likely to have a different cancer risk pattern than patients with T2DM, because the former patients are exposed to lower levels of exogenous administered insulin (Szablewski, 2014). Obtained results showed that patients with type 1 diabetes had elevated risks of cancers of the stomach, cervix, and endometrium (Szablewski, 2014).

Researchers have extensively investigated the link between T2DM and cancer, as they are both independent major public health problems. Zhang et al. (2012) conducted a study to investigate the association between T2DM and the risk of developing common cancers in a Chinese population. The population-based retrospective cohort study took

place in the Nan-Hu District, Jiaxing City, Zheijang Province, China, using a Diabetic Surveillance and Registry Database with the Cancer Database from January 2002 to June 2008. Zhang et al. estimated the standardized incidence ratio (SIR) and 95% CI for the risk of cancer among patients with type 2 diabetes. The results of the study revealed that the overall incidence of cancer in the participants was 1083.6 per 10 subjects in male T2DM patients and 870.2 per 105 subjects in the female population (Zhang et al., 2012).

An increased risk of developing cancer existed in both male and female T2DM patients, with a SIR of 1.33, 95% CI [1.14–1.51] and 1.73, CI [1.47–1.99], respectively (Zhang et al., 2012). Both male and female participants had a significantly increased risk of pancreatic cancer with SIRs of 2.97, CI [1.73–4.21] and 2.68, CI [1.44–3.92], respectively (Zhang et al., 2012). Elevated risk of liver and kidney cancers occurred only in male T2DM patients with SIRs of 1.53, CI [1.00–2.07] and 4.091, CI [1.41–6.76], respectively (Zhang et al., 2012). Zhang et al. (2012) found increased risks of developing breast cancer, 2.209, CI [1.487–2.93], and leukemia, SIR: 4.167, CI [1.584–6.749], in female patients, but no significant correlation between T2DM and increased risk of cancer of the lung, stomach, esophagus, bladder, prostate, uterine cervix, uterine corpus or ovary. Significant SIRs in T2DM were observed for almost all site-specific cancers, including study-related cancers such as breast, melanoma/skin, colorectal, endometrial, ovarian, prostate, and lung, with the highest observed for liver and pancreatic, but decreased risks for prostate and melanoma (Harding, Shaw, Peeters, Cartensen, & Magliano, 2015; Zhang et al., 2012).

Hsieh, Chiou, Wang, and Lin (2014) conducted a study to determine the risk for cancers in patients with and without T2DM stratified by BMI in an Asian population. Patients hospitalized from January 2000 to December 2010 with a diagnosis of malignant cancer were included and categorized according to their BMI for Asians, where a normal weight was a BMI of less than 24 kg/m^2, overweight was a BMI of greater than 24 kg/m^2, and obese was a BMI of greater than 27 kg/m^2 (Hsieh et al., 2014). The results revealed that, of the 42,229 patients included, there were 4,195 (16.9%), 2,056 (20.4%), and 1,625 (22.4%) patients with T2DM in the normal weight, overweight, and obese groups, respectively (Hsieh et al., 2014). Irrespective of weight, the T2DM patients were more likely to have pancreatic, liver, urinary tract, prostate, skin, hematological, lung, secondary, and gastric cancers, but were surprisingly less likely to have cervical, oropharyngeal, nasopharyngeal, breast, or thyroid cancer, some of which had a known association with obesity (Hsieh et al., 2014). Regardless of sex or the presence or absence of T2DM, the patients with more than one cancer were more likely to die than were those with only one malignancy (Hsieh et al., 2014). The obese patients diagnosed with T2DM had higher mortality than did the obese patients without T2DM with an equal number of cancers (Hsieh et al., 2014).

Attner et al. (2012) discussed how the incidence of cancer relates to diabetes, obesity, or abnormal blood lipids. Diagnosis of diabetes, obesity, or abnormal blood lipids was examined 0–10 years prior to the diagnosis of 19,756 cases of various cancers and in 147,324 controls matched regarding age, sex, and the county where they lived (Attner et al., 2012). The result revealed that diabetes was much more common among

those with cancer cases than among the controls, RR 1.14, 95% CI [1.09–1.21] (Attner et al., 2012). The results also revealed that diabetes was 14% more common in participants with liver, pancreatic, colon, urinary tract/bladder, and breast cancer (Attner et al., 2012). Participants with diabetes had a significantly reduced risk of prostate cancer, especially if the case was younger than 65 years of age, RR 0.66, 95% CI [0.50–0.87] (Attner et al., 2012). Among younger male and younger female participants, there was a significant increase in the risk of diabetes and liver, pancreatic, and colon cancers (Attner et al., 2012). However, for pancreatic cancer, a higher risk was seen for diabetes close to diagnosis, which could imply a reverse causality (Attner et al., 2012).

The diagnosis of obesity was not significantly (9%) common in cancer cases when compared to controls, RR 1.09, 95% CI [0.95–1.27] (Attner et al., 2012). Obesity was also more prevalent prior to diagnosis among participants with endometrial, colon, and kidney cancers, RR 2.45, 95% CI [1.39–4.36], RR 1.59, 95% CI [1.03–2.46], and RR 2.89, 95% CI [1.21–6.87] (Attner et al., 2012). Nead et al. (2015) further supported a causal association of higher insulin levels independent of BMI with endometrial cancer risk. Obesity was more common prior to diagnosis in patients with endometrial cancer, RR 2.45, 95% CI [1.39–4.36]; colon cancer, RR 1.59, 95% CI [1.03–2.46]; and kidney cancer, RR 2.89, 95% CI [1.21–6.87; Attner et al., 2012). The increase in the risk for breast cancer observed in participants above the age of 40 years was not significant (Attner et al., 2012). A no significantly increased risk for breast cancer was seen above the age of 60 years for participants, RR 1.55, 95% CI [0.96–2.50]. A nonsignificant risk of obesity was also observed in participants with nonmelanoma skin cancer, RR 0.45,

95% CI [0.18–1.12]. Colon cancer was expressed in male participants only, and renal cancer risks were more substantial in younger female participants (Attner et al., 2012).

With T2DM classified as a major public health burden worldwide and the prevalence of T2DM continuing to increase, Saito et al. (2016) conducted a 2016 study to estimate the burden of cancer associated with T2DM in Japan between 2010 and 2030 using the prevalence estimates of T2DM in Japan from 1990 to 2030. Summary hazard ratios of diabetes and cancer risk from a pooled analysis of eight large-scale Japanese cohort studies observed incidence/mortality for 2030 derived from an age-period-cohort model. Cancers of the esophagus, colon, rectum, liver, bile duct, pancreas, breast, corpus uteri (endometrium), kidney, bladder, and lymphoma were also included in the study (Saito et al., 2016). The results revealed that the percentage of cancer incidence and mortality was predicted to be 31.2% and 3.9% in both men and women over the age 20 years between 2010 and 2030. The total cancer incidence rate is projected to increase by 49.6%, and that of mortality will increase by 20.4%. The age-adjusted incidence rate for all sites for adult men showed a slight increase (595.1 in 2010 to 610.4 in 2030 per 100,000; Saito et al., 2016). However, a decrease was noted for the age-adjusted total cancer mortality rate in adult men (252.7 in 2010 to 179.2 in 2030 per 100,000). The age-adjusted cancer incidence rate for adult women showed an increase (400.9 in 2010 to 502.7 in 2030 per 100,000), but the mortality rate was predicted to fall in 20 years (127.2 in 2010 to 106.4 in 2030 per 100,000).

The results revealed that between 2010 and 2030, Saito et al. (2016) predicted the population attributable fraction of all cancer incidence due to diabetes would increase

modestly from 1.4% in 2010 to 1.7% in 2030. The site-specific PAF of cancer showed a modest increase in colon (4.5–5.8%), liver (9.3–11.7%), bile duct (4.1–5.2%), and pancreatic cancer (5.6–7.1%) among men (Saito et al., 2016). The PAF of cancer in women showed a similar trend in esophagus (16.6–18.8%), liver (4.3–5.0%), and pancreatic cancer (6.4–7.4%; Saito et al., 2016). Based on the number of excess incident cancer cases, the expected increase in men was 26.5% between 2010 and 2030 (from 6,218 to 7,862 cases) and 53.2% in women (from 2,223 to 3,406 cases; Saito et al., 2016). The PAFs of cancer by age group showed an increase in men aged 60 years and over, whereas women aged 60 years and over showed no significant change in PAF for the same period (Saito et al., 2016).

As previously mentioned, NHANES includes data from a multiethnic sample. African Americans have the highest death and shortest survival rates of any racial and ethnic group in the United States for most cancers (ACS, 2016; CDC, 2015). Researchers have revealed that an association exists between T2DM and CRC, but the exact mechanisms remain unclear (Khalili & Chan, 2012). T2DM also disproportionately affects African Americans (13.8%), followed by Mexican Americans (13.2%), and then European Americans (7.8%; Cavicchia et al., 2013). With respect to race, researchers had not examined the relationship between T2DM and CRC extensively (Cavicchia et al., 2013). Therefore, Cavicchia et al. (2013) studied a retrospective cohort to examine the association between T2DM and CRC and subsites of the colon and rectum among European Americans and African Americans in South Carolina. Of the 91,836 participants who were at least 30 years of age, 6,006 had T2DM (Cavicchia et al., 2013).

The results indicated that more than 50% of those diagnosed with T2DM are more likely to be diagnosed with CRC compared to those without T2DM (*n* = 85,681; Cavicchia et al., 2013). The association between T2DM and colon cancer was higher in Blacks (*OR* = 1.72, 95% CI [1.21–2.46], *n* = 47,984) than among Whites (*OR* = 1.24, CI [0.73–2.11], *n* = 43,703; Cavicchia et al., 2013). Individuals with T2DM were over twice as likely to be diagnosed with in situ or local colon cancer (*OR* = 2.12, CI [1.40–3.22], *n* = 191) compared to those without T2DM, with a higher likelihood among Blacks (*OR* = 2.49, CI [1.52–4.09], *n* = 113; Cavicchia et al., 2013). The results further revealed that the study population residing in a high-risk region of the United States showed an increased likelihood of CRC with T2DM and indicated a racial disparity that disfavors African Americans and provides further motivation for diabetes preventive efforts aimed toward this group (Cavicchia et al., 2013).

T2DM and Leptin

Obesity is a well-established risk factor for type 2 diabetes (Obesity Society, 2015). Obesity in humans is generally characterized by high levels of the adipocyte-secreted hormone leptin, which researchers have experimentally demonstrated to inhibit insulin secretion, possibly by binding to the functional leptin receptors expressed in pancreatic β-cells, as well as high BMI levels (Chen, Qin, & Ye, 2014). As a result, researchers believe leptin to be involved in the etiology of type 2 diabetes through its effect on the regulation of insulin secretion (Chen et al., 2014). Prospective epidemiologic studies regarding the association between leptin and the risk of T2DM have included questionable findings, which indicates that the relationship may be gender-

specific, with a positive association found in men only (Chen et al., 2014). To obtain a detailed understanding of the relationship between gender-specific T2DM and leptin, a gender-specific meta-analysis summarizing prospective studies was conducted to gain a more comprehensive understanding of the relationship between circulating leptin levels and risk of T2DM (Chen et al., 2014). Of the 11 relevant articles used in the meta-analysis published between 1999 and 2013, Chen et al. (2014) found 4,124 diabetic patients and 22,737 nondiabetic subjects. Chen et al. (2014) assessed dose–response relationships using a generalized least squares trend estimation and summary RR, with a 95% CI using the random-effects model.

The summary RR for an increment in leptin levels was 1.37, 95% CI [1.13–1.66], for men and 0.96, 95% CI [0.90–1.03] women (Chen et al., 2014). The differences between genders were statistically significant (p = .006). Lilja, Rolandsson, Norberg and Soderberg (2012) showed leptin is an independent predictor in men, but not in women. The gender-associated differences related to the leptin–T2DM relationship may be attributed to fat distribution, which varies significantly between men and women (Chen et al., 2014). Men tend have more visceral fat, which is the possible catalyst in the development of T2DM, and women carry more subcutaneous fat, which produces more leptin (Chen et al., 2014). However, men may be at greater risk of T2DM per unit increase in leptin levels when compared with women (Chen et al., 2014). Moreover, estrogen deficiency may also play a role by causing impaired central leptin sensitivity, which indicates a possible gender association in leptin transport across the blood–brain barrier (Chen et al., 2014).

The nonlinear leptin–diabetes association found among men might indicate that the central effect of leptin, rather than its peripheral effect, contributes to the inhibitory effect of leptin on insulin secretion because of the already saturated free leptin levels in the cerebrospinal fluid at low circulating levels of leptin (Chen et al., 2014). Additionally, Chen et al. (2014) revealed that ethnic disparities in the association between leptin and T2DM possibly exist because Blacks had significantly higher leptin levels, which indicated the need for future prospective studies to assess ethnicity-specific associations. Finally, high circulating leptin levels were independent of the level of adiposity and associated with increased risk of T2DM in men, but not in women (Chen et al., 2014).

Researchers have shown that obesity and leptin have an association with increased cardiovascular disease risk, particularly when coexisting with T2DM, although some researchers have shown conflicting results (Mohammadzadeh & Zarghami, 2013). Obesity also has an association with hyperleptinemia and leptin resistance. Leptin levels increase in proportion to the degree of adiposity, while the association of increased leptin with T2D is still unclear (Rajkovic et al., 2014). The relationship between obesity, T2DM, and leptin is not clear, which motivated Rajkovic et al. (2014) to analyze the impact of obesity in those with T2DM on adipocytokines (leptin, adiponectin, and resistin) and inflammatory markers; for the purpose of my study, leptin was the focus.

In a cross-sectional study, Rajkovic et al. (2014) examined 65 T2DM patients with a mean age of 57.8 years and 15 control subjects. Elevated leptin levels indicate that an association exists between obesity and increased levels of leptin in proportion to the amount of fat an individual carries (Rajkovic et al., 2014). The results revealed no

difference in leptin levels between nonobese T2DM patients and nonobese controls (Rajkovic et al., 2014). The highest concentrations of leptin were among obese patients with T2DM, with a significant difference in leptin found among overweight and obese individuals with T2DM (Rajkovic et al., 2014). The data revealed and confirmed that increased leptin levels in T2DM patients had a stronger relationship to the degree of adiposity than to the presence of T2DM (Rajkovic et al., 2014). The results indicate that obesity may influence risk of cardiovascular disease, and leptin and resistin may serve as the principal mediators of the impact of obesity on inflammatory markers involved in cardiovascular disease risk in T2DM patients (Rajkovic et al., 2014).

The growing prevalence of obesity is the leading cause of T2DM prevalence (Coimbra, Proenca, Santos-Silva, & Neuparth, 2014). Given that the world population is aging rapidly and T2DM is more common among middle-aged and older adults, along with the fact that insulin resistance and the correlation between obesity and T2DM not quite understood, Coimbra et al. conducted a cross-sectional study to examine the relationship between aging and the levels of adipokines, chemerin, adiponectin, and leptin in T2DM patients by observing middle-aged (38–64 years) and elderly (65 years and above) patients.

Coimbra et al. (2014) observed 73 Portuguese men and women and matched T2DM patients and controls for gender, age, and BMI. T2DM patients had higher leptin levels (Coimbra et al., 2014). Concerning gender, female T2DM patients had significantly higher leptin levels compared to controls, even though the controls had significantly high levels of leptin (Coimbra et al., 2014). When considering the age of the

T2DM patients, age correlated significantly and positively with leptin levels in both male and female patients according to the results of a multiple linear regression analysis (Coimbra et al., 2014). Furthermore, in T2DM patients, BMI significantly and positively correlated with chemerin (r = .407, p < .001) and leptin (r = .490, p < .001; males: r = .450, p < .005; females: r = .277, p = .102) and inversely correlated with adiponectin (r = −.419, p < .001; Coimbra et al., 2014). Multiple linear regression analysis showed that Lg10 leptin and Lg10 adiponectin had a significant association with the BMI of T2DM patients (β = 0.352, p = .003 and β = −.266, p = .025, respectively). After a statistical adjustment for length of disease, there was a loss of significance for adiponectin (p = .119) and for leptin in female patients (p = .117; Coimbra et al., 2014). When compared among age groups, leptin levels were significantly higher among the elderly group in both males and females, but levels of chemerin and adiponectin were lower (Coimbra et al., 2014). In the middle-aged group, BMI correlated with adiponectin (r = −.345, p = .032), leptin (r = .485, p = .002) at least in females (r = .517; p = .024), males lost statistical significance (p = .069) and chemerin (r = .527; p < .001). In the older group, BMI correlated with adiponectin (r = −.475, p < .005) and with leptin when considering both genders together (r = .423, p = .013), but not with chemerin (r = .190, p = .282; Coimbra et al., 2014). Adiponectin and leptin levels in elderly patients with T2DM appear associated closely with obesity and to the length of the disease, but not chemerin levels, which were independent of the length of the disease (Coimbra et al., 2014).

Socioeconomic Status and Cancer

Cancer disparities have plagued the U.S. population in terms of SES (income, education, and insurance status), race/ethnicity, geographic location, sex, and sexual orientation, and eliminating these disparities is the primary goal of the ACS (2017), DHHS, and the NCI (Clegg et al., 2009; Parise, & Caggiano, (2013). The causes of health disparities within each of these groups are complex and include interrelated social, economic, cultural, environmental, and health system factors (ACS, 2017). However, disparities predominantly arise from inequalities in work, wealth, education, housing, and standard of living as social barriers to high-quality cancer prevention, early detection, and treatment services (ACS, 2017).

According to the CDC (2014), individuals' SES affects major areas in life and the ability to obtain health care. The more education above high school individuals have, the more likely they are to obtain a job that pays well, offers health insurance, and provides paid sick leave (CDC, 2014). People with a higher SES and with health insurance are more likely to receive the necessary tests that can detect cancer early (CDC, 2014). This benefit also affords them the opportunity to receive the proper treatment (ACS, 2017; CDC, 2014). As a result, people with a higher SES often have higher cancer survival rates (CDC, 2014). Furthermore, researchers have reported that people classified as having a low SES are more likely to engage in health-risk behaviors that put them at a higher risk of developing cancer and mortality, such as smoking, lack of physical activity, and an unhealthy diet (CDC, 2014; Rametta et al., 2013).

Despite the many advances in knowledge concerning risk factor reduction and improvements in early detection and treatment for several cancers, socioeconomic inequalities persist in cancer incidence, morbidity, mortality, and survival (Clegg et al., 2009; Doubeni et al., 2012; Hystad, Carpiano, Demers, Johnson, & Brauer, 2013; Leuven, Plug, & Ronning, 2014; Liss & Baker, 2014). In some instances, such inequalities may even be widening (Clegg et al., 2009). The burden of disparities in cancer among racial and ethnic minorities and other disadvantaged groups prompted Public Law 104-208 in 1997, which mandates a review of research programs at the National Institutes of Health (Clegg et al., 2009).

According to researchers at the ACS (2017), advanced cancer mortality rates are much higher in individuals with lower SES than in those with higher SES, regardless of demographic factors such as race/ethnicity. Cancer mortality rates among both non-Hispanic Black and White men with 12 or fewer years of education are almost 3 times higher than those of college graduates for all cancers combined (ACS, 2017). The cause of this disparity is higher cancer incidence rates, again due to unhealthy behaviors, lower survival rates of cancer due to the detection of cancer at advanced stages as a result of the lack of standard treatment stemming from inadequate health insurance, personal barriers to health care, or low health literacy (ACS, 2017; Rametta et al., 2013).

Researchers have shown the relationship between cancer in various populations, including non-Hispanic Whites, non-Hispanic Blacks, American Indians or Alaska Natives, Asians or Pacific Islanders, Hispanics and the two subcategories Mexican Hispanic and other Hispanic; education; and income (Clegg et al., 2009). Clegg et al.

(2009) evaluated the impact of socioeconomic status on various cancer incidence rates and stages of diagnosis. The results revealed men and women with less than a high school education had elevated lung cancer rate ratios of 3.01 and 2.02, respectively, in relation to their college-educated counterparts (Clegg et al., 2009). Those with family annual incomes less than $12,500 had lung cancer incidence rates that were more than 1.7 times the rate of those with incomes of $50,000 or higher (Clegg et al., 2009). Lower income was also associated with a statistically significant increased risk of distant-stage breast cancer among women and distant-stage prostate cancer among men (Clegg et al., 2009). Racial/ethnic variations revealed that, compared to non-Hispanic White men, non-Hispanic Black men had a higher overall cancer rate (rate ratio = 1.49), with higher rates of lung cancer (rate ratio = 1.73) and prostate cancer (rate ratio = 1.87), while non-Hispanic Black women had a higher rate of cervical cancer (rate ratio = 2.00) relative to non-Hispanic White women (Clegg et al., 2009). Colorectal cancer rates were also higher among non-Hispanic Blacks (rate ratio = 1.44; Clegg et al., 2009).

Herndon, Komblith, Holland, and Paskett (2011) investigated the effect of SES as measured by education on the survival of breast cancer patients. The study revealed that being African American was a significant factor for poorer survival in both early stage and metastatic breast cancer (Herndon et al., 2011). An association existed between having not completed high school and poorer survival among early stage breast cancer patients (Herndon et al., 2011). Non-African American metastatic breast cancer patients who lacked a high school diploma had poorer survival rates than other metastatic breast cancer patients, and non-African American women who lacked a high school diploma

had poorer survival rates than other African American women (Herndon et al., 2011). Finally, African American women who did not earn a high school diploma had better survival rates than educated African American women (Herndon et al., 2011). Both race and education were independent predictors of survival among early stage breast cancer patients (Herndon et al., 2011). Among patients with metastatic disease, race also has a significant effect on survival (Herndon et al., 2011). However, education appears to have an effect on survival that is inconsistent across racial groups (Herndon et al., 2011). Additional research is necessary to gain a better understanding of the relationship between race, education, stage, clinical trial participation, and survival. An integral part of this additional research needs to be an examination of sociocultural and behavioral factors that contribute to long-term breast cancer survivors with low SES having poorer prognosis.

Education and income are strongly associated with various cancer outcomes, as demonstrated in one study performed to estimate the association between area-level SES, total and site-specific cancer incidence, and total cancer mortality and to assess whether observed associations remain after controlling for individual educational attainment and household income. The results revealed that when compared to higher SES areas, living in low-SES areas was associated with higher total lung (*HR*: 2.21, 95% CI [1.69–2.90] and CRC (*HR*: 1.52, 95% CI [1.11–2.09]) incidence and total cancer mortality (*HR*: 1.68, 95% CI [1.47–1.93] (Hastert, Beresford, Sheppard, & White, 2015). Risk for prostate cancer was low, and there was no association for breast cancer (Hastert et al., 2015). After accounting for individual education and household income, living in lower SES

areas remained associated with higher lung and CRC incidence and higher total cancer mortality (Hastert et al., 2015). Associations between area-level SES, cancer incidence, and mortality are partly explained by individual SES, but the places people live could also influence cancer outcomes, either directly or through other risk factors (Hastert et al., 2015).

