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Author manuscript

Risk factors for endometrial cancer in black and white women: A pooled analysis from the Epidemiology of Endometrial Cancer Consortium (E2C2)

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Abstract

Purpose—Endometrial cancer (EC) is the most common gynecologic cancer in the United States. Over the last decade, the incidence rate has been increasing, with a larger increase among blacks. The aim of this study was to compare risk factors for EC in black and white women.

Methods—Data from 7 cohort and 4 case-control studies were pooled. Unconditional logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals for each risk factor in blacks and whites separately.

Results—Data were pooled for 2,011 black women (516 cases and 1,495 controls) and 19,297 white women (5,693 cases and 13,604 controls). BMI 30 was associated with an approximate 3-fold increase in risk of EC in both black and white women (OR_{black}=2.93, 95% CI: 2.11, 4.07 and OR_{white}=2.99, 95% CI: 2.74, 3.26). Diabetes was associated with a 30–40% increase in risk among both groups. Increasing parity was associated with decreasing risk of EC in blacks and whites (p-value=0.02 and <0.001, respectively). Current and former smoking was associated with decreased risk of EC among all women. Both black and white women who used oral contraceptives for 10+ years were also at reduced risk of EC (OR=0.49, 95% CI: 0.27, 0.88 and OR=0.69, 95% CI: 0.58, 0.83, respectively). Previous history of hypertension was not associated with EC risk in either group.

Conclusions—The major known risk factors for EC exert similar effects on black and white women. Differences in the incidence rates between the two populations may be due to differences in the prevalence of risk factors.

Keywords

Introduction

More than 49,000 women will be diagnosed with endometrial cancer (EC) in 2013, making it the most common gynecologic cancer in the United States, and incidence rates have been rising since 2002 .[1] Data from the Surveillance, Epidemiology and End Results program (2006–2010) report the age-adjusted incidence rate of EC is lower among black women than white women (22.2 and 25.1 cases per 100,000 women, respectively).[2] Among women aged 50 and older there is a similar trend, with 60.9 cases per 100,000 black women and 78.8 cases per 100,000 white women. [3, 4] However, when the greater prevalence of hysterectomies in black women is accounted for, the incidence among black women has exceeded that of white women since 2000.[3] It is estimated that by 2030, endometrial cancer will become the 6th most common cancer overall, and the 3rd most common among women.[5] In addition, five year survival after an EC diagnosis is lower for black women compared to white women at every stage of diagnosis, and these rates have not changed substantially over the last three decades.[2] Thus, exploring factors associated with EC may

provide insight regarding racial differences that potentially impact incidence and ultimately, survival.

To a large extent, EC is a hormone-related cancer, with exposure to estrogen unopposed by progestin considered a major underlying mechanism.[6–8] It is well-established in both population- and hospital-based studies that tumor histology varies by racial group. Endometrioid tumors are the most common subtype of EC for all women, but black women have a higher proportion of non-endometrioid tumors, such as serous or clear cell cancers, which may be less hormonally-dependent.[9] As described by Setiawan et al, risk factors for endometrioid and non-endometrioid subtypes appear to be similar.[10] The foremost risk factor for EC, obesity, is strongly related to circulating estrogen levels in postmenopausal women, and appears to increase risk for all subtypes.[10, 11]. Other hormone-related factors associated with increased EC risk include later age at menopause and nulliparity.[12, 13] Reduced risk is associated with use of oral contraceptives, cigarette smoking, and later age at last birth.[13–15] As the prevalence of some of these biologic and behavioral factors differ between white and black women in the US population, it is possible that the strength of association between risk factors and EC may also differ, but the small number of black women in individual case-control and cohort studies has precluded analyses of black-white differences. The aim of this study was to investigate risk factors for endometrial cancer in black and white women using a pooled analysis.

Materials and Methods

Participating studies

Data were obtained from 7 cohort studies and 4 case-control studies that participate in the Epidemiology of Endometrial Cancer Consortium (E2C2). This international consortium was formed in 2006 to provide a collaborative environment to address questions by pooling data from existing studies that would be underpowered in individual studies.[16] Studies with at least 10 black cases and 10 black controls were asked to provide data for this analysis (see Table 1). Race was self-reported for each study participant. Cohort studies were analyzed as nested case-control studies, with up to 4 controls selected per case frequency-matched based on year of birth, date of cohort entry, race, and study. Controls had an intact uterus at the time of study participation, and did not have a previous history of EC. The number of black women with EC in each study ranged from 12 to 128. Informed consent was obtained from participants by each original study, in accordance with each study's institutional review board.

