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Racial disparities in risk of second primary cancers in endometrial cancer patients: Analysis of SEER Data

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Abstract

Introduction—Endometrial cancer (EC) is the most common gynecologic cancer in the United States. Racial disparities in the incidence and mortality of this cancer are apparent; black women are less likely to develop this malignancy, and yet are more likely to die when diagnosed. Racial differences of second primary cancer (SPC) have not been examined and are the goal of this study.

Methods—Using the National Cancer Institute's Surveillance, Epidemiology, and End Results database, SPC risk in white and black EC cases was compared to the general population and to women with other primary cancers. Standardized incidence ratios (SIRs) of SPC (overall and by tumor site) with 95% confidence intervals were calculated. Poisson regression was used to estimate the race-specific risk of SPC in EC cases treated with radiotherapy vs. non-irradiated cases.

Results—The analysis included 11,047 EC cases diagnosed between 1973 and 2007 that developed a SPC. Overall risk of SPC in white EC cases was significantly lower than the general population (SIR=0.85, 95% CI: 0.84, 0.87), but significantly higher in black EC cases (SIR=1.19, 95% CI: 1.08, 1.31). White EC cases treated with radiotherapy were more likely to develop SPC compared to non-irradiated cases (IRR=1.18, 95% CI: 1.14, 1.23).

Conclusions—This is the first analysis of race-specific SPC risk in EC cases and it suggests differences between white and black cases. Although exploratory, these data provide important clues about the etiology of SPC in patients with EC. This analysis also highlights the need for careful monitoring following diagnosis and treatment of EC.

INTRODUCTION

In the United States, endometrial cancer (EC) is the most common cancer of the lower female genital tract and mortality from this disease is rising.(1) In 2009, approximately

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42,160 new cases of EC were diagnosed with 7,780 reported deaths.(2) Important racial differences exist in the incidence and mortality of EC. Historical data show that the incidence of EC is higher in white women compared to black women, however blacks have a higher risk of dying when diagnosed with EC.(3) A large analysis using data from the Surveillance, Epidemiology, and End Results (SEER) program reported age-adjusted EC incidence rates among whites and blacks to be 23.4 and 15.3 per 100,000 women, respectively, whereas age-adjusted mortality rates were 3.1 and 5.0 per 100,000 women respectively.(4) Several studies have examined factors that may explain the racial disparity in EC mortality. Prevalence of aggressive histologies, such as papillary serous and clear cell, is higher among black cases compared to whites.(5,6) A SEER analysis reported 53% of EC-related deaths in blacks to be associated with serous and clear cell types compared to 36% of EC-related deaths in whites.(4)

Differences in tumor genetics could also play a role in mortality differences. Overexpression of p53, a tumor suppressor gene frequently inactivated in various cancers, is an independent prognostic factor for worse survival in EC.(7,8) In stage 1 EC cases, Clifford et al. showed that the prevalence of p53 overexpression was three times higher in black cases compared to white cases, and disease recurrence was twice as common in cases with p53 overexpression compared to normal immunostaining.(9) Other factors that may contribute to the racial disparity in EC mortality include decreased health care access, disparities in treatment options, and differences in the prevalence of risk factors that may affect treatment decisions. (3,4,10)

In addition to death following an EC diagnosis, outcomes such as EC recurrence and risk of second primary cancers (SPC) are important clinical considerations. With respect to recurrence, others(11), (12) have noted that black cases have a shorter time to recurrence compared to white cases, despite receiving similar treatments. To our knowledge, the risk of SPC following EC has been examined infrequently in the literature. One study investigated SPC following EC diagnosis and reported that the overall risk of SPC was not increased among cases with a primary diagnosis of EC; however, risk of SPC did vary by age and site of the SPC. Another SEER analysis examining the impact of radiotherapy on risk of SPC following EC(13) showed that any radiotherapy was associated with a significant excess risk of subsequent colon and lung cancer diagnoses, and the risk increased with latency since radiation exposure. Most recently, Lonn et al.(14) examined the effect of various radiotherapy modalities for EC treatment on risk of SPC; type of radiotherapy modified the overall effect of radiotherapy such that brachytherapy was associated with a reduced risk of SPC compared to any external beam therapy.

