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Racial Disparities in Type II Endometrial Cancer in the United States

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Abstract

Racial Disparities in Type II Endometrial Cancer in the United States

By Lin Lyu

Background: Population-based studies concerning racial disparities in type II endometrial cancer (EC) remain limited. Our study was designed to investigate racial disparities in the incidence trends, clinical presentation, treatment and survival of type II EC.

Method: Type II EC cases diagnosed between 2004 and 2015 were identified from the Surveillance, Epidemiology, and End Results (SEER) 18 Registries. Racial differences in age-adjusted incidence rates, annual percentage change (APC), clinicopathological characteristics, and five-year relative survival rates were examined. A multivariate Cox proportional hazards model was fit to identify potential independent predictors for overall survival (OS) and cause-specific survival (CS).

Results: A total of 35,906 type II EC cases were included in this study. Age-adjusted incidence rates for type II EC increased significantly for non-Hispanic Blacks, non-Hispanic Others and Hispanics (APC, 1.87, 1.62, and 1.42, respectively), and remained stable for non-Hispanic Whites. Compared with non-Hispanic Whites, non-Hispanic Blacks had a significantly higher overall incidence rate of type II EC (incidence rate ratio [IRR] and 95% confidence interval [CI]:1.89[1.83, 1.94]), while non-Hispanic Others (IRR and 95% CI: 0.89[0.85, 0.92]) and Hispanics (IRR and 95% CI: 0.91[0.88, 0.94]) had significantly lower overall incidence rates. Non-Hispanic Black patients were more likely to be diagnosed with advanced stage (46.4% vs. 39.7%, $p<0.0001$), were less likely to receive hysterectomy (84.1% vs 89.9%, $p<0.0001$), adequate lymphadenectomy (37.9% vs. 47.9%, $p<0.0001$) and radiation (36.9% vs. 40.3%, $p<0.0001$), and were more likely to receive chemotherapy (48.4% vs. 43.0%, $p<0.0001$), compared with non-Hispanic Whites. After adjusting for age at diagnosis, diagnosis period, histologic subtype, stage, hysterectomy, extent of lymphadenectomy, radiation, and chemotherapy, non-Hispanic Blacks had significantly worse OS (hazard ratio [HR] and 95% CI: 1.24[1.18, 1.30]) and CS (HR and 95% CI: 1.23[1.17, 1.30]) compared with non-Hispanic Whites.

Conclusions: The overall incidence of type II EC over the 12-year period increased in all racial/ethnic groups other than non-Hispanic Whites. Compared with non-Hispanic Whites, non-Hispanic Blacks demonstrated a considerably higher risk of type II EC, while non-Hispanic Others and Hispanics exhibited considerably lower levels of risk. Non-Hispanic Blacks had worse OS and CS after controlling for clinical covariates compared with other racial/ethnic groups.

Keywords: type II endometrial cancer, racial disparity, SEER

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Chapter I

Background/Literature Review

Introduction

As the most common gynecological malignancy, endometrial cancer represents 7% of the new cancer cases and 4% of the cancer-related deaths in females annually in the United States (1). It is usually divided into two types based on primary differences in pathologic and clinical features (2-5). Type I endometrial cancer is the predominant type, including grade 1 and grade 2 endometrioid carcinoma, which is considered to arise from abnormal glandular proliferation in an estrogen-dependent manner (5). Type II endometrial cancer, encompassing clear cell carcinoma, serous carcinoma, grade 3 endometrioid carcinoma, undifferentiated adenocarcinoma as well as carcinosarcoma, is estrogen-independent and often develops from atrophic endometrium (6-8). Moreover, type I endometrial cancer usually presents at an early stage with a relatively promising prognosis (9-11), whereas type II endometrial cancer generally displays a more aggressive biological behavior with a poor prognosis (7, 12-15).

Racial disparity has been recognized in a broad spectrum of diseases including endometrial cancer. Previous studies indicated that African Americans with endometrial cancer had a greater likelihood of experiencing poor survival as opposed to Whites (17). The reasons for the inequality are unclear, but always considered multifactorial. Addressing the inequalities existing across racial/ethnic groups is of great importance in endometrial cancer care. In this review, we examined the existing literature concerning racial disparity in endometrial cancer in order to identify areas where racial

differences exist, provide directions for future research, and propose possible ways to reduce racial disparities observed in endometrial cancer.

Factors concerning racial disparity in endometrial cancer

Incidence and mortality

Racial disparity exists in both the incidence and mortality of endometrial cancer. According to a study using the Surveillance, Epidemiology, and End Results (SEER) data from 2000 to 2011, the overall incidence rate of endometrial cancer for non-Hispanic Blacks was 19% lower while the overall mortality rate was 55% higher than non-Hispanic Whites (18). In contrast, Hispanic and Asian females exhibited both lower overall endometrial cancer incidence and mortality compared to non-Hispanic Whites (18). Several studies have also indicated that although African Americans have lower overall incidence of endometrial cancer, they have significantly higher incidence of more aggressive histologic subtypes (18-22). Trends for this type of cancer have varied during different time periods. Doung et al. examined the incidence trends for the period between the years 1999-2006 (22). This work showed that while the incidence rate was increasing for type I endometrial cancer, it remained stable for type II endometrial cancer during their study period (22). However, a recent study projecting new cases of endometrial cancer from 2015 to 2040 predicted a substantial increase in overall incidence within all relevant racial groups, with a greater increase occurring in aggressive histologic subtypes, disproportionately affecting Blacks (23). Thus,

exploring racial differences in recent incidence trends, and especially for type II endometrial cancer, is of great necessity.

Clinical presentation

Several studies have assessed differences in the clinical presentation of endometrial cancer across racial groups. A recent study evaluated the influence of age at diagnosis on racial disparities utilizing SEER data between 1991 and 2010 (24). The results indicated that Black patients with serous carcinoma and carcinosarcoma had a greater probability of being diagnosed at a younger age when compared to White patients, and larger racial disparities in survival were observed in younger patients, suggesting that interventions implemented in early ages may be helpful for reducing these disparities. Variations in stage at diagnosis and histologic subtype prevalence are also seen in different racial groups. According to multiple studies, Black patients with endometrial cancer had a higher likelihood of being diagnosed at more advanced stages and presenting with more aggressive histologic subtypes (25-30). In a prospective multiethnic cohort study, Black women were found to have a greater probability of presenting with endometrial cancer that was high-grade (32.7% vs. 19.2%), more aggressive histology (30.9% vs. 8.7%) or at advanced stage (38.2% vs. 15.4%) compared with White women (29). A recently published SEER analysis including data of 110,826 patients with endometrial cancer diagnosed between 1980 and 2008 found that fewer Black patients presented with localized or type I endometrial cancer (30). Advanced stage at diagnosis and aggressive histologic subtypes are often associated with worse

survival. The disproportionately higher occurrence of endometrial tumor with worse characteristics in Black patients, may to some extent explain the observed survival disparity. Doll et al. looked at the link shared by racial disparities and the recognition of postmenopausal bloody discharge in endometrial cancer (31). They discovered that lacking the recognition of the symptom of postmenopausal bleeding was related to the late detection of the disease in Black women, suggesting that improving the symptom recognition among both Black patients and providers may have a positive effect in reducing racial disparities in endometrial cancer. Little is known about why the histologic distribution of endometrial cancer differs across racial groups. Research assessing diversity in the exposure to risk factors as well as differences in genetic predispositions across racial groups may provide opportunities to gain a better understanding about racial differences in histologic presentation. In light of the disproportionate distribution of aggressive histologic subtypes in different racial groups, future research should focus more on type II endometrial cancer to help narrow racial disparity in both disease presentation and survival.

Treatment

Receipt of appropriate treatment has a positive impact on the outcome of endometrial cancer. Surgery, including total hysterectomy with bilateral salpingo-oophorectomy and lymphadenectomy, plays a fundamental role in endometrial cancer treatment. Inequalities in the receipt of surgery has been considered as a contributor to racial disparity in endometrial cancer. Much of the research has demonstrated that Black patients had a lower probability of receiving definitive surgery when

compared with White patients (21, 26, 32-34). Rauh-Hain et al. examined the trends in the receipt of treatment among 77,814 patients who presented with high-risk stage I endometrial cancer across different racial and ethnic groups (35). The study pointed out that Black and Hispanic patients had lower likelihood of receiving lymphadenectomy (35). While racial disparity in the receipt of surgery has persisted over time, few studies have aimed to develop interventions to narrowing these disparities.

Adjuvant therapy, mainly referring to chemotherapy and radiotherapy, is indispensable for those suffering from high-risk endometrial cancer as it aims to reduce disease recurrence and improve survival. National Comprehensive Cancer Network (NCCN) guidelines for endometrial carcinoma expand on the standards for the choice of adjuvant therapy according to disease stage, histologic subtype and grade, as well as other risk factors (36). Treatment response, typically measured by the percentage of patients with disease that has lessened after treatment (37), has a great influence on survival for those receiving chemotherapy or radiation. Maxwell et al. conducted a pooled reanalysis utilizing data that was gathered from 169 Black and 982 White patients suffering from recurrent or advanced endometrial cancer, who participated in one of four Gynecologic Oncology Group (GOG) clinical trials on chemotherapy (38). This study indicated that Black patients had significantly lower treatment response (34.9%) compared with White patients (43.2%) (38). Another retrospective cohort study from a single institute examined the racial differences in recurrence among early stage endometrial cancer patients with definitive surgery and postoperative

adjuvant therapy (39). The locoregional recurrence rate among Black patients with aggressive histology who underwent postoperative chemotherapy and brachytherapy was nearly twice that in White patients (39). Since survival disparities between Black and White patients are disproportionately obvious in endometrial cancer with worse tumor characteristics, for which adjuvant therapy is warranted by NCCN guidelines, some researchers speculated that the lower rate of receipt of necessary adjuvant therapy might be a contributor to this disparity. A recent NRG Oncology/ Gynecologic Oncology Group 210 Study assessed this hypothesis (40). However, contrary to their assumptions, the results revealed that Black patients with low-grade endometrioid carcinoma or serous carcinoma were more likely to receive chemotherapy plus radiation compared with their White counterparts. Besides, after results were stratified by European Society for Medical Oncology (ESMO) risk group, higher odds of receiving chemotherapy plus radiation were observed in Black patients with high-risk endometrial cancer. The reasons accounting for the racial discrepancies in the receipt and effect of adjuvant therapy are undetermined. Future prospectively designed research concerning adjuvant therapy in endometrial cancer is needed to address the observed racial discrepancies.

Molecular and genetic factors

Molecular and genetic differences across racial groups may to a certain extent explain the observed racial discrepancies in the incidence of histologic subtypes and survival outcomes. The two types of endometrial cancers have distinct genetic profiles. PTEN, K-ras and β-catenin gene mutations,

and Microsatellite instability (MSI) are usually detected in Type I endometrial cancer, whereas mutations in p53 and HER-2/neu genes are more frequent in Type II endometrial cancer (41). It is reported that mutation of the PTEN gene, which usually portends more favorable survival, is more frequent in Caucasian patients than in Black patients (42). In contrast, mutations in p53 and HER-2/neu genes that are usually associated with poor survival are more frequent in Black patients than in White patients (43-46). Differential epigenetic alternations across racial groups have also been observed in endometrial cancer. One study assessed the association between ribosomal DNA (rDNA) methylation and the prognosis of endometrial carcinoma (47). Their results implied that low-level rDNA methylation was related to worse survival in endometrial cancer and was more likely to present in African American patients, which may contribute to the observed Black-White survival disparity (47). Besides, evaluation of racial genetic admixture (RGA) provides a new insight to assess racial disparity in outcomes. A recent NRG Oncology/Gynecologic Oncology Group research evaluated the association of RGA with the outcomes of endometrial cancer, which demonstrated a trend of worsening progression-free survival associated with increasing African RGA (48). Research concerning molecular and genetic alterations in endometrial cancer can not only help explore the mechanisms behind the racial disparities in incidence and survival, but may also provide the possibility of developing targeted genetic therapy that could help diminish survival disparities.

Social determinants

Racial disparities cannot be fully explained by biological and medical factors. Social determinants, such as socioeconomic conditions, education, insurance status, social support, health literacy, and access to health care services, may have potential important effects on health inequalities across racial groups. A population-based research examined the link shared by racial disparity and socioeconomic status in the context of endometrial cancer (34). The authors demonstrated that Black women had a higher probability of living in undereducated tracts (34% vs. 80%) and having a lower household income (median: $22,829 vs. $51275) compared with white women. The analysis also indicated that lower socioeconomic status was related to advanced stage at the time of diagnosis, a lower rate of hysterectomy, as well as inferior survival. These results imply that socioeconomic status may partly account for the survival inequality observed among African American patients. Fedewa et al. reported that patients without private health insurance had poorer survival for uterine cancer (49). Since African American patients had a higher probability to be uninsured or insured by Medicaid, insurance status may be a contributor to the disproportionately poor survival in African American patients as well. Another study revealed that African-American and Hispanic women had a longer time to treatment interval compared with Caucasian women and there was a positive association between a longer time interval from diagnosis to treatment and an increased mortality for endometrial cancer patients (50). Interventions targeted on shortening the time to treatment interval and increasing the possibility of early diagnosis may be effective in reducing racial disparities (50).

Comorbidity

Due to the fact that Blacks have relatively higher rates of certain health conditions (51-53), such as diabetes, hypertension, obesity and heart disease, some studies go on to propose the hypothesis that the presence of these comorbidities might contribute to this population's observed discrepancies in terms of endometrial cancer. However, according to current studies, it appears that comorbidities have little impact on racial disparities in endometrial cancer. Olson et al. examined the association between comorbidities (e.g. diabetes, hypertension) and survival disparities in endometrial cancer across racial groups (54). They found that the association between diabetes and poorer disease-specific survival existed only in white patients, and the presence of comorbidities could not explain the survival disparities observed between Blacks and Whites. Another retrospective study including 271 black patients and 356 white patients diagnosed from 1990 to 2005 found that hypertension was linked with favorable survival for both racial groups (55).