Data collection

The individual, de-identified datasets were sent to the E2C2 data coordinating center at Memorial Sloan-Kettering Cancer Center for initial data harmonization and cleaning, with the exception of the data from the Women's Health Initiative, which was sent to Wayne State University (WSU). All datasets were then pooled and data analysis took place at WSU. Any questions regarding data inconsistencies or missing variables were referred back to the site study coordinator and/or principal investigator. All information, including race, was collected by self-report, either at baseline (for the cohort studies) or at the time of diagnosis

(for the case-control studies). Age was recorded at diagnosis (for cases in all studies), at interview (for controls in case-control studies) or at reference date (for controls in cohort studies).

Statistical methods

Race-specific odds ratios and 95% confidence intervals for the risk of EC were estimated using unconditional logistic regression. Available covariates of interest for this analysis were: age, body mass index, (BMI; wt(kg)/ht(m^2)), education, smoking history, oral contraceptive (OC) use and duration, parity, age at first birth, age at menarche, self-reported diabetes and hypertension. Risk factors found to be statistically significant in the univariate analysis were included in adjusted models. Multivariable unconditional logistic regression models were adjusted for age, study site, BMI (<25, 25–29.9, 30), smoking (ever/never), OC use (ever/never), diabetes (yes/no), age at menarche (age 11, 12–13, 14 years), and parity (continuous to 5+), where appropriate. The interaction between each variable and race was evaluated using an interaction term in the adjusted model. For significant interactions, forest plots were created to illustrate the effect of the risk factor on EC risk by race and study. Due to evidence of heterogeneity between the studies (I^2=51.2, Q=20.5 (10df), p=0.03), a random effects model was used to estimate a meta-OR. Analyses were completed using SAS Version 9.2 (Cary, North Carolina) and the R statistical package.[17]

Results

Descriptive characteristics of the 2,011 black women (516 cases and 1,495 controls) and 19,297 white women (5,693 cases and 13,604 controls) included in the study population are shown in Table 2, along with estimates of the risk of EC by race, adjusted for potential confounders. Obesity (BMI 30) was associated with EC in both black and white women, compared to those with BMI<25 (OR$_{black}$=2.93, 95% CI: 2.11, 4.07, and OR$_{white}$=2.99, 95% CI: 2.74, 3.26, respectively). Women who were overweight (BMI 25–29.9) were also at an increased risk of EC. In black and white women, past and current cigarette smoking was associated with reduced risk, as was oral contraceptive use of 10+ years, after adjustment. Increasing parity was associated with reduced risk of EC in both black women (p-value=0.02) and white women (p-value<0.001), and there was a significant interaction between parity and race (p-value=0.03, data not shown). No additional interactions by race were significant in the pooled analysis. Though increased age at first birth only showed a reduced risk for white women (p-value<0.001), there was a suggestion of a reduced risk in black women whose age at first birth was 30 or more years. White women who reported their age at menarche to be under 11 years of age were at a small increased risk of EC compared to those who were 12 or 13 years of age at menarche (OR=1.22, 95% CI: 1.11, 1.34) whereas individuals older than 14 at menarche were at a small decreased risk (OR=0.89, 95% CI: 0.82, 0.97). Risk estimates were similar but not statistically significant among black women. Diabetes was associated with similar increases in risk of EC among black women (OR=1.41, 95% CI: 1.07, 1.87) and white women (OR=1.30, 95% CI: 1.15, 1.46), after adjustment. A history of hypertension was not associated with increased risk of EC among black or white women. Histology, grade and stage at diagnosis among the cases are shown in Supplementary Table 1.

Because of the race-parity interaction we observed, we show in Figure 1 forest plots for the association between parity (on the continuous scale) and endometrial cancer risk by race. Among black women, results from the individual studies vary, with the meta-OR=0.93 (95% CI: 0.86, 1.01) (Figure 1a). For white women, 10 of 11 studies show an inverse association with EC, with a meta-OR=0.83 (95% CI: 0.80, 0.87), suggesting that every birth reduces the risk of EC by 17% (Figure 1b).

Discussion

This pooled analysis offers the first estimates of risk associated with EC in black women for common risk factors. Overall, we found estimates to be of similar magnitude between black and white women; however, as described below, the prevalence of these risk factors vary by race in the US population.

Obesity is the strongest risk factor for EC among all women examined in this study. A potentially modifiable risk factor, obesity is linked with a number of cancers, but the strongest association is with EC. The previously reported relative risk of 1.6 per 5 kg/m^2 incremental increase[18] is similar to the 3-fold increase among both black and white women we reported between women who were obese and those of normal weight. Overweight women are also at increased risk of EC, although the effect size is more modest. The racial disparity in obesity prevalence between black and white women has been widely reported.[19, 20] With a greater proportion of black women classified as obese, one would expect to see higher incidence of endometrial cancer among black women, as has been reported when the higher prevalence of hysterectomies is accounted for in the black population.[3]

Similar to our findings, the association between type II diabetes and EC has been reported in various studies, including a meta-analysis of 16 studies, reporting an approximate 2-fold increase in risk, after adjustment for BMI.[21] Diabetes is under-diagnosed in the general population, with a higher level of under-diagnosis among blacks, so it is likely our findings are conservative.[22] Prevalence of type II diabetes continues to rise in the United States, and remains relatively higher among black women.[23]

