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The Determinants of Endometrial Cancer Survival Disparities in the United States

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Walden University
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Abstract

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MA/MS, University of South Florida - College of Public Health, 2013

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Doctoral Study Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Endometrial cancer is the most common gynecologic cancer in the United States with recent trends showing a continued increase in incidence and mortality. Prognosis is influenced by cancer stage at diagnosis and differs by race/ethnicity. Researchers have documented poorer survival among Blacks than Whites diagnosed with endometrial cancer. The 5-year survival rates for women with endometrial cancer is 81%; while survival for White and Black women are 84% and 62%, respectively. There is a gap in literature examining the widening disparity in incidence and survival of women diagnosed with advanced stage disease among population subgroups across the United States. The purpose of this study was to ascertain the factors associated with endometrial cancer survival disparities in the United States. The social ecological model was utilized as a conceptual framework to guide this study. Using epidemiologic data obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results [SEER] database, the cross-sectional study included 115,997 women diagnosed with endometrial cancer between 2007 and 2016. Variables associated with the outcomes of interest were assessed using multilevel logistic regression and multilevel Cox-proportional hazards models. Multivariable analyses showed that race/ethnicity, increased age, aggressive histology, poor tumor grade, and advanced-stage disease were associated with increased risk of endometrial cancer mortality. This research provides insights into the contributing factors associated with disparities in endometrial cancer survival and can lead to positive social change by developing health programs and policies that improve the survival outcomes of women who have been diagnosed with late-stage endometrial cancer.

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Dedication

I give thanks to God for his grace throughout this journey. I want to dedicate this dissertation to my dear husband, Babatunde, my wonderful parents, and to my children, Maximillian, and Liam.

Acknowledgments

I would like to give special thanks to my committee chair, Dr. Richard C. Palmer, whose knowledge, guidance, and support made it possible for me to complete this dissertation. I truly appreciate your remarkable patience and excellent mentorship during this process; the timely responses and expert review of my work were critical to my academic progress and successful completion of this project. I would also like to thank my committee members, Dr. Nancy K. Rea and Dr. Vasileios Margaritis for your invaluable contributions, and excellent feedbacks in the review of my proposal and dissertation.

I also want to express my deepest appreciation to my family. I thank my dear husband, Babatunde, and my parents, Patrick, and Dorothy Anegbe, for their love and consistent support throughout my education. I could not have accomplished this without you. God bless you!

To all the women who have lost their lives to endometrial cancer or are currently battling this disease, it is my hope that an increased awareness of the issue may contribute to decrease the incidence and mortality of the disease both in the United States and globally.

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Section 1: Foundation of the Study and Literature Review

Introduction

Endometrial cancer survival disparities represent a significant public health problem in the United States despite several efforts at the local and national level to tackle inequalities in health care (O'Keefe et al., 2015). The number of women diagnosed with endometrial cancer has increased over the last decade, and incidence rates are projected to continue to rise (Sheikh et al., 2014). Based on National Cancer Institute (NCI) 2010–2016 cancer statistics, endometrial cancer accounts for 3.6% of all new cancer cases in the United States (NCI SEER, 2020). According to the Centers for Disease Control and Prevention (CDC), deaths from endometrial cancer increased by 2% each year for White and Black women from 2007 to 2014 (CDC, 2014). With prognosis strongly related to stage at diagnosis, the 5-year survival rate for all endometrial cancer cases is about 81.0% (NCI SEER, 2020).

Compared with Caucasians, African Americans in the United States are more likely to experience worse health outcomes across a range of diseases including obesity, cardiovascular diseases, diabetes, and other malignancies (Farley et al., 2007; Onstad et al., 2016; Randall & Armstrong, 2003; Ruterbusch et al., 2014). The same holds true for gynecologic cancers; several studies have documented that African American women report higher rates of morbidity and mortality for endometrial, ovarian and cervical cancers (Chatterjee et al., 2016; Collins et al., 2014; Rauh-Hain et al., 2018). Endometrial cancer exhibits particularly striking racial differences. Research shows a 30% decrease in incidence among African American patients diagnosed with endometrial cancer;

however, they are 2.5 times more likely than Whites to die from the disease (Jemal et al., 2010). Although histology and socioeconomics are the most consistent contributors to endometrial cancer incidence and mortality (Long et al., 2013), the cause of these disparities is multifaceted.

Despite a vast pool of literature describing disparities in endometrial cancer, the causes of these inequalities are not well understood; factors such as patient and disease characteristics, inconsistencies in treatment and socioeconomic differences may contribute significantly to observed disparities (Kish et al., 2014; Rauh-Hain et al., 2015; Setiawan et al., 2015). Hence, understanding the interplay of each of these factors can contribute to effective healthcare policy recommendations that could narrow the survival disparity gap significantly thus resulting in potential positive social change implications for this study. The findings from this study will provide insights into determinants of endometrial cancer racial/ethnic disparities, inform policy-makers about subpopulations that are disproportionately affected by the disease, and update knowledge on the trend of endometrial cancer racial/ethnic disparities based on a national level cancer registry data.

This section includes the problem, purpose, and nature of this study. The section also includes the research questions and hypotheses, the theoretical framework on which the study is based, as well a comprehensive review of literature. I will also discuss the study assumptions, limitations, and significance. I discuss the potential implications for positive social change in relation to understanding that factors associated with survival disparities are a potential public health component for developing interventions targeted toward lessening the burden of endometrial cancer.

Problem Statement

According to the National Cancer Institute (NCI), endometrial cancer accounts for 95% of cancer of the uterine corpus cases (NCI, 2018). The American Cancer Society (ACS) describes endometrial cancer as cancer of the endometrium i.e. the lining of the uterus. It occurs when cells of the endometrium grow too quickly and may thicken at certain areas to form a mass of tissue called a tumor (ACS, 2018). The cancer statistic review published by Cronin et al. (2018) based on data from the NCI's Surveillance Epidemiology and Ends Results Program (SEER) described endometrial cancer, sometimes called uterine cancer, as the fourth most commonly diagnosed cancer and the seventh leading cause of cancer-related deaths among U.S. women. In 2013, an estimated 50,560 women were diagnosed, and 9,325 women died from uterine cancer in the United States (Siege et al., 2013). According to the American Cancer Society (2018), it is estimated that 61,880 women in the United States will be diagnosed with endometrial cancer and 12,160 will die from the disease in 2019.

Endometrial cancer health disparities include differences in incidence, prevalence, mortality, and survival particularly among marginalized segments of the population (DeSantis et al., 2016). Several researchers have suggested that racial differences exist in the incidence and mortality of endometrial cancer (DeSantis et al., 2016; Smotkin et al., 2012). According to the Centers for Disease Control and Prevention (CDC), the incidence rate for malignant tumors of the uterine corpus is 30% lower in African-American women compared to White women (CDC, 2013); however, the mortality rate is much higher at 85% for African American women.

Epidemiological evidence as documented in numerous studies has shown that survival disparity in Black women is thought to be multifactorial including the potential influence of race/ethnicity, socioeconomic status, histologic subtypes, and treatment factors on disease-specific mortality (Cote et al., 2015; Kost et al., 2019; Long et al., 2013; Rauh-Hain et al., 2015). However, it remains unclear why racial differences in survival persist after accounting for these factors. Disparities in endometrial cancer diagnosis, treatment, and survival outcome using current national-level cancer registry data have not been thoroughly examined. It remains unclear whether racial/ethnic disparities in endometrial cancer outcomes have changed over the last decade. There is a gap in literature examining the widening disparity in incidence and survival for increasing rates of aggressive tumor subtypes among African American women. In a cancer statistics report by Chatterjee et al. (2016), African American women are more likely than White women to be diagnosed with late-stage cancer, high-grade tumors (Grade III or Grade IV), and poorer prognosis due to histological subtypes. Additionally, Tarney et al. (2018) found that Black women with endometrial cancer suffer significantly worse outcomes regardless of age, stage, and grade of disease.

Furthermore, there is also a gap in knowledge surrounding the role of access to care and its association with racial differences in uterine cancer survival. Hence, the need to examine socioeconomic factors, specifically the impact of insurance status and stage of diagnosis on endometrial cancer survival. For several cancer types including uterine cancer, uninsured and Medicaid insured patients experience higher mortality and lower survival outcomes than patients with private insurance (Fedewa et al., 2011; Niu et

al., 2013; Sohn, 2017). There are limited studies on the differential effects of insurance status on endometrial cancer outcomes. Even fewer uterine cancer survival studies have been carried out using population-based datasets such as SEER to examine differences in survival of women diagnosed with endometrial cancer (Fedewa et al., 2011; Niu et al, 2013). This might be due to the fact that insurance information was not released on the SEER database until 2012 when data were first published for cancer cases diagnosed from 2007 upwards (NCI SEER, 2013). Hence, exploring the determinants that contribute to endometrial cancer survival disparities is an important public health approach toward reducing the burden of disease.

Purpose of the Study

The purpose of this study was to conduct a retrospective, cross-sectional, quantitative analysis to ascertain the determinants of endometrial cancer survival disparities in the United States over the past decade. The main outcome variables (dependent variables) were endometrial cancer stage at diagnosis, treatment, and survival. The key independent variables for this study were insurance coverage, and three other factors that have been shown to be associated with disparities in endometrial cancer mortality: race/ethnicity, histologic subtype, and tumor grade. The covariables included in study analysis were women's age at diagnosis and marital status.

Research Questions and Hypotheses

In this study I addressed the following questions and hypotheses:

Research Question 1 (RQ1): Are race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status associated with

late-stage diagnosis of endometrial cancer (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis?

Null Hypothesis ($H_0$1): The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are not associated with late-stage endometrial cancer diagnosis (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis.

Alternative Hypothesis (H_a1): The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are associated with late-stage endometrial cancer diagnosis (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis.

Research Question 2 (RQ2): Are race/ethnicity, age at diagnosis, histologic, subtype, tumor grade, insurance, stage at diagnosis, and marital status associated with receipt of surgery in women diagnosed with endometrial cancer in the United States?

Null Hypothesis ($H_0$2): The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are not associated with receipt of surgery in women diagnosed with endometrial cancer in the United States.

Alternative Hypothesis (H_a2): The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are associated with receipt of surgery in women diagnosed with endometrial cancer in the United States.

Research Question 3 (RQ3): Are there racial/ethnic differences in 5-year survival

of women diagnosed with endometrial cancer in the United States?

Null Hypothesis ($H_0$3): There is no significant difference by racial/ethnicity in 5-year survival of women diagnosed with endometrial cancer in the United States.

Alternative Hypothesis (H_a3): There is a significant difference by racial/ethnicity in 5-year survival of women diagnosed endometrial cancer in the United States.

Research Question 4 (RQ4): Is there a significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States?

Null Hypothesis ($H_0$4): There is no significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States.

Alternative Hypothesis (H_a4): There is a significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States.

I conducted the quantitative data analysis to examine the relationship between the independent and dependent variables while controlling for confounding factors. I will discuss the results in Section 3 in detail.

Theoretical Foundation for the Study

The theoretical framework that I used to guide this study was the social-ecological model (SEM). The SEM, developed by Bronfrenbrener and McLeroy, provides insights into the interrelationships between an individual and population-level factors that influence behavior (Bronfenbrenner, 1979; McLeroy et al., 1988). The social-ecological model is a systems model with five bands of influence; the individual level lies at the

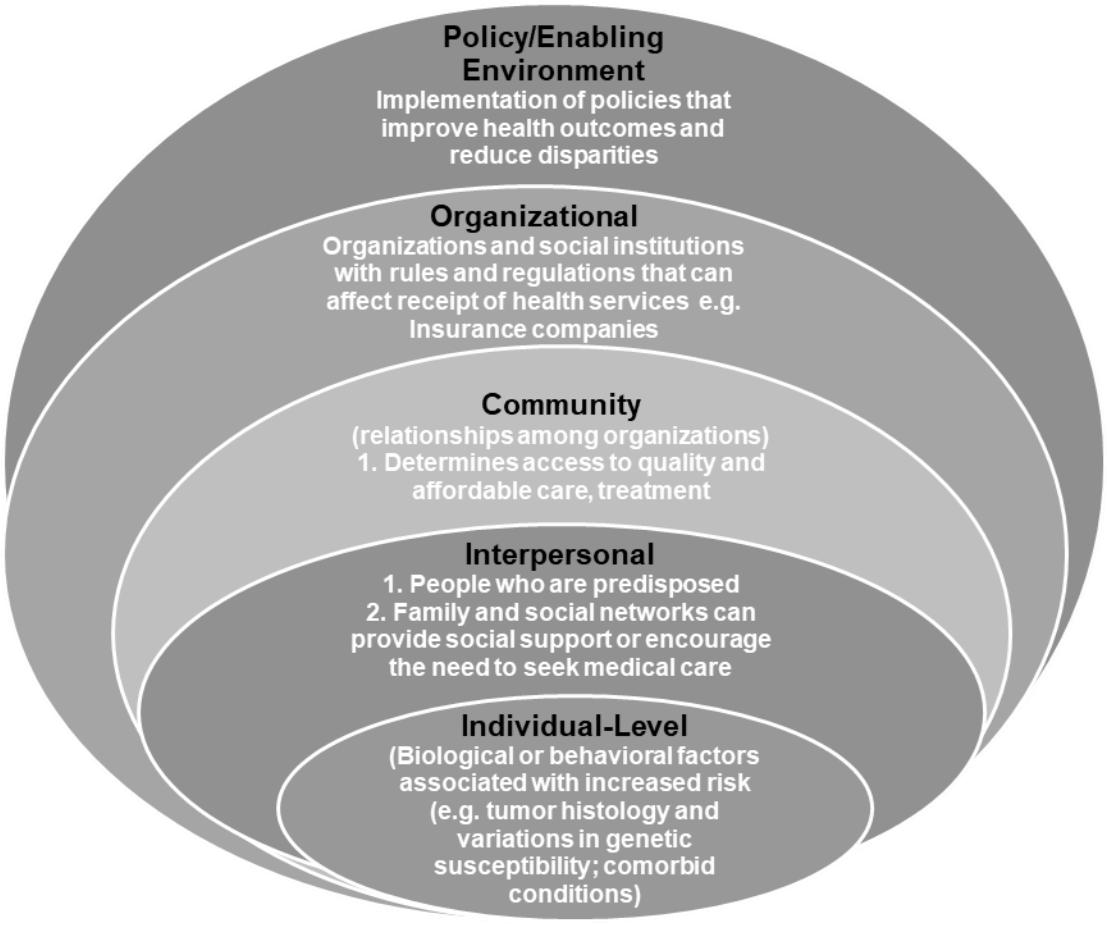
core of the model, surrounded by the other bands of influence i.e., the interpersonal, organizational, community, and policy levels (McLeroy, et al., 1988). This conceptual framework has been adopted by several public health organizations including the CDC to develop health promotion and disease prevention because of its multilevel approach to facilitate behavior change and promote health outcomes (Glanz et al., 2015). Research demonstrates that SEM has also been adapted in cancer-specific multilevel interventions including cervical and colorectal cancer screening (Daley et al., 2011; Joseph, et al., 2011; Smith & Brawley, 2014) as well as enhance communication and implement programs that support initiatives for breast cancer survivors (Buchanan et al., 2013). Additionally, this model has been applied to guide the development of public health programs that optimize the health of an individual before and after a cancer diagnosis.

The SEM relates to the study approach and research questions in this study because it is a useful framework for understanding the determinants i.e., the array of individual- and contextual-level factors that influence endometrial cancer survival outcomes. At the individual level, SEM is useful in describing biological factors and behaviors associated with increased risks such as tumor histology and variations in genetic susceptibility, and comorbid conditions (Moore et al., 2015); as well as demographic characteristics i.e., age, race/ethnicity, and economic status. Studies have shown that women at lower income levels were more likely to present with advanced-stage disease and were less likely to receive surgery (hysterectomy) as their primary treatment thus contributing to poorer survival rates (Kish et al., 2014; Madison et al., 2004; Williams et al., 2016). Consequently, at the interpersonal level, SEM can be

adapted by health care workers, patient navigators, and social support systems to influence individual behaviors. For instance, in delivering interpersonal messages that encourage an individual to seek medical care, especially predisposed individuals or those with a family history of disease. In addition, SEM can be adapted to promote initiatives that improve access to quality health care services among low-income women to facilitate earlier diagnosis and high-quality treatment. SEM would also prove an effective approach for influencing characteristics of organizations, institutions, and implementing policies that improve endometrial cancer survival outcomes.