Research associated with racial disparity in type II endometrial cancer

Although type II endometrial cancer accounts for a much lower proportion of endometrial cancers, it contributes the majority of endometrial cancer deaths (16). Besides, type II endometrial cancer has a disproportionate distribution across racial groups. Thus, assessing the racial disparity in type II endometrial cancer is indispensable for elucidating the factors contributing to racial disparity, developing targeted interventions to reduce disparities, and consequently improving the overall survival of type II endometrial cancer. Despite the fact that several studies have been conducted to

address racial disparities in endometrial cancer, very few have specifically focused on type II endometrial cancer. According to our knowledge, only four published studies aimed to assesses the racial differences in type II endometrial cancer. Details of these four research studies are summarized in Supplementary Table S1. One study using SEER data from 1988 to 2009 examined the differences in tumor characteristics, treatment and prognosis between non-Hispanic White patients and Hispanic White patients (56). One study linked the SEER and Medicare data to evaluate the discrepancies in the treatment and survival between Black and White patients (26). Neither of these studies included all racial/ethnic groups. The other two studies utilized state-level data. A study utilizing data in Florida's Cancer Data System evaluated the risk of type II endometrial cancer across racial and Hispanic subgroups (57). A California Registry study examined factors affecting the survival by race and ethnicity (58). None of these four studies evaluated the incidence trends of type II endometrial cancer. Federation International of Gynecology and Obstetrics (FIGO) staging for endometrial cancer was revised in 2009, which resulted in corresponding changes in how the disease was diagnosed and treated. However, three of the four studies only included data before the change. Even in the one study which included data after the change of the FIGO staging system, no comparison was made before and after the change. Thus, comprehensive, contemporary, population-based research focused on the racial disparities in type II endometrial cancer is needed.

Conclusions

Racial disparities in endometrial cancer pervasively exist and are pronounced. At present, the majority of existing studies concerning racial disparity in endometrial cancer have mainly focused on evaluating Black-White differences and were not concentrated on type II endometrial cancer. Moreover, although the existing studies have already identified various areas where racial disparities exist, research aimed to develop interventions for reducing racial disparities is limited. Our study will be designed to address racial disparity specifically in type II endometrial cancer covering other minority groups in addition to Blacks and Whites using the most recent population-based data that is available to augment the existing body of literature. This work will provide opportunities to help develop a deeper and more comprehensive understanding of the root of racial discrepancies in type II endometrial cancer and may assist others in developing targeted interventions for eliminating existing disparities.

Chapter II

Manuscript

Racial Disparities in Type II Endometrial Cancer in the United States

By Lin Lyu

Abstract

Background: Population-based studies concerning racial disparities in type II endometrial cancer (EC) remain limited. Our study was designed to investigate racial disparities in the incidence trends, clinical presentation, treatment and survival of type II EC.

Method: Type II EC cases diagnosed between 2004 and 2015 were identified from the Surveillance, Epidemiology, and End Results (SEER) 18 Registries. Racial differences in age-adjusted incidence rates, annual percentage change (APC), clinicopathological characteristics, and five-year relative survival rates were examined. A multivariate Cox proportional hazards model was fit to identify potential independent predictors for overall survival (OS) and cause-specific survival (CS).

Results: A total of 35,906 type II EC cases were included in this study. Age-adjusted incidence rates for type II EC increased significantly for non-Hispanic Blacks, non-Hispanic Others and Hispanics (APC, 1.87, 1.62, and 1.42, respectively), and remained stable for non-Hispanic Whites. Compared with non-Hispanic Whites, non-Hispanic Blacks had a significantly higher overall incidence rate of type II EC (incidence rate ratio [IRR] and 95% confidence interval [CI]:1.89[1.83, 1.94]), while non-Hispanic Others (IRR and 95% CI: 0.89[0.85, 0.92]) and Hispanics (IRR and 95% CI: 0.91[0.88, 0.94]) had significantly lower overall incidence rates. Non-Hispanic Black patients were more likely to be diagnosed with advanced stage (46.4% vs. 39.7%, $p<0.0001$), were less likely to receive hysterectomy (84.1% vs 89.9%, $p<0.0001$), adequate lymphadenectomy (37.9% vs. 47.9%, $p<0.0001$) and radiation (36.9% vs. 40.3%, $p<0.0001$), and were more likely to receive chemotherapy (48.4% vs. 43.0%, $p<0.0001$), compared with non-Hispanic Whites. After adjusting for age at diagnosis, diagnosis period, histologic subtype, stage, hysterectomy, extent of lymphadenectomy, radiation, and chemotherapy, non-Hispanic Blacks had significantly worse OS (hazard ratio [HR] and 95% CI: 1.24[1.18, 1.30]) and CS (HR and 95% CI: 1.23[1.17, 1.30]) compared with non-Hispanic Whites.

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Keywords: type II endometrial cancer, racial disparity, SEER

Introduction

Uterine cancer is the most common malignancy of the female reproductive system and the sixth leading cause of cancer-related death for women in the United States (1). In 2019, 61,880 new cases and 12,160 deaths of uterine cancer are expected (1). Endometrial cancer is the main type of uterine cancer, which is often classified into two distinct subtypes based on the clinical and pathological characteristics (2,9). Type I endometrial cancer is the predominant type, which is suggested to be estrogen-dependent with a low-grade endometrioid morphology and has a relatively promising prognosis (6,9). Type II endometrial cancer is considered as estrogen-independent, which includes clear cell carcinoma, serous carcinoma, undifferentiated adenocarcinoma, carcinosarcoma, as well as high grade endometrioid carcinoma (6-8). It often displays a more aggressive biological behavior with a poor prognosis (11,59-63). Though type II endometrial cancer merely accounts for 10-20% of endometrial cancers, it contributes to approximately 40% of endometrial cancer deaths (2,6,7,64). Improving the outcome of type II endometrial cancer is the current focus of endometrial carcinoma treatment.

Racial disparities have been recognized as one of the most important issues in cancer care. Racial differences may exist in the distribution of risk factors, incidence, clinical manifestations, diagnosis and treatment, as well as prognosis. Previous studies indicated that although Black women had lower overall incidence of endometrial cancer in comparison with White women, they had higher likelihood of being diagnosed at more advanced stage, presenting with more aggressive histologic

types (e.g. type II endometrial cancer), and having inferior survival (19, 34, 54, 65-69). Although these studies addressed part of the racial disparities in endometrial cancer, comprehensive, contemporary, population-based studies specifically focused on type II endometrial cancer remain limited. Prior studies concerning racial disparities in type II endometrial cancer either mainly assessed differences in tumor characteristics and outcomes among specific race groups without exploring incidence trends (26, 56-58), or reported incidence and survival statistics for earlier time periods (18). Besides, Federation International of Gynecology and Obstetrics (FIGO) staging for endometrial cancer was revised in 2009, which led to corresponding changes in how the disease was diagnosed and treated. Some of these existing studies concerning racial disparities in type II endometrial cancer did not include data after the change of FIGO staging system. Even those including cases diagnosed after 2009 did not compare the differences before and after the change. Factors triggering the racial disparities in type II endometrial cancer are unclear. A comprehensive population-based evaluation of racial disparities in type II endometrial cancer is essential for clarifying the possible mechanisms of racial disparities, helping eliminate disparities and eventually improving the survival of type II endometrial cancer.

In order to systematically investigate racial disparities in the incidence trends, clinical presentation, treatment and survival for type II endometrial cancer in the United States, we conducted a retrospective analysis of type II endometrial cancer cases registered from 2004 to 2015 in the Surveillance, Epidemiology, and End Results (SEER) Program.

Material and methods

Dara source

This study used existing data from the SEER Program which covers approximately 34.6% of the U.S. population. The data were based on the November 2017 submission and released in April 2018 (70).

Study population

Type II invasive endometrial cancer cases diagnosed between 2004 and 2015 were identified from the SEER 18 Registries. Tumor site, histology, behavior and grade in SEER are coded according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3). We used the following ICD-O-3 primary site codes to identify the malignancies of uterine corpus: C54.0–C54.3, C54.8–C54.9, and C55.9. In this study, type II endometrial cancer was defined as high grade (grade 3 or undifferentiated endometrial cancer) endometrioid carcinoma (histologic codes 8140, 8210, 8211, 8260, 8261, 8262, 8263, 8340, 8380, 8381, 8382, 8383, 8384, 8560, 8570), high grade mixed adenocarcinoma (histologic codes 8323, 8255), serous carcinoma (histologic codes 8441, 8460, 8461), clear cell carcinoma (histologic codes 8005, 8310), and carcinosarcoma/malignant mixed müllerian tumor (CS/MMMT, histologic codes 8950, 8951, 8980, 8981). Cases with unknown race/ethnicity, unknown age at diagnosis, and those diagnosed by autopsy only or death certificate only were excluded (N=188), resulting in a study cohort of 35,906 cases eligible for descriptive analyses. In survival analysis, we excluded cases with second

primaries. Figure 1 shows the selection of type II endometrial cancer cases for inclusion in this study.

Data on demographics, clinicopathological characteristics, treatment, and survival were extracted from the SEER data. Cases included in this study were classified into four groups based on race/ethnicity: non-Hispanic White, non-Hispanic Black, non-Hispanic Other (including non-Hispanic American Indian/Alaska Native and Asian or Pacific Islander), and Hispanic. FIGO stage is not directly collected in SEER. To ensure consistency, FIGO stage for each case was determined by information on tumor extension, lymph node involvement, and presence or absence of distant metastasis, based on FIGO 2009 staging system definitions for endometrial cancer (71). In order to compare the incidence, treatment and survival before and after the revision of FIGO staging system in 2009, the period covered by this study was divided into to two time windows: 2004-2009 (period 1) and 2010-2015 (period 2).

Statistical analysis

Incidence rates (IRs) were calculated per 100,000 person-years and age-standardized to the 2000 US standard population. Incidence rate ratios (IRRs) along with 95% confidence intervals (CIs) were calculated to compare age-adjusted incidence rates and age-specific incidence rates by race/ethnicity. Time trends for incidence rates were examined by estimating the annual percent change (APC). Comparison of clinicopathological characteristics across racial groups was

performed. Chi-square tests were used for analyzing the association between categorical variables, while a t-test was used for assessing the difference in two group means for continuous variables. Five-year relative survival rates (RSRs) were calculated by actuarial methods. Differences in 5-year RSRs across racial groups and different time periods were analyzed using a z-test. Proportional hazards assumptions were assessed for each variable by using graphical methods, goodness-of-fit tests and time-dependent variables. A multivariate Cox proportional hazards model was fit to identify potential independent predictors for overall survival (OS) and cause-specific survival (CS). An alpha level of 0.05 was considered statistically significant. SEER*Stat software was used for the analyses of incidence rates and RSRs (72). Temporal trends were analyzed by using the SEER*Stat and Joinpoint software (73). Other analyses were performed by using SAS software package (version 9.4).

Results

Age-adjusted incidence rates for type II endometrial cancer

There were 35,906 cases of type II endometrial cancer reported in the SEER 18 registries between 2004 and 2015. Table 1 displays the case counts, age-adjusted incidence rates, and incidence rate ratios of type II endometrial cancer between 2004 and 2015 by race/ethnicity and histologic subtype. Non-Hispanic White women accounted for the majority of type II endometrial cancer cases (N=23,367, 65.1%), followed by non-Hispanic Blacks (N=5,910, 16.4%), Hispanics (N=3,655, 10.2%), and non-Hispanic Others (N=2,974, 8.3%). The overall age-adjusted incidence rate of type II endometrial cancer between 2004 and 2015 was significantly higher for non-Hispanic Blacks when compared with non-Hispanic Whites (IRR and 95% CI:1.89[1.83, 1.94]). All histologic subtypes showed excess risk for non-Hispanic Blacks in comparison with non-Hispanic Whites (IRRs and 95% CIs: high grade endometrioid carcinoma, 1.21[1.15, 1.28]; high grade mixed adenocarcinoma, 1.50[1.36, 1.66]; serous carcinoma, 2.54[2.39, 2.65]; clear cell carcinoma, 1.98[1.73, 2.25]; Carcinosarcoma/MMMT, 2.78[2.62, 2.94]). Different from non-Hispanic Blacks, both non-Hispanic Others (IRRs and 95% CIs: 0.89[0.85, 0.92]) and Hispanics (IRRs and 95% CIs: 0.91[0.88, 0.94]) exhibited significantly lower overall age-adjusted incidence rates than non-Hispanic Whites.

Age-specific incidence rates for type II endometrial cancer

The overall incidence rate of type II endometrial cancer and the incidence rates of all histologic subtypes increased with age for all racial groups, except for a decrease after the age of 80 years (Figure 2). Non-Hispanic Blacks had the highest age-specific incidence rates for all histologic subtypes after the age of 50 years.

Temporal trends in incidence rates for type II endometrial cancer

Table 2 displays the trends in incidence rates for overall type II endometrial cancer and specific histologic subtypes by racial/ethnic group over the 2004-2015 period. Overall incidence rates for type II endometrial cancer remained stable during 2004 to 2015 (APC and 95% CI: 0.50 [-0.03, 1.04)]). When examining the overall trend for all racial/ethnic groups together over the full period using a joinpoint model, we found the inclination that the overall age-adjusted incidence rates decreased from 2004 to 2006, increased from 2006 until 2009, and decreased again thereafter (Supplementary Figure S1). However, the APCs in each segment indicated by the ioinpoint model were not statistically significant. The final models determined by the joinpoint trend analysis for each racial/ethnic group separately were all models with no joinpoints (Supplementary Figure S2-S5). Over the 12-year period from 2004 to 2015, incidence rates of all type II endometrial cancers increased significantly for non-Hispanic Blacks, non-Hispanic Others and Hispanics (APC, 1.87, 1.62, and 1.42, respectively), and remained stable for non-Hispanic Whites (Figure 3a). Furthermore, age-adjusted incidence rates for high grade endometrioid carcinoma decreased

significantly for non-Hispanic Whites, non-Hispanic Blacks, and Hispanics (APC, -3.99, -3.92, and -3.23, respectively), and were stable for non-Hispanic Others (Figure 3b). Age-adjusted incidence rates of both mixed high-grade adenocarcinoma and carcinosarcoma/MMMT significantly increased for Hispanic women (APC for mixed high-grade adenocarcinoma, 4.65; APC for carcinosarcoma /MMMT, 3.61, Figure 3c and 3f), but remained stable for the other three groups. Significant increases in the incidence rates of serous carcinoma were observed among all racial/ethnic groups and non-Hispanic others exhibited the highest increase (APC, 7.31, Figure 3d). During the entire study period, incidence rates for clear cell cancer were stable for all racial/ethnic groups. Incidence rates for all histologic subgroups remained highest for non-Hispanic Blacks.