Sharp et al. (2014) conducted a study to assess whether there were urban and rural variations in the incidence of 18 common cancers, after adjusting for SES in Northern Ireland, diagnosed from 1995 to 2007 (Sharp et al., 2014). The results revealed that, after adjusting for SES, significant urban–rural variations existed in the incidence of 12 of the 18 cancers assessed (Sharp et al., 2014). RR was calculated by negative binomial regression, adjusting for age, country, and SES (Sharp et al., 2014). Risks were significantly higher in both sexes in urban than in rural residents with head and neck (males: RR urban vs. rural = 1.53, 95% CI [1.42–1.64]; females: RR =1.29, 95% CI [1.15–1.45]), esophageal (males: RR = 1.21, CI [1.11–1.31]; females: 1.21, CI [1.08–1.35]), stomach (males: RR = 1.36, CI [1.27–1.46]; females: 1.19 CI [1.08–1.30], colorectal (males: RR = 1.14, CI [1.09–1.18]; females: RR = 1.04, CI [1.00–1.09]), lung (males: RR = 1.54, CI [1.47–1.61]; females: RR = 1.74, CI [1.65–1.84]), nonmelanoma skin (males: RR = 1.13, CI [1.10–1.17]; females: RR = 1.23, CI [1.19–1.27]), and bladder (males: RR = 1.30, CI [1.21–1.39]; females: RR = 1.31, CI [1.17–1.46]) cancers (Sharp et al., 2014). Risks of breast, cervical, kidney, and brain cancer were significantly higher in females in urban areas (Sharp et al., 2014). Prostate cancer risk was higher in rural areas (RR = 0.94, 95% CI [0.90–0.97]), which is possibly due to geographical variations in

prostate-specific antigen testing and prostate biopsy (Sharp et al., 2014). Other cancers showed no significant urban–rural differences (Sharp et al., 2014). Variations in health care use and known risk factors likely explain some of the observed associations (Sharp et al., 2014). Further explanations are necessary to explain unclear associations between SES and cancer.

Alberg et al. (2015) conducted a population-based, case-control study to assess the association between SES and ovarian cancer in African American women. Generally, the findings indicated that higher levels of education were associated with lower ovarian cancer risk or inverse association (Alberg et al., 2015). After adjusting for established ovarian cancer risk factors, women with a college degree or more education had an odds ratio of 0.71 (95% CI [0.51–0.99]) when compared with those with a high school diploma or less (p = .02); women with annual family incomes of $75,000 or more had an odds ratio of 0.74 (95% CI [0.47–1.16]) when compared with those with incomes less than $10,000 ($p$ = .055; Alberg et al., 2015). Although associations for income were not consistent, the possibility existed that an inverse association existed between the highest income levels and ovarian cancer risk (Alberg et al., 2015). Further studies are necessary to support the understanding of the potential association between SES and ovarian cancer.

Socioeconomic Status and Leptin

Researchers have associated lower SES with obesity, and many researchers have revealed that obesity has a strong correlation with BMI and leptin. Researchers do not seem to have specifically examined individual SES and leptin levels. However, Enroth et

al. (2016) conducted a related study to determine if education (since education often has a connection to SES) has an association with cholesterol levels, BMI, and leptin (cardio metabolic biomarkers) and inflammatory biomarkers for individuals age 90 years old and older living in Finland. The results revealed participants with low and mid-level education had greater odds of belonging to the high-risk group in the cardio metabolic markers than did those with high levels of education (Enroth et al., 2016). Statistically significant differences existed among cholesterol, leptin, and BMI and in a cardio metabolic score. No educational differences existed among the inflammatory biomarkers (Enroth et al., 2016). Biomarkers mediated part of the differences between mid- and high-level education after controlling for smoking, alcohol use, and disease (Enroth et al., 2016). Finally, high education had an association with healthier cholesterol, leptin, and BMI levels and functioning among the elderly (Enroth et al., 2016).

Leptin is closely related to obesity and its complications. Delgadillo et al. (2014) conducted a study with children aged 2 to 15 years to determine serum levels of leptin in children and adolescents and its associations to different variables such as age, gender, and socioeconomic status. The study involved assessing 166 children and adolescents (91 normal and 75 obese) from low SES households (Delgadillo et al., 2014). Leptin was significantly higher in the obese participants than in those with normal weight statuses, without differences by gender or age (Delgadillo et al., 2014). The results indicated that obese children had leptin resistance, independent of age and gender, which indicated the need to develop preventive programs for children and adults (Delgadillo et al., 2014).

Summary and Conclusions

With more than 1 million new cases and over 600,000 deaths expected in 2018, cancer continues to be a significant burden across the United States (ACS, 2018). Despite the many preventive and control measures established, cancer remains the second leading cause of death in the United States. With obesity reaching pandemic levels across the United States, obesity-associated diseases are becoming increasingly prevalent, including cancer, specifically obesity-associated cancers (ACS, 2017a; Obesity Society, 2015). Obesity and leptin have become synonymous in recent times. Studies on the relationship between leptin (level) and cancer have been epidemiological, prospective, retrospective, and cross-sectional and have demonstrated contradictory results (Aleksandrova et al., 2012; Alshaker et al., 2015; Baillargeion et al., 2006; Gupta et al., 2016; Harris et al., 2011; Ollberding et al., 2013; Rodriguez et al., 2013; Romero-Figueroa et al., 2013; Vona-Davis & Rose, 2007; Wang et al., 2017; Wu et al., 2009, 2014). Therefore, a need still exists to fill the gaps in literature on whether a significant difference exists in leptin levels among a multiethnic sample (non-Hispanic White, non-Hispanic Black, Mexican American/other races) of adults diagnosed with different types of obesity-associated cancers (breast, colorectal, endometrial [uterine corpus], ovarian, prostate) and common cancers (lung and skin).

This review of the literature demonstrated that age, BMI, overweight/obesity status, gender, race, smoking status, physical activity, T2DM, family history of malignancy, alcohol use, c-reactive protein, and at least one individual SES indicator have an association with relationship between cancer and leptin level. The review of the

current literature also demonstrated that these risk factors are the most common variables used as covariates in leptin and cancer research, and they could act as potential confounders of the relationship between leptin level and cancer.

Chapter 2 began with an introduction and a restatement of the problem and the purpose of the study. The literature search strategies and major sections of the chapter identified include the burden of cancer on the adult population, the economic impact of cancer, established obesity-associated cancers related to the study, the most commonly diagnosed cancers in the United States with a link to leptin, studies on the relationship between leptin level and cancer, and risk factors associated with the relationship between leptin (level) and cancer. The theoretical framework for this study was the social ecological perspective or model.

Chapter 3 includes a detailed discussion of the quantitative methodology used for this study. Chapter 3 begins with a description of the study design, study setting, and sample size, followed by a discussion of the data collection and analysis processes. An additional topic discussed will be the protection of human study participants.

Chapter 3: Research Method

Introduction

The purpose of this quantitative study was to examine if a significant difference exists between leptin levels in individuals with different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) and those without cancer, as well as to examine the association between cancer risk factors and leptin levels among a multiethnic sample of adults living in the United States from a periodic survey: the NHANES III. This study involved employing secondary analysis of data collected via the NHANES III. This chapter includes an outline of the research design and approach, setting and sample, instruments and materials, and data collection and data analysis methods used for this inquiry. This chapter also includes a discussion of the steps taken to ensure the protection of study participants.

Research Design and Rationale

The reason for conducting this quantitative study was to assess the leptin and cancer relationship among a multiethnic sample of adults living in the United States by conducting a secondary analysis of data collected via the NHANES III. The independent variable for this study was the type of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) reported. The dependent variable was leptin levels. Finally, the individual or interpersonal factors, variables, covariates, or risk factors examined were age, gender, BMI, race/ethnicity, dietary intake, physical activity, T2DM, and SES (education level, income level, and occupational status).

This study involved employing a quantitative approach and a descriptive cross-sectional study design, which is one of the most frequently used designs in public health research (Aschengrau & Seage, 2008; Crosby et al., 2006). The defining feature of a cross-sectional survey study is that researchers can compare different population groups or an exposure and a health outcome at a single point in time. This design was appropriate for determining if a significant difference exists in leptin levels in individuals with different types of cancer. The low cost and the capacity to generalize are major advantages of a cross-sectional study design (Aschengrau & Seage, 2008; Crosby et al., 2006). The collection of all data for the NHANES III took place at a single point in time via household interviews. Therefore, a cross-sectional design was an appropriate approach for this study.

Methodology

Target Population

The target population for this study was non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans/other race from the participants of the NHANES III Household Adult Questionnaire Data File (NCHS, 1996). The NHANES III Household Adult Questionnaire Data File contains all information collected amid the family household interviews for individuals who were at least 20 years old (NCHS, 1996). Demographic data, survey design variables, and sampling weights for this age cluster are accessible to the public (NCHS, 1996). Screeners assigned sampling weights to each participant to ensure the participant was representative of the civilian population of the United States (NCHS, 1996).

This study's sampling frame consisted of a multiethnic sample from the NHANES III household adult file (NCHS, 1996). The final sample size for this study depended upon the availability of, and responses to, all variables of interest for the multiethnic participants. Adult participants were excluded if data regarding the relevant cancers, dietary intake, physical intake, BMI, leptin levels, education, poverty income ratio, occupation, or T2DM status were missing or if respondents failed to provide the necessary data.

Setting and Sample

NHANES III is a stratified, multistage probability design, periodic, cross-sectional survey conducted by researchers for the NCHS (CDC, 2015a). NHANES III is also a nationwide probability sample of 39,695 persons aged 2 months and older (CDC, 2015a). NHANES III was the seventh in a series of these surveys based on a complex, multistage sample design (CDC, 2015a).

Researchers designed NHANES III to provide national estimates of the health and nutritional status of the U.S. civilian, noninstitutionalized population (CDC, 2015a). Researchers conducted NHANES III from 1988 to 1994 in two phases (CDC, 2015a). The first phase took place from October 18, 1988 to October 24, 1991, at 44 locations (CDC, 2015a). The second phase was conducted from September 20, 1991 to October 15, 1994, at 45 different locations (CDC, 2015a). In NHANES III, 39,695 persons were selected over the 6 years; of those, 33,994 (86%) participated in an interview in their homes (CDC, 2015a). All interviewed persons received an invitation to the mobile examination center (MEC) for a medical examination (CDC, 2015a). Seventy-eight

percent (30,818) of the selected persons were examined in the MEC, and an additional 493 persons were given a special, limited examination in their homes (CDC, 2015a). Children ages 2 months to 5 years, persons 60 years and older, Mexican Americans, and non-Hispanic Blacks were sampled at rates substantially higher than their proportion in the general population (CDC, 2015a).

Data release files in NHANES III are organized into three categories (CDC, 2015a). The first group of files is the original or core content of the survey (CDC, 2015a). The second group of files is augmented data files or special data files created after the core content of the survey (CDC, 2015a). The third group of files comes from later years and is the result of approved projects that used surplus sera specimens from the survey participants (CDC, 2015a).

Power Analysis

Determining an adequate sample size (*N*) to achieve a chosen statistical power is a necessary step during the planning phase of research (Cohen, 1992). To determine an adequate sample size *N*, researchers must know the desired statistical power, Type I error (α), and effect size. A statistical power of 80% (or .80) is the commonly accepted value (Whitley & Ball, 2002). The most common significance value is $\alpha = .05$ (Cohen, 1992; Whitley & Ball, 2002). Effect size is a measurement of the durability of the association between the independent and the dependent variables in the study. The effect size can be small, medium, or large. The estimated sample size for this study was determined by G*Power 3.1 software (Faul, Erdfelder, Buchner, & Lang, 2007, 2009).

Statistical power analyses using G* Power 3.1 tests were adopted for ANCOVA and regression analyses (Faul et al., 2007, 2009). This is a free, downloadable statistical analysis program frequently used in social, behavioral, and biomedical research (Faul et al., 2007, 2009). The software runs on most computer platforms and covers a wide variety of statistical tests, power analyses, effect size calculations, and graphic options (Faul et al., 2007, 2009). Because this was a quantitative, epidemiological study, G*Power 3.1 was appropriate in determining an adequate sample size for the study.

Data Collection

The original data collection procedures for the NHANES III study began with a household interview. Researchers administered Household Adult Questionnaires in households (NCHS, 1996). At the MEC, screeners performed an examination and administered automated questionnaires or interviews in the MEC Adult Questionnaire (NCHS, 1996). The well-being examination section incorporated an assortment of tests and techniques. The examinee's age at the phase of the interview and different components decided which methods were used (NCHS, 1996). Screeners acquired blood and urine samples and performed various tests and estimations, including body measurements, spirometry, fundus photography, x-rays, electrocardiography, allergy and glucose tolerance tests, and ultrasonography (NCHS, 1996). Screeners also took estimations of bone thickness; hearing; and physical, cognitive, and central nervous system functions (NCHS, 1996).

A physician completed a restricted standardized medical exam, and a dentist performed a standardized dental examination (NCHS, 1996). Though researchers

analyzed a portion of the blood and urine samples in the MEC laboratory, the majority of the analyses took place somewhere else by researchers at contract laboratories (NCHS, 1996). A home examination took place for those persons involved in the study aged 2 to 11 months and those 20 years or older who were not able to visit the portable examination facility (NCHS, 1996). The home examination comprised of a curtailed version of the tests and interviews performed in the MEC (NCHS, 1996). Contingent upon the age of the individual, the segments included body estimations, spirometry, venipuncture, physical function evaluation, and a questionnaire to inquire about infant feeding, selected health conditions, cognitive function, tobacco use, and reproductive history (NCHS, 1996).

The NHANES III data are available to the public via the NCHS's NHANES (CDC) website. Prior permission is not necessary to access and use the NHANES III questionnaires and data files located on the website. All variable data needed to test the hypotheses of this study were available in the data files on the NCHS website. However, I downloaded the public-use NHANES III data after receiving approval to conduct the study from the Walden University Institutional Review Board (IRB).

Screeners recorded data for the interview and examination components directly onto a computerized data collection form. With the exception of a few independently automated systems, the system was centrally integrated (NCHS, 1996). This operation allowed for the ongoing monitoring of much of the data. Before the introduction of the computer-assisted personal interview (CAPI), field editors and interviewers manually reviewed the household questionnaire data. CAPI questionnaires from 1992 to 1994

featured built-in edits to prevent entering inconsistencies and out-of-range responses (NCHS, 1996).

Instrumentation and Materials

Screeners used questionnaires to collect the data from the archival NHANES III cross-sectional survey. Screeners also administered several questionnaires in households to collect data: Household Screener Questionnaire, Family Questionnaire, Household Adult Questionnaire, and Household Youth Questionnaire (NCHS, 1996a). The NHANES III Household Adult Questionnaire Data File (ages 17 years and older) contains demographic data, health indicators, oral health status indicators, and other related information collected during household interviews. These files also contain all survey design variables and sample weights for these age groups (NCHS, 1996). These files may be linked to the serum leptin file using the unique survey participant (sample person) identifier (NCHS, 1996a). Depending on age of the sample person, the components included BMI; T2DM; blood pressure; spirometry; venipuncture; physical function evaluation; and a questionnaire to inquire about infant feeding, selected health conditions, cognitive function, tobacco use, and reproductive history (NCHS, 1996a). The variables of interest for this study were age, race/ethnicity, BMI, diagnosed cancers (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) T2DM, leptin levels, and SES (education level, income level, and occupational status).

Dependent Variable

The dependent variable for this study was leptin levels. This variable was also part of the NHANES III study. Leptin levels were established from 6,415 participants

aged at least 20 years old, who were randomly assigned to undergo an examination on the morning after an overnight fast. Leptin levels were indexed as LEP in the examination data set. The leptin level measurement in the data set recorded leptin levels from the minimum detectable concentration of 0.5 fg/L to a maximum recorded level of 100 fg/L. Normal leptin levels for adult males range between 1.2 and 9.5 ng/mL and normal leptin levels for adult females range between 4.1 and 25.0 ng/mL (Quest Diagnostics, n.d.). These ranges apply to men and women with a normal BMI ranging from 18 to 25 kg/m^2 (Quest Diagnostics, n.d.). For this study's purpose, leptin levels that fell outside the previously mentioned reference ranges were considered abnormal. Leptin levels are normal if they fall within the reference range for both genders. Normal leptin levels were recorded in the data set as continuous variables; therefore, the level of measure was continuous. However, distinguishing between normal and abnormal based upon the leptin level also allowed for a conversion to categorical variables. Being able to use measured leptin levels as either categorical or continuous variables based upon the type of analyses required by the inquiry is useful. This study involved conducting a comparison to determine if a significant difference exists in leptin levels among a multiethnic sample of adults who reported having different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, or lung).

Analysts at Quest Diagnostics measure leptin levels using radioimmunoassay. The analysts have established updated reference ranges for leptin levels and testing procedures since NHANES III was conducted, but researchers at the Food and Drug Administration had not yet approved them (Quest Diagnostics, 2017).

Independent Variables

The independent variables for this study were the types of cancer reported. The variables were a part of the NHANES III household adult file, and the variable names were HAC1N, HAC1O, and HAC3OR. HAC1N identified if a participant reported having skin cancer, and HAC1O indicated if a participant reported having any other type of cancer. Cancer was ascertained from study participants by self-report. The independent variables were dichotomous. Specifically, the study participants were asked, "Has a doctor ever told you that you had skin cancer? 1: Yes 2: No" and "Has a doctor ever told you that you had other cancer? 1: Yes 2: No." If yes, participants were also asked where was the cancer located when you were first told. HAC3OR was operationalized by assigning each type of cancer a specific numeric code to identify it in the correlational analyses. The levels of measure for each independent variable (cancer of interest) was breast (categorical), colorectal/colon and rectum (categorical), endometrial (categorical), prostate (categorical), lung (categorical), and skin (categorical).

Risk Factors

The NHANES III data set also includes self-reported and calculated information regarding the variables age; gender; BMI; race/ethnicity; T2DM; education level, occupational status, and income level; dietary intake; and physical activity, all of which were moderator variables. BMI is in the examination file of the NHANES III data set, and all others are in the household adult file. Secondary analyses involved examining the moderators' effect on any possible correlation found between the independent and the dependent variables.

Age and gender. Age was indexed as HSAGEIR in the NHANES III survey and was determined by asking participants their age in years (NCHS, 1996). The level of measure for age is continuous. The gender variable was indexed as HSSEX and was determined by asking participants if they were male or female (NCHS, 1996). This study included a multiethnic sample of men and women aged 20 years and older. The level of measure for gender is categorical.

Race/ethnicity. Race/ethnicity was indexed as DMARETHN (NCHS, 1996). Screeners derived the race/ethnicity analytic variable from many sources of data, and the variable was based on [self-reported race and ethnicity. Race/ethnicity was classified as non-Hispanic White, non-Hispanic Black, and Mexican American/other (NCHS, 1996). The other category includes all Hispanics, regardless of race, who were not Mexican American and includes all non-Hispanics from racial groups other than White or Black (NCHS, 1996). The level of measure for race/ethnicity is nominal.

Body mass index. The NHANES III BMI variable name was BMPBMI (NCHS, 1996). Screeners computed BMPBMI from weight and standing height using the following formula: BMPBMI = BMPWT / ((BMPHT/100) **2) (NCHS, 1996). The unit of measure for BMI is kilograms per square meter (kg/m^2). Ideal body weight is conventionally determined by the Metropolitan Life Tables. Body mass index is categorized as follows: 18.5–24.9 kg/m^2 is a normal weight status, 25.0–29.9 kg/m^2 is overweight, 30–34.9 kg/m^2 and 35.0–39.9 kg/m^2 are obese (CDC, 2015b, 2016a) and were used for this study.

Additionally, researchers at the NIH explained that obesity has additional classifications as Class I obese if BMI levels of men and women fall between 30 and 34.9 kg/m^2. Adults in this category are at high risk of developing associated diseases such as cancer, T2DM, hypertension, or cardiovascular disease (NIH, n.d.). An individual is Class II obese if BMI levels fall between 35.0 and 39.9 kg/m^2, and adults in this category are at a very high risk of developing associated diseases (NIH, n.d.). Class III which refers to extreme or severe obesity, exists when an individual's BMI is above 40.0 kg/m^2, and adults in this category are at an extremely high risk of developing associated diseases (NIH, n.d.). The levels of measure for BMI are continuous and interval. Interval measure was considered because the BMI ranges are equal (0.0–4.9 kg/m^2).

Education. Education level in the NHANES III study was indexed as HFA8R (NCHS, 1996). Screeners obtained education level by self-report by asking participants the highest grade or year of school they completed (NCHS, 1996). Education level categories were no high school, high school, or above high school. The level of measure for education is categorical.

Total family income level over last 12 months. Total income level was indexed as HFF19R (NCHS, 1996). HFF19R was a recoded variable based on response categories for Versions 1 and 2 (NCHS, 1996). This variable is the total family income variable. NCHS used the U.S. Bureau of the Census Current Population Survey (CPS) definition of "family" to group household members into one or more families (NCHS, 1996; U.S. Census Bureau, Population Division, Fertility & Family Statistics Branch, 2004). The CPS defines a family as: "a group of two people or more (one of whom is the

householder) related by birth, marriage, or adoption and residing together;" all such people (including related subfamily members) are considered to be members of one family (NCHS, 1996). Over eighty percent of the NHANES households were single-family households; the remaining households were comprised of 2 or more CPS families (NCHS, 1996). The level of measure for total family income is continuous.

Occupational status. Occupational status was indexed as HAS1 and HAS2 in NHANES III (NCHS, 1996). Occupational status was ascertained by self-report. Participants were asked if they were employed during the past two weeks (HAS1). If the response was no, the participants were asked, "Even though you did not work during the past two weeks, did you have a job or business" (HAS2). If participants answered yes to either of the questions, the researchers considered them employed. They considered all others unemployed. Researchers assigned a specific numeric code so that they could identify occupational status during correlational analyses. The level of measure for occupational status is categorical.

T2DM. T2DM was indexed as HAD1 in NHANES III (NCHS, 1996). Diabetes status was determined by self-report by asking the participants if they were ever told that they had sugar/diabetes. Study participants were assigned a specific code for identification during correlational analyses: diabetes or no diabetes. The level of measure for T2DM is categorical.

Dietary intake. Dietary intake was indexed as HAN3ES, HAN3FS, and HAN4GS in the NHANES III household adult file (NCHS, 1996). Researchers determined dietary intake by self-report by asking participants a series of questions

concerning their dietary habits, such as how often they had peaches, nectarines, apricots, guava, mango, and papaya in the past month. They were also asked how often they had any other fruits such as apples, bananas, pears, berries, cherries, grapes, plums, and strawberries, or plantains in the past month. Lastly, participants were asked how many times in the last month they had spinach, greens, collards, and kale. The level of measure for dietary intake is interval.

Physical activity. Physical activity was indexed as HAT1S, HAT18, and HAT2 in the NHANES III household data file (NHANES, 1996). Physical activity was determined by self-report by asking participants a series of questions, such as, "In the past month, how often did you walk a mile or more at a time without stopping?" They were also asked, "In the past month, have you done any other exercises, sports, or physically active hobbies not mentioned?" Finally, they were asked, "In the past month, did you jog or run?" The level of measure for physical intake is interval.

Data Analysis Plan

As previously discussed in Chapter 1, the purpose of this quantitative study was to examine if a significant difference exists between leptin levels in individuals with different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) and those without cancer after adjusting for cancer risk factors among a multiethnic sample of adults living in the United States from a periodic survey: NHANES III. The study involved conducting quantitative analysis to answer the research questions and test the null and alternative hypotheses and performing descriptive analysis to test the data for frequencies and distribution, which determined if parametric analyses

were appropriate. The correlational analysis included nonparametric tests. I planned to use certain statistical methods to answer the research questions and test the null and alternative hypotheses but altered the methods due to the data set.

I conducted multivariate analysis for the variables under study. Mean values of leptin levels of the different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) were assessed and compared within the parameters of the factors evaluated. The study included descriptive analysis, ANCOVA, correlational quantitative methods, and multiple linear regression. The descriptive analysis tested the data for frequencies and distribution to determine if parametric analyses were appropriate. The correlational analysis included both parametric and nonparametric tests. I organized and cleansed the raw data using Microsoft Excel, and I used SPSS to conduct all statistical analyses.

I used a one-way ANCOVA test to answer RQ1 and to determine if a difference exists between the dependent (continuous) variables and different types of (categorical) cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) after controlling for individual/interpersonal factors (dietary intake [interval] and physical activity [interval]) among a multiethnic sample of adults (non-Hispanic White, non-Hispanic Black, and other races) living in the United States. I also used Bonferroni post hoc tests and calculated an eta coefficient (Pearson correlation between a nominal variable and a continuous variable) to measure the strength of the relationship. ANCOVA was the appropriate statistical test for this study, as researchers use it to determine

whether there are any statistically significant differences between the means of three or more groups (Laerd Statistics, 2013).