Figure 1

Modified Social Ecological Model for Endometrial Cancer Risk among U.S. Women



Nature of the Study

This study was a quantitative, retrospective, cross-sectional study to ascertain the determinants of endometrial cancer survival disparities of women in the United States. Specifically, this observational study was a secondary data analysis of epidemiologic data collected by the National Cancer Institute's Surveillance Epidemiology and Ends Results Program. The data that I obtained were the most current data available on incidence and survival of endometrial cancer cases diagnosed from 2007 to 2016. I used study variables including independent variables, dependent variables, and covariates to address the research questions and hypotheses. The main outcome variables (dependent variables) were endometrial cancer stage at diagnosis, treatment, and survival. The key independent variables for this study were race/ethnicity, insurance, histologic subtype, and tumor grade. Other variables included in analyses to account for potential confounding effects were women's age at diagnosis and marital status.

I extracted all data using the 8.3.5 SEER*Stat Software (National Cancer Institute, 2019). I conducted statistical analyses using the IBM SPSS version 25 software application. I used multilevel logistic regressions for the analysis of racial/ethnic disparities in late-stage diagnosis and adjustment made for potential confounders. I used multivariate cox proportional hazards model to examine the influence of determinants on endometrial cancer survival measured as 5-year survival rates and reported as Hazard Ratio (HR). All hypothesis tests were two-tailed. I set the significance level at $p < .05$.

Literature Search Strategy

I conducted a literature review of peer-reviewed journal articles and seminal literature with a primary focus on disparities in survival for women treated for cancers of the uterine corpus for this study. To provide a complete, exhaustive summary of current evidence relevant to this topic, I examined articles published between the years 1980–2021, ensuring the citation of primary sources. My search included multiple electronic databases including MEDLINE, CINAHL, NCI, ProQuest, and PubMed. I also retrieved relevant articles from Google Scholar and EBSCO accessed through the Walden University Library. In addition, I conducted a search in the Walden dissertation database although no relevant articles related to my research topic was found. I used the following keywords and phrases for searches: *endometrial cancer, uterine cancer, late-stage cancer, diagnosis, incidence, mortality, survival, racial/ethnic disparities, histology, socioeconomic status, SEER, and insurance.* The literature search strategy that I used was comprehensive and I reviewed articles on endometrial cancer survival disparities, including epidemiology, disease and patient characteristics, and other multilevel factors that can influence endometrial cancer diagnosis, treatment, and survival outcomes.

Literature Review

This review includes the current body of literature that is relevant in identifying sociodemographic, pathological, and treatment factors that contribute to disparities in endometrial cancer survival.

Endometrial Cancer: Symptoms, Diagnosis, and Treatment

Endometrial cancer is the most common type of cancer that affects the female reproductive organs, specifically the endometrium, which is the lining of the uterus. According to the American Society of Clinical Oncology (ASCO, 2017), there are generally two types of this cancer: (a) endometrial cancer (Type 1), the most common, it grows slowly and is found only in the uterus; (b) endometrial cancer (Type II), spreads more quickly and affects other parts of the body. One of the earliest symptoms observed in women diagnosed with endometrial cancer is abnormal uterine bleeding (ASCO, 2017). Premenopausal women have reported irregular menstrual bleeding, spotting, and bleeding between menstrual periods, non-bloody vaginal discharge, and bleeding after menopause for postmenopausal women (Matteson et al., 2018). Patients with advanced-stage disease may have symptoms such as abdominal or pelvic pain, abdominal distension, sudden weight loss, and changes in bowel or bladder functions (ASCO, 2017). Based on the report by Howlader et al. (2017) on patients diagnosed with endometrial cancer between 2008 and 2014, endometrial cancer diagnosed at an early stage has a reported survival rate of 96%. For women with symptoms suspicious for endometrial cancer, or those with strong family history or genetic predisposition, the standard diagnostic evaluation performed to confirm an endometrial cancer diagnosis includes a pelvic ultrasonography, endometrial biopsy, dilatation and curettage (D&C), or a CA-125 blood test to test if cancer has spread (Bagaria et al., 2017; Tzur et al., 2017). A meta-analysis of studies examining the efficacy of several endometrial sampling devices including the Pipelle aspiration catheter showed that all devices analyzed had a high

specificity rate of 98% for endometrial cancer and endometrial hyperplasia (Dijkhuizen et al., 2000). Currently, endometrial biopsy remains the gold standard, the most accurate and commonly used test in the diagnostic evaluation for endometrial cancer, particularly in postmenopausal women (Burke et al., 2014).

After a confirmed diagnosis of endometrial cancer, it is important the stage of a tumor is determined. In 1988, the International Federation of Gynecologists and Obstetricians (FIGO) formally recommended surgical staging as part of the initial treatment for endometrial cancer (AJCC, 2017). Staging informs doctors of how far out the disease has spread in the body and helps determine how best to treat the disease. The American Cancer Society (2014a) classifies endometrial cancer from Stage I through IV; localized/early stage disease are depicted with lower numbers, while a higher number such as Stage IV represents advanced stage of disease i.e., cancer has spread to other parts of the body. The most recent AJCC Cancer TNM staging classifies endometrial cancer based on three factors: (a) the size of the tumor (T) i.e., how far the cancer has grown into the uterus, and adjacent organs, (b) the spread to adjacent lymph nodes (N) in the pelvis or around the aorta, and (c) the spread (metastasis) to distant sites (M) i.e., lymph nodes or organs in other parts of the body (AJCC, 2017). Hence the acronym T, N, and M characteristically used in cancer staging. The American Cancer Society (2014) suggested that current treatment options for endometrial cancer include surgery where in most cases the cervix and uterus are removed (total hysterectomy), as well as both ovaries and fallopian tubes (salpingo-oophorectomy). Lymph nodes and other tissue may also be removed and tested for cancer. In a process known as surgical staging, the

pathological stage of the tumor can be determined after examining tissue removed following an operation (AJCC, 2017). Staging is used by a doctor to decide if additional treatment, such as chemotherapy or radiation therapy, is needed.

Prevalence, Incidence, and Mortality

Endometrial cancer is the fourth most diagnosed and the seventh most common cause of death among women, with an estimated 772,245 diagnosed cases in the United States as of 2016 (Cronin et al., 2018). According to U.S. Cancer Statistics (2014), there has been a decline in overall cancer incidence in the United States. However, incidence rates for endometrial cancer have continued to increase over time. Based on incidence and mortality data obtained from the CDC's National Program of Cancer Registries (NPCR), the SEER program, and mortality data from the National Vital Statistics System, endometrial cancer incidence rates increased 0.7% per year from 1999–2015, and death rates increased 1.1% per year from 1999–2016 (Henley et al., 2018). Based on 2013–2017 cases, the prevalence of endometrial cancer in the United States was 27.8 per 100,000 women per year; while the number of deaths was 4.9 per 100,000 women per year based on 2014–2018 cases (NCI SEER, 2020). In 2017, there were an estimated 793,846 women diagnosed with endometrial cancer in the United States. In 2020, it was estimated that there would be 65,620 new cases of uterine cancer and an estimated 12,590 deaths from the disease (NCI SEER, 2020). The risk lifetime for developing endometrial cancer is about 3.1%, particularly among U.S. women aged 45–74 (NCI SEER, 2018). Although incidence rates for endometrial cancers are rising across all racial/ethnic

groups, there continues to be a widening disparity in endometrial cancer survival between races and ethnicities.

Several studies using large databases have shown the evident disparity in incidence and mortality of endometrial cancer among different races. Racial/ethnic disparities in survival is more prominent in endometrial cancer compared to other gynecologic cancers including ovarian and breast cancer (Cronin et al., 2018). Black women experience an 80% higher mortality rate compared to White women (DeSantis et al., 2016). Siegel et al. (2014) conducted an analysis examining 5-year survival rates in endometrial cancer and found a significant difference of about 22% in survival for Black women (64%) compared with White women (86%). As demonstrated by Henley et al (2018), non-Hispanic White (NHW) women and non-Hispanic Black (NHB) women report higher endometrial cancer incidence rates (27 cases per 100,000) than any other racial/ethnic groups (19–23 per 100,000), while endometrial cancer mortality rates are much higher among Black women (nine per 100,000) than among other racial/ethnic groups including White women (four to five per 100,000). Henley et al. (2018), comparing incidence and mortality rates among White and Black women in the U.S. found that Black women had a decreased risk of being diagnosed with endometrial cancer compared to White women (24.8 versus 26.3 new cases/100,000 per year) but a significantly higher risk of death from disease (8.1 versus 4.2 deaths/100,000 per year). Research has shown that observed disparities may be due to significantly higher incidence of advanced uterine corpus cancers and aggressive histologic subtypes such as serous and clear cell adenocarcinoma, malignant mixed Mullerian tumors and sarcomas

in Black women (Collins et al., 2014; Mahdi et al., 2016; Rauh-Hain et al., 2018). A recent study examining trends in endometrial cancer incidence from 2000 to 2011 found an even larger gap in incidence with NHB women representing an excess incidence of endometrial cancer for aggressive histologic subtypes (Cote et al., 2015). The 5-year cause-specific survival observed in this study was significantly less in Black women than White women (Cote, et al., 2015). Due to a lack of available data, there are currently limited studies examining endometrial cancer mortality rates in Asian and Hispanic women. However, results from a few studies suggest that survival rates in Asian and Hispanic women are similar to or better than those of White women (Mahdi et al., 2014). An understanding of incidence, mortality, and differences in survival can contribute significantly to additional research needed to address disparities in endometrial cancer outcomes.

Determinants of Endometrial Cancer Survival Disparities

Literature suggests that the reasons for disparities in endometrial cancer survival outcomes are multifactorial. They include the histopathologic, socioeconomic, and treatment factors discussed below.

Histopathologic Factors

Endometrial cancer stage at diagnosis, histology type, and grade of disease have been found to be important prognostic factors for survival (Fader et al., 2016; Long et al., 2013; Morice et al., 2016; Smotkin et al., 2012). Based on the statistics from the National Cancer Institute, SEER 18 Data 2009–2015, the relative 5-year survival rates by endometrial cancer stage are as follows: 95% for Stage I and II cancers (localized), 69%

for Stage III and IVA cancers (Regional), 16.8% for Stage IVB (Distant), and 52.9% for unknown (NCI SEER, 2018). When endometrial cancer is diagnosed at an early localized stage, the 5-year survival rate is about 95%; however, only 54% of Black women are diagnosed at this stage compared to 69% of White women (ACS, 2014b). Therefore, an important determinant of endometrial cancer survival is stage at diagnosis. Studies have shown that women with advanced stage at diagnosis of endometrial cancer, especially African American women, also present with other characteristics such as older age, higher tumor grade, and more aggressive histology (Madison et al., 2014; Oliver et al., 2011; Smotkin et al., 2012). Hence, the need for histopathological factors to be controlled for in modeling endometrial cancer disparities. Even after adjusting for these predictors, Madison et al (2014) found that African American women are still more likely to present with advanced-stage disease and have poorer prognoses.

The reasons for the higher mortality rates observed among Black women diagnosed with endometrial cancer are not completely understood. Numerous studies have shown that Black women are more likely to be diagnosed with later stage, higher grade disease, and with poorly-differentiated and aggressive non-endometrioid histologic types (Sheikh et al., 2014; Wartko et al., 2013). They also report less favorable survival outcomes regardless of histologic type, stage or grade of disease. Research conducted by Cote et al. (2015) using population-based SEER cancer registry data to examine endometrial cancer incidence and mortality disparities by race/ethnicity and tumor histologic subtype showed that compared to White women, Black women had significantly low incidence rates for low-grade endometrioid subtypes (well-differentiated

or moderately differentiated tumors) but higher incidence rates for high-grade endometrioid subtypes (poorly differentiated, undifferentiated, or anaplastic tumors). While these authors highlighted underlying complex biological pathways involved in carcinogenesis as a possible explanation, Black women experience poorer survival outcomes compared to other races, even when analyzing patients with similar stage of disease, tumor grade, and histologic subtypes.

Race/Ethnicity

Race/ethnicity is an important contributor to health disparities as it significantly impacts the diagnosis, treatment, and survival outcomes of patients with endometrial cancer. The effect of race/ethnicity on disparity outcomes suggest the trend in incidence and mortality of endometrial cancer in the United States over the last decade is quite distinct; African Americans have a 30% decreased incidence and a mortality rate 80% higher when compared to Whites (Farley et al., 2007). According to the NCI SEER 2013–2017 statistics, White women had the highest incidence rate of endometrial cancer per 100,000 women per year (28.3), followed by Black women (27.9), Hispanic (24.6), Asian/Pacific Islander (21.7), and American Indian/Alaska Native (19.9) women . Compared to other races, Black women had the highest mortality rate of endometrial cancer (8.7), followed by White (4.5), Hispanic (4.1), American Indian/Alaska Native (3.5), and Asian/Pacific Islander (3.2) women (NCI SEER, 2020).

Jemal et al. (2010) found that Black patients diagnosed with endometrial cancer are 2.5 times more likely to die from the disease compared to White patients. More recent studies have also shown similar disparate incidence trends of endometrial cancer. A

previous study based on incidence data from 1996 to 2006 found a considerable gap in incidence with African American women representing only 6.8% of all endometrial cancer cases and 17.4% of Type II endometrial cancers .i.e. poorly differentiated or high-grade tumors (Duong et al., 2011). This result is consistent with that of a previous study conducted using data from the California Cancer Registry database (CCR) to identify women with Type II endometrial cancers from 1998 to 2009, suggesting Black women have a higher incidence of more aggressive histologic subtypes even among a group of women with high-grade endometrial cancer and experience worse disease-specific survival even after adjusting for potential confounding factors such as age, stage at diagnosis, histologic subtype, tumor grade and type of treatment (Baskovic et al., 2018).

Rauh-Hain et al (2018) examined racial differences in treatment and survival using 1992-2009 SEER-Medicare linked data comprised of African American and White women with high-grade endometrial cancer. Results of study analysis showed that White women were more likely to receive definitive surgical treatment for endometrial cancer (88.7% versus 76.8%) than African American women. African American women also reported lower cancer-specific and all-cause survival compared with White women. However, there was no significant difference in disease-specific survival after adjusting for tumor characteristics, treatment, comorbidities, and sociodemographic factors. In examining racial differences in endometrial cancer outcomes, most of the reviewed studies have mainly focused on incidence and survival comparisons between African American and Caucasian subpopulations. Very few studies have been carried out on

Hispanics or Asians, two of the largest and fastest-growing minority ethnic groups in the United States.

The study conducted by Cote et al. (2015) was based on a study population that included Hispanic and Asian patients. Study results showed that Hispanic and Asian women have incidence and 5-year relative survival rates equal to or lower than White women even after controlling for stage of disease and histologic subtype. However, more research is needed to explore endometrial cancer incidence and survival outcomes among Hispanics and Asians compared to non-Hispanic Whites (NHWs) and non-Hispanic Blacks (NHBs).

Age

Age is an important risk factor for cancer, but data regarding whether patient age at diagnosis can contribute to disparities in endometrial cancer survival are conflicting. Cancer can be considered an age-related disease as the incidence of most cancers increases with age (White et al., 2014). In research from Singh et al. (2016), most endometrial cancer cases are diagnosed in post-menopausal women i.e. women over the age of 50. The average age at diagnosis for endometrial cancer is 60 years; the disease is not common in women younger than 45 (Singh et al., 2016). For several reasons, cancer research studies have demonstrated that age at diagnosis is associated with poorer prognosis and worse health outcomes especially among older persons over the age of 45 (Ory et al., 2014; White et al., 2014). Based on SEER (2018), 40% of women diagnosed with endometrial cancer are aged 65 or older, and 67% of deaths from endometrial cancer occur in women over 65.

Duska et al. (2016) found that older women are more likely to die of endometrial cancer compared with younger patients due to late-stage diagnosis, or more aggressive tumor biology. The presumed late-stage diagnosis common among older women may be due to social and cultural influences including financial concerns, educational barriers that limit access to health-related information, increasing risks of comorbidities that could cause reluctance to offer definitive surgery treatment to older patients, and complications of invasive therapies such as surgery and chemotherapy (Long et al., 2013; Madison et al., 2004; Ory et al., 2014). According to Long et al. (2013), age limits younger women from most government-funded insurance plans, thus limiting access to health care and contributing disproportionately to increased rates of advanced disease diagnosis particularly among minority populations. Age is often included as a predictor in survival analysis to account for its possible confounding effects. A meta-analysis investigating age at menopause and risk of developing endometrial cancer found that late menopausal age was associated with an increased risk of endometrial cancer (Wu et al., 2019); while the performed dose-analysis showed a statistically significant positive association when age at menopause was greater than 46.5 years old.