Figure 4 shows the age-adjusted incidence rates of type II endometrial cancer by histologic subtypes and race/ethnicity during period 1 (2004-2009) and period 2 (2010-2015). Age-adjusted incidence rates for non-Hispanic Blacks were highest for all histologic subtypes across all racial/ethnic groups in both periods. Overall incidence rates were significantly higher in period 2 than in period 1 in all racial/ethnic groups with the exception of non-Hispanic Whites (Figure 4a). Incidence rates for high grade endometrioid carcinoma were significantly lower in period 2 for all racial/ethnic groups with the exception of non-Hispanic Others. Incidence rates of mixed high-grade adenocarcinoma were significantly higher in period 2 for all racial groups other than non-Hispanic Others. Significantly increased incidence rates for serous carcinoma in period 2 were observed in all racial groups (Figure 4d). Significant increases in the incidence rates for

carcinosarcoma/MMMT in period 2 were only seen among non-Hispanic Others and Hispanics (Figure 4f). No significant differences in age-adjusted incidence rates for clear cell carcinoma were observed between the two periods for all racial/ethnic groups (Figure 4e). The estimates of age-adjusted incidence rates, incidence rate ratios, as well as the corresponding 95% CIs for both timeframes are presented in Supplementary Table S2-S7.

Clinical characteristics for type II endometrial cancer

Clinical characteristics for type II endometrial cancer cases are presented in Table 3. The mean age at diagnosis was younger in the non-Hispanic Black, non-Hispanic Other, as well as Hispanic groups than in the non-Hispanic White group (66.3, 63.2, 63.4, vs. 67.7 years, respectively, all $p<0.0001$). Non-Hispanic Blacks had higher likelihood of being diagnosed with certain more aggressive histologic subtypes (serous carcinoma and CS/MMMT) compared with non-Hispanic Whites (serous carcinoma, 33.1% vs. 22.9%; CS/MMMT, 28.3% vs. 19.3%, all $p<0.0001$). Patients in non-Hispanic Black, non-Hispanic Other, and Hispanic groups were more likely to be diagnosed with advanced stage in comparison with patients in the non-Hispanic White group (46.4%, 43.9%, 44.2%, vs. 39.7%, respectively, all $p<0.0001$). Patients in the non-Hispanic Black group had a lower probability of receiving hysterectomy as opposed to patients in non-Hispanic White group (84.1% vs 89.9%, $p<0.0001$), while no significant differences were found among non-Hispanic Others, Hispanics and non-Hispanic Whites. Besides, the proportion of patients who did not receive lymphadenectomy in non-Hispanic Black group was significantly higher than that in non-Hispanic

White group (35.3% vs. 28.2%, p<0.0001). Even among those who received lymphadenectomy, non-Hispanic Blacks were less likely to have 10 or more lymph nodes removed in comparison with non-Hispanic White patients (37.9% vs. 47.9%, p<0.0001). Patients in non-Hispanic Black, non-Hispanic Other, and Hispanic groups showed a lower probability of undergoing radiation therapy (36.9%, 36.5%, 37.9% vs. 40.3%, respectively, all p<0.05), but had a greater likelihood of receiving chemotherapy when compared with non-Hispanic Whites (48.4%, 48.1%, 45.8%, vs. 43.0%, respectively, all p<0.05).

Patients with type II endometrial cancer in the non-Hispanic Black group were less likely to receive hysterectomy and adequate lymphadenectomy (10 or more lymph nodes removed) in both time periods, compared with patients in the other three groups (Figure 5a and 5b, Supplementary Table S8). No significant differences were observed in the percentage of receiving hysterectomy and radiation therapy between period 1 and period 2 in any of the racial/ethnic groups (Figure 5a and 5c, Supplementary Table S8). The percentage of patients who had adequate lymphadenectomy was significantly higher in period 2 than in period 1 for non-Hispanic Whites and non-Hispanic Blacks, but had no significant changes during the two periods for non-Hispanic others and Hispanics (Figure 5b, Supplementary Table S8). The percentage of patient who received chemotherapy was significantly higher in period 2 than period 1 across all racial/ethnic groups (Figure 5d, Supplementary Table S8).

Survival analysis

The overall 5-year RSR of type II endometrial cancer was 60.3%, 43.5%, 59.5%, and 56.5% for non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic Others, and Hispanics, respectively. Non-Hispanic Blacks had the lowest overall 5-year relative survival for type II endometrial cancer regardless of the stage at diagnosis (Figure 6a). Compared with non-Hispanic Whites, patients in the non-Hispanic Black group had significantly lower 5-year relative survival for all histologic subtypes at every stage of diagnosis with the exception of clear cell carcinoma (Figure 6b-6f). Non-Hispanic Others and Hispanics had similar 5-year relative survival as non-Hispanic Whites across histologic subtypes and stages. Detailed information concerning 5-year RSRs of type II endometrial cancer by histologic types, stage and race/ethnicity were summarized in Supplementary Table S9.

No significant improvement in overall 5-year relative survival of type II endometrial cancer was observed in period 2 across any racial/ethnic group (Table 4). A significant decrease was found in the overall 5-year relative survival for those with late stage type II endometrial cancer in the Hispanic group in period 2 (28.8% vs. 34.2%, z value=-2.002). Significantly increased 5-year relative survival in period 2 was only observed in early stage high-grade mixed adenocarcinoma and late stage carcinosarcoma/MMMT among non-Hispanic Whites, as well as late stage serous and clear cell carcinoma among non-Hispanic Others (Table 4). A significant decrease in 5-year relative survival was observed in late stage clear cell carcinoma for non-Hispanic Blacks in period 2.

In the multivariate Cox proportional hazards model, after controlling for age at diagnosis, diagnosis period, histologic subtype, stage, hysterectomy, extent of lymphadenectomy, radiation, and chemotherapy, non-Hispanic Blacks had significantly worse OS (hazard ration [HR] and 95% CI: 1.24[1.18, 1.30]) and CS (HR and 95% CI: 1.23[1.17, 1.30]) compared with non-Hispanic Whites. There was no significant difference in OS and CS among non-Hispanic Whites, non-Hispanic Others, and Hispanics. Advanced stage, increasing age, serous or carcinosarcoma/MMT histology, not receiving hysterectomy, without lymph nodes removed or without adequate lymphadenectomy (≥10 lymph nodes removed), and absence of adjuvant radiation or chemotherapy were independent predictors of worse OS and CS for type II endometrial cancer (Table 5).

Discussion

Studies investigating the incidence pattern of endometrial cancer seldom specifically focused on type II endometrial cancer. Our analysis utilized the latest population-based data to evaluate the incidence trends of type II endometrial cancer, covering both non-Hispanic Others and Hispanics, in addition to non-Hispanic Whites and non-Hispanic Blacks. Previous studies stated that the overall incidence of endometrial cancer had increased during the first decade of the 21st century and would be expected to continuously increase in the coming 20 years (18, 74). Different from the increasing trend for overall endometrial cancer, the overall incidence of type II endometrial cancer remained relatively stable during the study period from 2004 to 2015 in our analysis. However, racial differences in temporal trends did exist by histologic categories and time periods. A considerable increase in the overall incidence rate of type II endometrial cancer was observed in all racial/ethnic groups under examination with the exception of non-Hispanic Whites. Similarly, when examining the incidence rates in two separate time periods, we discovered a significant increase of the overall incidence rates in period 2 for all the racial/ethnic groups with the exception of non-Hispanic Whites. Besides, a prominent increase in APCs for certain histologic subtypes was seen among non-Hispanic Others (serous carcinoma) and Hispanics (mixed high-grade adenocarcinoma and carcinosarcoma/MMMT). These findings suggest that continued surveillance on all populations is warranted, especially for non-Hispanic Others and Hispanics, which we used to ignore because of their relatively lower incidence as opposed to non-Hispanic Whites and non-Hispanic Blacks.

Our study provides evidence that the discrepancy in the risk of type II endometrial cancer exists among racial/ethnic groups. Although non-Hispanic Blacks only accounted for 16.4% of the overall type II endometrial cancer cases, their risk of developing type II endometrial cancer was 1.89 times that of non-Hispanic Whites. Furthermore, excess risks for non-Hispanic Black women were seen in all histologic subtypes. In contrast to non-Hispanic Blacks, patients in non-Hispanic Other and Hispanic groups commonly showed relatively lower risk of type II endometrial cancer compared with non-Hispanic Whites, which is in accordance with previous findings (18). Type II endometrial cancer is a complicated and heterogeneous disease with unclear etiology. Racial disparities in the incidence rate likely attribute to multiple factors which need further investigation. One pooled analysis revealed that the two types of endometrial cancer shared many common risk factors, including obesity, diabetes, cigarette smoking, as well as oral contraceptive use (75). Another analysis using data from the NIH-AARP Diet and Health Study indicated that women with first-degree blood relatives suffering from breast cancer had an increased risk for type II endometrial cancer (8). However, few studies examined whether the exposure to these risk factors differs in type II endometrial cancer patients in different racial/ethnic groups. Further investigation on the presence of risk factors across different racial/ethnic groups might be beneficial for elucidating the mechanisms beneath the racial disparities in the incidence rate. Biological differences may also account for the racial discrepancies of the incidence rates observed in type II endometrial cancer. It was reported that mutations of HER-2/neu and p53, the key gene changes involved in the carcinogenesis of type II endometrial cancer (41), were more frequent in Black women than in

White women, which may to some extent explain the observed higher risk of type II endometrial cancer for non-Hispanic Blacks (27, 44, 46). A prospective cohort study found a higher risk of serous endometrial carcinoma for women with BRCA1 mutations (76). Racial/ethnic variation in the prevalence of BRCA1 mutations has been found in breast cancer and ovarian cancer (77, 78). Evaluation of BRCA1 mutations in type II endometrial cancer across racial/ethnic groups may to some extent explain the disparities we observed, and provide an opportunity for implementing risk-reducing interventions. Carcinogenesis of type II endometrial cancer is a complicated process, which may include both changes of a genetic and epigenetic nature (41). Exploring genetic and molecular differences across racial and ethnic categories may help us get a better understanding of racial disparities in the incidence.

In present study, we found that non-Hispanic Blacks had poorer OS and CS of type II endometrial cancer than other racial/ethnic groups. No difference in OS and CS was found among non-Hispanic Others, Hispanics, and non-Hispanic Whites. These findings were in accordance with previous study using state-level data from California cancer registry between 1998 and 2009 (58). Discrepancy in the clinical presentation and treatment across racial/ethnic groups may preponderantly underlie the observed survival disparity. Stage at diagnosis has a strong influence on survival. High-risk histology, genetic predisposition, geographic position, health care quality as well as social determinants might be possible factors that would impact stage at diagnosis (32, 34, 79, 80). In our analysis, non-Hispanic Blacks, non-Hispanic Others and Hispanics were more likely

to present at a younger age with a more advanced stage as opposed to their non-Hispanic White counterparts. However, only non-Hispanic Blacks experienced worse survival, suggesting that there are other factors affecting survival. Aggressive histologic subtype is also associated with inferior survival. In present study, non-Hispanic Blacks had higher likelihood of being diagnosed with serous carcinoma or carcinosarcoma/MMMT, which have relatively worse prognosis than other histologic subtypes. At present, the reasons for this phenomenon remain unknown and suggest performing further epidemiological and biological researches on the etiology of these histologic subtypes to explain these differences.

Receipt of appropriate treatment has an important impact on prognosis. According to the National Comprehensive Cancer Network (NCCN) guidelines for endometrial carcinoma, the treatment for type II endometrial cancer consists of total hysterectomy with bilateral salpingo-oophorectomy, complete surgical staging and proper adjuvant therapy (36). In our review, we demonstrated the existence of racial disparities in the treatment. Patients in non-Hispanic Black group were less likely to receive hysterectomy and adequate lymphadenectomy compared with patients in other racial/ethnic groups. As opposed to non-Hispanic Whites, Patients in non-Hispanic Black, non-Hispanic Other, and Hispanic groups were less likely to undergo radiotherapy, but were more likely to receive chemotherapy. According to our analysis, after controlling for other covariates, not receiving hysterectomy, adequate lymphadenectomy, radiation or chemotherapy would increase the risk of overall death for patients with type II endometrial cancer by 160%, 103%, 35% and 32%,

respectively. This indicates that discrepancy in the treatment across racial/ethnic groups may be considered as a cause of survival disparity.

As we know, FIGO revised the staging system of endometrial cancer in 2009, resulting in some corresponding changes in the diagnosis and treatment. In addition, the publication of new research results in recent years has also led to the corresponding adjustment of therapeutic strategies. In order to assess whether the treatment and survival of type II endometrial cancer differs over time, we split the whole study period into two groups (period 1, 2004-2009 and period 2, 2010-2015). The situation that patients in the non-Hispanic Black group had the lowest rate of hysterectomy and lymphadenectomy remained consistent in both periods. Several previous studies reported the lower rate of surgery among Black patients with endometrial cancer (26, 32-34). However, few studies have been designed to elucidate the reasons for the disproportionate rate or to seek interventions to reduce disparity in surgical implementation rate. In our study, we found no obvious change in the hysterectomy rate during the two periods, but an improvement in lymphadenectomy in period 2. More patients in non-Hispanic White and non-Hispanic Black groups had adequate lymphadenectomy in period 2. Besides, we also observed an increase of chemotherapy administration in period 2 for all racial/ethnic groups, which may be attributed to the studies indicating that chemotherapy has a beneficial role for the survival of high-risk patients (81-83). However, it is so frustrating that we did not see significant improvement in the overall 5-year

relative survival of type II endometrial cancer for all racial/ethnic groups over the two periods and racial disparity in survival persisted.

After adjusting for the clinical covariates, we still found a poorer overall and cause-specific survival for non-Hispanic Black patients, which reminds us the necessity of seeking other factors accounting for this disparity. Non-medical social determinants, such as socioeconomic conditions, education, insurance status, social support, health literacy, access to health care services, et al., may have potential important effects on survival disparity. Madison and the colleagues examined the link shared by socioeconomic status and racial discrepancies in the context of endometrial cancer, indicating that lower socioeconomic status was associated with advanced stage at diagnosis, lower rate of hysterectomy as well as inferior survival (34). Fedewa et al. reported that patients without private health insurance had poorer survival for uterine cancer (49). Since American African patients were more likely to live in poverty and less like to be covered by private insurance, the socioeconomic status and insurance status may partly explain the poorer survival observed in American African patients. Another study revealed that African-American and Hispanic women had a longer time to treatment interval compared with Caucasian women and there was a positive association between a longer time interval from diagnosis to treatment and an increased mortality for endometrial cancer patients (50). In addition, the study also found that lacking private insurance was associated with a longer interval time from diagnosis to treatment. These results confirmed the hypothesis that social determinants had great influence on racial disparity in endometrial cancer.

While these studies made a good attempt to clarify the influence of social factors on racial disparity, none of them was comprehensive due to the variety of non-medical social determinants. Evaluating the association between non-medical social determinants and racial disparity in type II endometrial cancer is really a tough job, because individual data of social determinants are always difficult to collect and quantify. Besides, some indicators of social determinants (e.g. income) are correlated with race and are difficult to be disentangled. Thus, traditional research framework for evaluating the impact of social factors on racial disparity may not be effective.