To answer RQ2, I investigated if a significant difference existed in leptin levels among adults with different types of cancer (breast, colorectal, endometrial [uterine corpus], prostate, ovarian, and lung) after controlling for individual/interpersonal factors (i.e., dietary intake and physical activity) and known covariates (BMI and T2DM). I chose these covariates specifically because of both their known effects on cancer and their association with obesity/leptin levels. I used a one-way ANCOVA followed by Bonferroni post hoc tests. The covariates were dietary intake, physical activity, BMI, and diabetes. In addition, I calculated an eta coefficient (Pearson correlation between a nominal variable and a continuous variable) to measure the strength of the relationship.

I also used a one-way ANCOVA test to determine the presence or absence of (categorical) cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate and lung) with (continuous) leptin levels after controlling for individual/interpersonal factors (i.e., dietary intake (interval), physical activity (interval) for RQ3. I did not perform a Bonferroni post hoc test, as the only two categories identified were the presence or absence of cancer. I also calculated an eta coefficient (Pearson correlation between a nominal variable and a continuous variable) to measure the strength of the relationship.

I created a multiple regression model with the eight risk factors (age, gender, BMI, race/ethnicity, T2DM, occupation, education, SES) and the two individual/interpersonal factors (dietary intake and physical activity), and leptin level was

the dependent/criterion variable for RQ4. The parameter estimates in the model included the unstandardized and standardized beta weights, the standard error of estimate, the *t* ratio, the *p* value, and the 95% CI. The coefficient of determination (RR) measured the strength of the relationship between the predicted score and the dependent/criterion variable (leptin level).

After accessing the data, data analysis took place using the IBM Statistical Package for Social Sciences (SPSS). SPSS is a widely used and powerful tool for statistical analysis that facilitates both data collection and analysis (Techopedia, n.d.). SPSS is broadly adopted in the social sciences as a tool for quantitative, epidemiological studies, and the software contains several modules that enable researchers to create tables and databases for analysis. SPSS creates a database from which researchers can direct statistical treatment can be directed from simple drop-down menu options (Techopedia, n.d.). Researchers use the analytical capabilities of SPSS to read and assess the data entered through statistical means such as descriptive statistics, correlational, cross-tabulation and frequencies, and bivariate statistics. SPSS also generates linear regression and multiple regression generating data analyses in tabular and or graphical form (Techopedia, n.d.).

Research Questions and Hypotheses

The research questions and hypotheses used to direct the course of the study were as follows:

RQ1: Is there a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after

controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity)?

$H_0$1: There is not a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity).

H_a1: There is a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity).

Dependent variable: Leptin levels

Independent variable/groups: Different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung)

Covariates: Individual/interpersonal factors (dietary intake and physical activity); skin cancer

Test statistic: ANCOVA

Alpha: .05

Power: .80

Effect size: Medium (f =.25)

Calculated minimum sample size: 249

Software: G*power 3.1.9.2

RQ2: Is there a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, prostate, ovarian, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM)?

$H_0$2: There is not a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

H_a2: There is a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

Dependent variable: Leptin levels

Independent variables: Different types of cancer (breast, colorectal, endometrial, prostate, ovarian and lung)

Covariates: Dietary intake and physical activity, BMI and T2DM, skin cancer

Test statistic: ANCOVA

Alpha: .05

Power: .80

Effect size: Medium (f = .25)

Calculated minimum sample size: 279

Software: G*power 3.1.9.2

RQ3: Is there a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity)?

$H_0$3: There is not a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity).

H_a3: There is a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity).

Dependent variable: Leptin levels

Independent variable/groups: Diagnosis of cancer (yes/no)

Covariates: Dietary intake and physical activity

Test statistic: ANCOVA

Alpha: .05

Power: .80

Effect size: Medium (f =.25)

Calculated minimum sample size: 179

Software: G*power 3.1.9.2

RQ4: Is there a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and two individual interpersonal factors [dietary intake and physical activity]) and leptin

levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer?

$H_0$4: There is not a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and the two individual/interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer.

H_a4: There is a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and the two individual/interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer.

Dependent variable: Leptin Levels

Independent variable/groups: Cancer and cancer status (breast, colorectal, endometrial, ovarian, prostate, and lung)

Predictors: Eight cancer risk factors and two individual/interpersonal factors

Test statistic: Multiple linear regression

Alpha: .05

Power: .80

Effect size: Medium (f =.15)

Calculated minimum sample size: 118

Software: G*power 3.1.9.2

Threats to Validity

With the exception of leptin levels, analysts obtained all other data for the NHANES III from study participants mainly via self-report. As a result of using self-reported data in the NHANES III, the potential for significant threats to the validity was high, which could have potentially and negatively influenced the study's outcome. Self-reporting bias may result from the unintentional or intentional misreporting of information by study participants (Crosby et al., 2006; Frankfort-Nachmias & Nachmias, 2008). Such misreporting of information could lead to the potential misclassification of study participants (Crosby et al., 2006; Frankfort-Nachmias et al., 2008). Unintentional misreporting could result from misunderstanding the questions being posed or the inability of the NHANES III study participants to recall specific information accurately at the time of questioning (Crosby et al., 2006; Frankfort-Nachmias et al., 2008). Intentional misreporting of information by the NHANES III study participants could have resulted from such factors as social desirability (Crosby et al., 2006; Frankfort-Nachmias et al., 2008). For example, when respondents were asked how frequently they performed specified leisure time exercise or physical activities in the past month, recall bias and the estimated amount of time spent exercising may be overrepresented in this data set, as people often desire to be seen positively and may have overestimated the number of hours spent completing some form of aerobic activity per month.

Internal and external validity threats regarding this study could potentially arise from the lack of adequate sample representativeness and a reactive arrangement (Crosby et al., 2006; Frankfort-Nachmias et al., 2008). The inability to generalize study findings is

a threat to external validity concerns, and as the participants represented various races in the United States, the use of data concerning adults that are not a true representative of adults in the United States could result in the inability to generalize the findings of the study to a much larger population (Crosby et al., 2006; Frankfort-Nachmias et al., 2008).

Further, the use of secondary/archival data had disadvantages, such as the lack of in-depth information. A major drawback to using archival data is the inability to control the selection, quality, and methodology of data collection are when obtaining information, which causes difficulty in validating data. An additional drawback to using archival data is that research data may not have a particular purpose when collected, which in turn complicates the adoption of the data (Sorensen, Sabroe & Olsen, 1996). Another factor that may affect the significance of archival data in epidemiological research is the inability of the researcher to ensure the participants' registration is complete, the accuracy and comprehensiveness of the study variables, precision, and validity (Sorensen et al., 1996). It is necessary to abate such occurrences in tests and measures by conducting tests using multiple samples to achieve more reliable results.

To aid in maximizing the validity of the NHANES III data, all staff received intensive initial training (NCHS, 1996). Formal retraining procedures continued throughout the survey to main high skill levels (NCHS, 1996). The data collection system was automated in Phase 2 of the NHANES III survey, at which time interviews took place using CAPI. The developers designed CAPI to allow for ongoing monitoring of the data. CAPI also featured built-in edits to prevent entering inconsistencies and out-of-range responses (NCHS, 1996). Finally, a large oversampling took place with older

persons, Blacks, and Mexican Americans in the multistage probability sampling strategy of NHANES III to ensure an adequate sample size that was representative of all participants in the study.

Ethical Procedures

NHANES III researchers took steps to protect the confidentiality of the survey participants. Prior to conducting the survey, the researchers obtained IRB approval, and documented consent was obtained from participants (NCHS, 2015). NHANES III also restricted access to confidential information of the participants to avoid or prevent misuse of collected data. Specifically, all age-related variables were recoded to 90+ years for individuals who were 90 years of age and older (NCHS, 1996). This study involved conducting a study using archival data from the NHANES III survey. Household data files and serum leptin files (exam files) were deidentified. NHANES III is available to the public, and approval was obtained from the Walden University Institutional Review Board prior to conducting this study. All data from the NHANES III data files were stored on a password-protected personal computer hard drive. The IRB approval number provided by Walden University is 03-29-18-0063692.

Summary

Chapter 3 included the methodology used to conduct this quantitative study using archival data from the NHANES III cross-sectional survey. Specifically, the chapter outlined the cross-sectional study design, the sampling strategy, and the data collection methods used to examine if a significant difference in leptin levels existed among U.S. adults with and without various cancers (breast, colon and rectum/colorectal, endometrial

[uterine corpus], prostate, lung, and ovarian), Non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans/other living in the United States. This chapter also included a power analysis to determine the minimum number of participants needed for this study using G*Power 3 software (Cohen, 1988). Additional topics discussed in this chapter were the variables of interest, threats to validity, and ethical procedures to protect the study participants. Chapter 4 includes a description of the results of this research study.

Chapter 4: Results

Introduction

The purpose of this quantitative, cross-sectional study was to examine if a significant difference exists between leptin levels in individuals with different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) and those without cancer after adjusting for cancer risk factors among a multiethnic sample of adults living in the United States using the NHANES III periodic survey. Although the NHANES III data set consisted of more than 20,000 participants, the focus in this study was only those individuals who provided a leptin (level) sample. Leptin level was the dependent variable for this study and was obtained from 6,415 participants aged at least 20 years old and randomly assigned to be examined the morning following an overnight fast (CDC, 2015). The independent variable for this study was the type of cancer reported. Age, gender, BMI, race/ethnicity, T2DM, education level, dietary intake, physical activity, income level, and occupation (SES) were the covariates or risk factors examined. Descriptive statistics were established to demonstrate the characteristics of the population studied. Statistics were also established to make inferences regarding the population based on the data and findings.

Research Questions and Hypotheses

The research questions and hypotheses used to direct the course of the study were as follows:

RQ1: Is there a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after

controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity)?

$H_0$1: There is not a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity).

H_a1: There is a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity).

RQ2: Is there a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, prostate, ovarian, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM)?

$H_0$2: There is not a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

H_a2: There is a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

RQ3: Is there a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity)?

$H_0$3: There is not a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity).

H_a3: There is a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity).

RQ4: Is there a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and two individual interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer?

$H_0$4: There is not a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and the two individual/interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer.

H_a4: There is a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and the two individual/interpersonal factors [dietary intake and physical activity]) and

leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer.

Data Collection

The date range of the NHANES III archival data was 1988 to 1994. I downloaded and imported the data into SPSS Version 24 and used inclusion and exclusion criteria to obtain the final number of participants from which cases were identified. The original archival data set included records for 20,050 individuals, but I retained only those individuals with leptin values (n = 6,415) for this study. I calculated Mahalanobis distance statistics to identify the presence of multivariate outliers that are not representative of the majority of respondents. The chi-square value for 15 degrees of freedom used as the threshold was 37.697. Removing those individuals with multivariate outliers (n = 273) left the final number of participants as N = 6,142. Additionally, there was a deviation from the original plan, as some of the research questions were altered slightly due to the manner in which some variables of interest were reported. Most of the respondents were non-Hispanic White (n = 4,282; 69.7%), Black (n = 1,763; 28.7%), and Mexican American/other race (n = 97; 1.6%), with 2,803 males (45.6%) and 3,339 females (54.4%). The final sample size for this study was dependent upon the availability of, and responses to, all variables of interest for the multiethnic participants. I used the final sample size (N = 6,142) to answer the research questions following the Mahalanobis calculations.

I also used the final sample size consisting of 6,142 participants to produce descriptive statistics to further describe the study population using SPSS. The software

was also suitable for performing ANCOVA and multiple regression analyses to answer the four research questions. The results of the analyses served as the basis for rejecting or accepting the null or alternative hypotheses.

Before performing the analyses, I determined whether the assumptions for the desired tests were met. Addressing the assumptions for the ANCOVA and multiple regression models involved using several statistical and graphical tests, including normality of the dependent variable, independence of observations, a linear relationship at each level of the independent variable, homogeneity of regression slopes, normal distribution of dependent variable for each group, homoscedasticity of the standardized residuals, homogeneity of variances, and a normal distribution of residuals for each category of the independent variable. The original archival data set included records for 20,050 individuals. The individuals retained were relevant to the study because they provided a leptin score (n = 6,415). Mahalanobis distance statistics were calculated. I detected and addressed multivariate outliers using the SPSS Mahalanobis distance function. I removed individuals with multivariate outliers (n = 273), which were values above 37.697, thereby leaving a final sample size of N = 6,142. The primary dependent variable for this study (leptin level) had an extreme positive skew (skewness = 2.713, SE = .031; kurtosis = 17.797, SE = .062). I transformed this variable using a log transformation that resulted in a normally distributed dependent variable (skewness = -0.114, SE = .031; kurtosis = -.584, SE = .062). This assumption was met after I performed the transformation. I addressed the assumption in two ways: (a) the Durbin Watson statistic (1.99), which indicated that no autocorrelation existed, and (b)

the design of this study, which involved using only one set of answers for each individual (there were not any repeated measurements for the same person). This assumption was met.

To examine the assumption regarding the linear relationship at each level of the independent variables, I created grouped scatterplots with fit lines for each subgroup for nine independent variables (consumption of fruit, consumption of other fruits, consumption of greens, walking, exercise, jogging, presence of skin cancer, BMI, and T2DM). Inspection of the scatterplots showed that this assumption was not met. Examining the homogeneity of the regression slopes assumption involved creating interaction effects between the independent variable (type of cancer) and each of the covariates. The standardized residuals were found to be normally distributed for each of the six types of cancer based upon the Shapiro-Wilk test. The assumption was ultimately met. Homoscedasticity of the standardized residuals was tested by creating scatterplots for the standardized residuals against the predicted values to determine homoscedasticity for each cancer of interest. The sample size for several of the cases was not large enough to generate a significant scatterplot. This assumption was indeterminate. All scatterplots are shown in Figures 1 through 9.

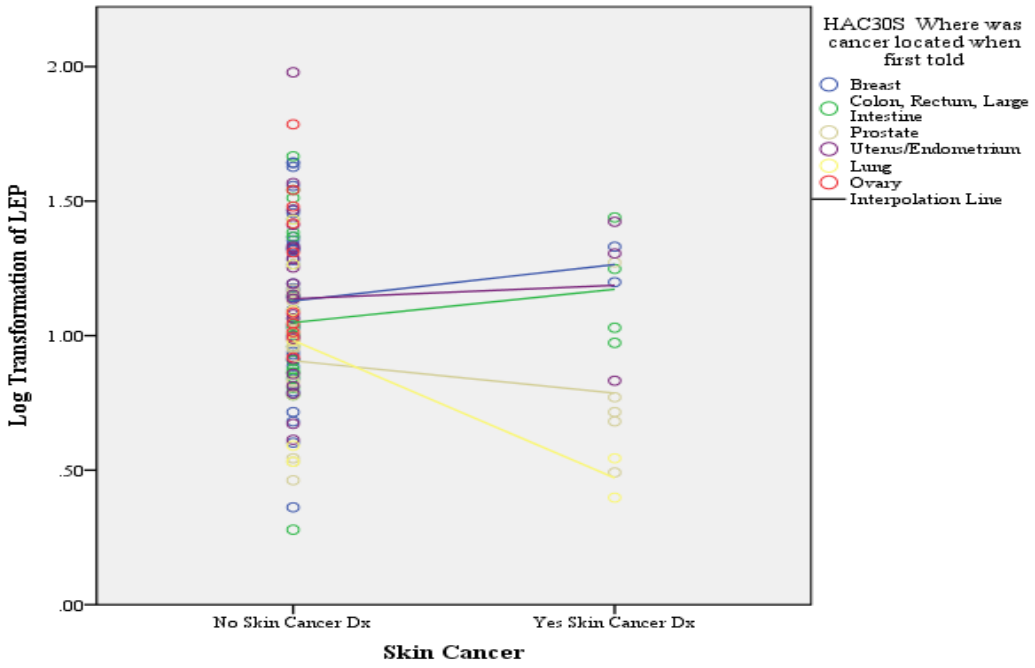

Figure 1. Scatterplots and trend lines for presence of skin cancer and the log transformation of LEP based on cancer location.

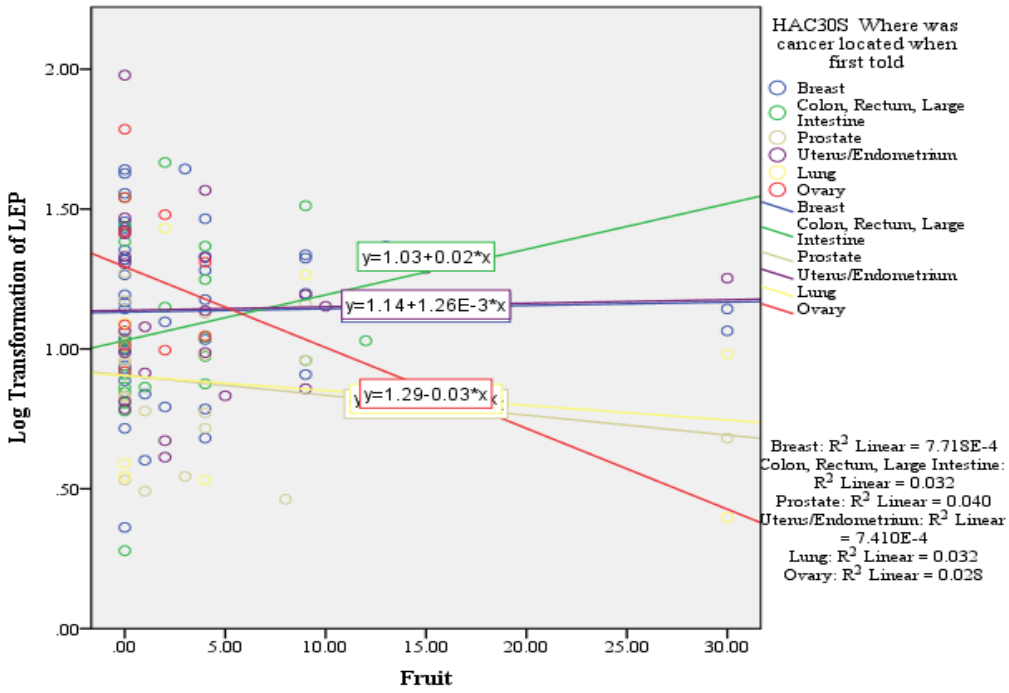

Figure 2. Scatterplots and trend lines for fruit consumption and the log transformation of LEP based on cancer location.

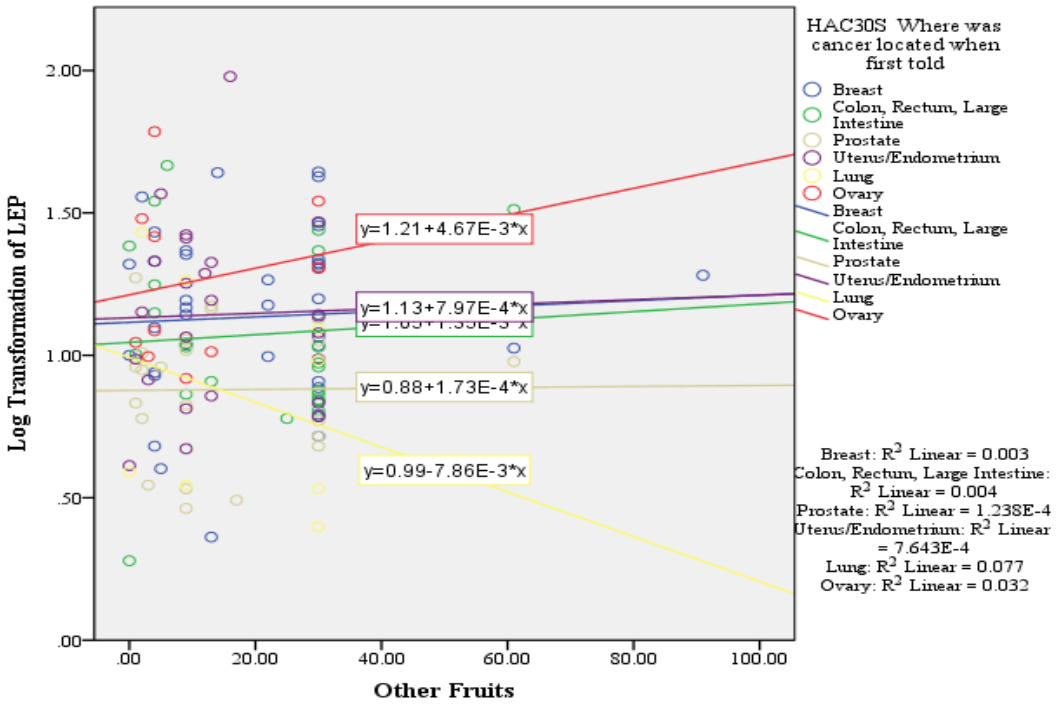

Figure 3. Scatterplots and trend lines for other fruit consumption and the log transformation of LEP based on cancer location.

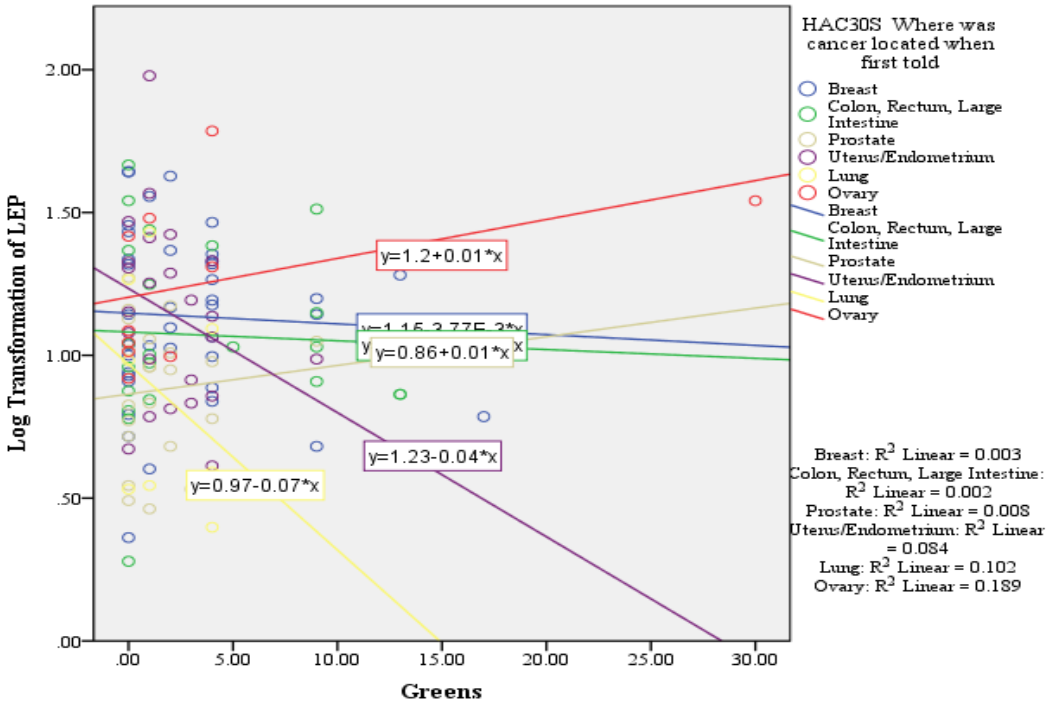

Figure 4. Scatterplots and trend lines for consumption of greens and the log transformation of LEP based on cancer location.