The previously cited literature does not address the risk of SPC separately for white and black EC cases. The current study has been designed to address this gap in the existing research and examine SPC risk in a large SEER cohort of white and black EC cases. We hypothesized that race-specific differences in development of subsequent cancers may provide further insights into the epidemiology of EC.

MATERIAL AND METHODS

Study population

The Surveillance, Epidemiology, and End Results (SEER) database is the source of population-based cancer information provided by the National Cancer Institute (NCI). For the current analysis the SEER 9 registries were used, which include Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah. Women who had a primary invasive EC between 1973 and 2007 and who developed a second primary cancer (SPC) at least 2 months subsequent to their EC diagnosis were

included. We defined SPC as a new cancer occurrence, as opposed to a metastatic disease or a recurrence of the first neoplasm based on time of diagnosis, histological type, and site.(15)

Statistical Analysis

Standardized incidence ratios (SIR) were calculated for all females with a first diagnosis of EC to determine the lifetime risk associated with the development of a SPC. We used the Multiple Primary-Standardized Incidence Ratio (MP-SIR) program of the SEER Stat software to calculate the SIR of SPC using data compiled between 1973 and 2007. Follow-up time was counted from 2 months after the initial EC diagnosis until the diagnosis of a SPC, death, or end of the study (34 years after diagnosis). A single outcome analysis was used which caused individuals to exit the study when a SPC or death occurred; thus, these individuals contributed no additional person time at risk. For each tumor site, the SIR was calculated with the following equation: observed number of cancer cases at a particular tumor site/expected number of cancer cases at that particular tumor site.(15) The observed number of cancer cases refers to the exact number of SPCs in this cohort while the expected number of SPCs was calculated using age and race-specific cancer incidence rates in the general population. In order to uniformly describe the burden of SPCs between white and black cases, the SPC risk was examined for all sites, solid tumors, digestive system, colon and rectum, liver, pancreas, respiratory system, breast, female genital system excluding the endometrium, and urinary system.

Excess risk was calculated to verify whether an excess in the number of cases of SPC in EC patients compared to the population of females with other cancers (excluding EC) was present. The expected number of SPC cases was determined by applying the stratum-specific incidence rates for the female cancer population to the stratum-specific person-years of the EC patients ((observed number of cases in the female cancer population/female cancer population's person-years at risk) $\times$ EC patients' person-years at risk).(15) The excess risk of SPC per 10,000 persons per year for each tumor site was calculated as ((observed number of SPC for EC patients – expected number of SPC when females with other cancers were used as the reference group) $\times$ 10,000)/EC patients' person years at risk.(15)

Categorical variables related to the primary EC diagnosis (stage at diagnosis, radiotherapy use, histology type, age at diagnosis, and calendar year of diagnosis) were extracted using a rate session from SEER stat. Histology type was re-categorized to reflect the Type I and Type II groups commonly referred to in the literature.(16) We reported the distributions of these variables by race; however we did not include chi-square *p*-values as the large sample size contributed to significant *p*-values even when differences by race were subtle. Furthermore, a Poisson regression model was used for grouped data to examine the relative risk of developing site-specific SPC in EC cases treated with radiotherapy vs. those who were not. Incidence rate ratios (IRR) and 95% confidence intervals stratified by race and adjusted for age group (<45, 45-54, 55-64, 65-74, and >75) are presented. SEER Stat and STATA version 10 (StataCorp, College Station TX) were used for this analysis. This study was approved by the University of Pittsburgh Institutional Review Board.