In addition, genetic or molecular differences may also contribute to survival inequity across racial/ethnic groups. A recent study evaluated the association of racial genetic admixture (RGA) with the outcomes of endometrial cancer and demonstrated a trend of worsening progression-free survival associated with increasing African RGA (48). While this study did not focus on type II endometrial cancer and the association between progression-free survival and RGA observed was not statistically significant, it does provide us a new insight to assess racial disparity by correlating ancestral genetic background with individual's self-report racial classification. Due to the rapid development of gene technology and the wide application of next generation sequencing technology in recent years, more and more research has been concentrated on the molecular changes in endometrial cancer. Recent data indicate that genomic classification of endometrial cancer identified by the Cancer Genome Atlas Research (TCGA) is diagnostic, therapeutic, and prognostic predictive (84). Assessing the molecular alterations in endometrial cancer across

racial/ethnic groups may provide us opportunities to get a better understanding of racial disparities in survival.

There are some limitations in our study. First, we integrated American Indian/Alaska Native and Asian or Pacific Islander into one group in our analysis due to the small sample size in each group if we categorized them separately, which led to heterogeneity in this racial group. Second, pathologic review was unable to be performed in our analysis. Thus, there might be misclassification of histologic subtypes among cases included in our study. Third, there is an absence of surveillance data on recurrence in SEER registry. Failure to analyze the differences in recurrence in our study is a defect that would affect the comprehensive understanding of racial disparities in type II endometrial cancer. Fourth, SEER does not include information concerning comorbidities. We cannot measure the effect that comorbidities produce on racial disparities in our study. Finally, we need to consider the limitations on under ascertainment of adjuvant treatment data in SEER. As more therapy is offered in outpatient settings, data on these therapies are more challenging for registries to collect. In addition, factors determining the receipt of adjuvant therapy, such as physician recommendations, comorbidities, patient choice, et al. are not captured in SEER. As such, analyses using these treatment data need to be interpreted with caution.

Despite the limitations, our study provided a comprehensive population-based evaluation of racial disparity in type II endometrial cancer, which augmented the existing literature by integrating the

most recent data available. Our study indicates that racial disparity persists in the incidence, presentation, treatment and survival of type II endometrial cancer. Further research should not only focus on clarifying the possible mechanisms beneath racial disparities, but also aim to develop targeted interventions to reduce the existing racial disparities in type II endometrial cancer.

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Tables

Table 1. Racial Difference in Age-adjusted Incidence Rate of Type II Endometrial Cancer by Histologic Subtype in the SEER Registry Data Between 2004 and 2015

	N	IR (95% CI)	IRR (95% CI)	*P* value
All types				
NHW*	23,367	3.14 (3.09, 3.18)	1.00	
NHB	5,910	5.92 (5.77, 6.08)	1.89 (1.83, 1.94)	<0.0001
NHO	2,974	2.78 (2.68, 2.88)	0.89 (0.85, 0.92)	<0.0001
Hispanic	3,655	2.85 (2.75, 2.95)	0.91 (0.88, 0.94)	<0.0001
HG endometrioid				
NHW*	9,801	1.32 (1.29, 1.34)	1.00	
NHB	1,597	1.60 (1.52, 1.68)	1.21 (1.15, 1.28)	<0.0001
NHO	1,240	1.13 (1.07, 1.19)	0.86 (0.81, 0.91)	<0.0001
Hispanic	1,408	1.03 (0.97, 1.08)	0.78 (0.73, 0.83)	<0.0001
HG mixed				
NHW*	2,477	0.33 (0.32, 0.34)	1.00	
NHB	496	0.50 (0.45, 0.54)	1.50 (1.36, 1.66)	<0.0001
NHO	300	0.27 (0.24, 0.31)	0.83(0.73, 0.94)	0.0026
Hispanic	337	0.26 (0.23, 0.29)	0.79 (0.70, 0.89)	0.0001
Serous				
NHW*	5,358	0.72 (0.70, 0.74)	1.00	
NHB	1,836	1.82 (1.73, 1.91)	2.54 (2.40, 2.68)	<0.0001
NHO	730	0.70 (0.64, 0.75)	0.97 (0.90, 1.05)	0.4688
Hispanic	938	0.78 (0.73, 0.83)	1.09 (1.01, 1.17)	0.0279
Clear cell				
NHW*	1,212	0.16 (0.16, 0.17)	1.00	
NHB	309	0.32 (0.29, 0.36)	1.98 (1.73, 2.25)	<0.0001
NHO	171	0.17 (0.14, 0.19)	1.01 (0.85, 1.18)	0.9708
Hispanic	218	0.18 (0.16, 0.21)	1.11(0.95, 1.29)	0.1798
CS/MMMT				
NHW*	4,519	0.61 (0.59, 0.63)	1.00	
NHB	1,672	1.69 (1.60, 1.77)	2.78 (2.62, 2.94)	<0.0001
NHO	533	0.51 (0.47, 0.56)	0.85 (0.77, 0.93)	0.0003
Hispanic	754	0.60 (0.56, 0.65)	0.99 (0.91, 1.07)	0.8100

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other; HG, high grade; CS/MMMT: carcinosarcoma/malignant mixed müllerian tumor.

Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population. *Reference group

Table 2. Time Trends of Type II Endometrial Cancer by Histologic Subtype and Race/Ethnicity in the SEER Registry Data Between 2004 and 2015

Histologic Types	Race/ ethnicity	APC (95% CI)		
		Period 1 2004-2009	Period 2 2010-2015	Full Period 2004-2015
All types	Overall	1.70 (-0.22, 3.64)	-0.56 (-1.26, 0.15)	0.50 (-0.03, 1.04)
	NHW	1.25 (-1.22, 3.78)	-1.74 (-2.74, -0.72)*	-0.14 (-0.85, 0.57)
	NHB	4.91 (2.14, 7.76)*	1.85 (-0.99, 4.77)	1.87 (0.84, 2.90)*
	NHO	2.17 (-3.76, 8.46)	-0.62 (-4.69, 3.63)	1.62 (0.16, 3.09)*
	Hispanic	-0.06 (-5.93, 6.18)	1.19 (-2.19, 4.69)	1.42 (0.16, 2.69)*
HG endometrioid	Overall	-1.94 (-3.86, 0.03)	-7.10 (-8.75, -5.42)*	-3.76 (-4.83, -2.69)*
	NHW	-2.10 (-4.24, 0.10)	-7.39 (-9.04, -5.70)*	-3.99 (-5.08, -2.88)*
	NHB	2.24 (-4.36, 9.29)	-10.07 (-13.78, -6.19)*	-3.92 (-6.52, -1.24)*
	NHO	-0.44 (-6.36, 5.86)	-3.10 (-8.16, 2.25)	-1.36 (-2.88, 0.19)
	Hispanic	-6.05 (-8.14, -3.90)*	-7.00 (-9.71, -4.20)*	-3.23 (-4.76, -1.67)*
HG mixed	Overall	14.69 (8.11, 21.67)*	-1.93 (-4.59, 0.79)	3.62 (0.45, 6.88)*
	NHW	14.73 (7.86, 22.05)*	-2.93 (-6.54, 0.83)	3.38 (-0.06, 6.93)
	NHB	26.64 (3.06, 55.60)*	-1.22 (-16.06, 16.24)	5.96 (-0.51, 12.84)
	NHO	14.59 (5.87, 24.03)*	-0.56 (-6.26, 5.49)	1.94 (-1.54, 5.55)
	Hispanic	5.89 (-5.58, 18.74)	4.03 (-7.57, 17.08)	4.65 (1.40, 8.00)*
Serous	Overall	3.83 (0.89, 6.86)*	7.11 (5.14, 9.12)*	5.74 (4.91, 6.58)*
	NHW	2.33 (-1.78, 6.62)	6.28 (3.53, 9.10)*	4.89 (3.78, 6.01)*
	NHB	6.23 (3.17, 9.38)*	9.58 (3.48, 16.05)*	7.23 (5.75, 8.73)*
	NHO	8.02 (-3.11, 20.42)	4.98 (-6.01, 17.26)	7,31 (4.14, 10.57)*
	Hispanic	4.99 (-6.89, 18.38)	5.05 (-6.18, 17.63)	5.06 (2.00, 8.20)*
Clear cell	Overall	0.26 (-8.55, 9.92)	0.89 (-2.47, 4.37)	0.40 (-1.34, 2.17)
	NHW	0.58 (-5.98, 7.60)	-0.27 (-3.87, 3.46)	0.56 (-0.83, 1.98)
	NHB	3.07 (-8.18, 17.13)	2.50 (-8.15, 14.37)	-0.36 (-3.56, 2.95)
	NHO	-7.14 (-23.16, 12.21)	0.30 (-6.41, 7.49)	-1.81 (-5.32, 1.83)
	Hispanic	-1.23 (-26.40, 32.56)	1.56 (-18.53, 26.61)	0.60 (-5.85, 7.50)
CS/MMMT	Overall	2.52 (1.07, 4.00)*	1.02 (-1.21, 3.31)	1.23 (0.64, 1.81)*
	NHW	2.43 (-0.53, 5.48)	-0.55 (-4.52, 3.59)	0.58 (-0.47, 1.64)
	NHB	2.77 (-1.38, 7.09)	4.09 (-0.11, 8.47)	1.29 (-0.10, 2.69)
	NHO	-1.08 (-12.26, 11.53)	-4.43 (-13.13, 5.14)	1.75 (-1.69, 5.31)
	Hispanic	4.08 (-5.18, 14.23)	6.80 (2.45, 11.33)*	3.61 (1.66, 5.59)*

Abbreviations: APC, annual percentage change; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other; HG, high grade; CS/MMMT: carcinosarcoma/malignant mixed müllerian tumor. *Statistically significant.

Table 3. Clinical Characteristics for Type II Endometrial Cancer by Race/Ethnicity, SEER 2004-2015

	NHW* (N=23,367)	NHB (N=5,910)	NHO (N=2,974)	Hispanic (N=3,655)	*P* value
Age at diagnosis (years)					
Mean (SD)	67.7 (11.5)	66.3 (9.9)	63.2 (11.4)	63.4 (11.8)	All <0.0001
Median (IQR)	67 (60-76)	66 (60-73)	63 (56-71)	64 (56-71)	
Histologic type [N (%)]					
HG endometrioid	9,801 (42.0)	1,597 (27.0)	1,240 (41.7)	1,408 (38.5)	All <0.0001
HG mixed	2,477 (10.6)	496 (8.4)	300 (10.1)	337 (9.2)	
Serous	5,358 (22.9)	1,836 (31.1)	730 (24.5)	938 (25.7)	
Clear cell	1,212 (5.2)	309 (5.2)	171 (5.8)	218 (6.0)	
CS/MMMT	4,519 (19.3)	1,672 (28.3)	533 (17.9)	754 (20.6)	
Stage [N (%)]					
I/II	13,111 (56.1)	2,844 (48.1)	1,562 (52.5)	1,906 (52.2)	All <0.0001
III/IV	9,274 (39.7)	2,741 (46.4)	1,304 (43.9)	1,616 (44.2)	
Unknown	982 (4.2)	325 (5.5)	108 (3.6)	133 (3.6)	
Hysterectomy [N (%)]					
Yes	21,015 (89.9)	4,969 (84.1)	2,702 (90.9)	3,270 (89.5)	NHB vs. NHW: <0.0001
No	2,259 (9.7)	907 (15.3)	263 (8.8)	376 (10.3)	NHO vs. NHW: 0.1458
Unknown	93 (0.4)	34 (0.6)	9 (0.3)	9 (0.2)	Hispanic vs. NHW: 0.2518
Lymphadenectomy [N (%)]					
None	6,585 (28.2)	2,083 (35.3)	760 (25.5)	1,114 (30.5)	NHB vs. NHW: <0.0001
1-9 LNs removed	5,017 (21.5)	1,408 (23.8)	642 (21.6)	760 (20.8)	NHO vs. NHW: 0.0069
≥ 10 LNs removed	11,187 (47.9)	2,240 (37.9)	1,,498 (50.4)	1,688 (46.2)	Hispanic vs. NHW: 0.0147
Unknown	578 (2.5)	179 (3.0)	74 (2.5)	93 (2.5)	
LN positive [N (%)]					
Yes	4,191 (17.9)	1,207 (20.4)	603 (20.3)	714 (19.5)	NHB vs. NHW: <0.0001
No	12,428 (53.2)	2,563 (43.4)	1,589 (53.4)	1,797 (49.2)	NHO vs. NHW: 0.0207
Unknown	6,748 (28.9)	2,140 (36.2)	782 (26.3)	1,144 (31.3)	Hispanic vs. NHW: 0.0006
Radiation [N (%)]					
Yes	9,421 (40.3)	2,181 (36.9)	1,086 (36.5)	1,385 (37.9)	NHB vs. NHW: <0.0001
No	13,426 (57.5)	3,570 (60.4)	1,819 (61.2)	2,148 (58.8)	NHO vs. NHW: <0.0001
Unknown	520 (2.2)	159 (2.7)	69 (2.3)	122 (3.3)	Hispanic vs. NHW: 0.0222
Chemotherapy [N (%)]					
Yes	10,056 (43.0)	2,861 (48.4)	1,431 (48.1)	1,675 (45.8)	NHB vs. NHW: <0.0001
No	13,311 (57.0)	3,049 (51.6)	1,543 (51.9)	1,980 (54.2)	NHO vs. NHW: <0.0001
					HISP vs. NHW: 0.0015

Abbreviations: NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other; SD, standard deviation; IQR, interquartile range; HG, high grade; CS/MMMT: carcinosarcoma/malignant mixed müllerian tumor; LN, lymph node. *Reference group.