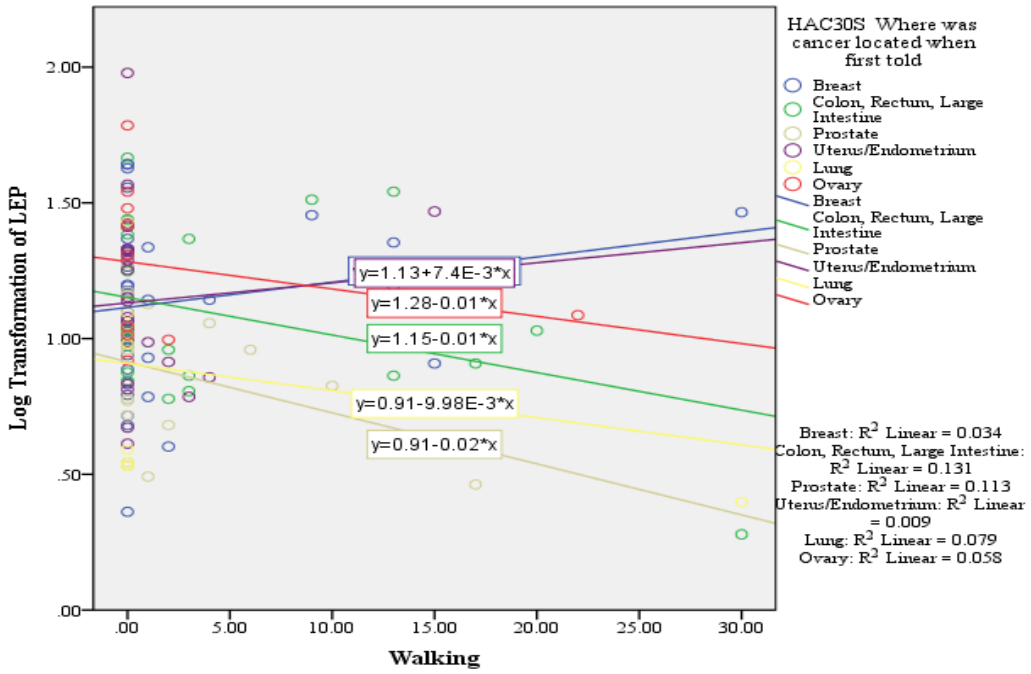

Figure 5. Scatterplots and trend lines for amount of walking and the log transformation of LEP based on cancer location.

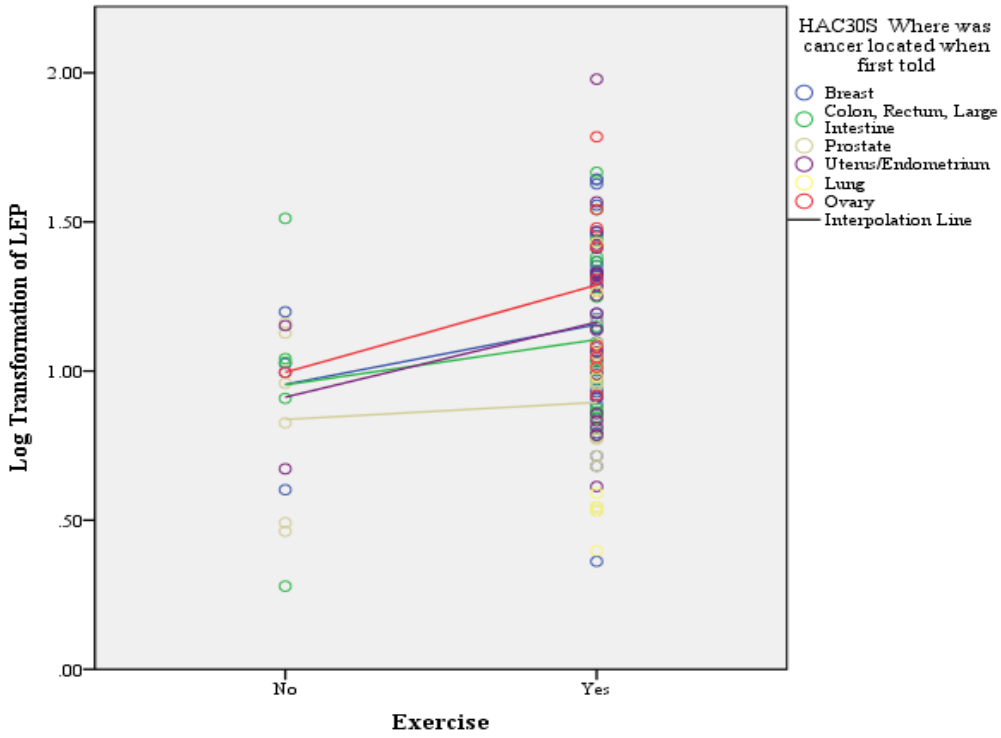

Figure 6. Scatterplots and trend lines for exercise and the log transformation of LEP based on cancer location.

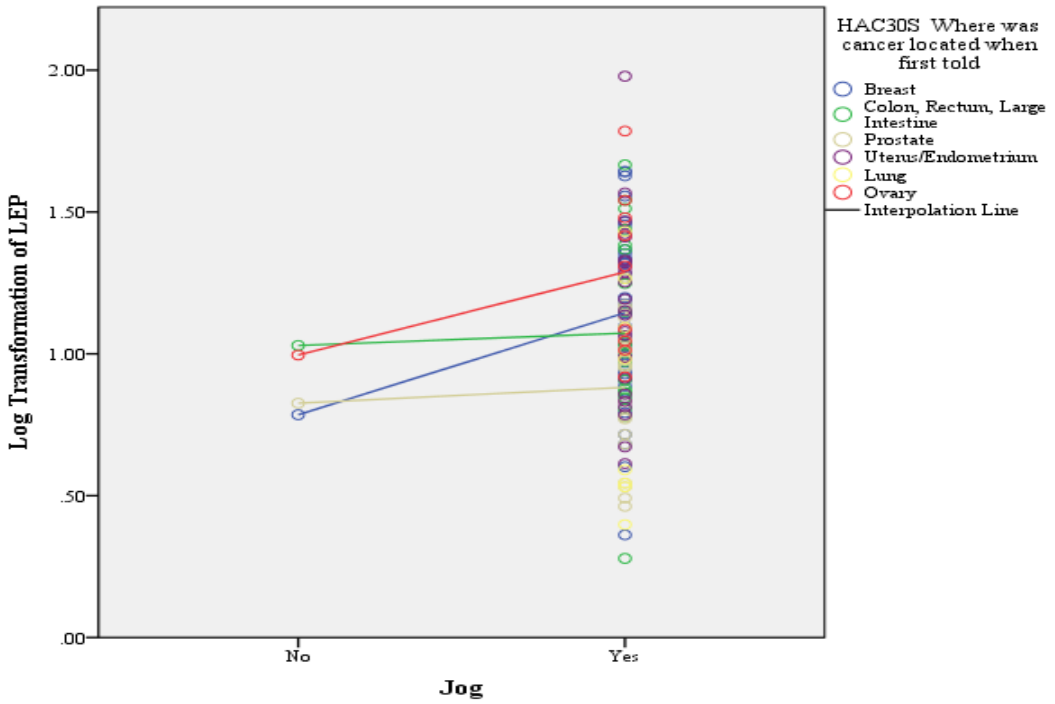

Figure 7. Scatterplots and trend lines for jogging and the log transformation of LEP based on cancer location.

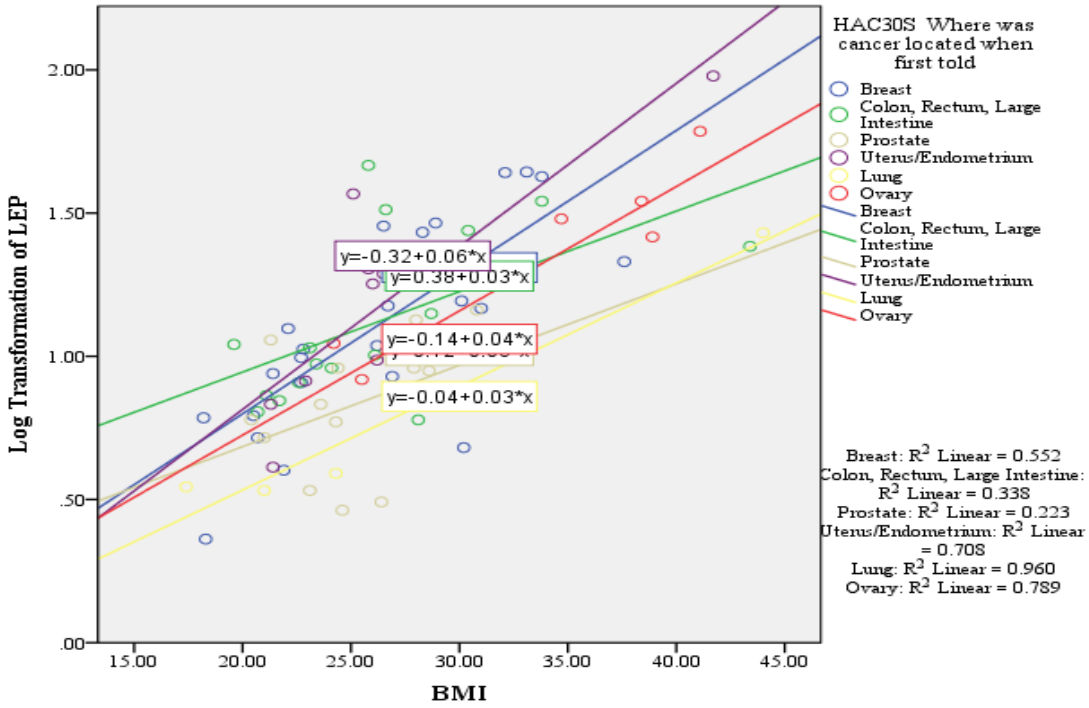

Figure 8. Scatterplots and trend lines for BMI and the log transformation of LEP based on cancer location.

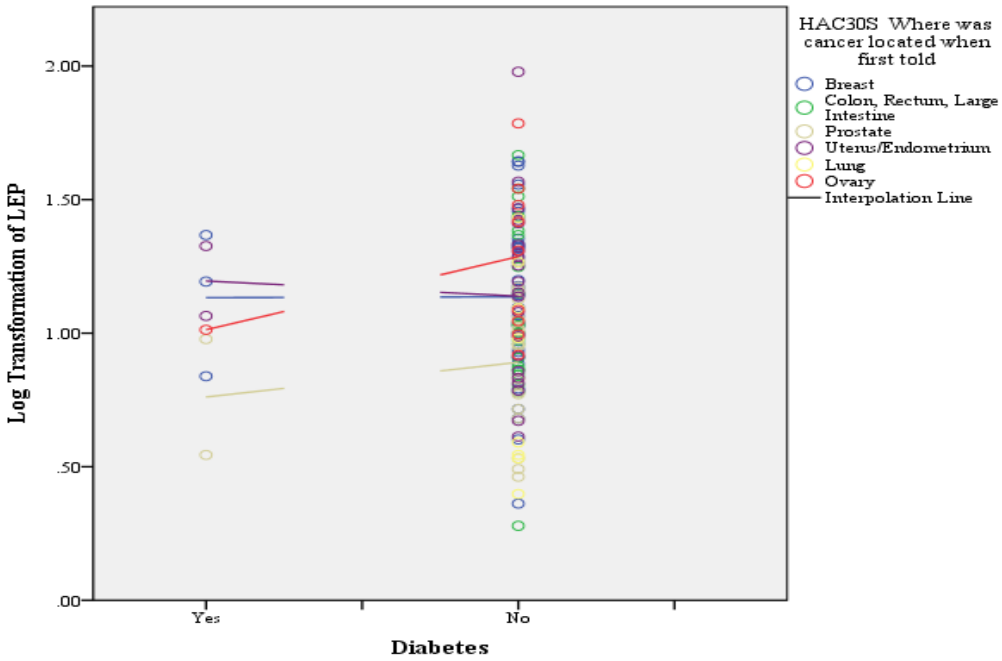

Figure 9. Scatterplots and trend lines for presence of diabetes and the log transformation of LEP based on cancer location.

A homogeneity of variances assumption was tested based on Levene's test of equality of error variances. For the three ANCOVA models, the Levene's test was nonsignificant ($p > .05$), which indicated this assumption was met. The normal distribution of residuals for each category of independent variable revealed that none of the standardized residuals for any of the categories were greater than ±3 *SD*, which indicated that this assumption was met.

The following statistical assumptions were met: normality of the dependent variable, independence of observations, homogeneity of regression slopes, normal distribution of dependent variable for each group, homogeneity of variances, and normal distribution of residuals for each category of the independent variable. The following assumptions were not met: linear relationship at each level of the independent variable and homoscedasticity of the standardized residuals. Collectively, six of the eight

assumptions for ANCOVA and multiple regression were met. However, interpretive caution should be exercised given the violation of some of the statistical assumptions.

Most of the 6,142 respondents were Non-Hispanic White (*n* = 4,282; 69.7%) or Non-Hispanic Black (*n* =1,763; 28.7%) and Mexican American/other race (*n* = 97; 1.6%), with 2,803 males (45.6%) and 3,339 females (54.4%). As outlined in Table 3, total family annual income ranged from $13,999 and under to $40,000 and over (22.3%), with a median income of $30,000. Two hundred thirty-two participants had a doctor tell them they had skin cancer (3.8%), and 215 participants had a doctor tell them they had some other form of cancer (3.5%). The number of respondents having an identified type of cancer was 126 (2.1%). Of those 126 participants; 40 reported having breast cancer (31.7%); 24 reported having cancer of the uterus/endometrium (19.0%); 22 reported having cancer of the colon/rectum/large intestine (17.5%); and 22 reported having prostate cancer (17.5%). In total, 377 participants reported being told by a doctor that they had sugar/diabetes (T2DM; 6.1%). Of the more than 6,000 participants with a leptin value, only 628 respondents ran or jogged in the previous month (10.2%), but 1,195 respondents reported doing some form of exercise during the same time frame (19.5%). A skin cancer diagnosis was found for 232 (3.8%) of the participants, and just more than half reported having a job or doing some type of work (*n* = 3,648; 59.4%). The frequency totals for health marker and demographic variables significant to this study appear in Table 2.

Table 2

Frequency Counts for Health Markers and Demographic Variables

Variable and category	*n*	%
Race		
White	4,282	69.7
Black	1,763	28.7
Other	97	1.6
Sex		
Male	2,803	45.6
Female	3,339	54.4
Total family 12-month income group (median salary $30,000)		
$13,999 and under	1,614	26.3
$14,000–$19,999	903	14.7
$20,000–$39,999	2,255	36.7
$40,000 and over	1,370	22.3
Doctor ever told you had: skin cancer		
Yes	232	3.8
No	5,910	96.2
Doctor ever told you had: other cancer		
Yes	215	3.5
No	5,927	96.5
Have cancer		
No	6,016	97.9
Yes	126	2.1
Where was cancer located when first told (n = 126)		
Breast	40	31.7
Colon, rectum, large intestine	22	17.5
Prostate	22	17.5
Uterus/endometrium	24	19.0
Lung	8	6.3
Ovary	10	7.9
Ever been told you have sugar/diabetes		
Yes	377	6.1
No	5,765	93.9
In the past month, did you jog or run?		
Yes	628	10.2
No	5,514	89.8
Past month, any other exercises or sports?		
Yes	1,195	19.5
No	4,947	80.5
Work		
No	2,494	40.6
Yes	3,648	59.4

Serum leptin levels ranged from 0.50 to 192.50, with *M* = 12.64 and *SD* = 11.83, while log-transformed leptin levels ranged from -0.30 to 2.28, with *M* = 0.94 and *SD* = 0.39. Average highest grade or year of school completed in school was *M* = 11.03. The age at interview ranged from 20 to 90 years, with *M* = 47.02 years and *SD* = 18.81. Participants reported average servings per month of peaches or nectarines (*M* = 2.95), any other fruits (*M* = 13.67), or spinach (*M* = 2.80), as well as the number of times of walking a mile in the past month without stopping (*M* = 5.40). Body mass index ranged from 16.00 to 62.00, with *M* = 27.01 and *SD* = 5.54, although BMI was only available for 3,610 individuals (58.8% of the sample). The descriptive statistics for the health markers and demographic variables in the study appear in Table 3.

Table 3

Descriptive Statistics for Health Markers and Demographic Variables

Score	*M*	*SD*	Low	High
Serum leptin	12.64	11.83	0.50	192.50
Log transformation for leptin	0.94	0.39	-0.30	2.28
Age at interview	47.02	18.81	20.00	90.00
Education (years completed)	11.03	3.86	0.00	17.00
Peaches, nectarines, and so forth (times/month)	2.95	5.86	0.00	30.00
Any other fruits (times/month)	13.67	13.31	0.00	91.00
Spinach, greens (times/month)	2.80	4.37	0.00	30.00
Walk mile without stopping (number in past month)	5.40	10.05	0.00	65.00
Body mass index (*n* = 3,610)	27.01	5.54	16.00	62.00

The results of the analysis revealed significantly more White participants (as anticipated due to the sample size) reported having cancer (*n* = 106; 2.5%) than Black participants (*n* = 19; 1.1%) or those from other racial/ethnic groups (*n* = 1; 1.0%; *p* < .002). Significantly more female respondents reported having cancer (*n* = 89; 2.7%) than

did the male respondents (n = 37; 1.3%; $p < .001$). In addition, significantly more participants who reported not having run or jogged in the past month did not have cancer (n = 122; 2.2%) than those who had cancer (n = 4; 0.6%; $p < .001$). Significantly more respondents who reported not having worked had cancer (n = 86; 3.4%) than those who did work or have a job (n = 40; 1.1%; $p < .001$). There were no significant differences for having been told by a doctor about having sugar/diabetes ($p > .05$) or doing any exercise or sports in the past month ($p > .05$). All of the Cramer V statistics (Pearson correlation between two nominal variables) were small or weak based on the Cohen (1988) criteria. The results of the bivariate chi-square tests for the health markers and demographic variables based on whether the respondent answered in the affirmative for having cancer appear in Table 4.

Cohen (1988) suggested guidelines for interpreting the strength of linear correlations. For example, Cohen noted that a weak correlation typically had an absolute value of r = .10 (about 1% of the variance explained), a moderate correlation typically had an absolute value of r = .30 (roughly 9% of the variance explained), and a strong correlation normally had an absolute value of r = .50 (about 25% of the variance explained). This chapter's results report all significant findings ($p < .05$), but moderate strength correlations (an absolute value of r = .30 and greater) will be emphasized.

Table 4

Health Markers and Demographic Variables Based on Cancer Status

Item and category	No cancer		Have cancer	
	N	%	*n*	%
Race[a]				
White	4,176	97.5	106	2.5
Black	1,744	98.9	19	1.1
Other	96	99.0	1	1.0
Sex[b]				
Male	2,766	98.7	37	1.3
Female	3,250	97.3	89	2.7
Ever been told you have sugar/diabetes[c]				
Yes	369	97.9	8	2.1
No	5,647	98.0	118	2.0
In the past month, any other exercises, sports[d]				
Yes	1,177	98.5	18	1.5
No	4,839	97.8	108	2.2
In the past month, did you jog or run[e]				
Yes	624	99.4	4	0.6
No	5,392	97.8	122	2.2
Work[f]				
No	2,408	96.6	86	3.4
Yes	3,608	98.9	40	1.1

Note. [a] χ^2 (2, N = 6,142) = 12.65, $p < .01$. Cramer's $V = .05$. Pearson correlation between two categorical variables
[b] χ^2 (1, N = 6,142) = 13.73, $p < .001$. Cramer's $V = .05$.
[c] χ^2 (1, N = 6,142) = 0.10, $p < .05$. Cramer's $V = .00$.
[d] χ^2 (1, N = 6,142) = 2.20, $p < .05$. Cramer's $V = .02$.
[e] χ^2 (1, N = 6,142) = 6.97, $p < .001$. Cramer's $V = .03$.
[f] χ^2 (1, N = 6,142) = 40.77, $p < .001$. Cramer's $V = .08$.

Analysis of the data revealed that participants with cancer had significantly higher non-transformed leptin levels (M = 15.44, SD = 12.85) than those participants who did not have cancer (M = 12.58, SD = 11.88; $p = .007$, $\eta = .03$). Significantly higher log transformed leptin levels existed between those with cancer (M = 1.07, SD = 0.32) than those without cancer (M = 0.93, SD = 0.39; $p < .001$, $\eta = .05$). Those with cancer were

significantly older (*M* = 65.88, *SD* = 15.90) than those without cancer (*M* = 46.62, *SD* = 18.66; $p < .001$, $\eta = .15$).

In addition, there was significantly higher frequency for eating any other fruits times per month between those with cancer (*M* = 17.12, *SD* = 15.15) and those without cancer (*M* = 13.59, *SD* = 13.26; $p = .003$, $\eta = .04$). Finally, there was a significantly lower occurrence of walking a mile without stopping in the past month among those with cancer (*M* = 2.89, *SD* = 6.42) than those without cancer (*M* = 5.46, *SD* = 10.10; $p = .005$, $\eta = .04$). All the eta coefficients (Pearson correlation between a categorical variable and a continuous variable) were small based on the Cohen (1988) criteria. The results of the *t*-test comparisons for the health markers and demographic variables based on whether the respondent had cancer appear in Table 5.

Table 5

Comparison of Health Markers and Demographic Variables Based on Whether the Respondent Had Cancer: t Tests for Independent Means

Item	*N*	*M*	*SD*	H	*T*	*p*
Serum leptin				.03	2.69	.007
	6,01					
No cancer	6	12.58	11.80			
Have cancer	126	15.44	12.85			
Log-transformation leptin				.05	3.97	.001
No cancer	6,016	0.93	0.39			
Have cancer	126	1.07	0.32			
Age at interview						
No cancer	6,016	46.62	18.66			
Have cancer	126	65.88	15.90			
Years of education				.00	0.91	.36
No cancer	6,016	11.03	3.87			
Have cancer	126	10.71	3.67			

(table continues)

Item	*n*	*M*	*SD*	H	*t*	*p*
Income in dollars				.01	0.25	.80
No cancer	6,016	18.88	6.83			
Have cancer	126	18.72	6.53			
Peaches, nectarines, etc. (times/month)				.02	1.49	.14
No cancer	6,016	2.94	5.84			
Have cancer	126	3.72	6.76			
Any other fruits (times/month)				.04	2.95	.003
No cancer	6,016	13.59	13.26			
Have cancer	126	17.12	15.15			
Spinach, greens, etc. (times/month)				.00	0.25	.80
No cancer	6,016	2.80	4.37			
Have cancer	126	2.71	4.19			
Past month, how often walk mile without stop				.04	2.84	.005
No cancer	6,016	5.46	10.10			
Have cancer	126	2.89	6.42			
Body mass index [a]				.00	0.03	.97
No cancer	3,528	27.01	5.54			
Have cancer	82	27.03	5.82			

Note. [a] n = 3,610.

The log-transformed leptin levels were significantly correlated with 13 of the 15 variables at the $p < .05$ level, and two were strong correlations per the Cohen (1988) criteria. Specifically, elevated log-transformed leptin levels were associated with higher BMI ($r = .58$, $p < .001$) and being female ($r = .61$, $p < .001$). Among respondents who did not report having cancer, log-transformed leptin levels were significantly correlated with 13 of the 15 variables at the $p < .05$ level, with two of those correlations having a strong strength according to the Cohen (1988) criteria. Additionally, higher log leptin levels were associated with higher BMI ($r = .58$, $p < .001$) and being female ($r = .62$, $p < .001$) for respondents without cancer. With regard to those respondents with cancer ($n = 126$), log-transformed leptin levels significantly correlated with five of 15 variables at the $p < .05$ level, with four of those correlations having moderate or strong strength per the Cohen (1988) standards. Lastly, increased log leptin levels were associated with higher

BMI (r = .70, p < .001), being female (r = .41, p < .001), and being Black (r = .35, p < .001) for those who reported having cancer. Pearson's correlations for the 15 health markers and demographic variables with the log-transformed leptin levels for all respondents (N = 6,142), for respondents without cancer (n = 6,016), and for respondents with cancer (n = 126) were outlined in Table 6.