Insurance Status

Insurance status is also an important contributor to endometrial cancer survival disparities. Measures such as income, education, occupation, and insurance status are typically used in public health research as proxy variables to estimate socioeconomic status (SES) for patients (Krieger et al., 1997; Montgomery et al., 2000). Previous studies have shown that uninsured and Medicaid insured patients with common cancers in the

United States have poorer health outcomes including more advanced disease, higher mortality, and are less likely receive cancer-directed therapy than patients with private insurance (Grant et al., 2016; Niu et al., 2013; Rosenberg et al., 2015). Studies have also established that uninsured and Medicaid insured patients diagnosed with endometrial cancer have lower survival than do patients with private insurance or Medicare, even after adjustment for other factors (Dolly et al., 2016; Fader et al., 2016; Fedewa et al., 2011).

Fedewa et al (2011) based on data from the National Cancer Database (NCDB) examined the impact of race and insurance on endometrial cancer survival. African American and Caucasian patients without private health insurance experienced worse survival outcomes thus contributing to endometrial cancer survival disparities. A retrospective study based on the Rush University Medical Center Cancer database examined patients diagnosed with and/or treated for endometrial cancer from 2005 to 2012 and found that although majority of the patients had insurance (Private insurance 49.6%; Medicare 42.1%; Medicaid 4.4%), patients with Medicare and Medicaid insurance experienced significantly longer interval time to treatment compared to patients with private insurance. Study analysis showed that Medicaid patients had the longest treatment interval with a mean treatment delay of 78 days, followed by Medicare patients with 54 days; patients with private insurance had the shortest interval at 38.4 days which was found to be clinically significant ($p < 0.001$) even when stratified by stage of disease. In addition, longer interval time from diagnosis to treatment was associated with decreased endometrial cancer survival. This study supports findings by Elit (2015),

whose analysis of a Canadian population also found that a delay in treatment was associated with a decrease in overall survival for patients with uterine cancer. Although the causes of these delays are likely multifactorial, the findings from these studies are significant because Medicaid beneficiaries in the United States include a disproportionately high percentage of minorities, especially Blacks (21%) and Hispanics (25%), although a higher percentage of total Medicaid beneficiaries are White (40%) (Kaiser Family Foundation, 2013). It is evident that individuals with Medicaid or without health insurance are more likely to present with advanced-stage disease at diagnosis as they tend not to seek timely treatment or may experience increased interval wait time from diagnosis to treatment.

Marital Status

There is a well-established association between marital status and survival in cancer patients; married patients compared to unmarried patients have decreased mortality in several malignancies such as prostate, breast, cervical and colon cancers irrespective of age, tumor grade, and disease stage (Hanske et al., 2016; Hinyard et al., 2017; Liu et al., 2019; Tyson et al., 2013; Wang et al., 2011). Few studies have examined the impact of marital status on survival in patients with endometrial cancer. A study based on 1991-2010 SEER data was used to assess the effect of marriage on survival outcomes for women diagnosed with uterine cancer (Lowery et al., 2015). Study results suggest that as opposed to widows, married women benefit significantly from personalized care and social support from their partners and thus have improved survival

outcomes. More studies are needed to examine the effect of marital status as a prognostic factor for the survival of endometrial cancer patients.

Treatment

Treatment factors have been suggested as a contributor to endometrial cancer survival disparities. Invasive treatments such as surgery, radiation therapy, and systemic therapy are often recommended by clinicians in the management of endometrial cancer. The standard treatment for most endometrial cancer cases is surgery, typically hysterectomy (removal of the uterus, cervix, and bilateral fallopian tubes and ovaries). In most cases, surgery alone may be curative for early-stage, low-grade disease; however, adjuvant therapy such as chemotherapy and/or radiation therapy may be recommended for patients with advanced disease and less favorable clinicopathologic features. Several studies have examined survival outcomes of surgical and adjuvant treatment on endometrial cancer patients. In terms of age, population-based studies conducted over the last decade suggest that there is a difference in treatment received, specifically in performing surgery for older patients with endometrial cancer. Two different SEER analyses demonstrated that older patients with endometrial cancer were less likely to receive surgical treatment, hysterectomy, and thus experienced poorer survival outcomes (Ahmed et al., 2008; Wright et al., 2011). Duska et al. (2016) suggest that older women are more likely to have high-grade uterine cancer tumors, poor histology, and advanced disease; consequently, require adjuvant treatment and/or surgery. In another study evaluating survival in endometrial cancer patients administered similar surgery and adjuvant radiation treatment (Gayar et al., 2011), elderly patients (≥ 75 years) diagnosed

with FIGO stage I–II endometrial cancer were found to have poorer histopathological features, and worse disease-specific and overall survival than younger patients (< 75 years). A more recent study by Rauh-Hain et al (2015) using data from the National Cancer Database found that elderly women with advanced-stage (stage III or IV) disease were less likely to be treated with surgery, chemotherapy, or radiation.

While examining the effect of race on disparity in treatment and survival, it has been shown that African American women with endometrial cancer have higher cancer-specific mortality. Black women with endometrial cancer are less often to receive surgical treatment at every stage and grade of disease (Rauh-Hain et al., 2015). An analysis of data from the National Cancer Database (NCDB) examined Stage I-III endometrial cancer patients who underwent surgery, African American women were less likely to receive postoperative radiation therapy and are more likely to die of endometrial cancer compared to Caucasians (Cho & Viswanathan, 2018). Rauh-Hain et al. (2018) also using NCDB data from 20042014 examined trends over the past 10 years in treatment and survival among different racial groups including White, Black, Asian, and Hispanic women diagnosed with endometrial cancer. Compared to other racial groups, Hispanic women with high-grade endometrial cancer were less likely to undergo surgery, lymphadenectomy (80.7% versus 74.5%). In addition, Black women diagnosed with endometrial cancer had lower five-year survival than other racial groups.

Definitions

This section reviews definitions of study variables included in analysis. The variables examined in this study include the outcome variables: endometrial cancer stage

at diagnosis, treatment, and survival. The key independent variables for this study are race/ethnicity, histologic subtype, tumor grade and insurance. Other potential covariates included in study analysis are age at diagnosis and marital status.

Stage at diagnosis

For the purpose of this study, *staging* refers to the process of finding out how much cancer is in a person's body and where it is located (ACS, 2018). Hence, it can be used to determine the stage of a person's cancer. The SEER database grouping of endometrial cancer is based on how far the cancer has spread; specifically, localized, regional, and distant stages (NCI SEER, 2013). Stage I and II endometrial cancers are localized and have not spread outside the uterus (AJCC, 2017). Stage III and IVA endometrial cancers that have spread from the uterus to nearby tissues, organs or lymph nodes are said to be regional (AJCC, 2017). Distant cancers include Stage IVB cancers and have spread to the lungs, livers or bones (AJCC, 2017). For this study, the variable "stage at diagnosis" was classified as "Non-advanced stage" and "Advanced stage". Non-advanced /Early-stage endometrial cancer was for localized cases, while it was dichotomized as advanced-stage disease for regional or distant cancers.

Survival time

Survival time was defined as the date of endometrial cancer diagnosis to the date of endometrial cancer-cause specific death or the cut-off time for follow-up (NCI SEER, 2018). For patients who were still alive, data were censored based on the date of the last follow-up visit.

The event in the survival analyses was endometrial cancer-cause specific death within 5 years of endometrial cancer diagnosis. The survival outcome was measured as 5-year endometrial cancer-cause specific mortality and reported as Hazard Ratio (HR).

Treatment

According to the National Cancer Institute, treatment can be described as a detailed plan with information about a patient's disease, the purpose of treatment, the treatment options for the disease including possible side effects, the expected length of treatment, and potential plans for follow-up care after treatment ends (NCI, 2018). Data for the primary treatment of surgery were obtained from SEER records. According to the American Cancer Society (2018), surgery (hysterectomy) to remove the uterus is typically the primary treatment for uterine corpus cancers. However, in some cases, depending on cancer subtype and stage of disease, adjuvant therapy such as chemotherapy, radiotherapy, or hormone therapy may also be used (ACS, 2018). For study analysis, treatment information was measured as "No surgery", "Surgery".

Other individual-level factors obtained from SEER included tumor histopathologic characteristics, race/ethnicity, insurance status, age at diagnosis, and marital status.

Histologic subtype

Histological classification of cancer subtypes is based on the type of tissue in which the cancer originates and by primary site, or the location in the body where the cancer first developed (AJCC, 2017). Data coding in SEER for tumor site, grade, and histology was classified in accordance with the third edition of the International

Classification of Diseases for Oncology [ICD-O-3] (Jack et al., 2000). For this analysis, major tumor histologic subtypes was categorized as follows: “endometroid", “uterine carcinosarcoma”, “serous carcinoma”, “clear-cell carcinoma” and “other” (includes squamous cell carcinoma, small cell carcinoma, transitional carcinoma). Endometroid (also called endometrial adenocarcinoma) is the most diagnosed histologic subtype; they are low-grade tumors and have a high cure rate (Jack et al., 2000). Serous carcinoma is the second most common type of endometrial carcinoma; they tend to be more aggressive and are often diagnosed at advanced stage of disease (Jack et al., 2000). Uterine carcinosarcoma (CS), is also referred to as *malignant mixed mesodermal tumors* or *malignant mixed mullerian tumors* (MMMTs), make up about 3% of endometrial cancer cases (Murali et al., 2019).

Furthermore, studies have shown that non-Hispanic Black (NHB) women suffer worse survival outcomes as they are more likely to be diagnosed with aggressive histologic subtypes, such as serous carcinomas, clear-cell carcinomas, and carcinosarcomas compared with other racial/ethnic groups (Long et al., 2013). Uterine sarcomas, which include uterine leiomyosarcomas and endometrial stromal sarcomas, develop in the muscle layer (myometrium) or supporting connective tissue of the uterus (Murali et al., 2019), were excluded from this analysis.

Tumor grade

A tumor is described based on how abnormal the cancer cells and tissue look under a microscope and how quickly the cancer cells are likely to grow and spread (NCI, 2018).

Grading systems vary for each type of cancer and are used to inform treatment plans and determine disease prognosis. Grade is based on how different endometrial cells tumor cells differ from normal cells. Grade is usually grouped between 1 and 3. The lower the grade, the better the prognosis (SEER 2018). For endometrioid tumors, grade can either be 1, 2 or 3. However, serous carcinoma or clear-cell carcinomas are usually graded 3 and indicate a worse prognosis (Jack et al., 2000). Endometroid tumors can also be further classified as "low-grade" endometrial cancers (for well-differentiated to moderately differentiated tumors), while carcinosarcomas, serous carcinomas and clear cell carcinomas are classified as "high-grade" endometrial cancers (for poorly differentiated to undifferentiated tumors). Endometrioid adenocarcinomas are type 1 endometrial cancers that generally present as low-grade tumors. They occur as a result of excess estrogen in the body; they look like normal cells, are slow-growing, not aggressive and less likely to spread (Soslow, 2013). Type II tumors are high-grade endometrial carcinomas such as carcinosarcomas, serous carcinomas, and clear cell carcinomas. Setiawan et al (2013) described type II tumors as poorly differentiated tumors, estrogen-independent, more aggressive, and present with poorer prognoses than type I tumors.

For this analysis, the classification of tumor grade was based on the 7th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual (Edge & Compton, 2010); the variable tumor grade was coded as "well-differentiated", "moderately-differentiated", "poorly-differentiated", "undifferentiated", with all other histologic subtypes categorized as "unknown."

Race/ethnicity

Race/Ethnicity was defined as Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Hispanic, Non- Hispanic Asian/Pacific Islander (NHAPI), and Non-Hispanic American Indian/Alaska Native (NHAIAN).

Insurance

The insurance variable was defined as the type of insurance reported by patients at the time of diagnosis: "Insured" (Medicare and private insurance), "Medicaid", and "Uninsured". Private insurance includes fee-for-service plans, managed care plans, health maintenance organizations, VA/TRICARE/Military/Public Health Service, and preferred provider Organizations (NCI SEER, 2013). Medicaid includes managed care plans, public health service insurance, and other state-administered insurance programs (NCI SEER, 2013); Medicare includes insurance administered through managed care plans, and Medicare with supplemental coverage (NCI SEER, 2013). Previous research conducted by Niu et al (2013) demonstrated an association between stage at diagnosis and insurance among women with uterine cancer; as patients who were uninsured or had Medicaid as opposed to private insurance, were more likely to present with advanced-stage disease, even after adjusting for other factors.

Age at diagnosis

The measure "Age at diagnosis" was categorized into five groups. They are 18-45 years, 46-55 years, 56-65 years, 66-75 years, and 76 years and older.

Marital status

In the SEER dataset, self-reported data on marital status was documented at the time of diagnosis of patients. For analysis, marital status was grouped as "single" (never married), "married", "separated/divorced", and "widowed". Where patients do not specify marital status, cases will be grouped as "Unknown".

Assumptions

This study was conducted based on the assumption that all information abstracted from the SEER database was accurate in its representativeness of data collated from a coordinated system of cancer registries located across the United States. Furthermore, it was assumed that although individual records could not be reviewed to ensure accuracy of the data, source registries ensured that all the individuals who consented to participate in the study and met the inclusion criteria, provided complete information that was de-identified in the SEER database. Utilizing the SEER database was necessary for the context of this study because it generates incidence, mortality, treatment, and survival data for cancer subtypes, including information on histopathology and its implications across demographic groups, geographic regions, and time (Duggan, Anderson, Altekruse, Penberthy, & Sherman, 2016). In addition, it was the assumption that based on the research questions and hypotheses, the SEER dataset was the best fit for this study, in terms of the selected patient population, large sample size, and available data on measures of the variables of interest including predictors, outcomes, and potential confounders.

Scope and Delimitations

The specific aspects of the research problem addressed in this study aimed at elucidating the factors associated with disparities in endometrial cancer survival among US women; while focusing specifically on multiple factors have been linked including differences in race/ethnicity, stage at diagnosis, tumor histopathology, insurance, and treatment type. For this study, the main outcome measures were endometrial cancer stage at diagnosis, treatment, and survival. This specific focus was selected because significant disparities in endometrial cancer outcome persist based on race/ethnicity, socioeconomic status, and other factors. A report by Siegel, Miller& Jemal (2015) showed that 5-year all-stage survival for White women with endometrial cancer was 84%, compared with 61% for Black women. Previous studies have elucidated that factors such increasing age, higher tumor grade, more aggressive histology, and insurance are associated with advanced stage at diagnosis; particularly among African American women even after adjusting for these predictors (Cote et al., 2015; Fader et al., 2016; Niu et al, 2013). Hence the need to identify the factors associated with disparities in stage at diagnosis and receipt of surgery; specifically, how these determinants influence survival of women with endometrial cancer.

This study was based on a large nationwide population of uterine cancer patients diagnosed between 2007 and 2016 in the SEER Database. The study population included women aged 18 and older diagnosed with endometrial cancer in the United States. However, there were some limitations associated with using the SEER dataset. One of which was ensuring that all data reported on the SEER database was complete and

accurate. It was difficult to evaluate the data collection method used by source registries to obtain personal information, as well as patient and disease characteristics; thus, a major limitation of this study. In addition, since this was an observational study, a causal relationship could not be established between race/ethnicity, tumor subtype, insurance, treatment, stage at diagnosis and survival based upon the possible findings. Also, survival outcome could not be fully evaluated as the collected data did not distinguish whether initial treatment received was curative. Finally, another potential limitation of this study was not examining other potential risk factors that have been known to be associated with increased risk of most gynecologic cancers. Till date, SEER does not collect individual-level data on health information such as socioeconomic status (SES), smoking, alcohol consumption, educational level, income level, obesity, and co-morbidities; therefore, these potential confounding factors could not be controlled for during the data analysis.

This was a retrospective study consisting of secondary data obtained from the SEER National Cancer Database of women diagnosed with endometrial cancer between 2007 and 2016. The target population examined included a group of women aged 18 years and over diagnosed with Stage I - IV endometrial cancer. Using the SEER program was a potential strength of this study, with regard to representativeness and generalizability to the U.S. population. The population-based data was obtained from 18 Cancer Registries and contains information on cancer incidence, diagnoses, treatment and survival for approximately 30% of the U.S. population (Park, Lloyd, Decker, Wilson, & Yu, 2012). Duggan et al (2016) also highlight other strengths of the SEER data including

large numbers of cases, reporting of cancer-specific outcomes, and the lengthy period of data collection largely due to patient follow-up.