Table 4. Five-year relative survival rates for type II endometrial cancer by histologic subtypes, race/ethnicity and stage during period 1 (2004-2009) and period 2 (2010-2015)

Histologic Types	Race/Ethnicity	Stage I/II			Stage III/IV		
		RSR (%) 2004-2009	RSR (%) 2010-2015	Z value	RSR (%) 2004-2009	RSR (%) 2010-2015	Z value
All types	**Overall**	78.9	80.4	0.924	32.2	30.8	-1.004
	NHW	81.1	82.9	0.706	34.1	33.4	-0.193
	NHB	66.1	70.0	1.614	22.4	21.7	0.133
	NHO	82.7	81.4	-0.613	35.7	36.2	0.097
	Hispanic	78.9	78.7	0.302	34.2	28.8	-2.002*
HG endometrioid	**Overall**	84.3	85.6	0.297	39.0	38.6	-0.435
	NHW	85.9	86.3	-0.461	40.3	41.4	0.075
	NHB	74.1	79.0	1.126	25.6	27.1	0.492
	NHO	85.5	87.0	-0.005	47.2	42.7	-1.190
	Hispanic	82.4	85.1	0.994	40.2	34.4	-0.519
HG mixed	**Overall**	78.8	84.5	2.109*	42.6	39.8	-0.948
	NHW	79.5	87.7	2.361*	44.9	40.2	-0.881
	NHB	67.1	72.7	0.524	21.7	38.2	1.241
	NHO	85.1	80.1	0.192	46.6	43.4	0.019
	Hispanic	83.9	78.7	-0.295	43.4	36.0	-1.591
Serous	**Overall**	77.3	78.6	1.379	24.9	28.6	1.897
	NHW	79.1	81.7	1.141	26.5	29.6	1.281
	NHB	68.6	10.8	1.014	20.9	21.2	0.539
	NHO	86.1	74.2	-1.616	22.7	36.8	2.317*
	Hispanic	75.7	75.7	1.077	26.0	30.3	-0.207
Clear cell	**Overall**	81.9	80.3	-0.482	33.9	30.2	-0.667
	NHW	83.9	78.7	-0.731	34.0	34.4	0.075
	NHB	71.1	86.1	1.684	35.9	13.1	-2.130*
	NHO	85.3	80.3	-0.522	18.6	38.7	2.293*
	Hispanic	77.3	76.5	-0.278	37.2	N/A	N/A
CS/MMMT	**Overall**	60.9	65.5	1.098	17.5	17.4	1.192
	NHW	64.4	69.9	1.284	18.5	20.0	2.101*
	NHB	46.5	48.1	-0.375	14.3	11.9	0.724
	NHO	59.2	69.7	1.542	16.4	22.7	-0.404
	Hispanic	68.4	65.9	-0.176	18.7	14.4	0.530

Abbreviations: RSR, relative survival rate; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other (including non-Hispanic American Indian/Alaska Native and Asian or Pacific Islander); HG, high grade; CS/MMMT: carcinosarcoma/malignant mixed müllerian tumor. *Statistically significant.

Table 5. Multiple Cox Proportional Hazards Models of Predictors of Overall and Disease-specific mortality in patients with Type II Endometrial Cancer

	Overall mortality			Disease-specific mortality		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Race/ethnicity						
NHW	1.00			1.00		
NHB	1.24	1.18, 1.30	<0.0001	1.23	1.17, 1.30	<0.0001
NHO	0.95	0.88, 1.02	0.1380	0.95	0.88, 1.03	0.2126
Hispanic	1.01	0.95, 1.08	0.7289	1.04	0.96, 1.11	0.3362
Age at diagnosis						
Per year	1.02	1.02, 1.03	<0.0001	1.01	1.01, 1.02	<0.0001
Time period						
2004-2009	1.00			1.00		
2010-2015	0.96	0.92, 1.00	0.0458	0.97	0.93, 1.02	0.2234
Histologic type						
HG endometrioid	1.00			1.00		
HG mixed	1.06	0.99, 1.14	0.0819	1.07	0.99, 1.16	0.0836
Serous	1.11	1.05, 1.16	<0.0001	1.16	1.10, 1.23	<0.0001
Clear cell	1.01	0.93, 1.10	0.8639	1.03	0.93, 1.13	0.6273
CS/MMMT	1.73	1.65, 1.82	<0.0001	1.87	1.76, 1.97	<0.0001
Stage						
I/II	1.00			1.00		
III/IV	3.84	3.67, 4.01	<0.0001	5.00	4.74, 5.23	<0.0001
Hysterectomy						
Yes	1.00			1.00		
No	2.60	2.45, 2.75	<0.0001	2.71	2.54, 2.89	<0.0001
Lymphadenectomy						
≥ 10 LNs removed	1.00			1.00		
1-9 LNs removed	1.38	1.32, 1.45	<0.0001	1.41	1.34, 1.50	<0.0001
None	2.03	1.93, 2.13	<0.0001	2.03	1.92, 2.14	<0.0001
Radiation						
Yes	1.00			1.00		
No	1.35	1.30, 1.41	<0.0001	1.37	1.31, 1.43	<0.0001
Chemotherapy						
Yes	1.00			1.00		
No	1.32	1.27, 1.38	<0.0001	1.29	1.23, 1.35	<0.0001

Abbreviation: HR, hazard ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other (including non-Hispanic American Indian/Alaska Native and Asian or Pacific Islander); HG, high grade; CS/MMMT: carcinosarcoma/malignant mixed müllerian tumor; LN, lymph node.

Figures

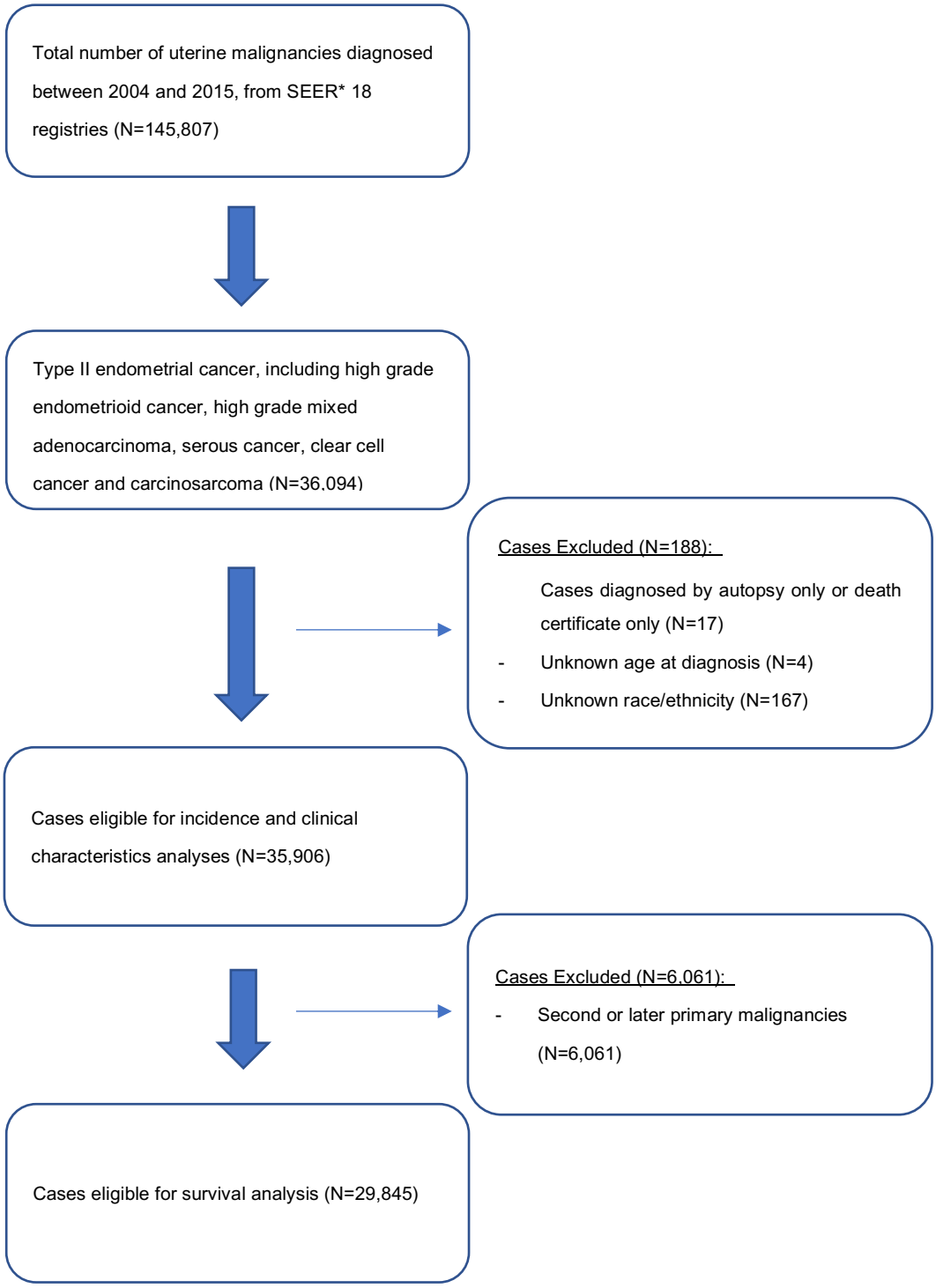

Figure 1. Selection of type II endometrial cancer study cohort

*SEER: Surveillance, Epidemiology, and End Results

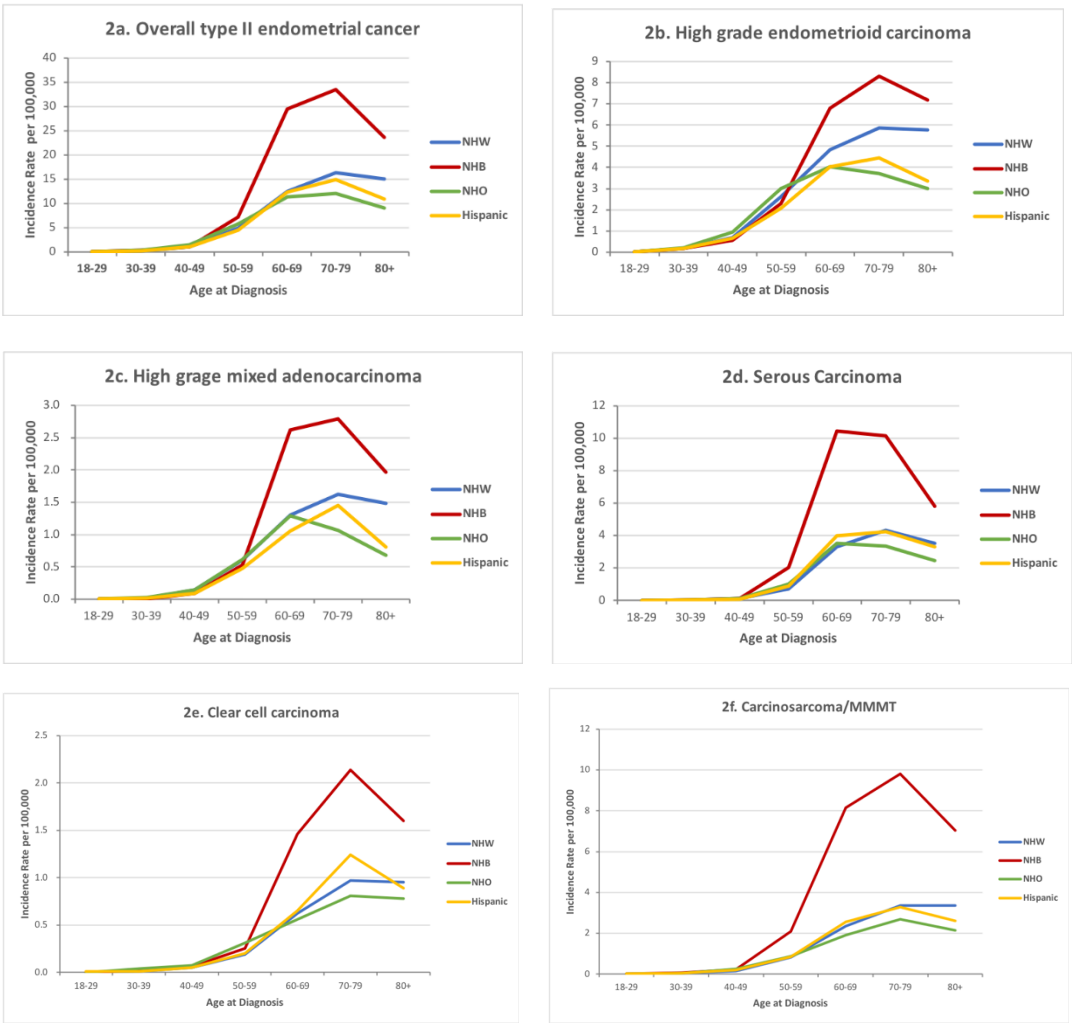

Figure 2. Age-specific incidence rates for type II endometrial cancer by histologic subtype and race/ ethnicity in the SEER registry data between 2004 and 2015. Abbreviations: NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other.

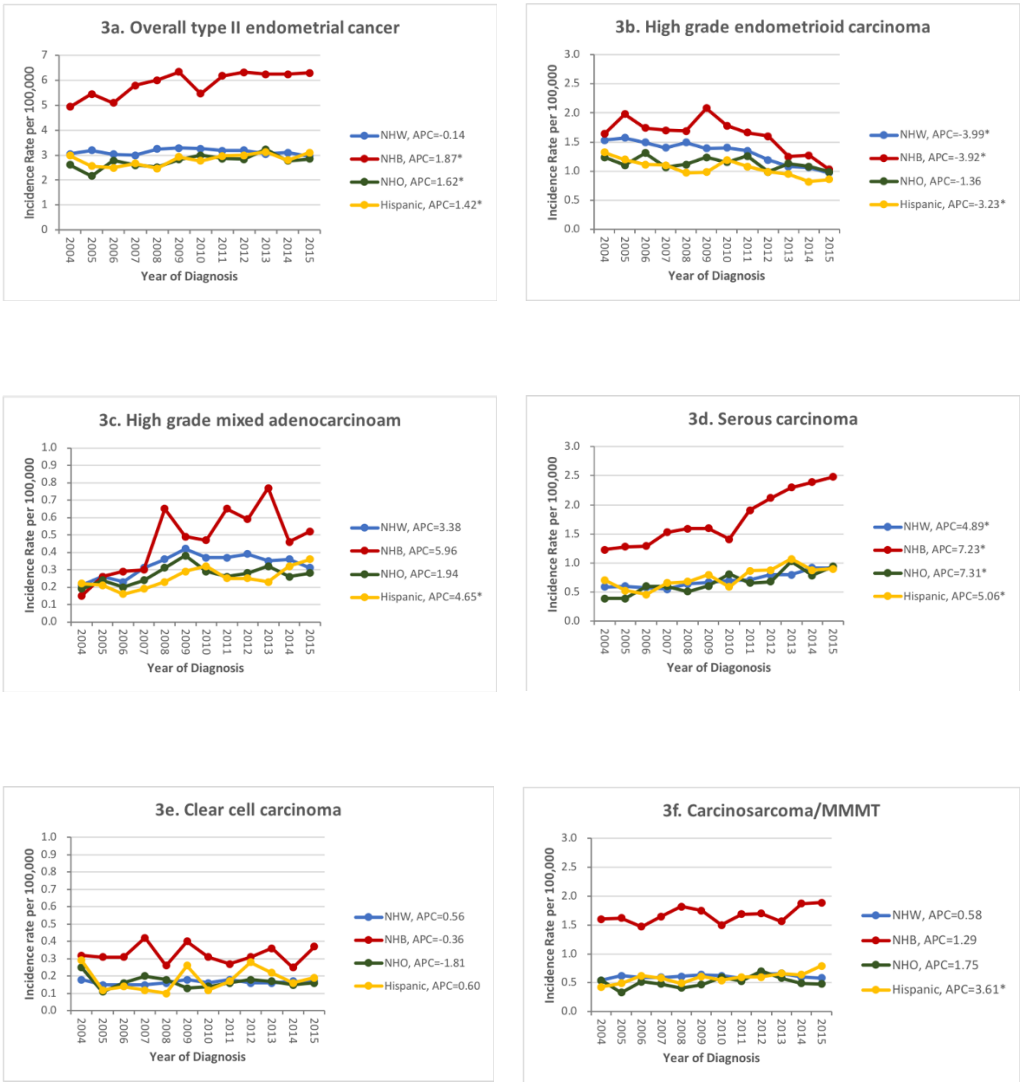

Figure 3. Age-adjusted incidence rate trends for type II endometrial cancer by histologic subtypes and race/ethnicity in the SEER registry data between 2004 and 2015. Abbreviations: NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other; APC, annual percentage change. *Statistically significant.