Table 6

Pearson's Correlations for Health Marker and Demographic Variables With Log Leptin Levels for Groups of Participants

	All (N = 6,142)	No cancer (n = 6,016)	Have cancer (n = 126)
Fruit	.03**	.03**	-.07
Other fruit	.06****	.06****	.03
Greens	.04****	.04***	.07
Walking	-.08****	-.07****	-.12
Exercise	.20****	.20****	.21*
Jogging	.18****	.18****	.09
Body mass index	.58****	.58****	.70****
Diabetes	-.06****	-.07****	.03
Age at interview	.11****	.11****	-.07
Sex [a]	.61****	.62****	.41****
White [b]	-.03*	-.03**	-.34****
Black [b]	.04**	.03**	.35****
Work [b]	-.14****	-.14****	.01
Education	.00	-.01	.05
Income	-.02	-.02	-.09

Note. * p < .05. ** p < .01. *** p < .005. **** p < .001.
[a] Coding: 1 = *male*, 2 = *female*. [b] Coding: 0 = *no*, 1 = *yes*.

Research Question 1

RQ1 was as follows: Is there a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity)?

$H_0$1: There is not a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity).

H_a1: There is a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity).

I conducted a one-way ANCOVA to test the first research question and to determine if a significant difference existed between the dependent variables and different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity) among a multiethnic sample of adults (non-Hispanic White, non-Hispanic Black, Hispanic, and other races) living in the United States. The total model was statistically significant ($p = .02$), although weakly, and thus accounted for 18.4% of the difference in the log-transformed leptin level. After controlling for the covariates (skin cancer, dietary intake and physical activity), the types of cancer were significant ($p < .01$). The Bonferroni post hoc tests revealed that the log-transformed leptin levels were higher among participants with ovarian cancer ($M = 1.26$) than those with prostate cancer ($M = 0.90$; $p = .061$). This combination of findings provided support to reject the null hypothesis for RQ1. The relevant model concerning RQ1 appears in Table 7, and the post hoc results for RQ1 appear in Table 8. I then address RQ2.

Table 7

ANCOVA Model for Log-Transformed Leptin Levels Based on Cancer Type Controlling for Skin Cancer and Individual/Interpersonal Factors and Physical Activity

Variable	*SS*	*Df*	*MS*	*F*	*P*	Partial eta squared
Full model	2.33	12	0.19	2.12	.02	.184
Fruits	0.00	1	0.00	0.00	.97	.000
Other fruits	0.02	1	0.02	0.23	.63	.002
Greens	0.00	1	0.00	0.01	.92	.000
Walking	0.06	1	0.06	0.63	.43	.006
Exercise	0.22	1	0.22	2.39	.12	.021
Jogging	0.03	1	0.03	0.35	.56	.003
Skin cancer	0.04	1	0.04	0.39	.53	.003
Type of cancer	1.42	5	0.28	3.09	.01	.120
Error	10.33	113	0.09			
Total	12.66	125				

Note. $N = 126$. Levene's test of equality of error variances: $F(5, 120) = 0.99$, $p = .43$. Model for Research Question 1.

Table 8

Post Hoc Test Results for Research Question 1

Type of cancer[a]	*n*	*M*	*SE*
1. Breast	40	1.12	0.05
2. Colon, Rectum, Large Intestine	22	1.10	0.07
3. Prostate	22	0.90	0.07
4. Uterus/endometrium	24	1.13	0.06
5. Lung	8	0.85	0.11
6. Ovary	10	1.26	0.10

Note. [a] Bonferroni post hoc test results: No. 6 > No. 3 ($p = .06$); no other post hoc test was significant at the $p < .10$ level.

Research Question 2

RQ2 was as follows: Is there a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, prostate, ovarian, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM)?

$H_0$2: There is not a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

H_a2: There is a significant difference in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

To answer RQ2, I investigated if a significant difference existed in leptin levels among adults with different types of cancer (breast, colorectal, endometrial [uterine corpus], prostate, ovarian, and lung) after controlling for skin cancer, individual/interpersonal factors (i.e., dietary intake and physical activity), and known covariates (BMI and T2DM). These covariates were chosen specifically because of both their established correlation with cancer and their association with obesity or leptin levels. The investigation involved a one-way ANCOVA followed by Bonferroni post hoc tests. In addition, I used an eta coefficient (Pearson correlation between a nominal variable and a continuous variable) to measure the strength of the relationships.

The overall model was significant ($p < .001$) and accounted for 66.3% of the difference in the log-transformed leptin level. After controlling for the covariates, the type of cancer was significant ($p = .004$). Bonferroni post hoc tests found the log-transformed leptin levels were higher for individuals with uterine/endometrium cancer ($M = 1.23$) than for those with prostate cancer ($M = 0.92$; $p = .031$). The post hoc tests also

found the log-transformed leptin levels were higher than those with lung cancer (M = 0.80; p = .031). This combination of findings provided support to reject the null hypothesis in RQ2. The relevant model and the post hoc results concerning RQ2 appear in Tables 9 and 10. I then address RQ3.

Table 9

ANCOVA Model for Log-Transformed Leptin Levels Based on Cancer Type Controlling for Skin Cancer and Individual/Interpersonal Factors, Physical Activity, BMI, and Presence of Diabetes

Variable	*SS*	*df*	*MS*	*F*	*p*	Partial eta squared
Full model	6.21	14	0.44	9.40	.001	.663
Fruits	0.01	1	0.01	0.13	.720	.002
Other fruits	0.22	1	0.22	4.76	.030	.066
Greens	0.05	1	0.05	1.12	.290	.016
Walking	0.02	1	0.02	0.42	.520	.006
Exercise	0.05	1	0.05	1.02	.320	.015
Jogging	0.00	1	0.00	0.02	.880	.000
Skin cancer	0.04	1	0.04	0.92	.340	.013
BMI	4.11	1	4.11	87.24	.001	.566
Diabetes	0.06	1	0.06	1.24	.270	.018
Type of cancer	0.90	5	0.18	3.82	.004	.222
Error	3.16	67	0.05			
Total	9.36	81				

Note. n = 82. Levene's test of equality of error variances: F (5, 76) = 0.49, p = .781. Model for Research Question 2.

Table 10

Post Hoc Test Results for Research Question 2

Type of cancer[a]	*n*	*M*	*SE*
1. Breast	27	1.12	0.04
2. Colon, rectum, large intestine	17	1.14	0.05
3. Prostate	16	0.92	0.06
4. Uterus/endometrium	11	1.23	0.07
5. Lung	4	0.80	0.11
6. Ovary	7	1.08	0.09

Note. [a] Bonferroni post hoc test results: No. 4 > No. 3 (p = .031); No. 4 > No. 5 (p = .031); no other post hoc test was significant at the p < .10 level.

Research Question 3

RQ3 was as follows: Is there a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity)?

$H_0$3: There is not a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity).

H_a3: There is a significant difference in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity).

The study involved running a one-way ANCOVA to determine the presence or absence of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate, and lung) with leptin levels after controlling for individual/interpersonal factors (i.e., dietary intake, physical activity [interval]) for RQ3. A Bonferroni post hoc test was not suitable, as there were only two categories identified (the presence or absence of cancer). I calculated an eta coefficient (Pearson correlation between a nominal variable and a continuous variable) to measure the strength of the relationship. The total model was significant ($p < .001$) and thus accounted for 6.7% of the variance in the log-transformed leptin level. After controlling for the covariates (dietary, intake, and physical activity), the types of cancer were significant ($p = .002$). Those without cancer had lower log-transformed leptin levels ($M = 0.93$, $SE = 0.01$) than those with cancer ($M = 1.04$, $SE =$

0.03). This combination of findings provided support to reject the null hypothesis of RQ3. The relevant model for RQ3 appears in Table 11. I then address RQ4.

Table 11

ANCOVA Model for Log-Transformed Leptin Levels Based on the Presence of Cancer Controlling for Individual/Interpersonal Factors and Physical Activity r

Variable	*SS*	*Df*	*MS*	*F*	*P*	Partial eta squared
Full model	63.38	7	9.05	62.76	.001	.067
Fruits	0.52	1	0.52	3.60	.060	.001
Other fruits	1.95	1	1.95	13.54	.001	.002
Greens	1.37	1	1.37	9.46	.002	.002
Walking	2.52	1	2.52	17.44	.001	.003
Exercise	23.12	1	23.12	160.23	.001	.025
Jogging	15.74	1	15.74	109.11	.000	.017
Have cancer [a]	1.45	1	1.45	10.02	.002	.002
Error	885.01	6,134	0.14			
Total	948.39	6,141				

Note. N = 6,142. Levene's test of equality of error variances: $F(1, 6140) = 9.53$, $p = .002$.
[a] Have cancer: No (M = 0.93, SE = 0.01) versus yes (M = 1.04, SE = 0.03). Model for Research Question 3.

Research Question 4

RQ4 was as follows: Is there a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and two individual interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer?

$H_0$4: There is not a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and the two individual/interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer.

H_a4: There is a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] and the two individual/interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer.

The overall multiple regression model for log-transformed leptin levels based on cancer status and controlling for selected variables was significant ($p < .001$) and accounted for 67.9% of the variance in the log transformed leptin levels. Those with cancer had higher leptin levels ($p = .031$), although the partial correlation regarding cancer status ($r_{ab.c} = .04$) was 17 times smaller than the partial correlation for either gender/sex ($r_{ab.c} = .68$) or BMI ($r_{ab.c} = .68$). This combination of findings provided support to reject $H4_0$. The multiple regression prediction model for log-transformed leptin levels based on cancer status and controlling for selected variables for RQ4 appear in Table 12.

Table 12

Prediction of Log-Transformed Leptin Levels Based on Cancer Status Controlling for Selected Variables

Variable	*B*	*SE*	β	*p*	*R*	$r_{ab.c}$
Intercept	-1.17	0.05		.001		
Age	0.00	0.00	.09	.001	.12	.13
Sex [a]	0.44	0.01	.56	.001	.61	.68
BMI	0.04	0.00	.53	.001	.58	.68
Race	0.00	0.01	.00	.860	-.03	.00
Diabetes	0.04	0.02	.02	.010	-.08	.04
Work	0.00	0.01	.00	.910	-.14	.00
Education	0.00	0.00	.04	.001	-.02	.06
Income	0.00	0.00	.02	.060	-.05	.03
Fruit	0.00	0.00	.00	.770	.04	.00
Other fruit	0.00	0.00	.00	.930	.05	.00
Greens	0.00	0.00	.00	.940	.05	.00
Walking	0.00	0.00	-.02	.030	-.08	-.04
Exercise	0.03	0.01	.03	.005	.23	.05
Jog	0.06	0.01	.04	.001	.21	.07
Have cancer	0.06	0.03	.02	.030	.06	.04

Note. Full model: $F(15, 3594) = 507.24$, $p < .001$. $R^2 = .679$. Durbin-Watson = 1.99. n = 3,610. Sex [a] = (1 Male) (2 Female) Regression model for Research Question 4.

Summary

This chapter included descriptive statistics on the differences between leptin levels and cancer status. Analysis involved using archival data concerning 6,142 individuals to examine if a significant difference exists between leptin levels in individuals with different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, lung, and prostate) and those without cancer after adjusting for risk factors with an association with malignancy among a multiethnic sample of adults living in the United States from NHANES III (CDC, 2015). Data analysis led to rejecting the null hypothesis in support of the alternative hypothesis for each of the four research questions. The results indicated that a significant difference existed, although the

relationship was weak (.10) in leptin levels among adults with different types of cancer and those without cancer after controlling for skin cancer and interpersonal/individual factors (dietary intake/physical activity) relating to RQ1, RQ2, and RQ3. Regarding RQ4, the results revealed that a correlation existed between the 10 predictor variables (eight cancer risk factors (age, gender, BMI, race or ethnicity, T2DM, occupational status, education, SES) plus the two individual/interpersonal factors (dietary intake and physical activity) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer. In Chapter 5, I will compare these findings to the literature, draw conclusions and implications, and suggest a series of recommendations.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this quantitative, cross-sectional study was to determine if a significant difference exists between leptin levels in individuals with different types of cancer (breast, colorectal, endometrial [uterine corpus], ovarian, prostate and lung) and those without cancer after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM) to cancer. The study also involved searching for a correlation between 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES]), two individual interpersonal factors (dietary intake and physical activity), and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, lung) and those without cancer.

Despite the many preventive and control measures established, cancer remains the second leading cause of death in the United States and claims the lives of half a million Americans each year (CDC, 2016k). Additionally, cancer cases are likely to rise in both men (24%) and women (21%) by 2020 (CDC, 2016k). Biological, social, and environmental determinants influence both cancer and obesity (increased leptin levels). With the prevalence of obesity having more than doubled and obesity becoming a national epidemic among the U.S. population, it is important from a social ecological perspective to have a better understanding of leptin and the role it plays in the progression of adiposity or obesity in the human body as well as its overall correlation to cancer, particularly types of cancer known to have an association with obesity (increased

leptin levels). My study, in turn, may aid in determining if leptin is an independent risk factor for the prevalence of obesity associated cancers and possibly aid in the efforts to reduce the incidence and mortality rates of the disease through research, clinical practice, and policy changes and may improve prevention efforts with lifestyle and behavior changes.

Summary of Key Findings

The results of this quantitative study indicated that a significant difference, although a weak relationship, exists in leptin levels among adults with different types of cancer and those without cancer after controlling for skin cancer and interpersonal/individual factors (dietary intake/physical activity) relating to RQ1, RQ2, and RQ3. The results concerning RQ4 revealed that a correlation exists between 10 predictor variables (eight cancer risk factors [age, gender, BMI, race-ethnicity, T2DM, occupational status, education, SES] and two individual/interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung), as well as those without cancer. The results of each of the four research questions supported rejecting the four null hypotheses.

Interpretation of the Findings

I used a periodic survey: the NHANES III (CDC, 2015). Researchers for NCHS conducted the NHANES III by collecting, analyzing, and disseminating data on the health status of residents residing in the United States (CDC, 2015). NHANES III was the seventh survey in a series based upon a complex plan with multiple stages conducted

from 1988 through 1994 and created to provide national estimates of the health and nutritional status of residents in the United States (CDC, 2015). The independent variables for this study were the types of cancer reported. The dependent variable was leptin level(s).

In the current study, I examined significant differences in leptin levels and various obesity associated cancers after adjusting for multiple covariates, and I interpreted the findings within the context of the SEM. According to the SEM, health is the result of the interaction between behavior and the social environment. The results of this study revealed that a statistically significant difference exists in leptin levels and different types of obesity-associated cancers. Factors such as low physical activity, poor diet, obesity, elevated leptin levels, BMI levels, gender, race/ethnicity, and other covariates influenced the outcome of this study and previous studies. The results help support the SEM and previous research that indicated various individual, social, and environmental factors influenced obesity and cancer outcomes (Moore et al., 2015).

Additionally, the results of the study yielded expected and unexpected results. In accordance with existing literature, serum leptin levels were significantly higher in women than in men, even after adjusting for total body fat mass (BMI) and with levels decreasing as age progresses (Gupta et al., 2016; Havel et al., 1996; Rosenbaum et al., 1996). This result was consistent with the findings of the study, as an association existed between increased log leptin levels and higher BMI ($r = .70$, $p < .001$), being female ($r = .41$, $p < .001$), and being Black ($r = .35$, $p < .001$) for those who reported having cancer. An association existed between higher log leptin levels and higher BMI ($r = .58$, $p <$

.001) and being female ($r = .62$, $p < .001$) for respondents without cancer as well. However, the results of the study revealed that being female and White presented higher leptin and cancer incidence. African American participants presented the second highest leptin and cancer incidence (1.1%) even though existing literature revealed that they tend to have the higher levels than those from other racial/ethnic groups (1.0%; $p = .002$). The sample size serves as an explanation for this finding, as significantly more White participants took part in the study. Significantly more female respondents reported having cancer (2.7%) than did male respondents (1.3%; $p < .001$).

The gap in literature reflected the lack of specific studies conducted to examine if a significant difference exists in leptin levels among adults with different types of obesity-associated cancers (breast, colorectal, endometrial [uterine corpus], ovarian, prostate) and commonly diagnosed cancers (lung and skin) that have an association with leptin in a single study. As such, there was no true benchmark to compare leptin levels and various cancers when aggregating by multiple racial ethnicities. Thus, the focus was toward relevant studies that investigated the leptin (level) and cancer relationship.

I have summarized the additional findings of this study into subheadings in accordance with the four research questions and corresponding hypotheses. I have interpreted the results of the study in the framework of existing literature and have established concepts relating to the area of cancer and obesity (leptin) research. The findings from this study follow.

Finding 1

Finding 1 was as follows: A significant difference exists in leptin levels among adults with different types of cancer after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity). In RQ1, I investigated if a significant difference exists in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity). I found that the total model was statistically significant ($p = .02$), although the relationship was weak, and accounted for 18.4% of the difference in the log-transformed leptin levels. After controlling for the covariates (skin cancer, dietary intake, and physical activity), the types of cancer were significant ($p < .01$). The Bonferroni post hoc tests found the log-transformed leptin levels to be higher for individuals with ovarian cancer ($M = 1.26$) than those with prostate cancer ($M = 0.90$; $p = .06$). The combination of findings provided support to reject the null hypothesis to RQ1.

Finding 2

Finding 2 was as follows: A significant difference exists in leptin levels among adults with different types of cancer after controlling for skin cancer and individual/interpersonal factors (dietary intake and physical activity) and known covariates (BMI and T2DM). In RQ2, I investigated if a significant difference exists in leptin levels among adults with different types of cancer (breast, colorectal, endometrial, prostate, ovarian, and lung) after controlling for skin cancer, individual/interpersonal factors (dietary intake and physical activity), and known covariates (BMI and T2DM).

The results revealed that a significant difference exists in leptin levels among adults with different types of cancer after controlling for skin cancer, dietary intake, physical activity, and known covariates. I also found that the model was significant ($p < .001$) and accounted for 66.3% of the difference in the log-transformed leptin level. After controlling for the covariates, the type of cancer was significant ($p = .004$). The Bonferroni post hoc tests found the log-transformed leptin levels to be higher for individuals with uterine/endometrium cancer ($M = 1.23$) than for those with prostate cancer ($M = 0.92$; $p = .03$) or those with lung cancer ($M = 0.80$; $p = .03$). This combination of findings provided support to reject the null hypothesis for RQ2.

Finding 3

Finding 3 was as follows: A significant difference exists in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors (dietary intake and physical activity). In RQ3, I investigated if a significant difference exists in leptin levels among adults with and without cancer after controlling individual/interpersonal factors (dietary intake and physical activity). I found that the total model was significant ($p < .001$) and accounted for 6.7% of the variance in the log-transformed leptin level. After controlling for the covariates (dietary, intake, and physical activity), the types of cancer were significant ($p = .002$). Those without cancer had lower log-transformed leptin levels ($M = 0.93$, $SE = 0.01$) than those with cancer ($M = 1.04$, $SE = 0.03$). These results indicated that a significant difference exists in leptin levels among adults with and without cancer after controlling for individual/interpersonal factors

(dietary intake and physical activity), and thus this combination of findings provided support to reject the null hypothesis for RQ3.

Finding 4

Finding 4 was as follows: There is a correlation between the 10 predictor variables (eight cancer risk factors [age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES] plus the two individual/interpersonal factors [dietary intake and physical activity]) and leptin levels among adults with different types of cancer (breast, colorectal, endometrial, ovarian, prostate, and lung) and those without cancer. In RQ4, I investigated if a correlation existed between the 10 predictor variables and leptin levels among adults with different types of obesity associated cancer and those without cancer. I found a correlation between the 10 predictor variables and leptin levels among adults with different types of cancer and those without cancer. The overall model was significant ($p < .001$) and accounted for 67.9% of the difference in the log-transformed leptin levels. The results also revealed that six of the 10 variables in the model (age, sex/gender, BMI, education, diabetes, exercise) were statistically significant in the model. However, based upon the partial correlation, sex/gender and BMI were several times more significant than the other predictor variables relevant to leptin levels. Additionally, those with cancer displayed higher leptin levels ($p = .03$). The partial correlation regarding cancer status ($r_{ab.c} = .04$) was 17 times smaller than the partial correlation for either sex ($r_{ab.c} = .68$) or BMI ($r_{ab.c} = .68$). This combination of findings provided support to reject the null hypothesis for RQ4.

As previously mentioned, the results of this study coincided and differed from earlier research. Several researchers had examined the association between prostate cancer and leptin level and revealed an unclear, not statistically significant, or null association (Allot et al., 2013; Hsing et al., 2001; Lai, et al., 2011; Li et al., 2010; Stattin et al., 2003a). Stattin et al. (2003a) demonstrated a potentially nonlinear relationship between leptin levels and prostate cancer and revealed an association between very elevated leptin levels and reduced cancer incidence. However, the results of this study revealed a statistically significant difference in leptin levels in those with prostate cancer after controlling for skin cancer, dietary intake, physical activity, BMI, and T2DM, which is also consistent with another study conducted by Barrington et al (2015), where BMI increased the risk of prostate cancer incidence in participants, who were mainly Black men, with a BMI of 35 kg/m^2 or above and also revealed an inverse relationship in both White and Hispanic men. Also consistent with this study's findings was the mean age of those afflicted with prostate and other relevant cancers related to this study, which was 65 years (65.88 this study) of age and older (Barrington et al., 2015).

Results differed from another study conducted in Hong Kong, China, where obesity rates are generally lower among the Chinese population and there is different overall body fat distribution when compared to European Americans. Yeung et al. (2013) found no difference in leptin levels between participants who developed all-incident cancer and those who did not, though most of the participants who did develop cancer were obese (22.1 vs. 16.1%) or had central obesity (36.6 vs. 24.5%). The findings

revealed that those who developed cancer were most likely male and, similar to this study, were older, had higher BMI levels, and reported being told they had T2DM.

Further inconsistencies to the results of this study and existing literature related to ovarian cancer. Jin et al. (2016) conducted a study to explore differences in plasma adiponectin and leptin concentrations between patients with ovarian cancer and women without ovarian cancer with the same BMI to determine whether adiponectin and leptin related to ovarian carcinogenesis. The results of the study revealed that both adiponectin and leptin concentrations were significantly lower in patients with ovarian cancer than in those in the control groups. Significantly lower leptin levels also occurred in patients with ovarian cancer versus those of healthy individuals (9.26 ± 4.04 ng/ml and 15.25 ± 2.82 ng/ml [$p < .0001$], respectively) in a similar study conducted to examine serum leptin levels in various ovarian cancer patients and those without the obesity-associated malignancy (Grabowski et al., 2014). The study revealed that leptin levels were significantly higher in individuals with ovarian cancer even after controlling for known covariates. Wu et al.'s (2014) nested case control study revealed significantly higher leptin levels in both UCC and ovarian cancers. The median leptin level was 22.53 ng/ml (IQR: 19.47–29.05 ng/ml) in UCC cases versus 9.81 ng/ml (6.16–14.56) in the age and menopause-matched controls, and 23.58 ng/ml (14.92–42.61) in ovarian cancer cases versus 9.79 ng/ml (6.50–14.74) in their matched controls, which were congruent with the findings in this study, where the results revealed a significant difference in leptin levels among adults with both uterine (endometrial) and ovarian cancers. After adjusting for age and risk covariates, patients with leptin in the highest tertile 3 had an increased risk of

incident gynecological cancer as compared with those in tertile 1 (*OR* =10.68, 95% CI [2.09–54.67], *p* = .005 and *OR* = 11.83, 95% CI [1.40–1.11], *p* = .023 for UCC and ovarian cancer, respectively (Wu et al., 2014).