RESULTS

Baseline characteristics of patients with primary EC by race are shown in Table 1. Of the primary EC cases, 98,205 were white (94%) and 6,511 were black (6%). Age and calendar year of diagnosis differed between white and black EC cases; a higher percentage of black cases (10%) were younger than 45 at time of diagnosis compared to whites (6%), while white cases were more likely to be diagnosed between the ages of 45-54. Black cases were also more likely to be diagnosed between 2000 and 2007 compared to white cases. EC tumor stage differed between black and white cases with relatively more black cases

diagnosed with regional or distant stage tumors compared to white EC cases. Sequence of treatment was similar among black and white cases. Approximately 9% and 6% of white and black EC cases had radiation prior to surgery, respectively, while 21% had radiation after surgery in both races, and 1% had radiation before and after surgery in both races. Radiotherapy modality was similar between whites and blacks. Beam radiation was used in 17% and 19% of white and black EC cases, respectively; 3% of white and black EC cases had radioactive implants or radioisotopes; 8% and 9% of white and black EC cases had combination therapy. The remaining patients had an unspecified or unknown radiotherapy modality. Histology type was significantly different between white and black EC cases; approximately 19% of black EC cases had Type II histologies compared to 7% of white EC cases. In this cohort of 103,441 white and black primary EC cases 11,047 SPC were observed; the prevalence of SPC was higher in white cases (11%) compared to black cases (7%).

The race-specific risk of developing selected SPCs is shown in Table 2. The SIR for all second cancers was lower than expected for white EC cases (SIR=0.85, 95% CI: 0.84, 0.87). Site-specific analyses showed decreased risks for solid tumors (SIR=0.85, 95% CI: 0.83, 0.87), liver (SIR=0.58, 95% CI: 0.41, 0.80), pancreas (SIR=0.88, 95% CI: 0.79, 0.98), and female genital system cancers (SIR=0.65, 95% CI: 0.59, 0.71) in white cases. A higher than expected risk of subsequent urinary system cancers was observed in white EC cases (SIR=1.19, 95% CI: 1.11, 1.28). Black EC cases had an increased overall risk of SPC (SIR=1.19, 95% CI: 1.08, 1.31). Elevated risks in development of solid tumors (SIR=1.19, 95% CI: 1.08, 1.31), digestive system (SIR=1.37, 95% CI: 1.16, 1.61), colon and rectum (SIR=1.53, 95% CI: 1.24, 1.87), female genital system (SIR=1.48, 95% CI: 1.03, 2.07), and urinary system cancers (SIR=1.80, 95% CI: 1.25, 2.52) were significant among black EC cases compared to the general population.

The age-adjusted relative risk of SPC associated with radiotherapy stratified by race is shown in Table 3. In white EC cases, the relative risk of developing SPC at all sites was significantly higher in cases treated with any radiotherapy modality vs. non-irradiated cases (IRR=1.18, 95% CI: 1.14, 1.23). Risk of solid tumors (IRR=1.17, 95% CI: 1.12, 1.22), digestive system (IRR=1.30, 95% CI: 1.20, 1.40), colon and rectum (IRR=1.34, 95% CI: 1.22, 1.47), respiratory system (IRR=1.19, 95% CI: 1.07, 1.33), female genital system (IRR=1.30, 95% CI: 1.07, 1.58), and urinary system cancers (IRR=1.72, 95% CI: 1.49, 1.98) were increased among white cases exposed to radiotherapy. We also examined the individual SPC risk of cervical, ovarian, vaginal, and vulvar cancers and noted a significant risk of vaginal (IRR=1.72, 95% CI: 1.07, 2.75) and vulvar cancers (IRR=1.77, 95% CI: 1.17, 2.67) associated with radiotherapy in white cases. In black EC cases, an overall increased risk of female genital system cancers was observed in irradiated cases (IRR=2.07, 95% CI: 1.03, 4.18); however no significant risk of subsequent cancers in individual female genital sites was observed.

The excess risk of SPC was examined by comparing the lifetime risk of SPC observed in EC cases to that observed for all other female cancer cases (Figures 1-2); white and black EC cases had excess risks for development of digestive system, colon and rectum, pancreas and urinary system cancers, however the magnitude of risk was greater among black cases. For example, the excess risk of digestive tumors was 3.3 and 11.7 per 10,000 for white and black EC cases, respectively. Moreover, black EC cases had an excess risk of developing female genital system cancers compared to other female cancer patients.