Significance, Summary, and Conclusions

This chapter introduced the study, stated the problem statement and purpose of the study, presented a detailed background of the study while highlighting the research questions and hypotheses, as well as the theoretical foundation on which the study was based. It also provided an exhaustive review of the current literature and research related to endometrial cancer survival disparities among women in the United States. In addition, information on assumptions, limitations, and importance of the study was also discussed. Data obtained from the SEER program was used to answer the research questions and address the gap in literature on what determinants contribute to survival disparities in women diagnosed with endometrial cancer in the United States.

Currently, the reason for survival disparities in women with endometrial cancer is multifactorial; however, age, race/ethnicity, histologic subtype, treatment, insurance, and other determinants have been identified in the literature as contributory factors for advanced stage endometrial cancer diagnosis and poorer survival (Long et al., 2013; Smotkin et al., 2012; Niu et al, 2013). Due to the complexity of interactions between potential risk factors, there is a need for continued research in this area. By identifying determinants of endometrial cancer survival, this study may highlight the potential influence of socioeconomic, histopathologic and treatment factors on survival disparity. Consequently, this study may encourage the development of effective endometrial cancer prevention and health promotion programs aimed at improving health outcomes in

women across the United States. Other potential contributions of this study include advancement in health policies such as the Affordable Care Act to promote access to healthcare services for women without adequate insurance, which is the case for a disproportionate number of African American women and other minorities. The implications for social change for this research include a better understanding of disparities associated with advanced stage diagnosis, primary treatment received, and endometrial cancer survival. Study findings could serve as a foundation for reducing the gap in survival by increasing awareness and education among women regarding the signs and symptoms of endometrial cancer and providing quality information on seeking appropriate treatment.

Endometrial cancer is the most common gynecologic cancer among American women (Siegel et al., 2013); incidence and mortality been shown to vary by race and ethnicity with the highest rates reported among Black women (Edwards et al., 2014). The current study updates knowledge about racial/ethnic disparities in endometrial cancer diagnosis and survival based on most recent national-level cancer research data. Identifying the determinants of endometrial cancer survival disparities will allow government and non-governmental agencies apply more focused efforts aimed at eliminating racial inequities and improving health outcomes. By expanding insurance coverage and promoting equal access to medical care for all women especially those in underserved communities will go a long way in decreasing mortality rates. Also, encouraging continued cancer health disparities research will advance knowledge in this discipline.

Section 2: Research Design and Data Collection

Introduction

This section includes a description of the research design and data collection methods utilized in this quantitative study. The purpose of this study was to examine the determinants of endometrial cancer survival disparities in the United States. As stated in Section 1, the purpose of this quantitative study was to explore histologic and socioeconomic factors that contribute to disparities in mortality and survival of women with endometrial cancer in the United States and identify ways to address these inequalities.

This focus of this section is the quantitative research paradigm and the rationale for this study. There is also a discussion on research methodology, the operationalization for each variable, the data collection process and data analysis plan, a description of study participants, as well as the inclusion and exclusion criteria used in the study. In addition, biases and threats to validity were discussed to ensure data quality. Finally, the potential confidentiality and ethical issues of the study were addressed.

Research Design and Rationale

This was a quantitative, cross-sectional study of a population-based cancer registry database. The data obtained from the SEER database included diagnosed cases of endometrial cancer reported from 2007 to 2016. The study population included three dependent variables (endometrial cancer stage at diagnosis, treatment, and survival) and four independent variables (race/ethnicity, histologic subtype, tumor grade, and insurance coverage).Health information and sociodemographic factors such as women’s age at

diagnosis and marital status were included in the analysis to account for possible confounding.

The retrospective, cross-sectional design was the most appropriate design for this study. Gordis (2009) described a cross-sectional study as an observational epidemiologic design that measures the prevalence of health outcomes or determinants of health, or both, in a population at a given point in time or over a short period. Cross-sectional studies measure simultaneously the exposure and health outcome in a given population at a certain time. The cohort of subjects selected from the SEER database were reported cases of patients diagnosed with endometrial cancer selected based on the inclusion and exclusion criteria set for the study. To examine multiple outcomes simultaneously, the data for outcome variables i.e. endometrial cancer stage at diagnosis, surgery treatment, and survival (measured from the date of diagnosis to date of death/ date of last follow-up visit) were reclassified for analysis. In addition, cross-sectional data was used in this study to evaluate the research question exploring 5-year survival among the varying racial/ethnic groups of women diagnosed with endometrial cancer in the United States. This was because the sufficiently large sample size could lead to statistically stable estimates, making it easier to evaluate trends in these data. In addition, the cross-sectional study design was suitable to effectively assess associations between multiple exposures and multiple outcomes as demonstrated in this study.

In cross-sectional studies, data on study population has been collected and follow-up already completed before the onset of research. Therefore, regardless of the original purpose for which the data were collected, data can be used in other secondary research

analysis. Due to potential barriers such as time and resource constraints consistent with the recruitment process in cross-sectional studies (Klebanoff & Snowden, 2018), individual recruitment of participants for this study would have been extremely difficult. Only a small sample size of endometrial cancer patients can be recruited in hospitals and clinics based on medical records at a single point in time. There is a significant benefit in having the NCI SEER database, an established cancer registry that reports information on cancer incidence and survival in the United States.

Cross-sectional studies can be effective in advancing knowledge in cancer research since data were typically made up of medical records that have already been collected and stored in an electronic database. According to Sedgwick (2014), the goal of observational study designs such as the cross-sectional study is to ensure that data were collected from patients before, during, and after a clinical diagnosis and for a long period so as to ensure all important data on disease etiology, incidence, treatment, follow-up, and outcome is well documented. The SEER database is a unique resource that is relevant for epidemiologic research as it allows researchers investigate disease trends, including access to information on cancer screening, incidence, treatment, and survival outcomes across demographic and socioeconomic groups. A major strength of the SEER cancer registry is that it collects population-based data on individual cancer cases using standardized methods of data collection to ensure validity and generalizability of study outcomes (Howe et al., 2003). Using cross-sectional analysis of the SEER program for this research study was relatively cheap, quick, and easy to perform due to the expeditious process of accessing secondary data from the SEER database. Information on

sociodemographic variables including cancer staging, treatment, and outcome available on the SEER database makes this study a potential resource to advance knowledge in cancer disparities research that examines endometrial cancer mortality trends.

Methodology

Population

I selected the target population from the SEER Program of the National Cancer Institute (NCI), a population-based cancer registry database, and obtained demographic, histopathological, diagnosis, treatment, and survival information for women diagnosed with endometrial cancer from 2007 to 2016. The SEER*Stat 8.3.5 software was used to extract cases from SEER 18 registry, generating the dataset from "Cervix Uteri" limited to women with uterine corpus tumors. Eligible patients included Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Hispanic, Non- Hispanic Asian/Pacific Islander (NHAPI), and Non-Hispanic American Indian/Alaska Native (NHAIAN) women diagnosed with primary cancer of the uterine corpus; while patients diagnosed before the age of 18, women who had in situ cancers, uterine sarcomas, or a previous history of cancer or prior malignancy were excluded from the analysis.

Sampling and Sampling Procedures

For the purpose of this study, data on endometrial cancer cases in the United States (N =130,375) were obtained from the original SEER datafile (NCI SEER, 1975–2016) on the SEER database. Insurance status, one of the key variables, has only been reported in the SEER database since 2007, so data extraction was limited to 2007–2016 to prevent missing data. The non-probability sampling method was the preferred

technique for this observational study as it allowed for the use of inclusion and exclusion criteria; the study population was limited to participants that met the eligibility criteria thus allowing for a more focused outcomes research. Data obtained from SEER database were readily accessible and available to answer the research questions posed in this study. Since predictor, outcome, and potential confounding variables were readily available on the SEER database, convenience sampling, a non-probability sampling method (Tyrer & Heyman., 2016), was most appropriate for this retrospective study. Data analysis was based on estimations and comparisons carried out on each variable. The sample size was based on the total population of patients selected from the SEER database who satisfied the inclusion criteria for the study. Specifically, the study sample comprised of abstracted data distributed into several subgroups that share common characteristics such as age, race or ethnicity thus ensuring a more representative sample of the population. The study population included women between the ages of 18 and 80 years diagnosed with endometrial cancer from different racial/ethnic population subgroups.

The NCI SEER database is the leading population-based resource for incidence and survival data in the United States. This secondary data source includes information on patient demographics, clinical information such as cancer diagnosis, treatment, follow-up and/or death for approximately 30% of the U.S. population (Duggan et al., 2016). The database is made up of information abstracted for several sources including patient medical records, diagnostic imaging reports, chemotherapy clinics, and death certificates (Duggan et al., 2016). Typically, cancer registry staff members abstract data from the sources listed above using standardized data collection templates that are

checked for accuracy and completeness, then edited, before reviewed information is inputted into an electronic database. The SEER data is de-identified and available for public use. Access to the SEER website (www.seer.cancer.gov) is unrestricted, and information on the website may be copied without permission. However, approval is necessary to view individual records such as cancer incidence data and mortality data. I received authorization to access and use the SEER dataset for this research study, after a signed permission form was submitted to SEER. Since the SEER data were publicly available, approval was waived by the local ethics committee.

Power Analysis

The power of a statistical test is defined simply as the probability of rejecting a null hypothesis when it is false (Jones et al., 2003). There are three interrelated parameters that affect the statistical power of a study: the sample size, the alpha level, and the effect size (Faul et al., 2009). In research studies, commonly used values for power is 0.80 or 80% i.e. beta {β} equals 0.20 (Lenth, 2001). An increase in statistical power is usually achieved by increasing sample size, as well as selecting stronger effect sizes and significance levels (Jones et al., 2003). Generally, in sample size calculations, a small sample size may potentially lead to inaccurate results not representative of the study population (Jones et al., 2003).To determine the estimated sample size needed for this study, a priori analyses were carried out using G*Power to estimate the power of the data collected from the SEER database.

It is critically important to determine the optimal sample size necessary to provide precise estimates and reliable answers to study hypotheses. That is, the likelihood of (a)

the rejection of the null hypothesis that there is no association between the variables: race/ethnicity, age at diagnosis, histologic subtype, insurance, other determinants and late stage endometrial cancer diagnosis, (b) the rejection of the null hypothesis that there is no association between the variables: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, marital status and receipt of surgery in women diagnosed with endometrial cancer in the United States, (c) the rejection of the null hypothesis that there is no significant difference by racial/ethnicity in 5-year survival of women diagnosed with endometrial cancer in the United States, or (d) the rejection of the null hypothesis that there is no significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States. Research is based on the widely used convention of 95% confidence interval or 5% level of significance and 10% margin of error.

Power analysis for multilevel logistic regression was conducted to assess the relationship among factors specific to this population-based cross-sectional study using the G*power software. According to Long (1997), maximum likelihood estimations including logistic regression analysis should not be done with less than 100 cases, citing 500 cases as adequate, with at least 10 cases per predictor. Peduzzi et al. (1996) stated that 10 times the number of predictors (k), should be required for the proportion (p) of successes.

Where *p* is the prevalence or proportion of event of interest for the study; and k is the number of covariates i.e. the number of independent variables in the study (race/ethnicity, tumor grade, histologic subtype, and insurance coverage).

The proportion of women diagnosed with endometrial cancer in the United States was 27.8 per 100,000 women per year based on 2014–2018 cases (NCI SEER, 2020). Therefore, the minimum number of cases to include is approximately:

$N = 10\ k / p$

$N = 10(4) / 0.0278 = 1{,}438$

Instrumentation and Operationalization of Constructs

Operationalization of the Variables

Study variables included four primary independent variables (race/ethnicity, histologic subtype, tumor grade, and insurance coverage), and three dependent variables (endometrial cancer stage at diagnosis, receipt of surgery, and survival). The demographic variables analyzed in this study included age, race/ethnicity, insurance, and marital status. Clinical variables included in analysis were stage of disease, tumor histology, tumor grade, and treatment. Table 1 below presents study variables.

Table 1

Research Variables, Measures, and Coding

Variable	SEER*Stat Variable Name	Operational Definition	Measurement
Race/Ethnicity	Race and Origin recode	NHW =1 NHB = 2 NHAIAN = 3 NHAPI = 4 Hispanic = 5	Nominal
Age at diagnosis	Age recode with single ages and 85+	18-45 years = 1 46-55 years = 2 56-65 years = 3 66-75 years = 4 >=76 years = 5	Ordinal
Tumor Histology	Histologic type ICD-O-3	Endometroid =1 Uterine carcinosarcoma = 2 Serous carcinoma = 3 Clear-cell carcinoma = 4 Other or unspecified = 5	Nominal
Tumor Histology	Histologic type ICD-O-3	Non-aggressive = 1 Aggressive = 2	Nominal
Tumor grade	Grade	Well differentiated = 1 Moderately differentiated = 2 Poorly differentiated =3 Undifferentiated/Anaplastic = 4 Unknown = 5	Nominal
Tumor Grade (dichotomized)	Grade	Low-grade = 1 High-grade = 2	Nominal

Table 2 Continued

Treatment	First course of treatment	Surgery (Yes) = 1 Surgery (No) = 2	Nominal
Insurance	Insurance recode	Uninsured = 1 Insured = 2 Medicaid = 3	Nominal
Stage of disease at diagnosis	Derived AJCC Stage Group, 7th ed (2010+)	Localized = 1 Regional = 2 Distant = 3	Nominal
Stage at diagnosis (dichotomized)	Derived AJCC Stage Group, 7th ed (2010+)	Non-advanced = 1 Advanced = 2	Nominal
Survival	Survival in months	MMMM = Survival time in months	Continuous
Marital status	Marital status at diagnosis	Single = 1 Married = 2 Separated/Divorced = 3 Widowed = 4	Nominal

Data Analysis Plan

Data were abstracted from the SEER database based on the assumption that the registry collects accurate, well-defined, and complete information on the key variables needed to address the research questions in this study, including characteristics of the study population; exposures of interest; patient outcomes; and potential confounding factors. After abstracting all necessary data for analysis, data cleaning and screening procedures were implemented to examine the quality of the data collected. Data cleaning and analyses were carried out between March and May 2020. Statistical screening methods involved using SPSS to carry out descriptive statistics to summarize and organize the data. According to Greenland and Finkle (1995), a common challenge when evaluating large datasets required for most multivariate analyses is the problem of handling missing data, whether the missing values are a function of a random or a systematic process. During the data screening process, it was important to check for the issue of missing data so as to identify and minimize the impact of errors or bias on study results. Dataset was also checked and corrected for errors. Descriptive analysis was done for all the variables using the cleaned dataset. Descriptive statistics were then presented as frequencies and percentages to describe the distribution of study variables including sociodemographic factors, tumor, and treatment characteristics. IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) was used to perform all analyses. Table 2 summarizes the data analysis plan for each research question.

Table 3

Research Questions, Variables, and Statistical Tests

Research Questions	Variables	Statistical Tests
Q1: What determinants are associated with late-stage diagnosis of endometrial cancer (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis?	Race/ethnicity; Age at diagnosis; Stage of disease; Histologic subtype; Tumor grade; Insurance; Marital status	Chi-square analysis; Multivariable logistic regression
RQ2: What determinants are associated with receipt of surgery in women diagnosed with endometrial cancer in the United States?	Race/ethnicity; Age at diagnosis; Stage of disease; Receipt of surgery; Histologic subtype; Tumor grade; Insurance; Marital status	Chi-square analysis; Multivariable logistic regression
RQ3: Are there racial/ethnic differences in 5-year survival of women diagnosed with endometrial cancer in the United States?	Race/ethnicity; Age at diagnosis; Histologic subtype; Tumor grade; Receipt of surgery; Marital status; Survival months; Advanced stage diagnosis; Endometrial cancer-cause specific mortality; endometrial cancer	Kaplan-Meier survival curves; Log-rank test; Multilevel Cox proportional hazards regression models
RQ4: Is there a significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States?	Race/ethnicity; Age at diagnosis; Histologic subtype; Tumor grade; Receipt of surgery; Marital status; Insurance status; Survival months; Advanced stage diagnosis; Endometrial cancer-cause specific mortality	Kaplan-Meier survival curves; Log-rank test; Cox proportional hazards regression models

Analysis Plan Addressing Research Questions and Hypotheses

RQ1: Are race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status associated with late-stage diagnosis of endometrial cancer (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis?

$H_0$1: The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are not associated with late-stage endometrial cancer diagnosis (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis.