Additionally, researchers found that serum leptin levels in obese women were higher among patients with newly diagnosed breast cancer among than those without cancer among 156 women (78 obese women with a BMI > 30 and newly diagnosed breast cancer and no current diagnosis of type II diabetes and 78 obese women with a BMI > 30 without breast cancer and type II diabetes among a Mexican population in Toluca, Mexico (Roman-Figueroa et al., 2013). Additionally, postmenopausal breast cancer and prostate cancers were the two most common primary cancer sites (24% and 18%, respectively) followed by gastrointestinal cancer, including colon and rectum (16%), of the total obesity associated cancers included in the study of the 190 (6.5%) men and women who developed an incident cancer in the median follow-up period of 12.0 years in the Dallas Heart Study (Gupta et al., 2016). Gupta et al. (2016) conducted this prospective study to examine the relationship between prediagnostic plasma leptin levels and the risk of relevant obesity associated cancer incidence relevant to this study (postmenopausal breast, endometrial cancers, prostate, and colorectal) among a group of multiethnic adults (aged 18–65 years). Leptin levels were 12.9 ng/ml in the cancer group and 12.3 ng/ml in the noncancer group (*p* = .341). Consistent with this study and prior research, median leptin levels were higher in females (23.2 ng/ml) than in males (5.6 ng/ml) and highest among Blacks (15.7 ng/ml), Whites (10.3 ng/ml), and Hispanics (11.1 ng/ml). However, when stratified by sex, race, T2DM, or BMI, there was not a

statistically significant relationship (Gupta et al., 2016). In contrast, BMI and sex/gender were significant and although race was not a statistically noteworthy correlate between 10 predictor variables, individual factors and leptin levels in those with and without cancer being African American were associated with the highest levels among race, followed by White participants in this study. Similarly, those with cancer in Gupta et al.'s (2016) study and in this study were older than those without cancer. Furthermore, no association existed between premorbid leptin levels and cancer, even though Gupta et al. (2016) identified preclinical basis and positive outcomes. Given the fact that leptin levels are higher in women than in men, it is practical to consider that leptin could have a positive association in women where leptin levels are higher, but not in men (Gupta et al., 2016). Both breast and endometrial cancer are obesity-associated cancers, which raises the possibility that leptin increases the risk of obesity-associated cancers (Gupta et al., 2016).

Finally, there has been limited research conducted concerning the association between skin cancer and obesity, and even less research includes leptin. Of the research conducted, the results indicated that, when compared to men and women with normal BMI, those classified as obese and morbidly obese had a 32% and 37%, respectively, lower risk of developing squamous cell carcinoma among women, but not men (Pothiawala et al., 2012). Additionally, when compared to participants who fell in the normal BMI category, those classified as obese had a 19% lower risk for developing basal cell carcinoma and those in the morbidly obese category had a 29% lower risk of developing basal cell carcinoma (Pothiawala et al., 2012). Ellerhorst et al. (2010) found that although elevated leptin levels showed an association with increased risk for

melanoma, the raised levels were surprisingly not attributed to obesity. Researchers also observed a nonsignificant risk of obesity in participants with nonmelanoma skin cancer (RR = 0.45, 95% CI [0.18–1.12], even though previous research has revealed that leptin tracks closely with BMI and most individuals with high leptin have elevated BMI and thus tend to be obese (Ellerhorst et al., 2010; Gupta et al., 2016). The high BMI and obesity relationship could be due to the fact people genetically predisposed to higher circulating leptin levels, regardless of body mass, are at a greater risk for the development of leptin-responsive tumors (Ellerhorst et al., 2010).

Moreover, in the study most related to this research, Gogas et al. (2007) explored the role of leptin whose levels increase with obesity in melanoma development among those with melanoma and matched healthy controls. Gogas et al. found that, of the 55 patients and controls, an excess melanoma risk was observed for sun-sensitive individuals and those with high circulating levels of leptin (*OR* = 1.56, 95% CI [1.07–2.28], $p = .02$), after controlling for age, smoking, diabetes mellitus, and education. Increased physical exercise, lower alcohol consumption, and plant food consumption seemed to play a protective role against melanoma development (Gogas et al., 2007). A positive association existed between melanoma risk and serum leptin levels, and an inverse relationship existed between melanoma risk and healthy lifestyle factors. However, further prospective studies are necessary to confirm the underlying pathophysiologic mechanisms and the role of the risk factors in predicting future risk of melanoma in humans (Gogas et al., 2007).

I used skin cancer as a covariate due to the manner of reporting it in the NHANES III data set. When adjusting for skin cancer and other covariates in the relevant research questions, the types of cancer were significant. However, skin cancer was not significant individually ($p = .531$; $p = .341$) concerning the relevant research questions. Additionally, when determining the correlation between age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES, dietary intake, physical activity, and leptin levels in adults with types of cancer that include skin cancer and those without, the results revealed that a correlation existed and the model was significant ($p < .001$): types of cancer were significant at $p = .04$. The results further revealed that those with cancer displayed higher leptin levels ($p = .03$). In addition, BMI, age, gender, education, and exercise were significant covariates, and the partial correlation regarding cancer status ($r_{ab.c} = .04$) was 17 times smaller than the partial correlation for sex ($r_{ab.c} = .68$) or BMI ($r_{ab.c} = .68$). Given the refuting results, further studies are necessary to determine the role of leptin in the progression of skin cancer.

Limitations of the Study

There were several limitations related to this study that warrant mentioning. The first is the cross-sectional design of the quantitative study. Researchers can use cross-sectional designs to determine an association but not causation, as data regarding each participant are recorded only once, which makes it a challenge to infer a time-based association between a risk factor and an outcome. Second, although purpose for gathering the NHANES III data was to serve as a nationally representative sample of individuals in the United States, the data were collected only from noninstitutionalized civilian

populations in the United States. As a result, individuals excluded included nursing home residents; those housed in juvenile detention centers, federal and state prisons, and halfway houses; and those serving in the military. The exclusion of the aforementioned populations may have had some impact or significance regarding the study's findings. Additionally, with the exception of leptin levels, participants self-reported all other data from the NHANES III data set from 1988 to 1994. Thus, the researchers could not eliminate the potential for discrepancies between cancer incidence and actual occurrence.

Self-reporting bias may result from the unintentional or intentional misreporting of information by the study participants (Crosby et al., 2006; Frankfort-Nachmias & Nachmias, 2008). Such misreporting of information could lead to misclassification (Crosby et al., 2006; Frankfort-Nachmias et al., 2008). Unintentional misreporting could result from misunderstanding the questions posed or from the inability of the NHANES III study participants to recall specific information accurately at the time of questioning (Crosby et al., 2006; Frankfort-Nachmias et al., 2008). On the contrary, intentional misreporting of information by the NHANES III study participants could result from such factors as social desirability (Crosby et al., 2006; Frankfort- Nachmias et al., 2008). For example, when respondents were asked how frequently they performed specified leisure time exercise or physical activities in the past month, recall bias and the estimated amount of time spent exercising may be overrepresented in this data set, as people most often desire to be seen positively and may have felt tempted to overestimate the number of hours spent completing some form of aerobic activity per month.

Internal and external validity threats regarding this study could arise from the lack of adequate sample representativeness and reactive arrangement. Regarding generalizing the findings, the external validity that address the generalizability can be ensured if the characteristics of the sample in this study are similar to the general population from another setting. I determined internal validity in this study when changes within the independent variables, notably the types of cancer, showed changes in the dependent variable, which in this study was leptin levels. Another limitation of this study was the use of archival data collected from 1988 to 1994. However, because of the requirements to adhere to the Health Insurance Portability and Accountability Act and to honor the rights of all patients (DHHS, n.d.), I was limited to data that are publicly available. Lastly, using data collected from a known source with a reputation for validity usually ensures the accuracy of the data collected, but not being able to cross-check these data for accuracy may have led to statistical errors. I could not determine cause and effect due to the cross-sectional study design, and additional unknown confounders could have affected the findings.

Recommendations for Further Research

As researchers have conducted little research concerning this topic, I have several recommendations for further research. For example, the data concerning this research study came from the publicly available NHANES III archival cross-sectional survey. I recommend researchers conduct a similar study using a more recent publicly available archival data set, particularly concerning the variable leptin level. I also recommend a larger sample size that adequately represents all races/ethnicities, including the Asian

population, as well as each covariate of interest (age, gender, BMI, race/ethnicity, T2DM, occupational status, education, SES, dietary intake, and physical activity) based upon previous research. Another recommendation could be to account adequately for additional cancer incidence, if reported, as I only accounted for the first cancer in the current study if participants reported more than one. Accounting for additional cancer incidence could lead to a better understanding of the association between obesity-associated cancers and leptin in not only the most negatively affected population (Blacks), but all populations.

Further, researchers calculated BMI as weight in kilograms divided by the square of height in meters (kg/m^2), following self-reported data from participants. Previous research has shown that BMI studies based on self-reported measurements tend to be inaccurate. In prior studies, researchers have revealed that BMI is strongly associated with obesity and leptin levels; I therefore recommend that trained personnel calculate and obtain BMI levels to yield accurate results. Lastly, researchers should determine the variable T2DM by blood sugar levels obtained in a laboratory setting, as opposed to self-reporting, to produce more accurate results.

Implications for Social Change

With cancer still classified as the second leading cause of death in the United States, despite the many preventive and control measures established, and because some reports indicate it will soon become the leading cause of death, a better understanding of its etiology is necessary (CDC, 2016a). This study adds to the literature because, at the time of this writing, there was no published research in which researchers investigated a

difference in leptin levels to established cancer risk factors (age, gender, BMI, race/ethnicity, T2DM, occupation, education, income level [SES]) and individual/interpersonal factors (dietary intake and physical activity). This study's findings revealed factors that significantly affected the relationship between leptin level and obesity-associated cancer among a multiethnic sample of adults in the United States. The information generated in this study may provide a reference for future studies that may promote a better understanding of how leptin levels may influence the risk of certain cancers among a set of correlates. By having an improved understanding of relationship between leptin level and cancer, health professionals may establish preventive strategies such as new medicines, clinical practice/health organizational efforts, and informed updates to existing policy to identify and thwart individual and environmental factors that contribute to increased leptin levels and obesity, thereby possibly reducing the risk of obesity-associated cancers among adults living in the United States and those living in other countries. This awareness may motivate persons at the individual/intrapersonal, interpersonal, organizational, community, and policy levels to take action toward preventing obesity (increased leptin levels) and obesity-associated cancers by focusing not only on those populations most negatively affected (i.e., African Americans, those with lower education levels, those with lower SES), but all populations in the United States and worldwide.

Using the SEM (individual, interpersonal, organizational, community, and policy levels) as a reference, for example, by establishing a preventive program concerning breast cancer at the individual level, the aim is to increase individuals' knowledge,

attitude, and beliefs concerning the need for breast cancer screening; the risks and benefits of screening; and possible access to affordable and convenient screening, diagnosis, and treatment of the disease (CDC, 2013). At the interpersonal level, providers and other support systems (friends, family churches, peers, etc.) help to reinforce recommendations toward breast screening, remind individuals of the need and importance of screening, and work to help remove any barriers to testing that may arise. Breast cancer prevention activities at the organizational (cancer control coalitions, local health departments, tribal urban health clinics and professional organizations) level influence individual behavior change by promoting reminder systems from the organizational level to the individual concerning breast cancer screening, providing an assessment and feedback of service rendered about breast cancer screening, the adoption of worksite policies that support preventive care and working to foster the coverage and expansion of benefits for screening, particularly to the underserved (CDC, 2013). Breast cancer prevention activities at the community level should facilitate individual behavior change by influencing the resources and participation of community-level institutions, for example by working in conjunction with coalitions to promote breast cancer screening and to expand resources; conducting public awareness and educational campaigns; and collaborating with health departments to expand breast cancer screening among the members of the community. At the policy level, the results of this study may influence federal, state, local, and tribal government agencies to support policies that promote healthy behavior by collaborating with coalitions to communicate policy decisions to the public or by translating local policies for members of the community via mayoral

proclamations for breast cancer awareness month (CDC, 2013; Moore et al., 2015). The aforementioned strategies could potentially lead to positive social change when health professionals and educators worldwide, through coordinated efforts, work to increase awareness and health literacy that empowers not only the current study population but all populations in adopting healthier lifestyles that in turn may aid in reducing the risk, incidence, and mortality rates of obesity and cancer at the individual, community, societal, and national levels.

Conclusion

This quantitative, cross-sectional study included archival data from the NHANES III data set to determine if a significant difference existed in leptin levels among a multiethnic sample of adults with different types of cancer and those without cancer, after controlling for covariates with a known association with cancer and obesity/leptin levels through the SEM. The findings supported and refuted previous similar research. The findings revealed that significant differences exist in leptin levels among adults with different types of cancer after controlling for different covariates. This study is likely the first of its kind to take a closer look at the relationship between leptin level and obesity-associated cancer, particularly as it pertains to age, sex/gender, BMI, race/ethnicity, physical activity, SES, level of education, dietary intake, skin cancer, and occupational status.

The findings revealed that age, sex/gender, BMI, education, diabetes, and physical activity (exercise) were statistically significant in the study (RQ4). However, the findings supported and refuted previous outcomes and revealed a need for further

research. For example, although race, SES, and occupational status were relevant factors concerning the obesity/leptin level and cancer risk/incidence in previous studies, they were not statistically significant when controlled for, along with other variables in this study. This finding further indicates that more studies are necessary to have a better understanding of the relationship between leptin levels and obesity-associated cancers. Additionally, a better understanding of leptin and the role it plays in the progression of adiposity in the human body and its correlation to cancer (particularly those known to be associated with obesity/leptin) could potentially aid health professionals and educators worldwide through coordinated efforts to reduce the risk, incidence, and mortality rates of cancer through research, clinical practice, and policy changes and possibly to improve prevention efforts with lifestyle and behavior changes, thereby promoting positive social change.

References

Adler, N. E., & Newman, K. (2002). Socioeconomic disparities in health: Pathways and policies. *Health Affairs, 21*, 60–76. doi:10.1377/hlthaff.21.2.60

The Agency for Healthcare Research and Quality (AHRQ) (2013). Medical expenditure panel survey. Retrieved from https://meps.ahrq.gov

Alberg, A. J., Moorman, P. G., Crankshaw, S., Wang, F., Bandera, E. V., Barnholtz-Sloan, J. S., . . . Schildkraut, J. M. (2016). Socioeconomic status in relation to the risk of ovarian cancer in African-American women: A population-based case-control study. *American Journal of Epidemiology*, *184*, 274–283. doi:10.1093/aje/kwv450

Aleksandrova, K., Boeing, H., Jenab, M., Bueno-de-Mesquita, B., Jansen, E., Franzel, J., . . . Pichon, T. (2012). Leptin and soluble leptin receptor in risk of colorectal cancer in the European prospective investigation into cancer and nutrition cohort. *Cancer Research*, 15; 72(20):5328-37. doi: 10.1158/0008-5472.CAN-12-0465.

Alemán, M. R., Santolaria, F., Batista, N., de La Vega, M. J., González-Reimers, E., Milena, A., . . . Gómez-Sirvent, J. L. (2002). Leptin role in advanced lung cancer. A mediator of the acute phase response or a maker of the status of nutrition? *Cytokine, 19*, 21-26. doi:10.1006/cyto.2002.1051

Alexe, D., & Petridou, E. (2009). Leptin and cancer. *In Leptin, 25*, 201–223. doi:10.1007/978-0-387-31416-7_11

Al-Habil, W. (2011). Positivist and phenomenological research in American public administration. *International Journal of Public Administration, 34,* 946–953. doi:10.1080/01900692.2011.615554

Allott, E. H., Masko, E. M., & Freedland, S. J. (2012). Obesity and prostate cancer: Weighing the evidence. *European Urology*, *63*(5), 800-809. doi: 10.1016/j.eururo.2012.11.013

Al Maskari, M. Y., & Alnaqdy, A. A. (2006). Correlation between serum leptin levels, body mass index and obesity in Omanis. *Sultan Qaboos University Medical Journal*, *6*(2), 27–31.

Alshaker, H., Sacco, K., Alfraidi, A., Muhammad, A., Winkler, M., & Pchejetski, D. (2015). Leptin signaling, obesity and prostate cancer: Molecular and clinical perspective on the old dilemma. *Oncotarget, 6*, 35556–35563. doi:10.18632/oncotarget.5574

American Cancer Society. (2015a). *Breast cancer facts and figures 2015-2016*. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2015-2016.pdf

American Cancer Society. (2015b). *Does body weight affect cancer risk?* Retrieved from https://www.cancer.org/cancer/cancer-causes/diet-physical-activity/body-weight-and-cancer-risk/effects.html

American Cancer Society. (2016a). *Cancer facts and figures 2016.* Retrieved from http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf

American Cancer Society. (2016b). *Cancer facts and figures for African-Americans.* Retrieved from http://www.cancer.org/research/cancerfactsstatistics/cancer-facts-figures-for-african-americans

American Cancer Society. (2016c) S*kin cancer*. Retrieved from https://www.cancer.org/cancer/skin-cancer.html

American Cancer Society. (2016d). *Colorectal cancer risk factors*. Retrieved from https://www.cancer.org/cancer/colon-rectal-cancer/causes-risks-prevention/risk-factors.html

American Cancer Society. (2016e). *What are the risk factors for ovarian cancer?* Retrieved from http://www.cancer.org/cancer/ovariancancer/detailedguide/ovarian-cancer-risk-factors

American Cancer Society. (2016f). *Endometrial (uterine) cancer.* Retrieved from https://www.cancer.org/cancer/endometrial-cancer/about/key-statistics.html

American Cancer Society. (2016g). *Lung cancer*. Retrieved from http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics

American Cancer Society. (2016h). *Hormone therapy for prostate cancer.* Retrieved from http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-treating-hormone-therapy

American Cancer Society. (2016i). *Stay healthy*. Retrieved from http://www.cancer.org/healthy/index

American Cancer Society. (2017a). *Cancer facts and figures 2017*. Retrieved from http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-048738.pdf

American Cancer Society. (2017b). *Cancer Statistics Center*. Retrieved from. https://cancerstatisticscenter.cancer.org/#/

American Cancer Society. (2017c). *Breast cancer*. Retrieved from https://www.cancer.org/cancer/breast-cancer.html

American Cancer Society. (2017d). *Prostate cancer*. Retrieved from http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-what-is-prostate-cancer

American Cancer Society. (2017e). *Key statistics for lung cancer*. Retrieved from https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/key-statistics.html

American Cancer Society. (2018). *Cancer facts & figures 2018.* Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf

American Cancer Society. (n.d.). *Economic impact of cancer*. Retrieved from https://www.cancer.org/cancer/cancer-basics/economic-impact-of-cancer.html

American Cancer Society. (2019). *Cancer Statistics Center*. Retrieved from. https://cancerstatisticscenter.cancer.org/#/

American Diabetes Association. (2017). *Diabetes and cancer.* Retrieved from http://www.diabetes.org/are-you-at-risk/lower-your-risk/diabetes-and-cancer.html

American Institute for Cancer Research. (2014). *Obesity: Nine cancers, 335 cases daily.* Retrieved from http://www.aicr.org/cancer-research-update/2014/november_19/cru_Obesity-nine-Cancers-335-Cases-Daily.html

American Institute for Cancer Research. (2015). *The AICR 2015 cancer risk awareness survey report.* Retrieved from http://www.aicr.org/assets/docs/pdf/education/aicr-awareness-report-2015.pdf

Applied Sociology. (2017). *Applying sociology within various society levels.* Retrieved from http://www.appliedsoc.org/society/

Artac, M., & Altundag, K. (2012). Leptin and breast cancer: An overview. *Medical Oncology, 29,* 1510–1514. doi:10.1007/s12032-011-0056-0

Aschengrau, A., & Seage, G. R., III. (2008). *Essentials of epidemiology in public health* (2nd ed.). Sudbury, MA: Jones and Bartlett.

Ashizawa, N., Yahata, T., Quan, J., Adachi, S., Yoshihara, K., & Tanaka, K. (2010). Serum leptin–adiponectin ratio and endometrial cancer risk in postmenopausal female subjects. *Gynecologic Oncology, 199, (1)* 65-69. doi:10.1016/j.ygyno.2010.07.007

Assiri, A. Kamel, H., & Hassanien, M. (2015). Resistin, visfatin, adiponectin, and leptin: Risk of breast cancer in pre- and postmenopausal Saudi females and their possible

diagnostic and predictive implications as novel biomarkers. *Disease Markers*, 15 1-9. doi: 10.1155/2015/253519.

Attner, B., Landin-Olsson, M., Lithman, T., Noreen, D., & Olsson, H. (2012). Cancer among patients with diabetes, obesity and abnormal blood lipids: A population-based register study in Sweden. *Cancer Causes & Control, 23,* 769–777. doi:10.1007/s10552-012-9946-5

Azvolinsky, A. (2016). Unraveling how obesity fuels cancer. *Journal of the National Cancer Institute*, *108*(4), djw116. doi:10.1093/jnci/djw116

Babaei, Z., Moslemi, D., Parsian, H., Khafri, S., Pouramir, M., & Mosapour, A. (2015). *Relationship of obesity with serum concentrations of leptin, CRP and IL-6 in breast cancer survivors*. doi:10.1016/j.jnci.2015.09.001

Baranowski, T., Cullen, K. W., Nicklas, T., Thompson, D., & Baranowski, J. (2003). Are current health behavioral change models helpful in guiding prevention of weight gain efforts? *Obesity Research, 11*(Suppl.), 23S-43S. doi:10.1038/oby.2003.222

Barrington, W. E., Schenk, J. M., Etzioni, R., Arnold, K. B., Neuhouser, M. L., Thompson, I. M., . . . Kristal, A. R. (2015). Difference in association of obesity with prostate cancer risk between US African American and Non-Hispanic White men in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA Oncology, 1*, 342–349. doi:10.1001/jamaoncol.2015.0513

Bartlett, J. E., Kotrlik, J. W., and Higgins, C. C. (2001). Organizational Research: Determining Appropriate Sample Size in Survey Research. Information Technology, *Learning, and Performance Journal*, 19(1), 43-50. 2001.

Bologna, M., Patrizia S., Vicentini C., & Angelucci A. (2013). *Aging influences the value of serum leptin as prostate cancer risk factor.* Retrieved from http://www.touchoncology.com/articles/aging-influences-value-serum-leptin-prostate-cancer-risk-factor

Bonnet, M., Delavaud, C., Laud, K., Gourdou, I., Leroux, C., Djiane, J., & Chilliard, Y. (2002). Mammary leptin synthesis, milk leptin and their putative physiological roles. *Reproduction Nutrition Development, 42*, 399–413. doi: 10.1051/rudL2002034

Boucher, J., Boudreau, A., Ahmed, S., & Atlas, E. (2015). In vitro effects of bisphenol A B-D-Glucuronide (BPA-G) on adipogenesis in human and murine preadipocytes. *Environmental Health Perspective*: Dec;123(12):1287-93. doi: 10.1289/ehp.1409143.

Brandon, E. L., Gu, J. W., Cantwell, L., He, Z., Wallace, G., & Hall, J. E. (2009). Obesity promotes melanoma tumor growth: role of leptin. *Cancer biology & therapy*, *8*(19), 1871-9.

Brann, D. W., Wade, M. F., Dhandapani, K. M., Mahesh, V. B., & Buchanan, C. D. (2002). Leptin and reproduction. *Steroids, 67*, 95–104.

Bravo, P. E., Morse, S., Borne, D. M., Aguilar, E. A., & Reisin, E. (2006). Leptin and hypertension in obesity. *Vascular health and risk management*, *2*(2), 163-9.

Bronfenbrenner, U. (1979). *The ecology of human development*. Cambridge, MA: Harvard University Press.