DISCUSSION

This is the first large scale study to examine racial differences in the risk of second primary cancers (SPCs) in endometrial cancer (EC) patients. Although numerous studies have examined racial disparities in mortality and recurrence associated with primary EC, none have explored whether a disparity exists in the occurrence of SPCs following an EC diagnosis. Furthermore, the risk of developing a SPC is highly relevant in EC due to long term survival associated with this cancer. In our analysis, white EC cases had a significantly lower overall risk of developing SPC compared to the general population. Conversely, black EC cases had a significantly increased risk of all second malignancies compared to that expected in the general population. Site-specific risk of SPC differed between whites and blacks; white EC cases had an increased risk of urinary system cancers and decreased risks of solid tumors, liver, pancreas, and female genital system cancers. Black EC cases had significantly elevated risks of subsequent solid tumors, digestive system, colon and rectum, female genital system cancers, and urinary system cancers compared to the general population.

Several mechanisms may contribute to the increased risk of SPC in black EC cases. First, certain risk factors such as obesity, physical inactivity, and diabetes, are important etiologic factors for development of multiple cancers, especially endometrial and colorectal cancers. (17-22) The prevalence of these risk factors is higher among black women compared to whites, which may indicate a shared etiology mechanism. (23,24) Second, genetic factors may play a role in development of several cancers. Lynch syndrome is an inherited disorder which predisposes patients to development of several cancers including endometrial, stomach, urinary tract, ovary, and colon cancers. The prevalence of Lynch syndrome in blacks is unknown, however, this may be a potential mechanism explaining increased risk of SPC in black EC cases compared to the general population. Further work in this area is needed to validate or reject this hypothesis. Genetic mutations in non-identified cancer predisposing genes may also play a role in multiple cancer development.

Radiation exposure is a known risk factor for cancer development. Several authors have reported that black EC cases are more likely to undergo radiotherapy treatment compared to white EC cases (25-27), which may be related to the higher prevalence of aggressive histologies in black EC cases. In the current study, black EC cases were more likely to have any radiotherapy compared to whites, however the large sample size available for this analysis may have enhanced slight differences between white and black cases. When the effect of radiotherapy use on site of SPC development was examined, in white EC cases, radiotherapy was significantly associated with higher risk of all tumor sites, solid tumors, digestive system, colon and rectum, respiratory system, female genital system, and urinary system cancers, while black EC cases only had an increased risk of female genital system cancers associated with radiotherapy. Although similar patterns of the IRR were not observed between white and black cases, the number of black cases with SPC may have prohibited similar observations. As noted, there was an increased risk of female genital cancers among white and black EC cases treated with radiotherapy. Typically, surgical resection for EC includes a hysterectomy and removal of both ovaries and both fallopian tubes. This would potentially preclude developing cancer at these sites, however risk of other female genital cancers such as cervical, vaginal, and vulvar remains. We observed a large number of ovarian SPCs which may imply that these cases had local radiotherapy treatment and no surgical intervention. Unfortunately, the SEER dataset did not allow for the subgroup of cases treated with radiotherapy only to be parsed out from the entire sample.

The general patterns in this study are similar to previously published reports. Kumar et al. (13) reported the relative risk associated with radiotherapy to be higher in organs closer to

the uterus compared to organs at distant sites. Likewise, Lonn et al.(14) reported significantly higher SIRs of the colon, rectum, and bladder in EC cases treated with radiotherapy vs. the general population. We also investigated the excess risk of developing SPC among EC cases compared to female patients with other primary cancers. Both white and black EC cases had excess risks of developing digestive system, colon and rectum, pancreas, and urinary system cancers compared to female patients with other primary cancers; however the magnitude of risk was greater in black EC cases. Furthermore, black EC cases had excess risks of female genital system and liver cancers. The excess risk of these tumors may be associated with radiotherapy treatment following EC, especially based on the proximity of these organs to the uterus.