H_a1: The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are associated with late-stage endometrial cancer diagnosis (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis.

To test this hypothesis, chi-square analysis was used to assess what determinants (race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, and marital status) were associated with late-stage diagnosis of endometrial cancer (Stage III and IV) in the US versus early-stage (I and II). Multivariate logistic regression analysis were performed to measure the association between study variables and late-stage endometrial cancer diagnosis. Both unadjusted and adjusted odds ratios (OR) with their corresponding 95% confidence interval (CI) were calculated. All tests were evaluated at a 2-sided

significance level of $p<0.05$. SPSS version 25 (IBM Corp., Armonk, N.Y., USA) was used for all analyses.

RQ2: Are race/ethnicity, age at diagnosis, histologic, subtype, tumor grade, insurance, stage at diagnosis, and marital status associated with receipt of surgery in women diagnosed with endometrial cancer in the United States?

$H_0$2: The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are not associated with receipt of surgery in women diagnosed with endometrial cancer in the United States.

H_a2: The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are associated with receipt of surgery in women diagnosed with endometrial cancer in the United States.

To test this hypothesis, chi-square analysis was used to assess what determinants (race/ethnicity, age at diagnosis, stage at diagnosis, histologic subtype, tumor grade, insurance, and marital status) were associated with receipt of surgery as primary treatment for endometrial cancer patients. Multivariate logistic regression analysis were performed to measure the association between study variables and receipt of surgery. Both unadjusted and adjusted odds ratios (OR) with their corresponding 95% confidence interval (CI) were calculated. All tests were evaluated at a 2-sided significance level of $p<0.05$. SPSS version 25 (IBM Corp., Armonk, N.Y., USA) was used for all analyses.

RQ3: Are there racial/ethnic differences in 5-year survival of women diagnosed with endometrial cancer in the United States?

$H_0$3: There is no significant difference by racial/ethnicity in 5-year survival of

women diagnosed with endometrial cancer in the United States.

H_a3: There is a significant difference by racial/ethnicity in 5-year survival of women diagnosed endometrial cancer in the United States.

Kaplan-Meier curves were constructed to assess differences in mortality over time; racial/ethnic differences in survival were evaluated with the log-rank test. Multilevel Cox proportional hazards regression models were applied to analyze the racial/ethnic disparities in endometrial cancer-cause specific mortality while controlling for potential confounders. All tests were evaluated at a 2-sided significance level of $p<0.05$. SPSS version 25 (IBM Corp., Armonk, N.Y., USA) was used for all analyses.

RQ4: Is there a significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States?

$H_0$4: There is no significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States.

H_a4: There is a significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States.

Chi-square tests were employed to analyze the relationship between insurance and all other covariates. Kaplan-Meier survival curves were used to calculate cumulative 5-year survival, and cox proportional hazards regression models were used to estimate hazard ratio (HR) and 95% confidence intervals (CIs) for cause-specific survival within 5 years after diagnosis. All tests were evaluated at a 2-sided significance level of $p<0.05$. SPSS version 25 (IBM Corp., Armonk, N.Y., USA) was used for all analyses.

Treatment of Missing Data

The goal was to conduct statistical analyses using complete data only. However, if necessary, multiple imputation method could be used to impute missing data and produce estimates of the parameter(s) of interest. Sensitivity analysis was conducted to examine whether missing data could have biased any of the study findings.

Threats to Validity

The primary goal of this research study was to generate valid results with minimal error. It was therefore important to ensure the internal and external validity of this study. The data used for this observational study were from the SEER database, a nationally representative population-based dataset. Studies have shown that a large sample size is a major advantage of using cancer registry datasets (Magee, Lee, Giuliano, & Munro, 2006; Park et al., 2012). Due to its large sample size, analytic results from this study were more generalizable and minimized threats to external validity. In contrast, internal validity is the "extent to which systematic error is minimized during the process of data collection" (Shadish, Cook, & Campbell, 2002). Threats to validity based on methods of data collection are quite common in secondary data analyses. SEER use of data collection and quality standards by registry personnel allowed for an internal consistency that minimized potential bias (Duggan et al., 2016). To avoid errors that could influence study conclusions, any degree of random error was evaluated using statistical methods. Additionally, statistical analysis was carried out to ensure data were not missing at random as this could impact incidence and survival estimates of endometrial cancer cases; it could also be a source of bias affecting internal validity. Any

potential threat to statistical conclusion validity like low statistical power that could prevent this retrospective study of cross-sectional data from detecting a true effect was mitigated by using a large sample size, selecting reliable outcome measures and using appropriate statistical tests for data analysis.

Ethical Procedures

The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute gave permission to access its Research Data File after signing a Research Data Agreement form with an option to download required files with the assigned username and password.

Human Subjects Protection

The SEER program emphasizes the need to protect the identities of cancer patients. Since study analysis was carried out using secondary data, there was no direct access to human participants in this research study. SEER data was de-identified i.e. all identifying information on individual patients have been removed from the data files thereby eliminating any risks of disclosure of confidential or private information that could constitute bias or conflict of interest by the researcher. This research study with information on data usage for the primary purpose of analysis was submitted to the Institutional Review Board (IRB) at Walden University for approval. IRB approval number #02-20-20-0588627.

Ethical Concerns

U.S. Cancer registries including the SEER registry do not have uniform procedures for identifying and contacting potential research participants so there is

limited information on ethical concerns related to recruitment materials and processes (Beskow, Sandler, & Weinberger, 2006). However, the implemented Health Insurance Portability and Accountability Act (HIPAA) mandates cancer registries to engage in ethical recruitment practices that maximize privacy protections such as educating patients about the registry, involving physicians in patient recruitment, and initiating contact with only patients who indicate an interest in participating after receiving an introductory letter about the study. Using secondary data is based on the assumption that recruitment activities in the SEER program take place within the context of well-established practices for ethically responsible research with the primary aim of minimizing risk to participants. SEER data quality improvement strategies also include cancer registry personnel involved in the data collection process to sign statements that prevent the use of data and safeguard patient confidentiality.

Treatment of Data

The data obtained from SEER were anonymous, and as specified in the Research Data Agreement form, there were no attempts made to identify individuals, and research results were presented such that they contained no patient identifiers. This researcher maintained the utmost integrity and professionalism in handling data throughout the research process. Data were stored as a password-protected file and securely saved on a personal computer. To maintain patient confidentiality, the SEER data file and all supporting documents will be permanently deleted from the computer on completion of this doctoral study.

Summary

In summary, this chapter presented a focused discussion on the research design and methodology used in this quantitative retrospective cross-sectional study. Secondary data obtained from the NCI SEER database was used to answer research questions aimed at ascertaining the determinants of endometrial cancer survival disparities in the U.S. Study results and findings were discussed in section 3.

Section 3: Presentation of the Results and Findings

Introduction

This section highlights the results and findings generated from the analyses of the research questions and hypotheses presented in this study. This is a quantitative secondary analysis using SEER data to ascertain the determinants associated with endometrial cancer survival disparities in the United States. The SEM is the conceptual framework used to guide this study. The following research questions and hypotheses were evaluated in this study:

RQ1: Are race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status associated with late-stage diagnosis of endometrial cancer (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis?

$H_0$1: The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are not associated with late-stage endometrial cancer diagnosis (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis.

H_a1: The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are associated with late-stage endometrial cancer diagnosis (Stage III and IV) in the United States as compared to women with Stage I and II endometrial cancer diagnosis.

RQ2: Are race/ethnicity, age at diagnosis, histologic, subtype, tumor grade,

insurance, stage at diagnosis, and marital status associated with receipt of surgery in women diagnosed with endometrial cancer in the United States?

$H_0$2: The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are not associated with receipt of surgery in women diagnosed with endometrial cancer in the United States.

H_a2: The determinants: race/ethnicity, age at diagnosis, histologic subtype, tumor grade, insurance, stage at diagnosis, and marital status are associated with receipt of surgery in women diagnosed with endometrial cancer in the United States.

RQ3: Are there racial/ethnic differences in 5-year survival of women diagnosed with endometrial cancer in the United States?

$H_0$3: There is no significant difference by racial/ethnicity in 5-year survival of women diagnosed with endometrial cancer in the United States.

H_a3: There is a significant difference by racial/ethnicity in 5-year survival of women diagnosed endometrial cancer in the United States.

RQ4: Is there a significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States?

$H_0$4: There is no significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States.

H_a4: There is a significant difference in 5-year survival by health insurance status of women diagnosed with endometrial cancer in the United States.

This section includes information on data collection, the descriptive and demographic characteristics of the sample, and a summary of results from the series of statistical analyses performed to test the research questions and hypotheses.

Data Collection of Secondary Data Set

Data were collected from the NCI's SEER database, which includes data on cancer incidence and survival from population-based cancer registries in the United States. The first step to accessing SEER data is to sign the SEER Data-Use Agreement form which emphasizes essential guidelines for using the data. I signed the SEER Data-Use Agreement form and received approval in November 2019 (Appendix A) to access to SEER 1975–2016 Research Database. I used the SEER*Stat software to download the SEER 18: 1975-2016 Research Data File (November 2018 Submission) through an internet connection i.e., SEER*Stat's client-server mode to specifically obtain data for women diagnosed with endometrial cancer from 2007 through 2016. The variables selected for data collection were race/ethnicity, age at diagnosis, tumor grade, stage of disease, histology, treatment, insurance, survival time, and marital status. The initial dataset consisted of 130,375 deidentified cases of endometrial cancer. The IBM SPSS version 25 software application was used to carry out further analysis of study variables.

Characteristics of the study population

The endometrial cancer (corpus uteri and uterus, NOS) incidence and mortality data were obtained from the NCI SEER database which includes women who were diagnosed with primary invasive stages I, II, III or IV uterine corpus tumors between 2007 and 2016. However, women with in-situ cancers, uterine sarcomas, or a previous

history of cancer were excluded from analysis (*N* = 130,375). The analysis was also restricted to women ages 18 to 99 (*N* = 130,366). Patients were excluded if they were missing data on or marital status (*N* = 7,629), race/ethnicity (*N* = 522), insurance (*N* = 2,557), treatment (*N* = 191), and stage at diagnosis (*N* = 3,150). Treatment information includes patients who did or did not receive surgery (hysterectomy) as primary therapy. The final analytic cohort contained 115,997 patients.

There were several factors taken into consideration to ensure the representativeness of the data sample to the target population with respect to the determinants of interest in this study. Based on tumor histology, each cancer was designated as one of the following types: endometrioid, uterine carcinosarcoma, serous carcinoma, clear-cell carcinoma, and other/unspecified endometrial cancer. The variable "stage at diagnosis" was classified as localized, regional, or distant; and further dichotomized as non-advanced stage (localized), and advanced stage (regional or distant). Tumor grade was classified as well differentiated, moderately differentiated, poorly differentiated, undifferentiated, and unknown. To ascertain the factors associated with advanced-stage disease, two groups were compared in this analysis; women diagnosed with late-stage endometrial cancer (Stage III and IV) and women diagnosed with early stage (Stage I and II) endometrial cancer. To explore survival disparities by race/ethnicity, the variable was categorized as non-Hispanic White (NHW), non-Hispanic Black (NHB), American Indian/Alaska Native (NHAIAN), Asian/Pacific Islander (NHAPI), and Hispanic women. For this analysis, Hispanics includes all "persons of specific Hispanic/Latino origins" (e.g., Mexican, Cuban, Puerto Rican (SEER, 2018).

The determinant, age at diagnosis, was categorized as follows: 18–45, 46–55, 56–65, 66–75, 76 and over. To examine whether types of insurance are associated with survival disparities for endometrial cancer patients, uninsured patients, insured patients (includes private insurance and Medicare), and Medicaid-insured patients were compared. The "marital status" variable was grouped into four main categories: single, married, separated/divorced, and widowed. The "treatment" variable was categorized as patients who received surgery (yes) or did not receive surgery (no) as primary treatment.

Chi-square test for univariate analysis was used to examine demographic and socioeconomic characteristics of endometrial cancer patients. The study population included 115,997 patients, the majority 80,275 (69.2%) being NHW women, 11,579 (10.0%) were NHB women, 733 (0.6%) were NHAIAN, 9,573 (8.3%) were NHAPI, and 13,837 (11.9%) were Hispanic. Patients over the age of 45 were more likely to be diagnosed with endometrial cancer. Most diagnosed patients were aged 56–65 (35.2%), followed by patients aged 66–75 (24.1%), then 46–55 (19.3%), with only about 7.9 % of patients diagnosed in the 18–45 age group. Histological characteristics showed that 85,157 (73.4%) of endometrial cancer patients presented with endometroid tumors, with less favorable subtypes such as uterine carcinosarcomas (11.5%), serous carcinomas (6.8%), clear cell carcinomas (1.3%), and other/unspecified cases consisted of 6.9% of all cases. Although 23.7% of patients reported unknown tumor grade, well differentiated (31.9%), moderately differentiated (20.7%), poorly differentiated (16.3%), and undifferentiated/anaplastic tumors (7.3%), made up endometrial cancer cases, respectively. Additionally, of the total number of women included in the study, 98,985

(85.3%) were insured, 13,383 (11.5%) had Medicaid, and 3,614 (3.1%) were uninsured. Most patients were married 61,594 (53.1%), while 23,474 (20.2%) of patients were single, 14,007 (12.1%) were separated/divorced, and 16,922 (14.6%) were widowed. The presentation of early or nonadvanced stage disease occurred in 80,052 (69.0%) of women compared to 35,945 (31.0%) of women who were diagnosed at advanced stage of disease. Only 6,721 (5.8%) of endometrial cancer patients received surgical treatment as their first course of cancer-directed therapy.

Results

Descriptive characteristics stratified by race/ethnicity are presented in Table 3.

Table 4

Characteristics of Women Diagnosed with Endometrial Cancer, SEER 2007 – 2016 by Race/Ethnicity

Characteristic	All patients (*N* = 115,997)	Non-Hispanic White (*N* = 80,275)	Non-Hispanic Black (*N* = 11,579)	Non-Hispanic American Indian/Alaskan Native (*N* = 733)	Non-Hispanic Asian/Pacific Islander (*N* = 9,573)	Hispanic (*N* = 13,837)	*Chi-square p*-value
Age at Diagnosis							
18-45	9217 (7.9)	4435 (5.5)	902 (7.8)	131 (17.9)	1294 (13.5)	2455 (17.7)	
46-55	22383 (19.3)	14387 (17.9)	1770 (15.3)	192 (26.2)	2650 (27.7)	3384 (24.5)	<0.001
56-65	40849 (35.2)	28656 (35.7)	4404 (38.0)	236 (32.2)	3189 (33.3)	4364 (31.5)	
66-75	27961 (24.1)	20445 (25.5)	3199 (27.6)	129 (17.6)	1671 (17.5)	2517 (18.2)	
76+	15587 (13.4)	12352 (15.4)	1304 (11.3)	45 (6.1)	769 (8.0)	1117 (8.1)	
Marital Status at Diagnosis							
Single	23474 (20.2)	13916 (17.3)	3786 (32.7)	231 (31.5)	1825 (19.1)	3716 (26.9)	
Married	61594 (53.1)	44625 (55.6)	3641 (31.4	345 (47.1)	5992 (62.6)	6991 (50.5)	<0.001
Separated/Divorced	14007 (12.1)	9529 (11.9)	2002 (17.3)	85 (11.6)	693 (7.2)	1698 (12.3)	
Widowed	16922 (14.6)	12205 (15.2)	2150 (18.6)	72 (9.8)	1063 (11.1)	1432 (10.3)	
Insurance Type							
Uninsured	3629 (3.1)	1795 (2.2)	617 (5.3)	19 (2.6)	304 (3.2)	894 (6.5)	
Insured	98985 (85.3)	72511 (90.3)	8842 (76.4)	473 (64.5)	7755 (81.0)	9404 (68.0)	<0.001
Medicaid	13383 (11.5)	5969 (7.4)	2120 (18.3)	241 (32.9)	1514 (15.8)	3539 (25.6)	
Tumor Grade							
Well Differentiated	37013 (31.9)	26619 (33.2)	2043 (17.6)	259 (35.3)	3292 (34.4)	4800 (34.7)	
Moderately Differentiated	24064 (20.7)	17549 (21.9)	1870 (16.1)	123 (16.8)	1830 (19.1)	2692 (19.5)	
Poorly Differentiated	18900 (16.3)	12055 (15.0)	2934 (25.3)	114 (15.6)	1636 (17.1)	2161 (15.6)	<0.001
Undifferentiated/Anaplastic	8511 (7.3)	5307 (6.6)	1535 (13.3)	35 (4.8)	738 (7.7)	896 (6.5)	
Unknown	27509 (23.7)	18745 (23.4)	3197 (27.6)	202 (27.6)	2077 (21.7)	3288 (23.8)	
Tumor Histology							
Endometroid	85157 (73.4)	61428 (76.5)	6111 (52.8)	573 (78.2)	7031 (73.4)	10014 (72.4)	
Uterine Carcinosarcoma	13348 (11.5)	8671 (10.8)	2161 (18.7)	69 (9.4)	999 (10.4)	1448 (10.5)	
Serous Carcinoma	7930 (6.8)	4646 (5.8)	1691 (14.6)	38 (5.2)	666 (7.0)	889 (6.4)	<0.001
Clear-cell Carcinoma	1563 (1.3)	980 (1.2)	252 (2.2)	10 (1.4)	135 (1.4)	186 (1.3)	
Other or Unspecified	7999 (6.9)	4550 (5.7)	1364 (11.8)	43 (5.9)	742 (7.8)	1300 (9.4)	
Stage at Diagnosis							
Non-Advanced	80052 (69.0)	57091 (71.1)	6500 (56.1)	515 (70.3)	6515 (68.1)	9431 (68.2)	
Advanced	35945 (31.0)	23184 (28.9)	5079 (43.9)	218 (29.7)	3058 (31.9)	4406 (31.8)	<0.001
Treatment (Surgery)							
No	109276 (94.2)	75881 (94.5)	10590 (91.5)	688 (93.9)	9056 (94.6)	13061 (94.4)	
Yes	6721 (5.8)	4394 (5.5)	989 (8.5)	45 (6.1)	517 (5.4)	776 (5.6)	<0.001