Buchanan, D. (2000) Social Epidemiology: *Health Education Research*, 18, (3), 404-407, https://doi.org/10.1093/her/cyg020

Burke, N. J., Joseph, G., Pasick, R. J., & Barker, J. C. (2009). Theorizing social context: Rethinking behavioral theory. *Health Education & Behavior*, *36*(50), 55S–70S. doi:10.1177/1090198109335338

Caro, J., Sinha, M., Kolaczynski, J., Zhang, P., & Considine, R. (1996). Leptin: The tale of an obesity gene. *Diabetes* 45(11): 1455-1462. https://doi.org/10.2337/diab.45.11.1455

Cavicchia, P. P., Adams, S. A., Steck, S. E., Hussey, J. R., Liu, J., Daguisé, V. G., & Hebert, J. R. (2013). Racial disparities in colorectal cancer incidence by type 2 diabetes mellitus status. *Cancer Causes & Control, 24*, 277–285. doi:10.1007/s10552-012-0095-7

Centers for Disease Control and Prevention. (2013a). *Social ecological model.* https://www.cdc.gov/cancer/nbccedp/sem.htm

Centers for Disease Control and Prevention. (2013b). United States Cancer Statistics Technical Notes 2013. Retrieved from https://www.cdc.gov/cancer/uscs/pdf/uscs-2013-technical-notes.pdf

Centers for Disease Control and Prevention. (2014a). *Chronic disease and health promotion*. Retrieved from https://www.cdc.gov/chronicdisease/index.htm

Centers for Disease Control and Prevention. (2014b). *Overweight and obesity*. Retrieved from http://www.cdc.gov/obesity/data/adult.html

Centers for Disease Control and Prevention. (2014c). *Gynecologic cancer (ovarian cancer).* Retrieved from https://www.cdc.gov/cancer/ovarian/index.htm

Centers for Disease Control and Prevention. (2014d). *Lung cancer.* Retrieved from https://www.cdc.gov/cancer/lung/basic_info/what-is-lung-cancer.htm

Centers for Disease Control and Prevention. (2015a). *About adult BMI.* Retrieved from https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html

Centers for Disease Control and Prevention. (2015b). *Basics about diabetes.* Retrieved from https://www.cdc.gov/diabetes/basics/diabetes.html

Centers for Disease Control and Prevention. (2016b). *Addressing the cancer burden at a glance.* Retrieved from http://www.cdc.gov/chronicdisease/resources/publications/aag/dcpc.htm

Centers for Disease Control and Prevention. (2016a). *Adult obesity facts.* Retrieved from https://www.cdc.gov/obesity/data/adult.html

Centers for Disease Control and Prevention. (2016c). *Cancer prevention and control.* Retrieved from http://www.cdc.gov/cancer/index.htm

Centers for Disease Control and Prevention. (2016d). *Chronic disease overview.* Retrieved from http://www.cdc.gov/chronicdisease/overview/#ref17

Centers for Disease Control and Prevention. (2016). *Expected new cancer cases and death in 2020.* Retrieved from https://www.cdc.gov/cancer/dcpc/research/articles/cancer_2020.htm

Centers for Disease Control and Prevention. (2016e). *What is breast cancer?* Retrieved from https://www.cdc.gov/cancer/breast/basic_info/what-is-breast-cancer.htm

Centers for Disease Control and Prevention. (2016f). *Basic information about breast cancer.* Retrieved from https://www.cdc.gov/cancer/breast/basic_info/index.htm

Centers for Disease Control and Prevention. (2016g). *Colorectal cancer statistics.* Retrieved from https://www.cdc.gov/cancer/colorectal/statistics/index.htm

Centers for Disease Control and Prevention. (2016h). *Lung cancer.* Retrieved from https://www.cdc.gov/cancer/lung/statistics/race.htm

Centers for Disease Control and Prevention. (2016i). *Skin cancer.* Retrieved from http://www.cdc.gov/cancer/skin/basic_info/index.htm

Centers for Disease Control and Prevention. (2016j). *Cancer prevention and control.* Retrieved from http://www.cdc.gov/cancer/

Centers for Disease Control and Prevention. (2016k). *Statistics for different kinds of cancer.* Retrieved from https://www.cdc.gov/cancer/dcpc/data/types.htm

Centers for Disease Control and Prevention, National Center for Health Statistics. (2015). *National health and nutrition examination survey.* Retrieved from http://www.cdc.gov/nchs/nhanes/nhanes3.htm

Chen, C., Chang, Y., & Lan, M. (2014). Leptin stimulates ovarian cancer cell growth inhibits apoptosis by increasing cyclin D1 and Mcl-1 expression via the activation of the MEK/ERK1/2 and Pi3K/Akt signaling pathways. *International Journal of Oncology* 42(3):1113-9. doi: 10.3892/ijo.2013.1789.

Chen, D., Chung, Y., Yeh, Y, Chaung, H., Kuo, F., Fu, O., . . . Yuan, S. (2006a). Serum adiponectin and leptin levels in Taiwanese breast cancer patients. *Cancer Letters 237,* 109–114. doi: 10.1016/canlet2005.05.047

Chen, G., Qin, L., & Ye, J. (2014). Leptin levels and risk of type 2 diabetes: Gender-specific meta-analysis. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity, 15,* 134–142. doi:10.1111/obr.12088

Clegg, L., Reichman, M., Miller, B., Hankey, B., Singh, G., Lin, Y., . . . Edwards, B. (2009). Impact of socioeconomic status on cancer incidence and stage at diagnosis: selected findings from the surveillance, epidemiology, and end results: National Longitudinal Mortality Study. *Cancer Causes & Control, 20,* 417–435. doi: 10.1007/s10552-008-9256-0 Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Erlbaum.

Cohen, J. (1992). Quantitative methods in psychology: A power primer. *Psychological Bulletin, 112,* 155–159. doi:10.1037/0033-2909.112.1.155

Cohen, S., Fowke, J., Cai, Q., Buchowski, M., Signorello, L., Hargreaves, M., . . . Matthews, C. (2012). Differences in the association between serum leptin levels and body mass index in Black and White women: A report from the Southern community cohort study. doi: 10.1159/000336180

Coimbra, S., Brandão Proença, J., Santos-Silva, A., & Neuparth, M. J. (2014). Adiponectin, leptin, and chemerin in elderly patients with type 2 diabetes mellitus: A close linkage with obesity and length of the disease. *Biomed Research International*, 8 pgs, 2014. doi:10.1155/2014/701915

Considine, R. V. (2011). *Increased serum leptin indicates leptin resistance in obesity. Clinical Chemistry 57, 10* doi: 10.1373/clinchem.2011.

Crosby, R., DiClemente, R., & Salazar, L. (2006). *Research methods in health promotion.* San Francisco, CA: Jossey-Bass.

Cust, A. E., Kaaks, R., Friedenreich, C., Bonnet, F., Laville, M., Lukanova, A., . . . Riboli, E. (2007). Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. *Journal of Clinical Endocrinology and Metabolism*, *92*, 255–263. doi: 10.1210/jc.2006-1371

Cymbaluk, A., Chudecka-Glaz, A., & Rzepka-Gorska, I. (n.d.). Leptin levels in serum depending on Body Mass Index in patients with endometrial hyperplasia and cancer. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *136*, 74–77. doi: 10.1371/journal.pone.0104630

Dagogo-Jack, S. (Ed.). (2015). *Leptin and regulation to clinical applications*. London, England: Springer.

Dallal, C. M., Brinton, L. A., Bauer, D. C., Buist, D. M., Cauley, J. A., Hue, T. F., . . . Lacey, J. J. (2013). Obesity-related hormones and endometrial cancer among postmenopausal women: A nested case-control study within the B~FIT cohort. *Endocrine-Related Cancer*, *20*, 151–160. doi:10.1530/ERC-12-0229

Delgadillo Guzmán, D., Marchat Marchau, L. A., Reyes, J. L., Loera Castañeda, V., Sosa Macías, M., García Vivas, J., & Asseff, I. L. (2014). Leptin levels and nutritional status of indigenous Tepehuán and Mestizo subjects in Durango, Mexico. *Disease Markers, 2014*, 974503. doi:10.1155/2014/974503

Donnelly, L. (2015) Obesity poised to overtake smoking as key cause of cancer. Retrieved from http://www.telegraph.co.uk/news/health/news/11640373/Obesity-poised-to-overtake-smoking-as-key-cause-of-cancer.html

Doubeni, C. A., Major, J. M., Laiyemo, A. O., Schootman, M., Zauber, A. G., Hollenbeck, A. R., . . . Allison, J. (2012). Contribution of behavioral risk factors and obesity to socioeconomic differences in colorectal cancer incidence. *Journal of the National Cancer Institute, 104*, 1353–1362. doi: 10.1093/jnci/djs346

Drew, J. E. (2012). Molecular mechanisms linking adipokines to obesity-related colon cancer: Focus on leptin. *Proceedings of the Nutrition Society, 71*, 175–180. doi:10.1017/S0029665111003259

Dutta, D., Ghosh, S., Pandit, K., Mukhopadhyay, P., & Chowdhury, S. (2012). Leptin and cancer: Pathogenesis and modulation. *Indian Journal of Endocrinology and Metabolism, 16, 596-600.* doi: 10.4103/2230-8210.10557

Ellerhorst, J. , Diwan, A., Dang, S., Uffort, D, Johnson, M., Cooke, C., & Grimm, E. (2010). Promotion of melanoma growth by the metabolic hormone leptin. *Oncology reports*, *23*(4), 901-7.

Enroth, L., Raitanen, J., Hervonen, A., Lehtimäki, T., Jylhävä, J., Hurme, M., & Jylhä, M. (2016). Cardiometabolic and inflammatory biomarkers as mediators between educational attainment and functioning at the age of 90 years. *Journals of Gerontology Series A: Biological Sciences & Medical Sciences, 71*, 412–419. doi:10.1093/gerona/glv105

Farag, A., Elnaidany, N., & El-Dien, M. (2016). Immunohistochemical Expression of Leptin in Non Melanoma Skin Cancer. *Journal of clinical and diagnostic research: JCDR*, *10*(8), WC08-12. doi: 10.7860/JCDR/2016/19755.8385

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2007). G*3 Power: A flexible statistical power analysis for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*, 175–191. doi:10.3758/BF03193146

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*power 3.1: Tests for correlation and regression analyses. Behavior research methods, *41*, 1149–1160. doi:10.3758/brm.41.4.1149

Frankfort-Nachmias, C., & Nachmias, D. (2008). *Research methods in the social sciences* (7th ed.). New York, NY: Worth.

Freedland, S. J., & Platz, E. A. (2007). Obesity and prostate cancer: Making sense out apparently conflicting data. Epidemiologic Reviews 2007; 29:88-97. doi: 10.1093/epirev/mxm006

Frezza, E. E., Wachtel, M. S., & Chiriva-Internati, M. (2005). Influence of obesity on the risk of developing colon cancer. *Gut*, 55, 285–291. doi:10.1136/gut.2005.073163

Gallagher, E., & LeRoith, D. (2015). Obesity and diabetes: The increased risk of cancer and cancer-related mortality. *Physiological Reviews*, *95*, 727–748. doi: 10.1152/physrev.00030.2014.

Garofalo, C., & Surmacz, E. (2006). Leptin and cancer. *J. Cell. Physiology. 207*, 12–22. doi:10.1002/jcp.20472

Gialamas, S. P., Sergentanis, T. N., Antonopoulos, C. N., Dessypris, N., Chrousos, G. P., & Petridou, E. Th. (2013). Circulating leptin levels and risk of colorectal cancer and adenoma: A case-control study and meta-analysis. *Cancer Causes Control, 24*, 2129–2141. doi:10.1007/s10552-013-0290-1

Glanz, K., Rimer, B. K., & Viswanath, K. (Eds.). (2008). Health behavior and health education: Theory, research, and practice (4th ed.). San Francisco, CA, US: Jossey-Bass.

Gogas, H., Trakatelli, M., Dessypris, N., Terzidis, A., Katsambas, G., Chrousos, P., & Petridou, E. (2007). *Melanoma risk in association with serum leptin levels and lifestyle parameters: A case-control study.* Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17925285

Gong, T.-T., Wu, Q.-J., Wang, Y.-L. & Ma, X.-X. (2015), Circulating adiponectin, leptin and adiponectin–leptin ratio and endometrial cancer risk: Evidence from a meta-analysis of epidemiologic studies. *International Journal of Cancer*, *137*, 1967–1978. doi:10.1002/ijc.29561

Gonzalez-Campoy, J. M. (2016). *Obesity in America: A growing concern.* Retrieved from http://www.endocrineweb.com/conditions/obesity/obesity-america-growing-concern

Goumenou, A., Matalliotakis, I., Koumantakis, G., & Panidis, D. (2003). The role of leptin in fertility. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 106*, 118–124. doi: https://doi.org/10.1016/S0301-2115(02)00359-7

Grabowski, J. P., Markowska, A., & Markowska, J. (2014). Evaluation of leptin serum concentrations during surgery and first-line chemotherapy in primary epithelial ovarian cancer patients. *Contemporary Oncology, 18*, 318–322. doi:10.5114/wo.2014.46323

Gulen, S., Karadag, F., Karul, A., Kilicarslan, N., Ceylan, E., Kuman, N. K., & Cildaq, O. (2012). Adipokines and systemic inflammation in weight-losing lung cancer patients. Lung. 2012 Jun; 190 (3):327-32. doi: 10.1007/s00408-011-9364-6.

Gunnars, K., (2017). Leptin and leptin resistance: everything you need to know. Retrieved from https://authoritynutrition.com/leptin-101/

Gupta, A., Herman, Y., Ayers, C., Beg, M. S., Lakoski, S. G., Abdullah, S. M., Johnson, D. H., … Neeland, I. J. (2016). Plasma Leptin Levels and Risk of Incident Cancer: Results from the Dallas Heart Study. *PloS one, 11*(9), e0162845. doi:10.1371/journal.pone.0162845

Han, C., Zhang, H., Du, L., Liu, X., Jing, J., et al. (2005). Serum levels of leptin, insulin, and lipids in relation to breast cancer in China. *Endocrine, 26,* 19–24. https://doi.org/10.1385/ENDO:26:1:019

Harding, J., Shaw, J., Peeters, A., Cartensen, B., & Magliano, D. (n.d.). Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. *Diabetes Care, 38,* 264–270. doi: 10.2337/dc14-1996.

Hardwick, J., Van den Brink, G., Offerhaus, G., Van Deventer, S., & Peppelenbosch, M. (2001). Leptin is a growth factor for colonic epithelial cells. *Gastroenterology. 121*, 79–90. doi:10.1053/gast.2001.25490

Hastert, T. A., Beresford, S. A., Sheppard, L., & White, E. (2015). Disparities in cancer incidence and mortality by area-level socioeconomic status: a multilevel analysis. *Journal of Epidemiology and Community Health, 69,* 168–176. doi:10.1136/jech-2014-204417

Havel, P. J., Kasim-Karakas, S., Dubuc, G. R., Mueller, W., & Phinney, S. D. (1996). *Gender differences in plasma leptin concentrations*. National Medicine *2,* 949–950.

Herndon, J., Kornblith, A., Holland, J., & Paskett, E. (2011). Effect of socioeconomic status as measured by education level on survival in breast cancer clinical trials. *Psycho-Oncology, 22,* 315–323. doi:10.1002/pon.2094

Heron, M., & Anderson, R. N. (2016). *Changes in the leading cause of death: Recent patterns in heart disease and cancer mortality* (NCHS data brief, no 254). Hyattsville, MD: National Center for Health Statistics.

Ho, G., Wang, T., Gunter, M., Strickler, H., Cushman, M., Kaplan, R., . . . Rohan, T. (2012). Adipokines linking obesity with colorectal cancer risk in postmenopausal women. Cancer Research. 72(12), 3029-37. doi: 10.1158/0008-5472

Hopkins, B. D., Goncalves, M. D., & Cantley, L. C. (2016). Obesity and cancer mechanisms: Cancer metabolism. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27903152

Hsieh, S., Chiou, W., Wang, M., & Lin, J. (2014). Association of body weight with the risk for malignancies in hospitalized patients with or without diabetes mellitus in Taiwan. *Journal of Investigative Medicine, 62,* 37–42. doi:10.2310/JIM.0000000000000004

Hsing, A., Chua, S., Jr., Yu-Tang, G., Gentzschein, E., Chang, L., Deng, J., . . . Gao, Y. (2001). Prostate cancer risk and serum levels of insulin and leptin: a population-based study. *Journal of National Cancer Institute.* 16;93(10):783-9.

Hystad, P., Carpiano, R. M., Demers, P. A., Johnson, K. C., & Brauer, M. (2013). Neighbourhood socioeconomic status and individual lung cancer risk: Evaluating long-term exposure measures and mediating mechanisms. *Social Science & Medicine, 97,* 95–103. doi:10.1016/j.socscimed.2013.08.005

Iles, M. M., Law, M. H., Stacey, S. N., Han, J., Fang, S., Pfeiffer, R., . . . Barrett, J. H. (2013). A variant in FTO shows association with melanoma risk not due to BMI. *Nature Genetics*, *45,* 428–432. doi:10.1038/ng.2571

Jackson, C. L., Yeh, H., Szklo, M., Hu, F. B., Wang, N., Dray-Spira, R., & Brancati, F. L. (2014). Body-mass index and all-cause mortality in us adults with and without diabetes. *Journal of General Internal Medicine, 29,* 25–33. doi:10.1007/s11606-013-2553-7

Jaffe, T., & Schwartz, B. (2008). Leptin promotes motility and invasiveness in human colon cancer cells by activating multiple signal-transduction pathways. *International Journal of Cancer. 123,* 2543–2556. doi: 10.1002/ijc.23821.

Jin, J. H., Kim, H.-J., Kim, C. Y., Kim, Y. H., Ju, W., & Kim, S. C. (2016). Association of plasma adiponectin and leptin levels with the development and progression of ovarian cancer. *Obstetrics & Gynecology Science*. 59, 279-85. doi: 10.5468/ogs.2016

Johnson, C. M., Wei, C., Ensor, J. E., Smolenski, D. J., Amos, C. I., Levin, B., & Berry, D. A. (2013). Meta-analyses of colorectal cancer risk factors. Cancer Causes & Control. 24(6):1207-22. doi: 10.1007/s10552-013-0201-5.

Joshi, R. K., Kim, W. J., & Lee, S. (2014). Association between obesity-related adipokines and colorectal cancer: A case-control study and meta-analysis. *World Journal of Gastroenterology, 20*, 7941–7949. doi:10.3748/wjg.v20.i24.7941

Jung, U., & Choi, M-S. (2014). Obesity and its metabolic complications: The role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *International Journal of Molecular Sciences, 15*, 6184–6223. doi:10.3390/ijms15046184

Kerenidi, T., Lada, M., Tsaroucha, A., Georgoulias, P., Mystridou, P., & Gourgoulianis, K. I. (2013). Clinical significance of serum adipokines levels in lung cancer. *Medical Oncology,* 2, 507. doi:10.1007/s12032-013-0507-x

Khalili, H., & Chan, A. T. (2012). Is diabetes a risk factor for colorectal cancer? *Digestive Diseases and Sciences, 57*, 1427–1429. doi:10.1007/s10620-012-2175-7

Khan, S., Shukla, S., Sinha, S., & Meeran, S. (2013). Role of adipokines and cytokines in obesity-associated breast cancer: Therapeutic targets. doi:10.1016/j.cytogfr.2013.10.001

Kimura, E., Matsumoto, K., Samori, T., Kato, S., & Kawahara, T. (2000). One-step enzyme-linked immunosorbent assay (ELISA) for measurement of serum free leptin. *Clinical Chimica Acta: International Journal of Clinical Chemistry, 296,* 45–57. doi: 10.1007/s12020-012-9788-7

Kitahara, C., Berndt, S., de Gonzalez, A., Coleman, H., Schoen, R., Hayes, R., & Huang, W. (2013). Prospective investigation of body mass index, colorectal adenoma, and colorectal cancer in the prostate, lung, colorectal, and ovarian cancer screening trial. Journal of Clinical Oncology. 31 (19) 2450-2459. doi: 10.1200/jco.2012.48.4691.

Koda, M., Sulkowska, M., Kanczuga-Koda, L., Surmacz, E., & Sulkowski, S. (2007). Overexpression of the obesity hormone leptin in human colorectal cancer. *Journal of Clinical Pathology. 60,* 902–906. doi: 10.1136/jcp.2006.041004.

Kumor, A., Daniel, P., Pietruczuk, M., & Małecka-Panas, E. (2009). Serum leptin, adiponectin, and resistin concentration in colorectal adenoma and carcinoma (CC) patients. *International Journal of Colorectal Disease*, *24,* 275–281. doi:10.1007/s00384-008-y

Lai, G. Y., Giovannucci, E. L., Pollak, M. N., Peskoe, S. B., Stampfer, M. J., Willett, W. C., & Platz, E. A. (2014). Association of C-peptide and leptin with prostate cancer incidence in the health professional's follow-up study. *Cancer Causes & Control*. 25, 625-632. doi: 10.1007/s10552-014-0369-3

Laird Statistics. (2013). *One-way ANOVA*. Retrieved from https://statistics.laerd.com/statistical-guides/one-way-anova-statistical-guide.php

Laiyemo, A. O. (2014). The risk of colonic adenomas and colonic cancer in obesity. *Best Practice & Research, 28*, 655–663. doi:10.1016/j.bpg.2014.07.007

Lee, J., Meyerhardt, J., Giovannucci, E., & Jeon, J. (2015). Association between body mass index and prognosis of colorectal cancer: a meta-analysis of prospective cohort studies. *PLOS one*, 10 (3). doi: 10.1371/journal.pone.0120706

Leuven, E., Plug, E., & Ronning, M. (2014). Education and cancer risk. Retrieved from http://ftp.iza.org/dp7956.pdf

Li, H., Stampfer, M. J., Mucci, L., Rifai, N., Qiu, W., Kurth, T., & Ma, J. (2010). *A 25-year prospective study of plasma adiponectin and leptin concentrations and prostate cancer risk and survival. Clinical Chemistry.* 56, 34-43. doi: 10.1373/clinchem.2009.133272

Li, W.-Q., Cho, E., Weinstock, M., Mashfiq, H., & Qureshi, A. (2016). *Epidemiological assessments of skin outcomes in the nurses' health studies. American Journal of Public Health.* 106, 1677-83. doi: 10.2105/AJPH.2016303315

Lilja, M., Rolandsson, O., Norberg, M., & Soderberg, S. (2012). The impact of leptin and adiponectin on incident type 2 diabetes is modified by sex and insulin resistance. *Metabolic Syndrome Related Disorders,* 10, 143–151. doi:10.1089/met.2011.0123

Liss, D. T., & Baker, D. W. (2014). Understanding current racial/ethnic disparities in colorectal cancer screening in the united states: the contribution of socioeconomic status and access to care. *American Journal of Preventive Medicine*, *46*, 228–236. doi:10.1016/j.amepre.2013.10.023

Luhn, P., Dallal, C. M., Weiss, J. M., Black, A., Huang, W., Lacey, J. J., . . . Brinton, L. A. (2013). Circulating adipokine levels and endometrial cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiology, Biomarkers & Prevention*, 22, 1304–1312. doi:10.1158/1055-9965.EPI-13-0258

Ma, Y., Liu, Z., Zhang, Y., & Lu, B. (2013). Serum leptin, adiponectin and endometrial cancer risk in Chinese women. *Journal of Gynecologic Oncology,* 24, 336–341. doi: 10.3802/jgo.2013.24.4.336

Martinez-Useros, J., & Garcia-Foncillas, J. (2016). Obesity and colorectal cancer: Molecular features of adipose tissue. *Portuguese Journal of Cardiology.* 31, 711-719. doi: 10.1016/j.repc.2012.08.002

Martins, M., Faleiro, L., & Fonseca, A. (2012). Relationship between leptin and body mass and metabolic syndrome in an adult population. *Journal of the Portuguese Society of Cardiology*. 31, 711-9. doi: 10.1016/j.repc.2012.08.002

McLeroy, K. R., Bibeau, D., Steckler, A., & Glanz, K. (1988). An ecological perspective on health promotion programs. *Health Education Quarterly, 15*, 351–377. doi: 10.1177/109019818801500401

Medicine Net. (2016). Hematopoiesis definition. Retrieved from https://www.medicinenet.com/script/main/art.asp?articlekey=19775#pregnancy_definition_and_facts

Mohammadzadeh, G., & Zarghami, N. (2013). Serum leptin level is reduced in non-obese subjects with type 2 diabetes. *International Journal of Endocrinology and Metabolism,* 11, 3–10. doi:10.5812/ijem.6535

Monalisa, R. (2015). Role of leptin in obesity. *Research Journal of Pharmacy and Technology, 8,* 1073–1076. doi: 10.5958/0974-360X.2015.00185.7

Moore, A. R., Buchanan, N. D., Fairley, T. L., & Smith, J. L. (2015). Public health action model for cancer survivorship. *American Journal of Preventive Medicine, 49,* S470–S476. doi:10.1016/j.amepre.2015.09.001

Münzberg, H., & Heymsfield, S. B. (2015). Leptin, obesity, and leptin resistance. In S. Dagogo-Jack (Eds.), *Leptin* (pp. 643-651). New York, NY: Springer.