The major strength of this study is use of the SEER database. The internal and external validity of this database has been previously highlighted.(28) Furthermore, as EC in black women is relatively rare(29), large databases of cases are needed to evaluate EC and its sequelae in this demographic. No other study has specifically examined racial differences in the incidence of SPC. An important limitation of using the SEER database is lack of information on other factors relevant to development of second cancers. Specifically, smoking, BMI, genetic information, and chemotherapy treatment are not available in the public use files; however these factors are certainly implicated in cancer development. Chemotherapy could potentially be viewed as a risk factor for SPC, as it results in immune dysfunction. Nevertheless, while chemotherapy is becoming more prevalent for the treatment of EC, the vast majority of EC patients are routinely administered radiotherapy, not chemotherapy. Future studies can address the limitations in this paper by taking into account other known risk factors for cancer development. In order to achieve sufficient sample sizes for this endeavor, pooled analyses of existing databases will need to be performed.

In summary, this is the first study to examine race-specific risks of developing SPCs in primary cases of EC. Overall patterns of second cancer development were dissimilar between white and black EC cases. The increased risk of cancers proximal to the uterus agrees with previously published data and stresses the need for continued patient monitoring after treatment for EC.

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Figure 1.

Excess risk per 10,000 for SPC in white EC cases

Description – Lifetime excess risk per 10,000 for second primary cancers in white endometrial cancer patients compared to white females with other cancers

Figure 2.

Excess risk per 10,000 for SPC in black EC cases

Description – Lifetime excess risk per 10,000 for second primary cancers in black endometrial cancer patients compared to black females with other cancers

Table 1

Characteristics of white and black primary EC cases, SEER 9 Registries (1973-2007)

	White (N=98,205)	Black (N=6,511)
Age at EC diagnosis (years)	N (%)	N (%)
<45	5,645 (6)	634 (10)
45-54	15,922 (16)	882 (14)
55-64	29,490 (30)	1,889 (29)
65-74	26,845 (27)	1,885 (29)
75+	20,296 (21)	1,219 (19)
Calendar year of EC diagnosis		
1973-1979	20,065 (20)	801 (12)
1980-1989	25,820 (26)	1,487 (23)
1990-1999	27,965 (28)	1,928 (30)
2000-2007	24,355 (25)	2,295 (35)
Tumor stage *		
Localized	72,872 (74)	3,430 (53)
Regional	12,380 (13)	1,379 (21)
Distant	7,764 (8)	1,153 (18)
Unstaged	5,189 (5)	549 (8)
Sequence of treatment		
No radiotherapy and/or surgery	67,599 (69)	4,707 (72)
Radiation prior to surgery	9,124 (9)	395 (6)
Radiation after surgery	20,197 (21)	1,349 (21)
Radiation before and after surgery	1,120 (1)	50 (1)
Sequence unknown	144 (<1)	8 (<1)
Radiotherapy modality		
None	62,023 (63)	3,990 (61)
Beam radiation	16,623 (17)	1,249 (19)
Radioactive implants or radioisotopes	3,246 (3)	213 (3)
Combination of beam with implants or isotopes	8,131 (8)	609 (9)
Radiation, NOS	6,549 (7)	243 (4)
Unknown	1,633 (2)	207 (3)
Histology type **		
Type I	80,195 (93)	3,699 (81)
Type II	6,118 (7)	878 (19)
Observed number of SPC ‡	10,584 (11)	463 (7)

‡ Excludes cancers of the uterine corpus

* SEER summary stage: Groupings based on The International Federation of Gynecology and Obstetrics (FIGO) stage criteria

** Type I: ICD-O-3 morphology codes: 8140, 8380, 8382, 8480, 8482, 8560, and 8570; Type II: ICD-O-3 morphology codes: 8260, 8310, 8441, and 8460

Table 2

Site-specific risk of SPC in EC cases according to race, (1973-2007)