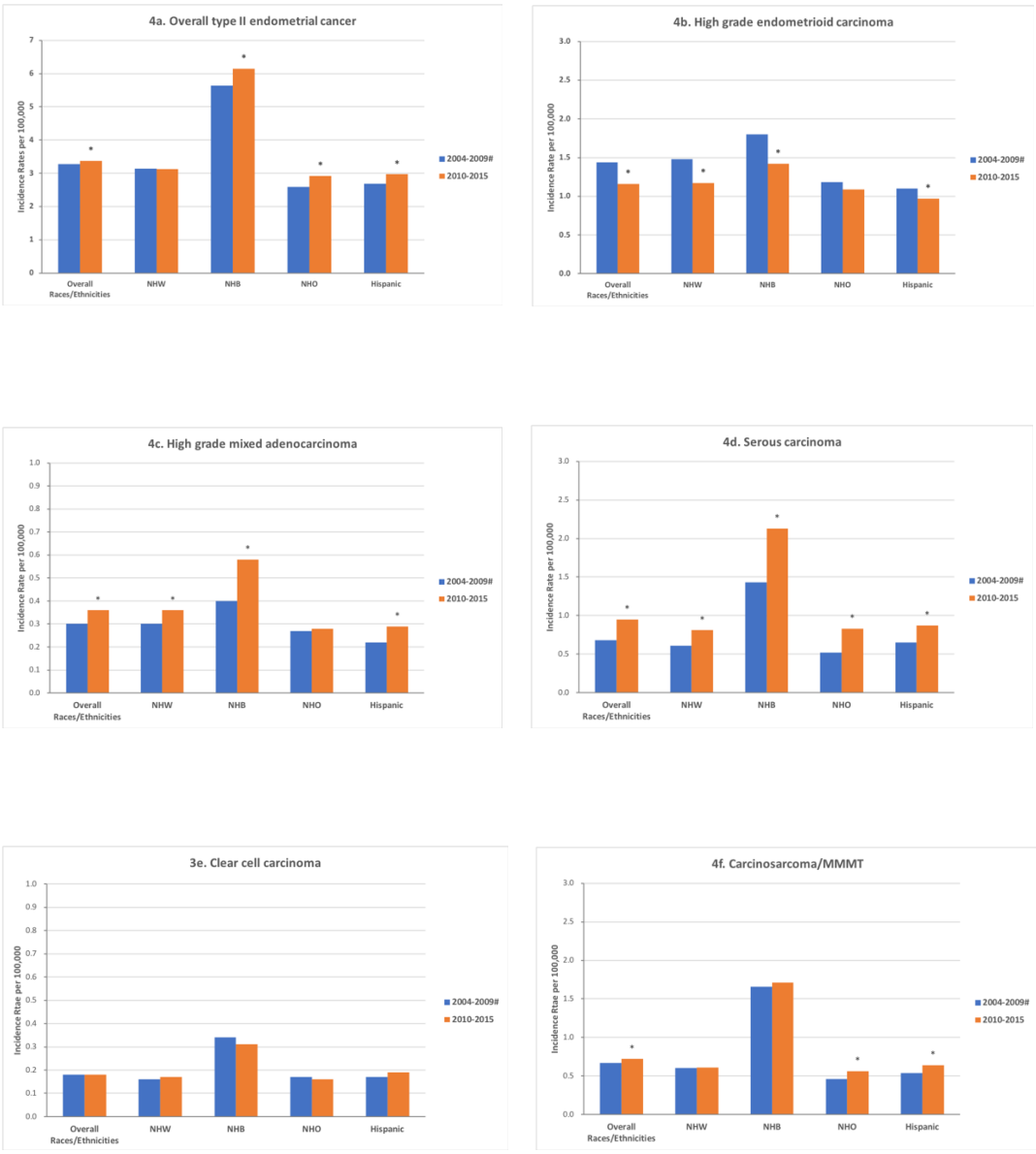

Figure 4. Age-adjusted incidence rates for type II endometrial cancer by histologic subtypes and race/ethnicity for 2004–2009 (period 1) and 2010–2015 (period 2). Abbreviations: NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other. # Reference group. *Statistically significant.

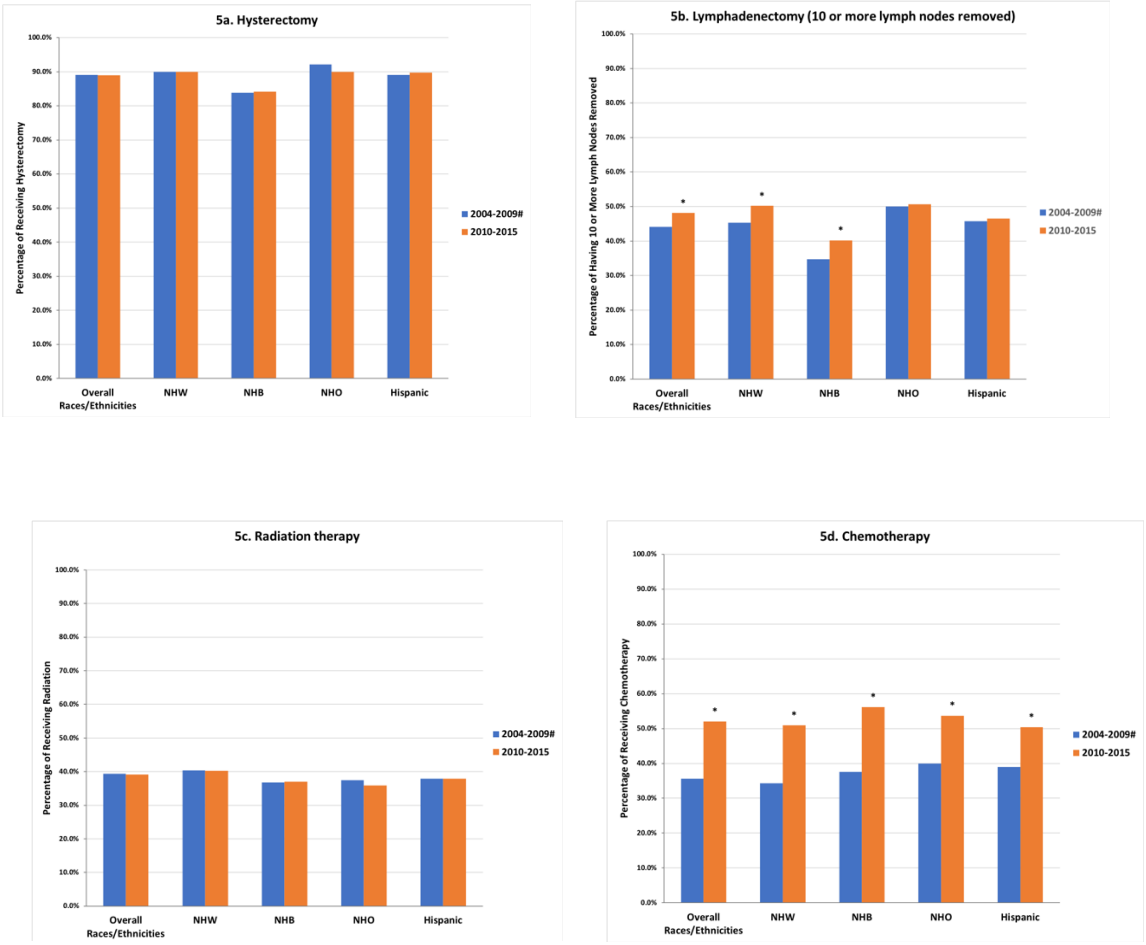

Figure 5. Treatment characteristics for type II endometrial cancer by race/ethnicity during 2004–2009 (period 1) and 2010–2015 (period 2). Abbreviations: NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other. # Reference group. *Statistically significant.

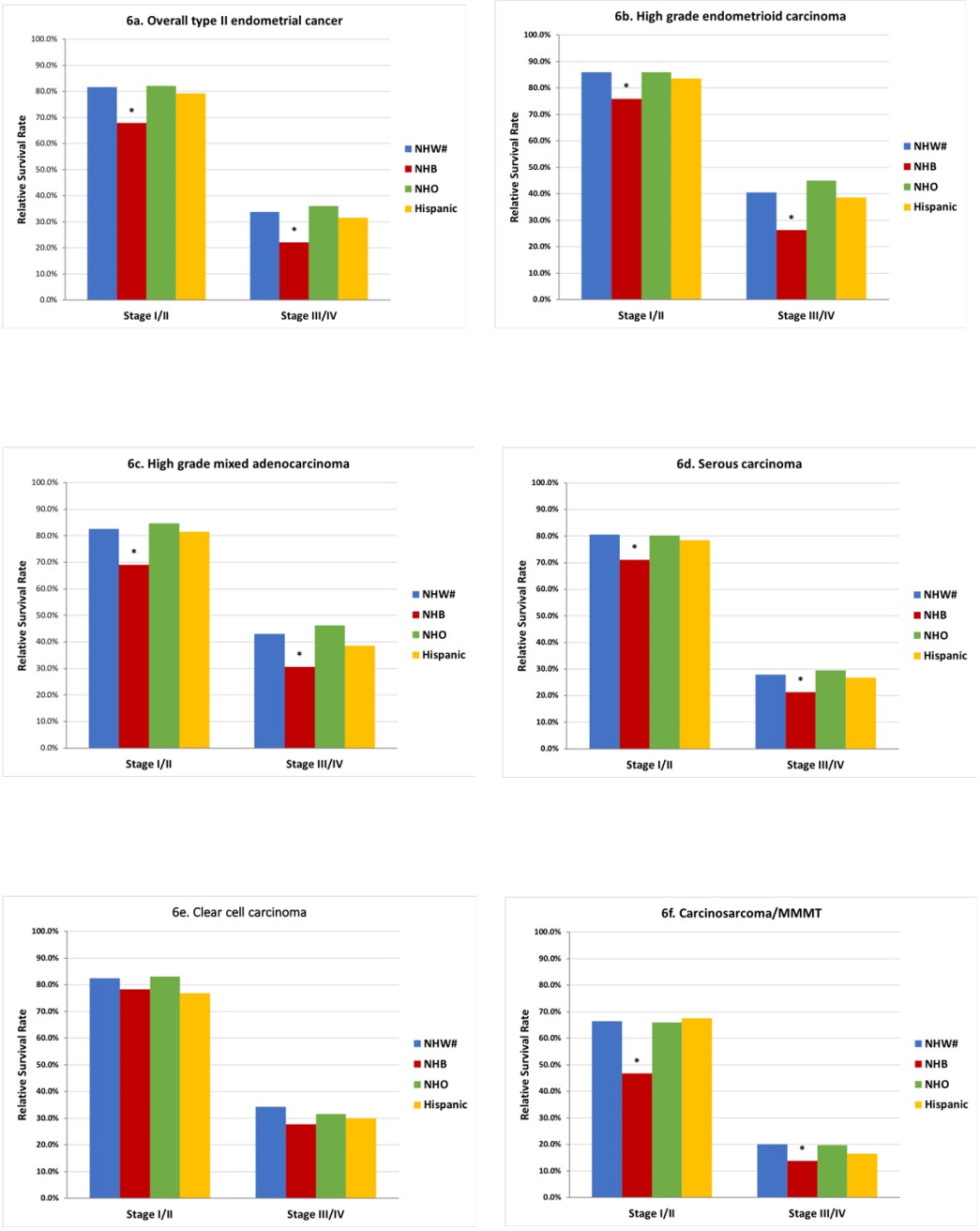

Figure 6. Five-year relative survival rates for type II endometrial cancer by histologic subtypes, Figo stage and race/ethnicity in the SEER registry data between 2004 and 2015. Abbreviations: NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other; MMMT, malignant mixed müllerian tumor. # Reference group. *Statistically significant.

Chapter III

Summary/Public Health Implications/Possible Future Directions

Summary

Racial disparities pervasively exist in the incidence, clinical presentation, treatment, as well as survival of type II endometrial cancer. The overall incidence of type II endometrial cancer increased in all racial/ethnic groups other than non-Hispanic Whites, with the highest APC for non-Hispanic Blacks. In comparison with non-Hispanic Whites, non-Hispanic Blacks exhibited significantly higher risk of type II endometrial cancer, while Hispanics and non-Hispanic Others had considerably lower risk. Non-Hispanic Blacks, non-Hispanic Others, and Hispanics were more likely to present with advanced stage in comparison with non-Hispanic Whites. Non-Hispanic Blacks were less likely to receive hysterectomy, adequate lymphadenectomy and radiation, but were more likely to receive chemotherapy. After controlling for clinical covariates, non-Hispanic Blacks had worse OS and CS than other racial/ethnic groups.

Public health implications

Our study indicated a growing burden of type II endometrial cancer among minorities, especially for non-Hispanic Blacks. Although the survival of type II endometrial cancer in all racial/ethnic groups is poor and has not improved during the past decade, non-Hispanic Black patients have disproportionately unfavorable survival when compared with patients in other racial/ethnic groups. The factors account for this disparity are multifactorial, including both biological contributors and social determinants. As the incidence rate of type II endometrial cancer is expected to increase in minority groups with a disproportionate impact on non-Hispanic Blacks, racial disparities would

persist and even broaden without further interventions. Exploring the drivers of this racial discrepancy and deploying targeted interventions are imperative for narrowing the racial gap in the survival of type II endometrial cancer.