According to chi-square results, there was a significant difference in age at diagnosis of endometrial cancer patients across race/ethnicity groups ($p < .001$). The youngest age group (18–45), NHAIAN (17.9%) and Hispanic (17.7%) women were more likely to be diagnosed with endometrial cancer compared to other racial/ethnic groups (NHW 5.5%; NHB 7.8%; NHAPI 13.5%). However, with increasing age, NHAPI (27.7%), NHAIAN (26.2%) and Hispanic (24.5%) women were more likely to be diagnosed with endometrial cancer in the age group 46–55 compared to NHW (17.9%) and NHB (15.3%) women. For the age group 56–65, although prevalence of endometrial cancer was high across all racial/ethnic groups (NHW 35.7%; NHAIAN 32.2%; NHAPI 33.3%; Hispanic 31.5%), NHB women (38.0%) still had a higher proportion of cases. NHB (27.6%) and NHW (25.5%) patients were more likely to be diagnosed at age of 66–75 compared to other racial/ethnic groups (NHAIAN 17.6%; NHAPI 17.5%; Hispanic 18.2%). NHW patients (15.4%) were more likely to be diagnosed over the age of 76 compared to other racial/ethnic groups (NHB 11.3%; NHAIAN 6.1%; NHAPI 8.0%; Hispanic 8.1%). NHB women were more likely to be unmarried at the time of diagnosis (32.7%) ($p < .001$). While NHW patients (55.6%) and NHAPI (62.6%) patients were more likely to be married compared to patients from other racial/ethnic groups (NHB 31.4%; NHAIAN 47.1%; Hispanic 50.5%) NHW patients were more likely have health insurance coverage (90.3%) and were less likely to be enrolled in Medicaid (7.4%), the lowest rate across other racial/ethnic groups

($p < .001$). Medicaid enrollees were more likely to be NHAIAN patients (32.9%), Hispanic (25.6%), NHB (18.3%), and NHAPI (15.8%). NHB patients (5.3%) and Hispanics (6.5%) were more likely to be uninsured.

NHB women were twice (43.9%) as likely to be diagnosed with advanced stage endometrial cancer compared with NHW (28.9%), NHAIAN (29.7%), NHAPI (31.9%), and Hispanics (31.8%; $p < .001$). In comparing tumor pathological characteristics, tumor histology and grade differed significantly by race/ethnicity ($p < .001$). NHB were more likely to have aggressive endometrial cancer based on tumor histology of all non-endometrioid carcinomas. In particular, uterine carcinosarcoma (NHW 10.8%; NHB 18.7%; NHAIAN 9.4%; NHAPI 10.4%; Hispanic 10.5%) and clear-cell carcinoma were two times more likely to occur in NHB patients (NHW 1.2%; NHB 2.2%; NHAIAN 1.4%; NHAPI 1.4%; Hispanic 1.3%), while cases of serous carcinoma (NHW 5.8%; NHB 14.6%; NHAIAN 5.2%; NHAPI 7.0%; Hispanic 6.4%) were three times more likely to occur in NHB patients compared to other racial/ethnic groups. In contrast, NHB women were less likely to be diagnosed with endometroid uterine corpus tumors. In addition, NHB were more likely to be diagnosed with higher grade disease. Compared to other racial/ethnic groups (NHW 5.5%; NHAIAN 6.1%; NHAPI 5.4%; Hispanic 5.6%), NHB patients (8.5%) were more likely to receive surgery as primary treatment of endometrial cancer ($p < .001$).

Factors Associated with Advanced Stage Diagnosis

In multivariable analysis (stepwise logistic regression), after adjusting for age, insurance, tumor histology and grade, NHB women were at an increased risk for

advanced stage disease. The risk for NHB women to present with advanced stage disease was significantly higher than for NHW women (odds ratio [*OR*] = 1.16; 95% confidence interval [*CI*] = 1.11, 1.22) (Table 4). NHAPI also reported an increased risk of late-stage disease compared to NHW women (*OR* = 1.16; 95% *CI* = 1.10, 1.22). However, this association was not significant in NHAIAN and Hispanic patients. Other factors associated with increased risk for advanced stage disease were increasing age, poor tumor grade, and aggressive tumor histology. Age was associated with advanced stage disease for each subgroup [46-55 years (*OR* = 1.12; 95% *CI* = 1.05, 1.20); 56-65 years (*OR* = 1.08; 95% *CI* = 1.02, 1.15); 66-75 years (*OR* = 1.13; 95% *CI* = 1.06, 1.21); 76+ (*OR* = 1.29; 95% *CI* = 1.20, 1.39)]. Tumor histology was stratified as "aggressive" and "nonaggressive" histology; study analyses showed a strong association between tumor histology and stage at diagnosis (*OR* = 2.22; 95% *CI* = 2.14, 2.30). Similarly, there was an increasingly strong association with tumor grade and advanced stage disease at these subgroups [moderately-differentiated tumors (*OR* = 2.74; 95% *CI* = 2.62, 2.86); poorly-differentiated tumors (*OR* = 5.86; 95% *CI* = 5.59, 6.14); undifferentiated tumors (*OR* = 6.01; 95% *CI* = 5.63, 6.41) when compared to well-differentiated tumors. In addition, having insurance was associated with a decreased risk for advanced stage disease (*OR* = 0.74; 95% *CI* = 0.68, 0.80). However, the association was not significant in the analysis of patients with Medicaid.

Receipt of Surgery Treatment

Depending on the extent of the disease in patients, the main treatment for endometrial cancer is hysterectomy, i.e., the surgical removal of a woman's uterus, and

cervix (ACS, 2018). Surgical treatment is most successful at early stage of disease. Only 5.8% of all endometrial cancer patients received surgery as their primary treatment (Table 3). In the univariate analysis, race/ethnicity was not associated with receipt of surgery. After controlling for stage at diagnosis in the multivariate analysis, race/ethnicity and marital status were not independently associated with receipt of surgery. Results from analysis also showed that insured patients (*OR* = 0.84; 95% *CI* = 0.73, 0.97) and patients with Medicaid (*OR* = 0.81; 95% *CI* = 0.69, 0.95) were less likely to receive surgery treatment (Table 4). With increase in age, patients were less likely to receive surgery as primary treatment [56–65 years (*OR* = 0.76; 95% *CI* = 0.67, 0.85); 66–75 years (*OR* = 0.77; 95% *CI* = 0.68, 0.86); 76+ (*OR* = 0.58; 95% *CI* = 0.51, 0.67). However, for the age group 46–55 years, the results were not significant (*OR* = 1.01; 95% *CI* = 0.94, 1.09). In the multivariate analysis, women of increased age were less likely to receive a hysterectomy. Although surgery as a first course of cancer-directed therapy is most frequently recommended for women with localized uterine corpus tumors, the analysis of predictors of receipt of surgery showed similar results of a strong association for patients who presented with aggressive histology (*OR* = 1.80; 95% *CI* = 1.68, 1.92, and advanced stage disease (*OR* = 3.20; 95% *CI* = 3.02, 3.40). In addition, tumor grade was associated with an increasingly strong association with receipt of surgery. Patients with [moderately-differentiated tumors (*OR* = 1.32; 95% *CI* = 1.20, 1.45); poorly-differentiated tumors (*OR* = 2.10; 95% *CI* = 1.92, 2.31); undifferentiated tumors (*OR* = 2.02; 95% *CI* = 1.80, 2.27)] were more likely to receive a hysterectomy.

Table 5

Variables Associated with Advanced-Stage Disease and Receipt of Surgery

Characteristic	Advanced Stage Diagnosis *OR*[a] (95% *CI*)	Receipt of Surgery *OR*[a] (95% *CI*)
Race/Ethnicity		
NH White	REF	REF
NH Black	1.16 (1.11 – 1.22)	1.04 (0.96 – 1.13)
NHAIAN	1.09 (0.92 – 1. 31)	1.09 (0.79 – 1.52)
NHAPI	1.16 (1.10 – 1.22)	0.82 (0.74 – 0.92)
Hispanic	1.09 (1.04 – 1.14)	0.89 (0.81 – 0.97)
Age at Diagnosis		
18-45	REF	REF
46-55	1.12 (1.05 – 1.20)	0.90 (0.79 – 1.01)
56-65	1.08 (1.02– 1.15)	0.76 (0.67 – 0.85)
66-75	1.13 (1.06 – 1.21)	0.77 (0.68 – 0.86)
76+	1.29 (1.20 – 1.39)	0.58 (0.51 – 0.67)
Marital Status at Diagnosis		
Single	REF	REF
Married	0.75 (0.72 – 0.78)	1.01 (0.94 – 1.09)
Separated/Divorced	0.84 (0.80 – 0.88)	0.92 (0.83 – 1.01)
Widowed	0.90 (0.86 – 0.95)	1.01 (0.92 – 1.12)
Insurance Type		
Uninsured	REF	REF
Insured	0.74 (0.68 – 0.80)	0.84 (0.73 – 0.98)
Medicaid	0.94 (0.86 – 1.03)	0.81 (0.69 – 0.95)
Stage at Diagnosis		
Non-advanced	-	REF
Advanced	-	3.21 (3.02 – 3.40)
Tumor Grade		
Well Differentiated	REF	REF
Moderately Differentiated	2.74 (2.62 – 2.86)	1.32 (1.20 – 1.45)
Poorly Differentiated	5.86 (5.59 – 6.14)	2.10 (1.92 – 2.31)
	6.01 (5.63 – 6.41)	2.02 (1.80 – 2.27)
Undifferentiated/Anaplastic		
Unknown	2.65 (2.54 – 2.77)	1.45 (1.32 – 1.59)
Tumor Histology		
Non-aggressive	REF	REF
Aggressive	2.22 (2.14 – 2.30)	1.80 (1.68 – 1.92)

Note.
NH = Non-Hispanic; AIAN = American Indian/Alaskan Native; API = Asian/Pacific Islander.
OR = odds ratio; CI = confidence interval;
aORs derived from the logistic regression model; REF=reference level.

Survival

Factors Associated with Endometrial Cancer-Specific Mortality

Cox proportional hazards model showing variables associated with risk for death are shown in table 5. Based on analysis of the 5-year study period, 14,053 (20.8%) women died of endometrial cancer. The number of deaths was disproportionately higher in NHB women (*N* = 2,748; 35.2%; $p < .001$) compared to NHW women (*N* = 8,570; 19.3%; $p < .001$). Among other minority women, NHB women had the highest overall mortality, followed by NHAIAN women (*N* = 443; 19.6%; $p < .001$), then Hispanic women (*N* = 9,064; 18.2%; $p < .001$), and then NHAPI (*N* = 5,760; 17.4%; $p < .001$). Using Cox proportional hazard multivariable analysis, after adjusting for age at diagnosis, marital status, tumor grade, histologic subtype, stage at diagnosis, type of treatment and insurance status, the hazard of disease-specific mortality was increased for NHB women compared to NHW women (Hazard ratio [HR] = 1.33; 95% *CI* = 1.27, 1.39; $p < .05$) (Table 5). There is no evidence of a difference between all other racial/ethnic groups and NHW women. Women aged 65 years and older had a higher risk of death due to endometrial cancer compared with women diagnosed below the age of 65 years (*HR* = 1.56; 95% *CI* = 1.50, 1.62; $p < .05$). Being married was a protective factor against endometrial cancer death; patients who were married were 18% less likely to die from endometrial cancer compared with unmarried patients (*HR* = 0.82; 95% *CI* = 0.79, 0.86; $p < .05$). The risk of death from endometrial cancer significantly increased in patients diagnosed with aggressive histologic subtype (*HR* = 1.58; 95% *CI* = 1.52, 1.65; $p < .05$); risk was 3 times higher in patients diagnosed with high-grade tumors (*HR* = 3.20; 95% *CI*

= 3.05, 3.35; $p < .05$), and 5 times higher in patients diagnosed with advanced stage disease (*HR* = 5.88; 95% *CI* = 5.65, 6.13; $p < .05$). Having insurance, whether private insurance or Medicare showed a protective effect against endometrial cancer cause-specific mortality as risk of death decreased by 32% (*HR* = 0.68; 95% *CI* = 0.63, 0.74; $p < .05$) compared to patients with no insurance. The hazard for patients with Medicaid also showed a decrease of 16% when compared to patients with no insurance (*HR* = 0.84; 95% *CI* = 0.77, 0.92; $p < .05$). Receipt of surgery treatment was independently associated with an increased risk (*HR* = 1.26; 95% *CI* = 1.20, 1.33; $p < .05$) for endometrial cancer death.

Table 6

Adjusted Hazard Ratios for Endometrial Cancer-Cause Specific Mortality

Characteristic	Endometrial Cancer-Cause Specific Mortality (*N* = 67,478) *HR* (95% *CI*)
Race/Ethnicity	
NH White	REF
NH Black	1.33 (1.27 – 1.39)
NHAIAN	1.08 (0.88 – 1. 33)
NHAPI	0.96 (0.90 – 1.02)
Hispanic	1.01 (0.96 – 1.07)
Age at Diagnosis	
< 65	REF
≥ 65	1.56 (1.50 – 1.62)
Marital Status at Diagnosis	
Single	REF
Married	0.82 (0.79 – 0.86)
Separated/Divorced	0.98 (0.93 – 1.04)
Widowed	1.23 (1.17 – 1.30)
Insurance Type	
Uninsured	REF
Insured	0.68 (0.63 – 0.74)
Medicaid	0.84 (0.77 – 0.92)
Stage at Diagnosis	
Non-advanced	REF
Advanced	5.88 (5.65 – 6.13)
Tumor Grade	
Low-grade	REF
High-grade	3.20 (3.05 – 3.35)
Unknown	2.60 (2.47 – 2.73)
Tumor Histology	
Non-aggressive	REF
Aggressive	1.58 (1.52 – 1.65)
Unknown	3.44 (3.28 – 3.61)
Treatment	
Non-aggressive	REF
Aggressive	1.26 (1.20 – 1.33)

Note.
HR = hazard ratio; *CI* = confidence interval.
[a]*HR*s derived from the Cox proportional hazards model.
Ref., reference group. * $p < .05$

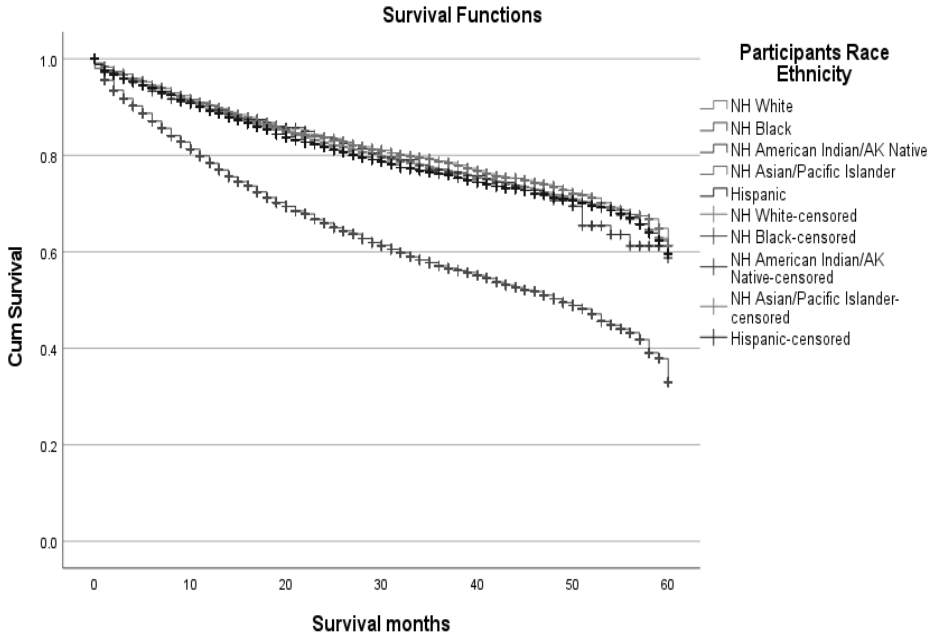
Disease-Specific Survival by Race/ethnicity and Disease Stage

Five-year survival rates were much lower in NHB women than other racial/ethnic groups diagnosed with endometrial cancer. The overall survival time was shorter among NHB women, compared to other racial/ethnic groups (Figure 2). The median survival time among NHB women was 49.0 months (95% *CI* = 46.8, 51.2); compared to NHW women who had a longer survival time. This disparity in survival remained the same with multivariable analysis (*HR* = 1.33; $p < .05$) (Table 5).