Second cancer site	White (N=10, 584)	Black (N=463)
	SIR (95% CI)	SIR (95% CI)
All sites (N=11,047)	0.85 (0.84, 0.87)	1.19 (1.08, 1.31)
Solid tumors (N=9,744)	0.85 (0.83, 0.87)	1.19 (1.08, 1.31)
Digestive system (N=2,854)	0.97 (0.93, 1.01)	1.37 (1.16, 1.61)
Colon and rectum (N=1,949)	1.02 (0.97, 1.07)	1.53 (1.24, 1.87)
Liver (N=40)	0.58 (0.41, 0.80)	1.17 (0.32, 2.99)
Pancreas (N=356)	0.88 (0.79, 0.98)	0.97 (0.56, 1.55)
Respiratory system (N=1,382)	0.72 (0.68, 0.76)	1.09 (0.84, 1.39)
Breast (N=3,448)	0.98 (0.95, 1.01)	1.01 (0.82, 1.23)
Female genital system (N=448)	0.65 (0.59, 0.71)	1.48 (1.03, 2.07)
Urinary system (N=801)	1.19 (1.11, 1.28)	1.80 (1.25, 2.52)

Digestive system: esophagus, stomach, small intestine, colon and rectum, liver, gallbladder, and pancreas

Respiratory system: lung and bronchus

Female genital system: ovary, cervix, vaginal, and vulva

Urinary system: urinary bladder and ureter, kidney and renal pelvis

Table 3
Incidence rate ratios (IRRs) and 95% CIs of selected SPC sites among EC patients, by radiotherapy and race

	No radiotherapy*	Any radiotherapy	IRR (95% CI)	Black	No radiotherapy*	Any radiotherapy	IRR (95% CI)
White	n[†]	n[†]	IRR (95% CI)	Black	n[†]	n[†]	IRR (95% CI)
All Sites	6,041	4,418	1.18 (1.14, 1.23)	All Sites	261	192	1.07 (0.88, 1.29)
Solid Tumors	5,353	3,870	1.17 (1.12, 1.22)	Solid Tumors	230	169	1.06 (0.87, 1.30)
Digestive System	1,480	1,188	1.30 (1.20, 1.40)	Digestive System	87	58	0.96 (0.68, 1.34)
Colon and rectum	1,003	826	1.34 (1.22, 1.47)	Colon and rectum	52	42	1.21 (0.80, 1.82)
Liver	18	17	1.53 (0.79, 2.97)	Liver	2	2	1.37 (0.19, 9.84)
Pancreas	194	139	1.14 (0.91, 1.41)	Pancreas	11	6	0.72 (0.26, 1.95)
Respiratory System	747	557	1.19 (1.07, 1.33)	Respiratory System	37	29	1.07 (0.65, 1.75)
Breast	2,078	1,232	0.95 (0.89, 1.02)	Breast	60	37	0.88 (0.58, 1.34)
Female Genital System	234	177	1.30 (1.07, 1.58)	Female Genital System	14	19	2.07 (1.03, 4.18)
Cervix	10	8	1.39 (0.54, 3.54)	Cervix	2	5	3.32 (0.64, 17.16)
Ovary	147	86	1.04 (0.80, 1.36)	Ovary	4	8	2.72 (0.82, 9.07)
Vagina	34	36	1.72 (1.07, 2.75)	Vagina	6	4	1.03 (0.29, 3.72)
Vulva	43	47	1.77 (1.17, 2.67)	Vulva	2	2	2.51 (0.32, 19.73)
Urinary System	366	386	1.72 (1.49, 1.98)	Urinary System	16	15	1.46 (0.71, 3.00)

Digestive system: esophagus, stomach, small intestine, colon, rectum, liver, gallbladder, and pancreas

Respiratory system: lung and bronchus

Female genital system: ovary, cervix, vaginal, and vulva

Urinary system: urinary bladder and ureter, kidney and renal pelvis

* Reference group

[†] Number of observed SPC