Possible future directions

Future researches should be designed to incorporate biological, environmental, and social factors to address racial disparities in type II endometrial cancer. Besides, current studies addressing health disparities often focus on factors directly related to patients and seldom concentrate on factors concerning providers and medical systems. Future attempt could be made on identifying the role that providers and medical systems play on racial disparities in type II endometrial cancer and developing corresponding interventions to effectively eliminate the health inequalities among different racial groups.

Appendices

Supplementary Tables

Table S1. Researches concerning racial disparity in type II endometrial

Author (Citation) (year of publication)	Data Source	Time period of data included	Racial groups	Factors examined
Mahdi H, et al. (56) (2014)	SEER (national)	1988-2009	HW NHW	Clinical characteristics Treatment Survival
Rauh-Hain JA, et al. (26) (2015)	Linked SEER and Medicare dataset (National)	1992-2009	White African American	Treatment Survival
Schlumbrecht M, et al. (57) (2017)	Florida's Cancer Data System	2004-2013	NHW NHB Cuban Mexican Puerto Rican SC American Hispanic, NOS	Risk of type II endometrial cancer
Baskovic M, et al. (58) (2018)	California Cancer Registry	1998-2009	NHW NHB Asian Hispanic	Factors affecting survival

Abbreviations: SEER, the Surveillance, Epidemiology, and End Results; HW, Hispanic White; NHW, non-Hispanic White; W, White; AA, African American; NHB, non-Hispanic Black.

Table S2. Age-adjusted Incidence Rates and Incidence Rate Ratios of Overall Type II Endometrial Cancer by Race/Ethnicity for 2004–2009 (Period 1) and 2010–2015 (Period 2)

	N	IR (95% CI)	IRR (95% CI)	*P* value
Overall				
2004-2009	16,229	3,27 (3.22, 3.32)	1.00	
2010-2015	19,677	3.37 (3.33, 3.42)	1.03 (1.01, 1.05)	0.0032
NHW				
2004-2009	11,074	3.14 (3.08, 3.20)	1.00	
2010-2015	12,293	3.12 (3.07, 3.18)	1.00 (0.97, 1.02)	0.7386
NHB				
2004-2009	2,481	5.63 (5.40, 5.86)	1.00	
2010-2015	3,429	6.15 (5.94, 6.37)	1.09 (1.04, 1.15)	0.0012
NHO				
2004-2009	1,207	2.59 (2.45, 2.75)	1.00	
2010-2015	1,767	2.92 (2.78, 3.06)	1.13 (1.04, 1.21)	0.0019
Hispanic				
2004-2009	1,467	2.68 (2.54, 2.83)	1.00	
2010-2015	2,188	2.97 (2.84, 3.10)	1.11 (1.03, 1.19)	0.0046

Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population.

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other.

Table S3. Age-adjusted Incidence Rates and Incidence Rate Ratios of High Grade Endometrioid Carcinoma by Race/Ethnicity for 2004–2009 (Period 1) and 2010–2015 (Period 2)

	N	IR (95% CI)	IRR (95% CI)	*P* value
Overall				
2004-2009	7,251	1.44 (1.41,1.48)	1.00	
2010-2015	6,795	1.16 (1.13, 1.19)	0.80 (0.78, 0.83)	<0.0001
NHW				
2004-2009	5,234	1.48 (1.44, 1.52)	1.00	
2010-2015	4,567	1.17 (1.13, 1.20)	0.79 (0.76, 0.82)	<0.0001
NHB				
2004-2009	806	1.80 (1.68, 1.94)	1.00	
2010-2015	791	1.42 (1.32, 1.53)	0.79 (0.71, 0.87)	<0.0001
NHO				
2004-2009	565	1.18 (1.08, 1.28)	1.00	
2010-2015	675	1.09 (1.01, 1.18)	0.93 (0.83, 1.04)	0.2098
Hispanic				
2004-2009	646	1.10 (1.01, 1.19)	1.00	
2010-2015	762	0.97 (0.90, 1.04)	0.88 (0.79, 0.98)	0.0254

Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population.

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other.

Table S4. Age-adjusted Incidence Rates and Incidence Rate Ratios of High Grade Mixed Adenocarcinoma by Race/Ethnicity for 2004–2009 (Period 1) and 2010–2015 (Period 2)

	N	IR (95% CI)	IRR (95% CI)	*P* value
Overall				
2004-2009	1,469	0.30 (0.28, 0.31)	1.00	
2010-2015	2,141	0.36 (0.35, 0.38)	1.23 (1.15, 1.32)	<0.0001
NHW				
2004-2009	1,054	0.30 (0.28, 0.32)	1.00	
2010-2015	1,423	0.36 (0.34, 0.38)	1.21 (1.11, 1.31)	<0.0001
NHB				
2004-2009	172	0.40 (0.34, 0.46)	1.00	
2010-2015	324	0.58 (0.51, 0.64)	1.45 (1.19, 1.76)	0.0001
NHO				
2004-2009	123	0.27 (0.22, 0.32)	1.00	
2010-2015	177	0.28 (0.24, 0.33)	1.06 (0.83, 1.35)	0.6731
Hispanic				
2004-2009	120	0.22 (0.18, 0.26)	1.00	
2010-2015	217	0.29 (0.25, 0.33)	1.32 (1.04, 1.68)	0.0209

Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population.

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other.

Table S5. Age-adjusted Incidence Rates and Incidence Rate Ratios of Serous Carcinoma by Race/Ethnicity for 2004–2009 (Period 1) and 2010–2015 (Period 2)

	N	IR (95% CI)	IRR (95% CI)	*P* value
Overall				
2004-2009	3,330	0.68 (0.65, 0.70)	1.00	
2010-2015	5,532	0.95 (0.92, 0.97)	1.40 (1.34, 1.46)	<0.0001
NHW				
2004-2009	2,125	0.61 (0.58, 0.63)	1.00	
2010-2015	3,233	0.81 (0.79, 0.84)	1.34 (1.27, 1.42)	<0.0001
NHB				
2004-2009	637	1.43 (1.32, 1.55)	1.00	
2010-2015	1,199	2.13 (2.00, 2.26)	1.49 (1.35, 1.65)	<0.0001
NHO				
2004-2009	237	0.52 (0.46, 0.59)	1.00	
2010-2015	493	0.83 (0.75, 0.90)	1.58 (1.35, 1.86)	<0.0001
Hispanic				
2004-2009	331	0.65 (0.58, 0.72)	1.00	
2010-2015	607	0.87 (0.80, 0.95)	1.35 (1.17, 1.55)	<0.0001

Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population.

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other.

Table S6. Age-adjusted Incidence Rates and Incidence Rate Ratios of Clear Cell Carcinoma by Race/Ethnicity for 2004–2009 (Period 1) and 2010–2015 (Period 2)

	N	IR (95% CI)	IRR (95% CI)	*P* value
Overall				
2004-2009	871	0.18 (0.17, 0.19)	1.00	
2010-2015	1,039	0.18 (0.17, 0.20)	1.03 (0.94, 1.13)	0.5850
NHW				
2004-2009	563	0.16 (0.15, 0.17)	1.00	
2010-2015	649	0.17 (0.15, 0.18)	1.05 (0.93, 1.18)	0.4629
NHB				
2004-2009	145	0.34 (0.29, 0.40)	1.00	
2010-2015	164	0.31 (0.26, 0.37)	0.91 (0.72, 1.16)	0.4739
NHO				
2004-2009	75	0.17 (0.13, 0.21)	1.00	
2010-2015	96	0.16 (0.13, 0.20)	0.95 (0.69, 1.31)	0.8106
Hispanic				
2004-2009	88	0.17 (0.14, 0.21)	1.00	
2010-2015	130	0.19 (0.16, 0.23)	1.10(0.83, 1.47)	0.5364

Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population.

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other.

Table S7. Age-adjusted Incidence Rates and Incidence Rate Ratios of Carcinosarcoma/MMMT by Race/Ethnicity for 2004–2009 (Period 1) and 2010–2015 (Period 2)

	N	IR (95% CI)	IRR (95% CI)	*P* value
Overall				
2004-2009	3,308	0.67 (0.65, 0.70)	1.00	
2010-2015	4,170	0.72 (0.70, 0.74)	1.07 (1.02, 1.12)	0.0077
NHW				
2004-2009	2,098	0.60(0.57, 0.62)	1.00	
2010-2015	2,421	0.61 (0.59, 0.64)	1.03 (0.97, 1.09)	0.3634
NHB				
2004-2009	721	1.66 (1.53, 1.78)	1.00	
2010-2015	951	1.71 (1.60, 1.83)	1.03 (0.93, 1.14)	0.5484
NHO				
2004-2009	207	0.46 (0.40, 0.53)	1.00	
2010-2015	326	0.56 (0.50, 0.62)	1.22 (1.02, 1.46)	0.0302
Hispanic				
2004-2009	282	0.54 (0.48, 0.61)	1.00	
2010-2015	472	0.64 (0.58, 0.71)	1.19(1.02, 1.40)	0.0276

Rates are per 100,000 and age-adjusted to the 2000 U.S. Standard Population.

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other.

Table S8. Treatment Characteristics by Race/Ethnicity for 2004–2009 (Period 1) and 2010–2015 (Period 2)

	Total		NHW		NHB		NHO		Hispanic	
	2004-2009*	**2010-2015**	**2004-2009***	**2010-2015**	**2004-2009***	**2010-2015**	**2004-2009***	**2010-2015**	**2004-2009***	**2010-2015**
Hysterectomy	p = 0.3819		p = 0.7025		p = 0.7886		p = 0.0530		p = 0.5691	
Yes	14,457 (89.1)	17,499 (89.0)	9,959 (89.9)	11,056 (89.9)	2,080 (83.8)	2,889 (84.2)	1,111(92.1)	1,591 (90.0)	1,307 (89.1)	1,963 (89.7)
No	1,693 (10.4)	2,112 (10.7)	1,061 (9.6)	1,198 (9.8)	384 (15.5)	523 (15.3)	92(7.6)	171 (9.7)	156 (10.6)	220 (10.1)
Unknown	79 (0.5)	66 (0.3)	54 (0.5)	39 (0.3)	17 (0.7)	17 (0.5)	4 (0.3)	5 (0.3)	4 (0.3)	5 (0.2)
Lymphadenectomy	p <0.0001		p<0.0001		p = 0.0004		p = 0.9897		p = 0.5812	
None	4,875 (30.0)	5,667 (28,8)	3,196 (28.8)	3,389 (27.6)	914 (36.8)	1,169 (34.1)	308 (25.5)	452 (25.6)	357 (31.2)	657 (30.0)
1-9 LNs removed	3,695 (22.8)	4,132 (21.0)	2,532 (22.9)	2,485 (20.2)	611 (24.6)	797 (23.2)	258 (21.4)	384 (21.7)	294 (20.0)	466 (21.3)
≥ 10 LNs removed	7,150 (44.1)	9,436 (48.1)	5,017 (45.3)	6,170 (50.2)	860 (34.7)	1,380 (40.2)	603 (50.0)	603 (50.7)	670 (45.7)	1,018 (46.5)
Unknown	509 (3.1)	415 (2.1)	329 (3.0)	249 (2.0)	96 (3.9)	83 (2.4)	38 (3.1)	36 (2.0)	46 (3.1)	47 (2.2)
Radiation	p = 0.3817		p = 0.3028		0 p =.4713		p = 0.7397		p = 0.5880	
Yes	6,392 (39.4)	7,681 (39.1)	4,472 (40.4)	4,949 (40.3)	913 (36.8)	1,268 (37.0)	451 (37.4)	635 (35.9)	556 (37.9)	829 (37.9)
NO	9.621 (59.3)	11,342 (57.6)	6,466 (58.4)	6,960 (56.6)	1,529 (61.6)	2,041 (59.5)	744 (61.6)	1,075 (60.8)	882 (60.1)	1,266 (57.9)
Unknown	216 (1.3)	654 (3.3)	136 (1.2)	384 (3.1)	39 (1.6)	120 (3.5)	12 (1.0)	57 (3.2)	29 (2.0)	93 (4.2)
Chemotherapy	p<0.0001		p<0.0001		p<0.0001		p<0.0001		p<0.0001	
Yes	5,783 (35.6)	10,240 (52.0)	3,796 (34.3)	6,260 (50.9)	933 (37.6)	1,928 (56.2)	482 (39.9)	949 (53.7)	572 (39.0)	1,103 (50.4)
No	10.446 (64.4)	9,437 (48.0)	7,278 (49.1)	6,033 (49.1)	1,548 (62.4)	1,501 (43.8)	725 (60.1)	818 (46.3)	895 (61.0)	1,085 (49.6)

Abbreviations: NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other; HG, high grade; CS/MMMT: carcinosarcoma/malignant mixed müllerian tumor; LN, lymph node.

*Reference group.

Table S9. The 5-year Relative Survival for Type II Endometrial Cancer by Histologic Subtype, Stage, Race/Ethnicity in the SEER Registry Data Between 2004 and 2015

	Stage I/II			Stage III/IV		
	RSR (%)	**Z value**	**P value**	**RSR (%)**	**Z value**	**P value**
All types						
NHW*	81.6			33.8		
NHB	67.8	-11.566	<0.0001	22.1	-9.976	<0.0001
NHO	82.2	0.370	0.7114	36.0	1.506	0.1321
Hispanic	79.3	-1.490	0.1362	31.5	-1.501	0.1334
HG endometrioid						
NHW*	85.9			40.5		
NHB	75.9	-5.410	<0.0001	26.2	-6.663	<0.0001
NHO	85.9	-0.092	0.9267	45.0	1.507	0.1318
Hispanic	83.6	-0.866	0.3865	38.6	-1.063	0.2878
HG mixed						
NHW*	82.6			43.1		
NHB	69.1	-2.970	0.0030	30.6	-2.743	0.0061
NHO	84.6	0.418	0.6760	46.3	0.342	0.7324
Hispanic	81.4	-0.626	0.5313	38.6	-0.430	0.6672
Serous						
NHW*	80.5			27.9		
NHB	71.0	-3.662	0.0003	21.3	-4.229	<0.0001
NHO	80.2	-0.524	0.6003	29.5	0.663	0.5073
Hispanic	78.4	-0.797	0.4255	26.8	-0.732	0.4642
Clear cell						
NHW*	82.4			34.3		
NHB	78.3	-0.971	0.3316	27.7	-1.557	0.1195
NHO	83.1	0.603	0.5465	31.5	0.196	0.8446
Hispanic	76.9	-0.777	0.4372	30.0	-0.997	0.3188
CS/MMMT						
NHW*	66.4			20.0		
NHB	46.7	-6.962	<0.0001	13.7	-1.953	0.0508
NHO	66.0	0.402	0.6877	19.7	-0.037	0.9705
Hispanic	67.6	0.839	0.4015	16.5	-0.525	0.5996

Abbreviations: RSR, relative survival rate; NHW, non-Hispanic White; NHB, non-Hispanic Black; NHO, non-Hispanic Other; HG, high grade; CS/MMMT: carcinosarcoma/malignant mixed müllerian tumor; LN, lymph node. *Reference group.