Additionally, of all the determinants included in the multivariable analysis, stage at diagnosis had a more significant impact on survival of women diagnosed with endometrial cancer. Sub-analysis of the interaction between race/ethnicity and stage at diagnosis shows racial/ethnic differences in survival time within each disease stage. The survival rate at five years from diagnosis showed that NHB women experienced worse survival outcomes for all stages combined. For localized disease, all racial/ethnic groups had similarly longer survival times (Figure 3); However, NHB women had a higher risk of death when presenting with advanced stage disease. For regional disease, the median survival time for NHB women was 34.0 months (95% *CI* = 31.4, 36.6) compared to 56.0 months (95% *CI* = 54.7, 57.3; $p < .05$) among NHW women; while distant-stage disease showed a median survival time of 9.0 months for NHB women (95% *CI* = 8.2, 9.7) versus 12.0 months (95% *CI* = 11.3, 12.7; $p < .05$) for NHW women. However, differences in survival time within each disease stage was less apparent among all other racial/ethnic groups when compared to NHW women.

Figure 2

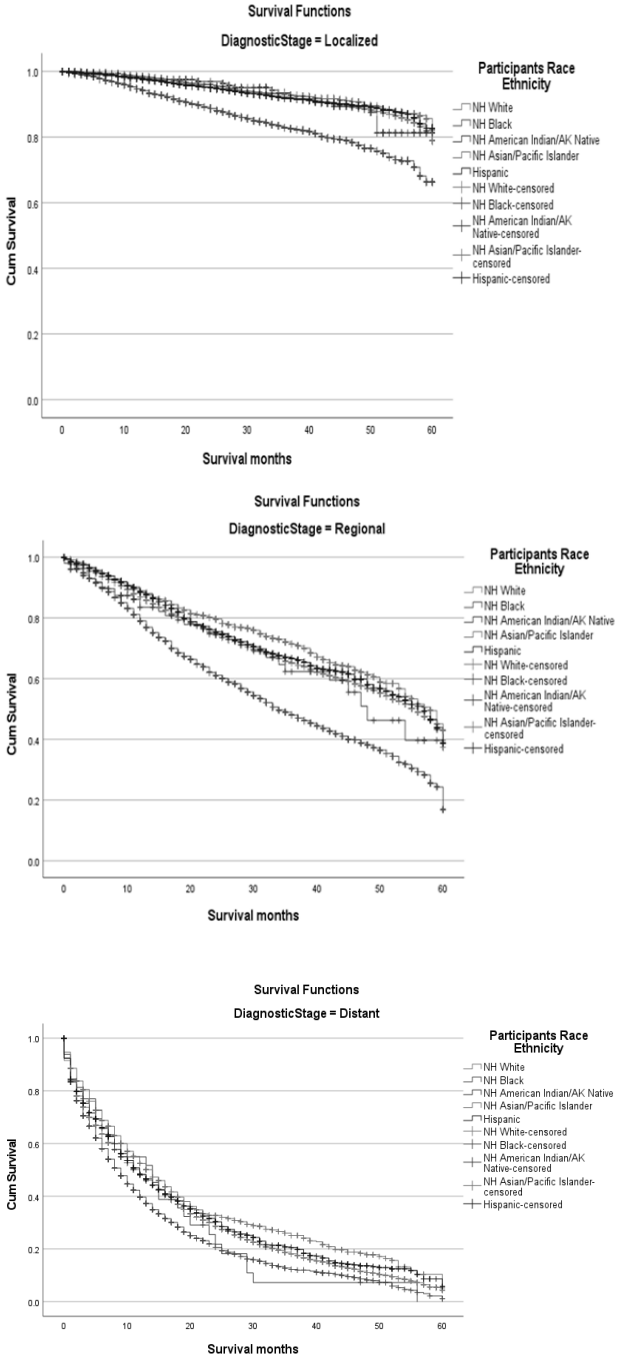
Cumulative 5-year Survival Curves for Women Diagnosed with Endometrial Cancer, by Race/Ethnicity



Note. Kaplan–Meier log-rank tests, * $p < .05$

Figure 3

Cumulative 5-year Survival Curves for Women Diagnosed with Endometrial Cancer, by Race/Ethnicity and Stage of Diagnosis



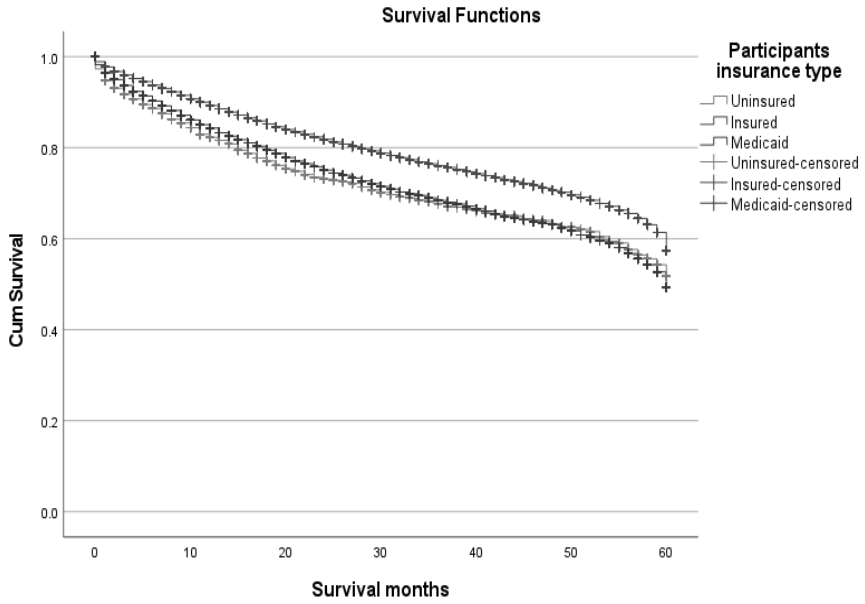
Note. Kaplan–Meier log-rank tests, * $p < .05$

Disease-Specific Survival by Insurance

Kaplan–Meier survival curves for insurance status of endometrial cancer patients are depicted in Figure 4. Of the women who died of endometrial cancer, 27.8% of patients had no insurance, 24.6% were enrolled in Medicaid, and 19.9% were privately insured. There was a significant difference in the estimated 5-year survival of women diagnosed with endometrial cancer ($p < .05$). In examining the association between health insurance status and survival, estimated 5-year cause-specific survival was higher for privately insured patients. Survival analysis for insurance status, stratified by stage at diagnosis, showed that uninsured patients and Medicaid enrolled patients with advanced stage disease had a significantly higher risk of death within 5 years of diagnosis (23.0 months; 95% *CI* = 18.8, 27.2) and (26.0 months; 95% *CI* = 24.0, 27.9) respectively, while privately insured patients had a longer survival time of 34.0 months (95% *CI* = 32.9, 35.1).

Figure 4

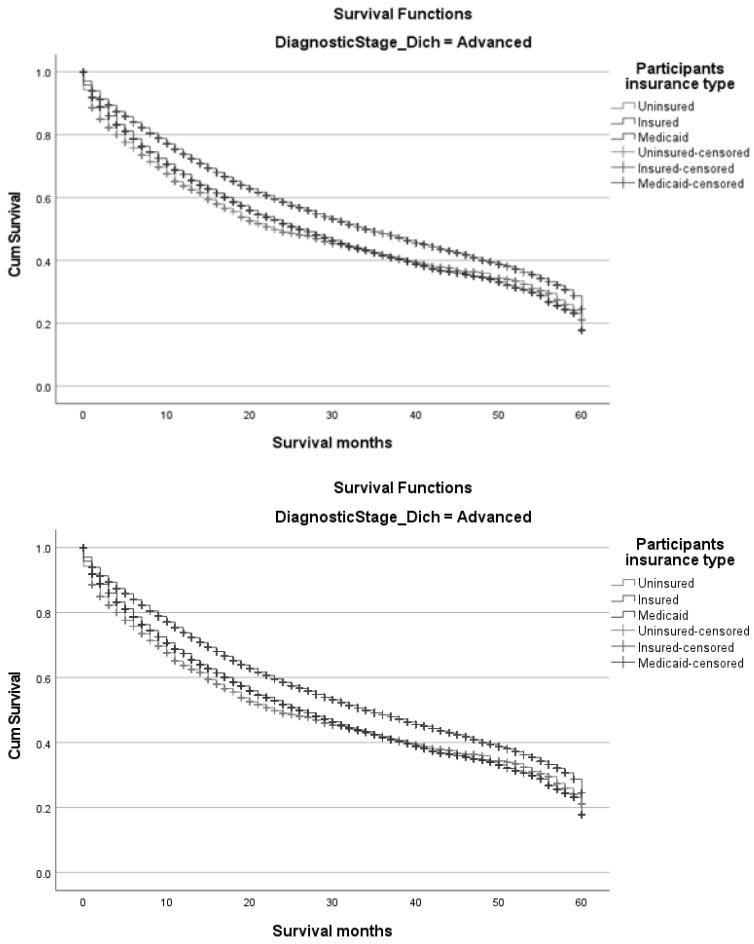
Cumulative 5-year Survival Curves for Women Diagnosed with Endometrial Cancer, by Insurance



Note. Kaplan–Meier log-rank tests, * $p < .05$

Figure 5

Cumulative 5-year Survival Curves for Women Diagnosed with Endometrial Cancer, by Insurance and Stage of Diagnosis



Note. Kaplan–Meier log-rank tests, * $p < .05$

This chapter presented results of descriptive statistics and hypotheses testing for the four research questions posed in this study. Specifically, to evaluate the independent effect of variables: race/ethnicity, age at diagnosis, marital status, stage at diagnosis, histologic subtype, tumor grade, treatment type, and insurance on endometrial cancer survival. Logistic regression analysis were used to test the null hypothesis against the alternative hypothesis (H_1 or H_a) for the first two research questions. The findings of research question one indicated that the determinants, race/ethnicity, age at diagnosis, tumor histology and grade significantly increased the risk of being diagnosed with late-stage endometrial cancer ($p < .001$). Therefore, the null hypothesis was rejected. However, insurance and marital status had no significant effect on late-stage diagnosis of endometrial cancer, so the null hypothesis was not rejected. The findings of the second research question showed that, tumor histology and grade, as well as stage at diagnosis were the only determinants that independently had an impact on receipt of surgery among women diagnosed with endometrial cancer ($p < .001$). Hence, the null hypothesis was rejected. However, the null hypothesis was not rejected for the independent variables race/ethnicity, age at diagnosis, insurance, and marital status as the results were not significant.

For research question three, hazard ratios adjusted for age at diagnosis, marital status, tumor grade, histologic subtype, stage at diagnosis, type of treatment and insurance status, showed that disease-specific mortality increased significantly when stratified by race/ethnicity ($p < .05$). Hence, the null hypothesis of no difference regarding survival times and racial/ethnic groups was rejected. Similarly, for question

four, there was a significant difference in the estimated 5-year survival of women diagnosed with endometrial cancer stratified by insurance status ($p < .05$). Hence, the null hypothesis that there is no difference in survival times between uninsured and insured patients with endometrial cancer was rejected.

Summary

The results of this study established that multiple determinants were significantly and consistently associated with late-stage endometrial cancer. The variables race/ethnicity, older age, poor tumor grade, and aggressive tumor histology were independent predictors of being diagnosed with late stage disease. NHB women were twice more likely to be diagnosed with advanced stage disease compare to NHW women. After adjusting for potential confounders in the multivariable analysis, health insurance status did not independently affect advanced-stage disease. NHB women were twice more likely to be diagnosed with advanced stage disease compare to NHW women. Increasing age affected the likelihood of receiving surgery as primary treatment. Also, patients who presented with aggressive histology, high grade tumors and advanced-stage disease were more likely to receive surgical treatment. Race/ethnicity was not independently associated with receipt of surgery after controlling for stage at diagnosis. Therefore, the influence of individual- and contextual-level factors contributed to racial/ethnic disparities in treatment for endometrial cancer.

Additionally, increasing age, race/ethnicity, aggressive histology, high grade tumors and advanced-stage disease were associated with an increased risk of endometrial cancer mortality; while having insurance was associated with a decreased risk for death.

NHB women had a disproportionately worse disease- specific survival even after adjusting for age, tumor histology and grade. There was a significant association between health insurance status and survival, estimated 5-year cause-specific survival was higher for privately insured patients. Survival analysis, stratified by stage of diagnosis, insured and Medicaid insured cancer patients with advanced stage disease had poorer survival outcomes compared to patients with insurance. A further review of study findings will be discussed in Chapter 4, including the study's application to professional practice and its implications for social change.

Section 4: Application to Professional Practice and Implications for Social Change

Introduction

The purpose of this study was to ascertain the determinants of endometrial cancer survival disparities in the United States. Specifically, my goal was to evaluate the independent effect of variables: race/ethnicity, age at diagnosis, marital status, stage at diagnosis, histologic subtype, tumor grade, treatment type, and insurance on endometrial cancer survival. The retrospective, cross-sectional study was carried out using epidemiologic data from NCI SEER Database which contained the most current data available on incidence and survival of endometrial cancer cases. The study sample included 115,997 women diagnosed with endometrial cancer from 2007 to 2016. The key findings suggest that causes of differences in endometrial cancer survival are multifactorial; race/ethnicity, increasing age, poor tumor grade, and aggressive tumor histology similarly influence the risk for presenting with advanced-stage endometrial cancer. Non-Hispanic Black women had a higher risk of being diagnosed with advanced stage endometrial cancer, and experienced worse disease-specific survival after controlling for factors such age at diagnosis, histologic subtype, tumor grade, and insurance. There were racial/ethnic disparities in survival rates; the 5-year overall survival for non-Hispanic White women with endometrial cancer was 81%, compared with 65% for non-Hispanic Black women. The interaction between race/ethnicity and stage of disease also showed that non-Hispanic Black women had a higher risk of death with advanced stage disease. Race/ethnicity was not an independent predictor of receipt of surgery after controlling for stage of diagnosis in the multivariate analysis. With

increased age, patients were less likely to receive surgery as primary treatment. However, aggressive histology, high grade tumors and advanced-stage disease were associated with receipt of surgery treatment in the multivariable analysis. There was a significant association between health insurance status and survival; estimated 5-year cause-specific survival was higher for privately insured patients. Survival analysis, stratified by stage of diagnosis, showed that among patients with advanced disease, those with insurance had better survival outcomes compared to patients with no insurance.