Murphy, N., Cross, A., Abubakar, M., Jenab, M., Aleksandrova, K., Boutron-Ruault, C., . . . Gunter, M. (2016). A nested cases-control study of metabolically defined body size phenotypes and risk of colorectal cancer in the European prospective investigation into cancer and nutrition (EPIC). *PLOS Medicine*. (13) 4, doi: 10.1371/journal.pmed.1001988

Mutschler, J., Abbruzzese, E., Wiedemann, K., Von, D. G., Dinter, C., Mobascher, A., . . . Kiefer, F. (2013). Functional polymorphism in the neuropeptide Y gene promoter (rs16147) is associated with serum leptin levels and waist-hip ratio in women. *Annals of Nutrition & Metabolism, 62*(4), 271–276. doi:10.1159/000346799

Nakajima, T. E., Yamada, Y., Hamano, T., Furuta, K., Matsuda, T., Fujita, S., . . . Shimada, Y. (2010). Adipocytokines as new promising markers of colorectal

tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. *Cancer Science,* 101, 1286–1291. doi:10.1111/j.1349-7006.2010.01518.x

National Cancer Institute. (2011). *Cancer costs projected to reach at least $158 billion in 2020.* Retrieved from http://www.cancer.gov/news-events/press-releases/2011/costcancer2020

National Cancer Institute. (2012). *Obesity and cancer.* Retrieved from https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/obesity-fact-sheet

National Cancer Institute. (2016a). Cancer prevention overview (pdq)-patient version. Retrieved from https://www.cancer.gov/about-cancer/causes-prevention/patient-prevention-overview-pdq#section/_199

National Cancer Institute. (2016). *Understanding cancer.* Retrieved from https://www.cancer.gov/about-cancer/understanding/statistics

National Center for Biotechnology Information. (2016). *LCN2 lipocalin 2 [Homo sapiens (human)]*. Retrieved from https://www.ncbi.nlm.nih.gov/gene/3934

National Center for Health Statistics. (1996a). *Analytic and reporting guidelines: The Third National Health and Nutrition Examination Survey, NHANES III (1988-94).* Retrieved from https://www.cdc.gov/nchs/data/nhanes/nhanes3/nh3gui.pdf

National Center for Health Statistics. (1996b). *NHANES III household adult data file documentation. Ages 17+*. Retrieved from https://wwwn.cdc.gov/Nchs/Data/Nhanes3/1A/ADULT-acc.pdf

National Center for Health Statistics. (2002). *Third National Health and Nutrition Examination Survey, 1988-1994, NHANES III serum leptin data file (Series 11, No. 12A).* Retrieved from https://wwwn.cdc.gov/nchs/nhanes/nhanes3/datafiles.aspx

National Health and Nutrition Examination Survey. (2015). NCHS research ethics review board (ERB) approval. Retrieved from https://www.cdc.gov/nchs/nhanes/irba98.htm

National Institutes of Health. (n.d.). *Classification of overweight and obesity by BMI, waist circumference, and associated disease risks*. Retrieved from https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm

Nead, K. T., Sharp, S. J., Thompson, D. J., Painter, J. N., Savage, D. B., Semple, R. K., . . . Wareham, N. J. (2015). Evidence of a causal association between insulinemia and endometrial Cancer: a mendelian randomization analysis. *Journal of the National Cancer Institute, 107*(9), 1–7. doi:10.1093/jnci/djv178

Neuman, W. L. (2000). Social research methods: qualitative and quantitative approaches (4th ed.). Boston, MA: Allyn & Bacon.

Neville, M. C., McFadden, T. B., & Forsyth, I. (2002). Hormonal regulation of mammary differentiation and milk secretion. *Journal of Mammary Gland Biology and Neoplasia, 7,* 49–66. https://link.springer.com/journal/10911

Niu, J., Jiang, L., Guo, W., Shao, L., Liu, Y., & Wang, L. (2013). Association between leptin level and breast cancer: A meta-analysis. *Plos ONE, 8*(6), 1–8. doi:10.1371/journal.pone.0067349

Obesity Society. (2015). *Cancer and obesity.* Retrieved from https://www.obesity.org/

Office of Minority Health. (2016). *African American profile.* Retrieved from http://www.minorityhealth.hhs.gov/templates/browse.aspx?lvl=2&lvlID=51

Office of Disease and Health Promotion. (2014). Cancer. Retrieved from https://www.healthypeople.gov/2020/topics-objectives/topic/cancer

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2013). *Prevalence of obesity among adults: United States, 2011-2012.* Retrieved from http://www.cdc.gov/nchs/data/databriefs/db131.htm

Ogunwobi, O. (2015). Leptin, cell cycle, and cancer. In S. Dagogo-Jack (Ed.), *Leptin*: *Regulation and clinical applications* (pp. 1-299). doi:10.1007/978-3-319-09915-6

Ohio Department of Health and Human Services. (2015). Non-modifiable, modifiable and environmental risk factors for cancer. Retrieved from https://odh.ohio.gov/

Ollberding, N. J., Kim, Y., Shvetsov, Y. B., Wilkens, L. R., Franke, A. A., Cooney, R. V., . . . Goodman, M. T. (2013). Prediagnostic leptin, adiponectin, c-reactive protein, and the risk of postmenopausal breast cancer. Cancer Prevention Research. 3, 188-195. doi: 10.1158/1940-6207.CAPR-12-0374

Pais, R., Silaghi, H., Silaghi, A., Rusu, M., & Dumitrascu, D. (2009). Metabolic syndrome and risk of subsequent colorectal cancer. *World Journal of Gastroenterology.* 41, 5141-5148. doi: 10.3748/wjg.15.5141

Papageorgiou, G., Papakonstatinou, A., Mamplekou, E., Terzis, I., & Melissas, J. (2002). Pre- and postoperative psychological characteristics in morbidly obese patients. *Obesity Surgery, 12,* 534–553. doi:10.1381/096089202762252307

Parise, C. A., & Caggiano, V. (2013). Disparities in race/ethnicity and socioeconomic status: risk of mortality of breast cancer patients in the California Cancer Registry, 2000-2010. *BMC Cancer,* 13, 449. doi:10.1186/1471-2407-13-449

Paz-Filho, G., Lim, E., Wong, M. L., & Licinio, J. (2011). *Associations between adipokines and obesity-related cancer. Frontiers in Bioscience*. 16, 1634-1650.

Petridou, E., Belechri, M., Dessypris, N., Koukoulomatis, P., Diakomanolis, E., Spanos, E., & Trichopoulos, D. (2002). Leptin and body mass index in relation to endometrial cancer risk. *Annals of Nutrition & Metabolism, 46*, 147–151. doi: 10.1159/000063081

Petridou, E., Mantzoros, C., Dessypris, N., Koukoulomatis, P., Addy, C., Voulgaris, Z., & ... Trichopoulos, D. (2003). Plasma adiponectin concentrations in relation to endometrial cancer: a case-control study in Greece. *Journal of Clinical Endocrinology and Metabolism, 88*, 993–997. doi: 10.1210/jc.2002-021209

Pothiawala, S., Qureshi, A., Yunhui, L., & Han, J. (2012). Obesity and the incidence of skin cancer US Caucasians. *Cancer Causes & Control*. 23, 717-726. doi: 10.007/s10552-012-9941-x

Præstegaard, C., Kjær, S. K., Christensen, J., Tjønneland, A., Halkjær, J., & Jensen, A. (2015). Obesity and risks for malignant melanoma and non-melanoma skin cancer: Results from a large Danish prospective cohort study. *Journal of Investigative Dermatology*, *135*, 901–904. doi:10.1038/jid.2014.438

Quest Diagnostics. (2017). *Leptin*. Retrieved from http://www.questdiagnostics.com /testcenter/BUOrderInfo.action?tc=90367&labCode=SJC

Quest Diagnostics. (n.d.). *Leptin 37109x.* Retrieved https://www.questdiagnostics.com/hcp/intguide/EndoMetab/EndoManual_AtoZ_PDFs/Leptin.pdf

Rajkovic, N., Zamaklar, M., Lalic, K., Jotic, A., Lukic, L., Milicic, T., . . . Lalic, N. (2014). Relationship between obesity, adipocytokines and inflammatory markers in Type 2 diabetes: Relevance for cardiovascular risk prevention. *International Journal of Environmental Research and Public Health, 11*, 4049–4065. doi: 10.3990/ijerph1104049

Rametta, S., Grosso, G., Galvano, F., Mistretta, A., Marventano, S., Nolfo, F., . . . Biondi, A. (2013). Social disparities, health risk behaviors, and cancer. *BMC Surgery, 13* Suppl 2S17. doi:10.1186/1471-2482-13-S2-S17

Redding, C. A., Rossi, J. S., Rossi, S. R., Velicer, W. F., & Prochaska, J. O. (2000). Health behavior models. *International Electronic Journal of Health Education, 3,* 180–193. Retrieved from https://pdfs.semanticscholar.org/5913/74764a22b4a570906662948e3da0294c03a9.pdf

Ren, J. (2004). Leptin and hyperleptinemia – from friend to foe for cardiovascular function. *Journal of Endocrinology*. 181, 1-10. doi: 10.002-0795/04/0181-001

Renehan, A., Tyson, M., Egger, M., Heller, R., & Zwahlen, M., (2008). Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. *Lancet*. 371, 569-78. doi: 10.1016/S0140-6736(08)60269-X

Riondino, S., Roselli, M., Palmirotta, R., Della-Morte, D., Ferroni, P., & Fiorella, G. (2014). Obesity and colorectal cancer: role of adipokines in tumor initiation and progression. *World Journal of Gastroenterology, 20, 5177-5190.* doi: 10.3478/wjg.v20.18.5177

Rodriguez, A., Mastronardi, C., & Paz-Filho, G. (2013). Leptin as a risk factor for the development of colorectal cancer. *Translational Gastrointestinal Cancer* 2, 4 doi: 10.3978/j.issn.2224-4778.2013.10.04

Romero-Figueroa, M., Garduno-Garcia, J., Duarte-Mote, J., Matute-Gonzalez, G., Gomez-Villanueva, A., & De la Cruz-Vargas, J. (n.d.). Insulin and leptin levels in obese patients with and without breast cancer. *Clinical Breast Cancer, 13*, 482–485. doi:10.1016/j.clbc.2013.08.001

Rosenbaum, M., Nicolson, M., Hirsch, J., Heymsfield, S. B., Gallagher, D., Chu, F., & Leibel., R. L. (1996). Effects of gender, body composition, and menopause on plasma concentration of leptin. *Journal of Clinical Endocrinology & Metabolism, 81*, 3424–3427. doi: 10.1210/jcem.81.9.8784109

Saito, E., Charvat, H., Goto, A., Matsuda, T., Noda, M., Sasazuki, S., & Inoue, M. (2016). Burden of cancer associated with type 2 diabetes mellitus in Japan, 2010-2030. *Cancer Science, 107*, 521–527. doi:10.1111/cas.12902

Sallis J. F., & Owen N. (2008). Ecological model of health behavior. In K. Glanz, B. K. Rimer, F. M. Lewis (Eds.), *Health behavior and health education.* 3rd Edition, Jossey-Bass, San Francisco, 462-464.

Saxena, N., & Sharma, D. (2013). Multifaceted leptin network: the molecular connection between obesity and breast cancer. *Journal of Mammary Gland Biology and Neoplasia.* 18, 309-320. doi: 10.007/s10911-013-9308-2

Sharp, L., Donnelly, D., Hegarty, A., Carsin, A., Deady, S., McCluskey, N., . . . Comber, H. (2014). Risk of several cancers is higher in urban areas after adjusting for socioeconomic status: Results from a two-country population-based study of 18 common cancers. *Journal of Urban Health, 91,* 510–525. doi:10.1007/s11524-013-9846-3

Shavers, V. L. (2007). Measurement of socioeconomic status in health disparities research. *Journal of the National Medical Association, 99,* 1013–1023.

Sheesley, A. P. (2016). Counselors within the chronic care model: Supporting weight management. *Journal of Counseling and Development*. 94, 234-245, doi: 10.1002/jcad.12079

Shirakami, Y., Ohnishi, M., Sakai, H., Tanaka, T., & Shimizu, M. (2017). Prevention of colorectal cancer by targeting obesity-related disorders and inflammation. *International Journal of Molecular Science.* 18 (5). doi: 10.3390/ijms18050908**.**

Smith, L., Brinton, L., Spitz, M., Lam, T., Park, Y, . . . Gierach, G. (2012). *Body mass index and risk of lung cancer among never, former, and current smokers. Journal National Cancer Institute.* 10, 778-789. doi: 10.1093/jnci/djs179

Society for Endocrinology. (2014). Leptin. Retrieved from http://www.yourhormones.info/hormones/leptin/

Song, C., Liao, J., Deng, Z., Zhang, J., Xue, H., Li, Y., Liang, C, … Yan, G. (2013). *Is leptin a predictive factor in patients with lung cancer? Oncotarget.* 12, 19699-19711. doi:10.18632/oncotarget.14963

Song, M., Zhang X., Wu, K., Ogino, S., Fuchs, C., Giovannucci, E., et al. (2013). Plasma adiponectin and soluble leptin receptor and risk of colorectal cancer: A prospective study. *Cancer Prevention Research, 6,* 875–885. doi:10.1158/1940-6207.CAPR-13-0169

Sorensen, H. T., Sabroe, S., & Olsen, J. (1996). A framework for evaluation of secondary data sources for epidemiological research. *International Journal of Epidemiology, 25*, 435–442. doi:10.1093/ije/25.2.435

State of Obesity. (2017). *Fast facts on the state of obesity in America*. Retrieved from https://stateofobesity.org/fastfacts/

Statistics Solutions. (2013). Data analysis plan: One-way ANCOVA. Retrieved from http://www.statisticssolutions.com/academic-solutions/member-resources/member-profile/data-analysis-plan-templates/data-plan-plan-one-way-ancova/

Stattin, P., Kaaks, R., Johansson, R., Gislefoss, R., Soderberg, S., Alfthan, H., Stenman, U., . . . Olsson, T. (2003). Plasma leptin is not associated with prostate cancer risk. Cancer Epidemiology Biomarkers & Prevention, *12*, 474-475

Stattin, P., Lukanova, A., Biessy, C., Söderberg, S., Palmqvist, R., Kaaks, R., . . . Jellum, E. (2004). Obesity and colon cancer: Does leptin provide a link? *International Journal of Cancer, 109*, 149–152. doi:10.1002/ijc.11668

Stattin, P., Palmqvist, R., Soderberg, S., Biessy, C., Ardnor, B., Hallmans, G., . . . Olsson, T. (2003). Plasma leptin and colorectal cancer risk: A prospective study in Northern Sweden. *Oncology Reports*, *10*, 2015–2021. doi: 10.3892/or10.62015

Stokols, D. (1996). Translating social ecological theory into guidelines for community health promotion. *American Journal of Health Promotion, 10*(4), 282–298. doi:10.4278/0890-1171-10.4.282

Szablewski, L. (2014). Diabetes mellitus: Influences on cancer risk. *Diabetes Metabolism Research and Reviews*, *30*, 543–553. doi:10.1002/dmrr.2573

Tamakoshi, K., Toyoshima, H., Wakai, K., Kojima, M., Suzuki, K., Watanabe, Y., . . . Tamakoshi, A. (2005*).* Leptin is associated with an increased female colorectal cancer risk: A nested case-control study in Japan. *Oncology, 68*, 454–461. doi:10.1159/000086988

Tang, J. Y., Henderson, M. T., Hernandez-Boussard, T., Kubo, J., Desai, M., Sims, S. T., . . . Stefanick, M. L. (2013). Lower skin cancer risk in women with higher body mass index: The women's health initiative observational study. *Cancer Epidemiology, Biomarkers & Prevention*, *22*, 2412–2415. doi:10.1158/1055-9965.EPI-13-0647

Techopedia. (n.d.). Statistical package for the social sciences. Retrieved from https://www.techopedia.com/definition/12401/statistical-package-for-the-social-sciences-spss

Terzidis, A., Sergentanis, T., Antonopoulos, G., Syrigos, C., Efremidis, A., Polyzos, A., . . . Petridou, E. (2009). Elevated serum leptin levels: A risk factor non-small-cell lung cancer? Oncology. *76*, 19-25. doi: 10.1159/000177952 http://www.ncbi.nlm.nih.gov/pubmed/19033693

Tessitore, L., Vizio, B., Jenkins, O., De Stefano, I., Ritossa, C., Argiles, J., . . . Mussa, A. (2000). Leptin expression in colorectal and breast cancer patients. *International Journal of Molecular Medicine, 5,* 421–426. doi: https://doi.org/10.3892/ijmm.5.4.421

Tewari, R., Rajender, S., Natu, S., Goel, A., Dalela, D., Goel., M., & Tondon, P. (2013). Significance of obesity markers and adipocytokines in high grade and high stage prostate cancer in north indian men. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23669251

Tilg, H., & Moschen, A. R. (2014). Mechanisms behind the link between obesity and gastrointestinal cancers: Best practice & research. *Clinical Gastroenterology, 28*, 599–610. doi:10.1016/j.bpg.2014.07.006

Trust for America's Health. (2017). State of obesity. Retrieved from https://stateofobesity.org/files/stateofobesity2017.pdf

University of Michigan. (2016). *Center for managing chronic disease.* Retrieved from https://cmcd.sph.umich.edu/about/about-chronic-disease/

USC Libraries. (n.d.) *Organizing your social sciences research paper: limitations of the study.* Retrieved from http://libguides.usc.edu/writingguide/limitations

U.S. Census Bureau, Population Division, Fertility & Family Statistics Branch. (2004). *Current population survey: Definitions and explanations.* Retrieved from http://www.census.gov/population/www/cps/cpsdef.html

U.S. Department of Health and Human Services. (n.d.). *Your rights under HIPAA.* Retrieved from http://www.hhs.gov/hipaa/for-individuals/guidance-materials-for-consumers/index.html

U.S. Department of Health and Human Services, National Center for Health Statistics. (1996). *Third national health and nutrition examination survey, 1988-1994, NHANES III examination data file* [CD-ROM]. Retrieved from https://wwwn.cdc.gov/nchs/data/nhanes3/1a/exam-acc.pdf

U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. (2003). Theory at a glance: A guide for health promotion practice. Retrieved from http://www.sbccimplementationkits.org/demandrmnch/wp-content/uploads/2014/02/Theory-at-a-Glance-A-Guide-For-Health-Promotion-Practice.pdf

Vona-Davis, L., & Rose, D. (2007). Adipokines as endocrine, paracrine, and autocrine factors in breast cancer risk and progression. Endocrine Related Cancer. 14, 189-206. doi: https://doi.org/10.1677/ERC-06-0068

Walker, J. J., Brewster, D. H., Colhoun, H. M., Fischbacher, C. M., Leese, G. P., Lindsay, R. S., . . . Wild, S. H. (2013). Type 2 diabetes, socioeconomic status and risk of cancer in Scotland 2001-2007. *Diabetologia, 56*, 1712–1715. doi:10.1007/s00125-013-2937-6

Wang, D., Gao, L., Gong, K., Chai, Q., & Wang, G. (2016). Increased serum leptin level in overweight patients with colon carcinoma: A cross-sectional and prospective study. *Molecular and Clinical Oncology, 6*, 75–78. doi: 10.3892/mco.2016.1087

Wang, P. P., He, X. Y., Wang, R., Wang, Z., & Wang, Y. G. (2014). High leptin level is an independent risk factor of endometrial cancer: a meta-analysis. *Cellular Physiological Biochemistry, 34,* 1377–1484. doi:10.1159/000366352

Wang, Y., & Beydoun, M. A. (2007). The obesity epidemic in the United States—Gender, age, socioeconomic, racial/ethnic, and geographic characteristics: A systematic review and meta-regression analysis. *Epidemiologic Reviews, 29*, 6–28. doi:10.1093/epirev/mxm007

Wauters, M., Considine, R. V., & Van Gaal, L. F. (2000). Human leptin: From an adipocyte hormone to an endocrine mediator. *European Journal of Endocrinology/European Federation of Endocrine Societies, 143,* 293–311. https://doi.org/10.1530/EJE.0.1430293

Weir H. K., Anderson R. N., Coleman King, S. M., Soman, A., Thompson, T. D., Hong, Y., . . . Ledbetter, M. S. (2016). Heart disease and cancer deaths-trends and projections in the United States, 1969-2020. *Preventing Chronic Disorder, 13,* 160–211. doi:10.5888/pcd13.160211

Whitley, E., & Ball, J. (2002). Statistics review 4: sample size calculations. *Critical care (London, England)*, *6*(4), 335–341.

Whittemore, R., Melkus, G., & Grey, M. (2004). Applying the social ecological theory to type 2 diabetes prevention and management. *Journal of Community Health Nursing, 21*(2), 87–99. doi:10.1207/s15327655jchn2102_03

World Health Organization. (2006). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of a who/idf consultation. Retrieved from http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf

World Health Organization. (2017). *Obesity and overweight fact sheet.* Retrieved from http://www.who.int/mediacentre/factsheets/fs311/en/

World Health Organization. (n.d.). *Obesity.* Retrieved from http://www.who.int/topics/obesity/en/

Wu, M., Chen, H., You, S., Cheng, W., Chen, C., Chen, C., . . . Chen, C. (2014) *A prospective study of gynecological cancer risk in relation to adiposity factors: cumulative incidence and association with plasma adipokine levels. PLOS One.* 8: doi:10.1371/journal.pone.0104630

Wu, W-H., Chou, Y-C., Chou, W-C., Hsu, G-C., Chu, C-H., Yu, C-P., . . . Sun, C-A. (2009). Circulating levels of leptin, adiposity and breast cancer risk. *British Journal of Cancer.* 4: 578-82. doi: 10.1038/sj.bjc.6604913

Xu, H., Fang, H., Xu, W., Qin, G., Yan, Y., Yao, B., & … Zhao, Y. (2015). Cancer incidence in patients with type 2 diabetes mellitus: A population-based cohort study in Shanghai. *BMC Cancer,* 15: 151–158. doi:10.1186/s12885-015-1887-4

Yang, Y., Dong, J., Sun, K., Zhao, L., Zhao, F., Wang, L., & Jiao, Y. (2012). Obesity and incidence of lung cancer: A meta-analysis. *International Journal of Cancer*. 132 (5), 1162-9. doi:10.1002/ijc.27719

Yeung, C-Y., Tso, A. W-K., Xu, A., Wang, Y., Woo, Y-C., Lam, T-H., . . . Lam, K. S-L. (2013). Pro-inflammatory adipokines as predictors of incident cancers in a Chinese cohort of low obesity prevalence in Hong Kong. *PLoS ONE, 8*(10), e78594. doi:10.1371/journal.pone.0078594

Yuan, S. F., Tsai, K., Chung, Y., Chan, T., Yeh, Y., Tsai, L., & Su, J. (2004). Aberrant expression and possible involvement of the leptin receptor in endometrial cancer. *Gynecologic Oncology, 92*, 769–775. doi: 10.1136/jcp.2005.035477

Zhang, P., Chen, Z., Lv, D., Xu, Y., Gu, W., Zhang, X., . . . Zhu, Y. (2012). Increased risk of cancer in patients with type 2 diabetes mellitus: A retrospective cohort study in china. *BMC Public Health, 12,* 567. doi:10.1186/1471-2458-12-567