Supplementary Figures

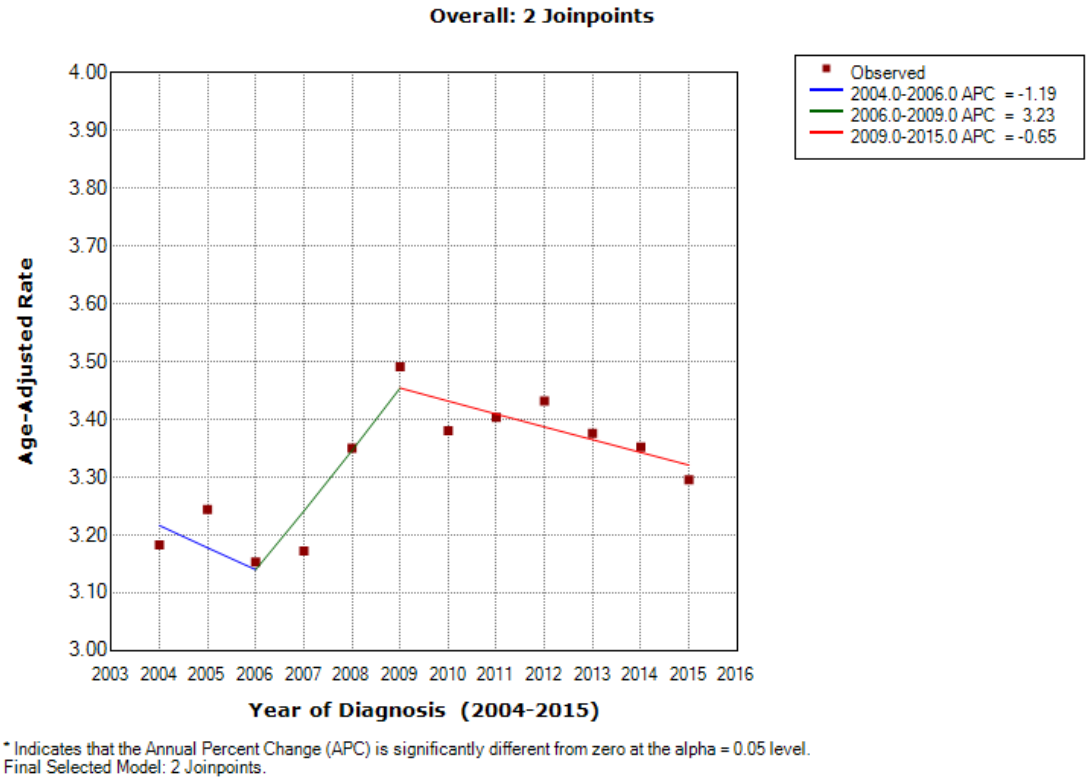

Figure S1. Joinpoint regression lines of overall type II endometrial cancer incidence for all racial/ethnic group together in the SEER registry data between 2004 and 2015. Abbreviations: APC, annual percentage change.

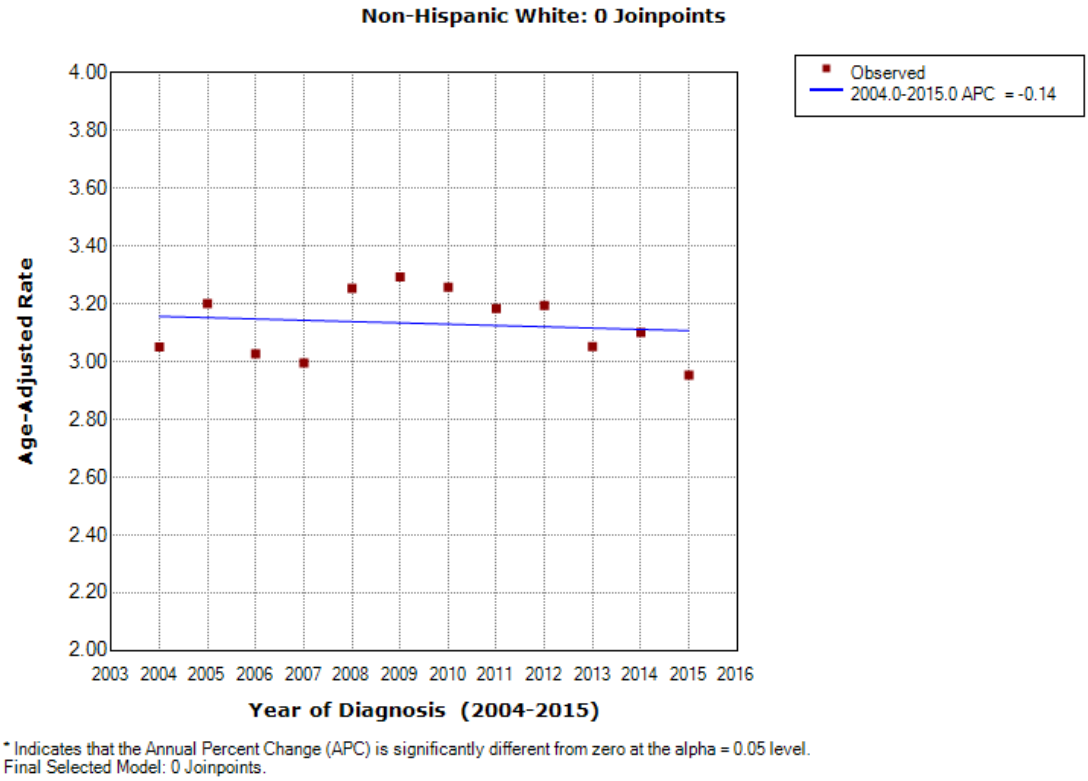

Figure S2. Joinpoint regression line of type II endometrial cancer incidence for non-Hispanic Whites in the SEER registry data between 2004 and 2015. Abbreviations: APC, annual percentage change.

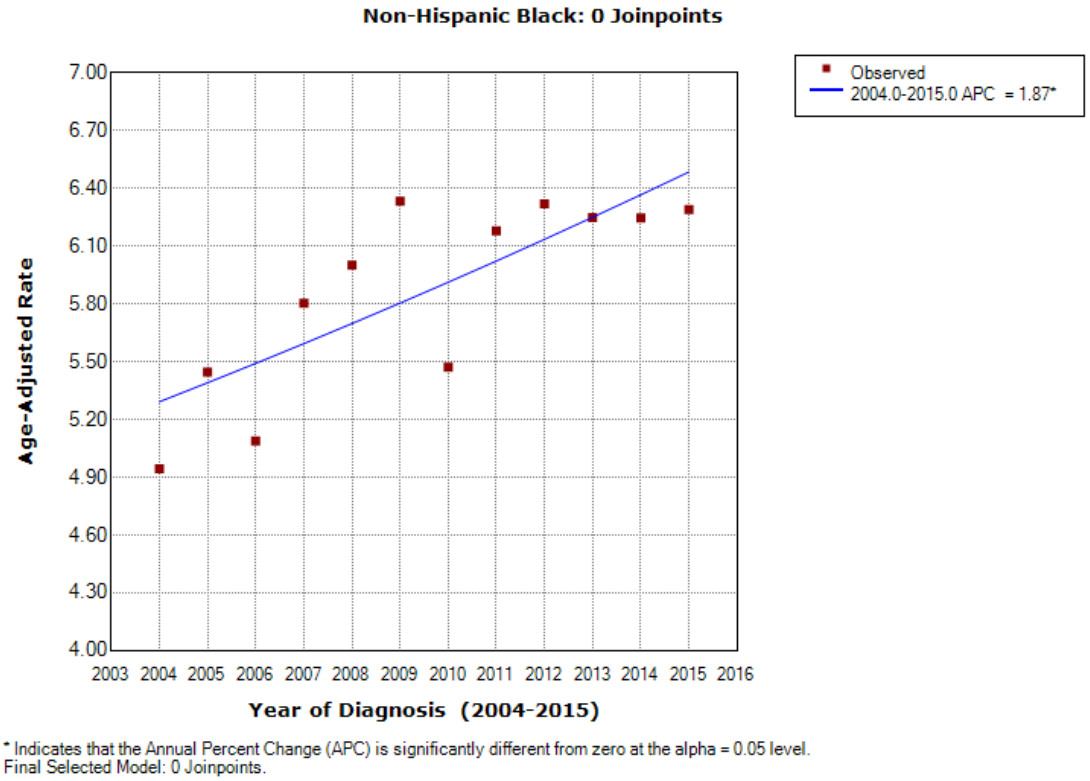

Figure S3. Joinpoint regression line of type II endometrial cancer incidence for non-Hispanic Blacks in the SEER registry data between 2004 and 2015. Abbreviations: APC, annual percentage change.

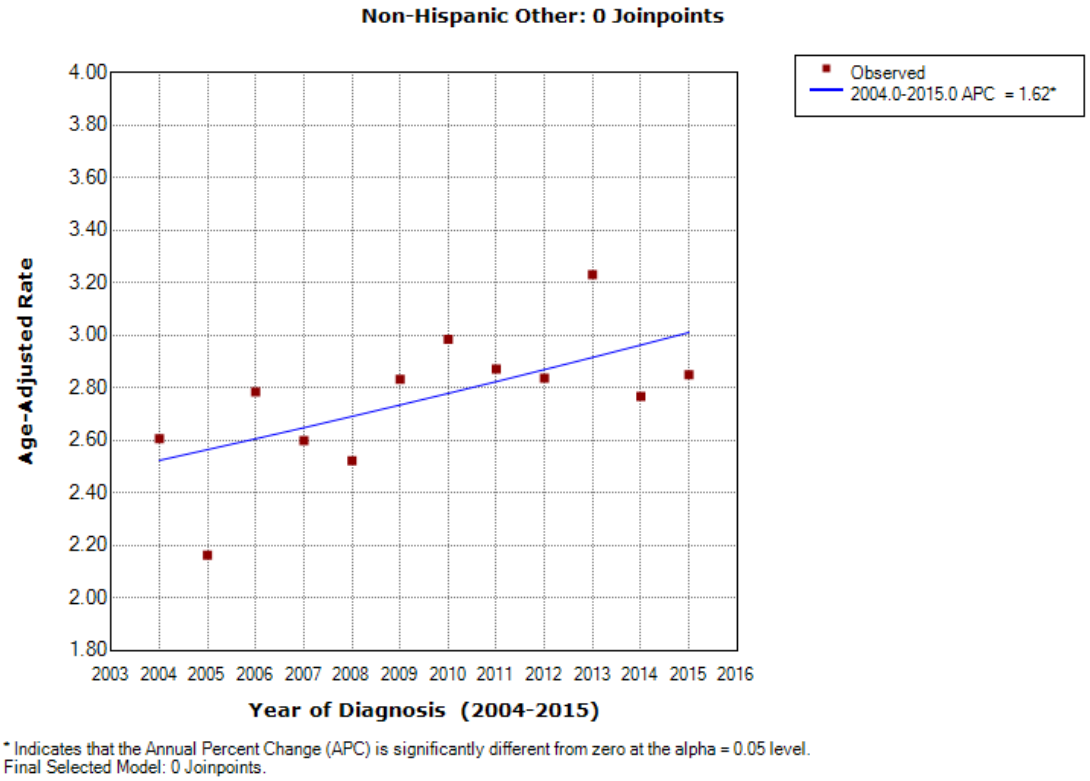

Figure S4. Joinpoint regression line of type II endometrial cancer incidence for non-Hispanic Others in the SEER registry data between 2004 and 2015. Abbreviations: APC, annual percentage change.

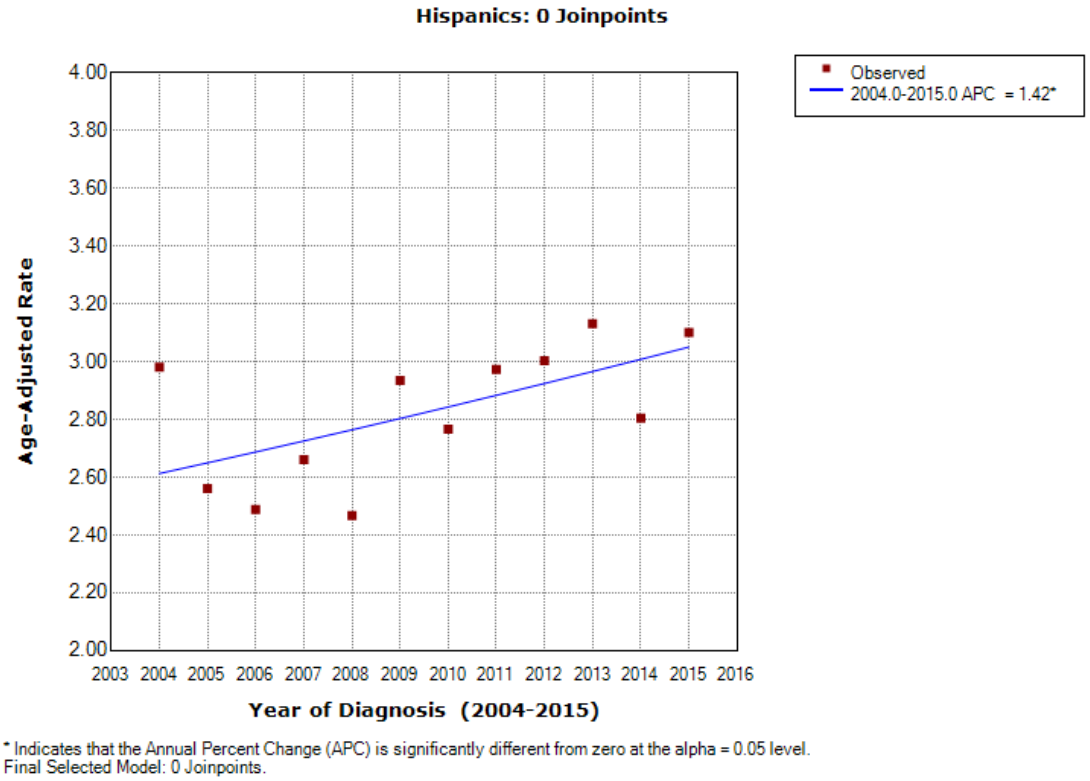

Figure S5. Joinpoint regression line of type II endometrial cancer incidence for Hispanics in the SEER registry data between 2004 and 2015. Abbreviations: APC, annual percentage change.