Interpretation of the Findings

Several studies have examined the racial/ethnic and socioeconomic factors associated with disparities in endometrial cancer survival across different population groups throughout the United States. It is well-documented that non-Hispanic Black women have disproportionally worse survival due to several potential factors that influence disease-specific mortality such as demographic and socioeconomic factors, tumor characteristics, and treatment factors (Cote, et al., 2015; Long et al., 2013; Rauh-Hain et al., 2015). However, it remains unclear why racial differences in survival persist after accounting for these factors. Chatterjee et al. (2016) found that African American women are more likely than White women to be diagnosed with advanced-stage disease, high-grade tumors (Grade III or Grade IV), and were more likely to suffer poorer prognosis. Additionally, Tarney et al. (2018) found that Black women with endometrial cancer suffer significantly worse survival outcomes regardless of age, stage and grade of disease. Findings from this study confirm these assumptions as increased age, African American ethnicity, aggressive histologic subtype, high-grade tumors and advanced-

stage disease were independently associated with increased risk for endometrial cancer death, and poorer survival outcomes. African American women had a higher risk of being diagnosed with aggressive histology, poor tumor grade, and advanced-stage disease. Increasing age was independently associated with being diagnosed with late stage disease across all racial/ethnic groups. The 5-year disease-specific survival was significantly higher at 81% for non-Hispanic White women, compared to 65% for non-Hispanic Black women; this racial/ethnic differences in survival was also evident within regional and distant disease stage.

Studies have demonstrated that older women are more likely to be diagnosed with high-grade uterine cancer tumors, poor histology, and advanced disease; thus, may require surgery and/or adjuvant therapy (Ahmed et al., 2008; Duska et al.,2016; Wright et al., 2011). Rauh-Hain et al. (2015) found that Black women with endometrial cancer are less often to receive surgical treatment at every stage and grade of disease and have poorer survival outcomes. While increasing age was not associated with receipt of surgery, study findings confirm that endometrial cancer patients with aggressive histology, poor tumor grade, and advanced-stage disease were more likely to undergo surgery. There was no racial/ethnic differences observed with receipt of surgery among women diagnosed with endometrial cancer.

The SEM was used as conceptual framework to explore the determinants of endometrial cancer survival disparities in the United States. This model takes into consideration the complexity of the multilevel interactions between individual, interpersonal, community, organization, and societal factors. Currently, there is no known

standard or routine screening test for endometrial cancer; hence the challenge to develop and implement evidenced-based policies that promote early detection and timely diagnosis. For this to happen, it requires a better understanding of perceived risk factors that influence health outcomes at these different levels. This includes the range of individual- and contextual-level factors such as the sociodemographic and tumor characteristics that can influence survival outcomes. At the community level, insurance plays a major role in predicting survival outcomes. The lack of adequate insurance coverage and other supplemental health programs could limit the number of women who seek medical care that could lead to early detection and timely diagnosis. Previous studies, albeit few, have examined the effects of insurance status on cancer outcomes including endometrial cancer. Findings have shown that uninsured and Medicaid insured patients have poorer survival outcomes compared to privately insured patients (Fedewa et al, 2011; Niu et al, 2013; Sohn, 2017). This is also consistent with study findings, except for patients on Medicaid, insured patients were less likely to be diagnosed with advanced stage endometrial cancer and reported significantly lower risks of death than uninsured and Medicaid insured patients.

Individual-level factors such as age, race/ethnicity, and marital status are also important demographic characteristics that can influence survival outcomes. There is a well-established association between marital status and survival in cancer patients; married patients compared to unmarried patients have decreased mortality in several malignances such as such as prostate, breast, cervical and colon cancers irrespective of age, tumor grade, and disease stage (Hanske et al., 2016; Hinyard et al., 2017; Liu et al.,

2019; Tyson et al., 2013; Wang et al., 2011). Lowery et al. (2015) examined the effect of marriage on survival outcomes for women diagnosed with uterine cancer, and found that compared to widows, married women experienced better uterine cancer survival outcomes. This study has examined the effect of marital status as a prognostic factor for survival of women diagnosed with endometrial cancer. The findings clearly indicate that being married is associated with a decreased risk of endometrial cancer mortality.

Limitations of the Study

The study was conducted using data obtained from SEER database, a national level cancer registry, which provides valid and reliable information related to endometrial cancer incidence and survival data, as well as individual-level data related to cancer diagnoses, histopathology and treatment characteristics across various demographic groups (SEER, 2018). The SEER program provides access to population-based data that is unique with regard to representativeness and generalizability to the U.S. population (Duggan et al., 2016). A major strength of this study is the large sample size and the representativeness of the study sample i.e., endometrial cancer patients diagnosed during the study period allowed for more reliable and generalizable results. In addition, using an appropriate sample size was critical to ensuring validity in this quantitative study. If the sample size is too small, it will not yield valid results in the multivariable analyses (Jones et al., 2003). Hence, a large sample size is necessary to estimate significant endpoints for this study including cause-specific survival.

One major limitation of this study is that adequate data related to SES, risky behavior, comorbidities, and other relevant health information are not available in the

SEER database. Although not included in study analysis, these variables including education, income, treatment regimen, smoking history, diabetes, and obesity have been known to affect endometrial cancer survival. It is possible that exempting these variables could have mitigated potentially confounding effects in this study. In addition, although cancer-specific mortality and survival outcomes for Black women diagnosed with endometrial cancer have improved over time, results from this study showed that the 5-year overall survival for Black women was 65%, compared to 81% for non-Hispanic White women, after controlling for confounding effects. This suggests that disparity in survival may be attributed to not just socioeconomic and histopathologic differences, but other unidentified factors not accounted for in this analysis.

Another limitation of this study is based on the underlying assumption that information obtained from the SEER database on cause-specific survival is correctly defined i.e., cause of death information obtained from death certificates was accurately documented during data abstraction. That is, any misclassification of cause of death is a major threat to the validity of study results for cause-specific survival. Finally, since this is a retrospective, cross-sectional study, results were based on the analysis of multiple variables captured at a specific point in time i.e., 2007 to 2016. Therefore, causality cannot be inferred from this analysis. Nevertheless, study limitations are less probable to influence the main conclusions of this study.

Recommendations

Research findings suggest that the determinants assessed in this study increased the likelihood of presenting with late-stage disease and may also account for increased

mortality from endometrial malignancy. However, they do not explain the differences in prognosis and survival observed between African American women and Caucasian women diagnosed with endometrial cancer. African American women were more likely to present with advanced stage disease, more aggressive histologic subtypes, and poorer tumor grade. There was also a significant decrease in survival among uninsured patients compared to privately insured patients. This might suggest that disparities in survival may be as a result of other influences such as comorbid conditions, socioeconomic status, access to appropriate and timely treatment. Hence, the findings of this study support the need for further research into the biologic mechanisms underlying differences in histopathology, as well as socioeconomic and treatment factors associated with disparities in endometrial cancer survival.

The survival disparity observed in African American women diagnosed with endometrial cancer is multifactorial, and its complexity highlights the need for continued research. Future studies should synthesize available evidence in literature to identify important research questions and facilitate designing targeted interventions that can have a real impact in reducing endometrial cancer disparities in the United States. Methodology recommendations for future researchers include having robust study methods and design to ensure validity of study results. It is important to ensure high quality method and measurements techniques targeted to measure exactly the outcome of interest. Some of the limitations of this study include data source, i.e. utilizing the SEER database was based on the assumption that data collected were complete and accurate. Researchers using information from large databases must assess the completeness and

accuracy of information contained in the database. This may include data source, geographic location of participant enrollment, techniques used in recruitment of participants, exclusion and exclusion criteria used to determine eligibility of study population, how patient demographics were defined and measured, and how outcome of interest was defined and measured. Comprehensive data should also be obtained for disease characteristics such as age at diagnosis, race/ethnicity, socioeconomic status, year of diagnosis, cancer stage at diagnosis, tumor grade and histology, comorbidities, and disease risk factors. In addition, the importance of developing specific research questions, selecting a rigorous study design, and expertise in analytic methods should not be underestimated.

Implications for Professional Practice and Social Change

The burden of endometrial cancer is significant. As the most commonly diagnosed gynecologic malignancy in the United States, it has become imperative to reverse the trend of increasing rates of endometrial cancer incidence and mortality. Future implications for professional practice include identifying ways to improve early detection of endometrial cancer, as well as advance professional practice and implement policies at the state and national levels that promote better survival outcomes. Over time, the Affordable Care Act (ACA) has expanded health insurance coverage for more women to have access to equitable, timely and quality health care (Holland et al., 2016). Low-income women who do not have insurance now benefit from the ACA's Medicaid expansion plan. Although uninsured rates in the United States have reduced substantially, racial and ethnic disparities in the receipt of adequate healthcare still exist. Early

diagnosis of disease improves overall prognosis so the significance of primary healthcare services for women cannot be understated. Access to care, especially primary health care practitioners can alleviate the burden of disease by earlier referrals to oncologists for proper diagnosis and treatment.

As previously discussed, the positive social change implications of this research study is primarily to improve survival outcomes for all women diagnosed with endometrial cancer in the United States. This includes identifying factors associated with increased mortality, and a better understanding of how those factors contribute to racial and ethnic disparities in endometrial cancer. Therefore, potential policy recommendations should focus largely on improving survival outcomes of subpopulations disproportionately affected by the impact of individual and contextual-level factors assessed in this study.

This includes:

1. Specific policy interventions targeted toward African American women who are at increased risk for advanced stage diagnosis, higher disease mortality, and are less likely to receive surgery treatment.
2. Advancing polices that ensure health insurance coverage includes potential treatments for subpopulations at risk.
3. Improving access to care by increasing the capacity and number of healthcare providers in underserved communities.

4. Promoting the use of standardized protocols and procedures by healthcare providers for the treatment of endometrial cancer so as to reduce racial/ethnic disparities.
5. Increasing awareness of racial and ethnic disparities among healthcare providers and the general public.

Conclusion

Endometrial cancer continues to be a major public health problem in the United States as incidence and mortality continue to rise. There is also a widening survival disparity observed among racial/ethnic groups, hence the need to examine multiple determinants associated with decreased survival among women with endometrial cancer. This study provided further evidence showing that disparities in survival cannot be fully explained by factors assessed in this study, elucidating the need for more research to explore other multilevel factors that may potentially contribute to disparities in endometrial cancer outcomes. The key to improving survival rates for women diagnosed with endometrial cancer is a better understanding of the complex interplay of multiple factors that have been suggested to contribute to inequalities in endometrial cancer outcomes. Population-based interventions should focus on increasing awareness of the significant benefits of early detection and implementing policies that ensure accessibility to quality health care services and treatment for all women.

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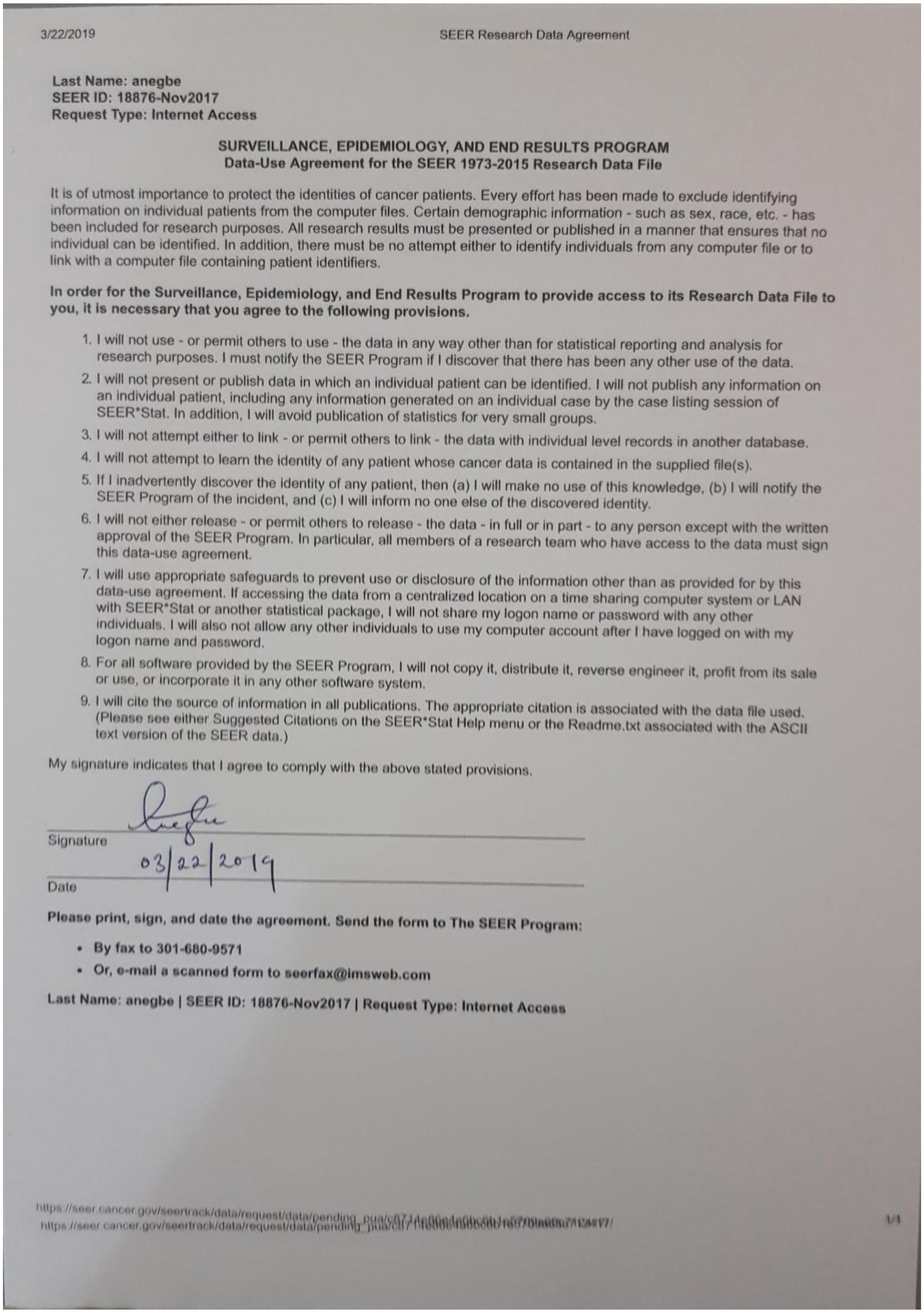
Appendix: SEER Data-Use Agreement



3/22/2019 SEER Research Data Agreement

Last Name: anegbe
SEER ID: 18876-Nov2017
Request Type: Internet Access

SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS PROGRAM
Data-Use Agreement for the SEER 1973-2015 Research Data File

It is of utmost importance to protect the identities of cancer patients. Every effort has been made to exclude identifying information on individual patients from the computer files. Certain demographic information - such as sex, race, etc. - has been included for research purposes. All research results must be presented or published in a manner that ensures that no individual can be identified. In addition, there must be no attempt either to identify individuals from any computer file or to link with a computer file containing patient identifiers.

In order for the Surveillance, Epidemiology, and End Results Program to provide access to its Research Data File to you, it is necessary that you agree to the following provisions.

1. I will not use - or permit others to use - the data in any way other than for statistical reporting and analysis for research purposes. I must notify the SEER Program if I discover that there has been any other use of the data.
2. I will not present or publish data in which an individual patient can be identified. I will not publish any information on an individual patient, including any information generated on an individual case by the case listing session of SEER*Stat. In addition, I will avoid publication of statistics for very small groups.
3. I will not attempt either to link - or permit others to link - the data with individual level records in another database.
4. I will not attempt to learn the identity of any patient whose cancer data is contained in the supplied file(s).
5. If I inadvertently discover the identity of any patient, then (a) I will make no use of this knowledge, (b) I will notify the SEER Program of the incident, and (c) I will inform no one else of the discovered identity.
6. I will not either release - or permit others to release - the data - in full or in part - to any person except with the written approval of the SEER Program. In particular, all members of a research team who have access to the data must sign this data-use agreement.
7. I will use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this data-use agreement. If accessing the data from a centralized location on a time sharing computer system or LAN with SEER*Stat or another statistical package, I will not share my logon name or password with any other individuals. I will also not allow any other individuals to use my computer account after I have logged on with my logon name and password.
8. For all software provided by the SEER Program, I will not copy it, distribute it, reverse engineer it, profit from its sale or use, or incorporate it in any other software system.
9. I will cite the source of information in all publications. The appropriate citation is associated with the data file used. (Please see either Suggested Citations on the SEER*Stat Help menu or the Readme.txt associated with the ASCII text version of the SEER data.)

My signature indicates that I agree to comply with the above stated provisions.

Signature

Date 03/22/2019

Please print, sign, and date the agreement. Send the form to The SEER Program:

- **By fax to 301-680-9571**
- **Or, e-mail a scanned form to seerfax@imsweb.com**

Last Name: anegbe | SEER ID: 18876-Nov2017 | Request Type: Internet Access

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