Increasing parity has been shown to be associated with a reduction in EC risk in white women. [24, 25] We see a similar association among black women; however, the pattern of decreasing risk with increasing parity was somewhat less strong for blacks. There are various potential mechanisms that could explain why nulliparous women are at greater risk of EC compared to parous women. Hormones produced during pregnancy, particularly high levels of progesterone, may inhibit estrogen-driven proliferation of the endometrium, resulting in a reduction of endometrial cancer risk.[26] It is also possible that the reduction of risk is due to the mechanical shedding of precancerous cells during delivery or during postpartum involution of the uterus.[27, 28] Data suggest nulliparity is increasing in the United States, with 18% of women ages 40–44 childless in 2008, compared to 10% of women of the same age in 1974.[29] The prevalence of childlessness increased more rapidly among black women than among white women during this time period (30% increase

among blacks compared to 11% in whites). Overall, 17% of black women and 20% of white women were childless (at ages 40–44) in 2008.[29]

Both black and white women who reported former or current cigarette smoking were at reduced risk of EC compared to never smoking women. This association has been fairly consistent in various populations. [30–32] The biological mechanisms linking smoking to endogenous sex hormones underlying this reduction in risk are unclear, but may be associated with a reduction in circulating estrogen.[33, 34] Cigarette smoking appears to increase circulating progesterone levels, and in vitro studies suggest it increases expression of progesterone receptors in endometrial stromal cells. [35, 36] Ever smoking women have also been shown to have lower ages at natural menopause compared to never smokers, and to be thinner.[37, 38] In 2011, 15.5% of adult black women and 18.8% of adult white women reported current smoking.[39] Prevalence of current smoking has been consistently lower among black women compared to white women.[40]

Extended duration of oral contraceptive use was shown to provide a 40–50% reduction of EC risk in this pooled analysis. Similar to our findings, a meta-analysis of 11 studies published between 1980 and 1993 reported a more pronounced negative association as the duration of oral contraceptive use increased, with a relative risk of 0.28 for women reporting 12 or more years of use (p-value<0.0001).[41] A more recent meta-analysis of 9 studies published from January 1, 2000 and forward suggested a similar reduction of risk among ever users of oral contraceptives, but did not account for duration (OR=0.57, 95% CI: 0.43, 0.77).[42] Thus, despite differences in formulations over the decades, oral contraceptive use is consistently associated with decreased risk of EC. Various studies suggest black women are less likely to use oral contraceptives compared to their white counterparts; however, in our pooled analysis white and black controls reported ever use of oral contraceptives to a similar degree.[43–45]

Two other reproductive variables, age at first birth and age at menarche, were associated with risk of EC only among white women. The risk estimates were similar for black women, but were not statistically significant. The association between later age at first birth and decreased risk of EC has been reported in some populations, but not others.[25, 28, 46] Earlier age at menarche has been associated with increased risk in several populations, but these studies did not include an adequate number of black women for stratified analysis. [25, 47–49]

Our analyses did not include an assessment of the possible role of postmenopausal hormone therapy on EC in black or white women, because details regarding the formulation of hormone therapy were not collected for many of the studies. Estrogen-only hormone therapy, a well-established risk factor for EC, was used by less than 25% of the study population, and was less frequent among black women. When we excluded women reporting using estrogen-only hormone therapy, the results were essentially unchanged (see Supplementary Table 2).

Our study had other limitations. First, despite the inclusion of 11 studies with participants from across the United States, our sample size in some subgroup analyses was not sufficient

to robustly estimate associations with EC. In particular, we were unable to examine race-stratified associations by histologic subtype, and thus our results apply primarily to type I cancers. Recent work utilizing the E2C2 data reported that common risk factors did not appear to vary substantially by subtype, with the exception of clear cell tumors. [10] Second, data harmonization across studies was challenging for certain variables due to the use of different questions. For example, we were unable to harmonize oral contraception duration in a manner that included a true "no exposure" category, as one of the studies collected duration as less than one year, and 20% of respondents who reported ever using oral contraception did not report duration. Thus, our multivariable models were adjusted for a dichotomous ever/never oral contraceptive use variable. Finally, there is the potential for recall bias for the case-control studies, which may lead to an overestimation of the effect, although estimates from cohort studies and case control studies were similar (data not shown). Lastly, all of variables in this pooled analysis were self-reported, which may have resulted in misclassification of exposures.

In conclusion, the results of our pooled analysis suggest that the major known factors associated with EC in white women—obesity, nulliparity, cigarette smoking, oral contraceptive use, and history of diabetes—also predispose to EC in black women. Increases in obesity, diabetes and nulliparity in both populations, but to a greater extent in blacks, may in part explain some of the racial differences seen in EC incidence both now and in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix

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1a: Black women
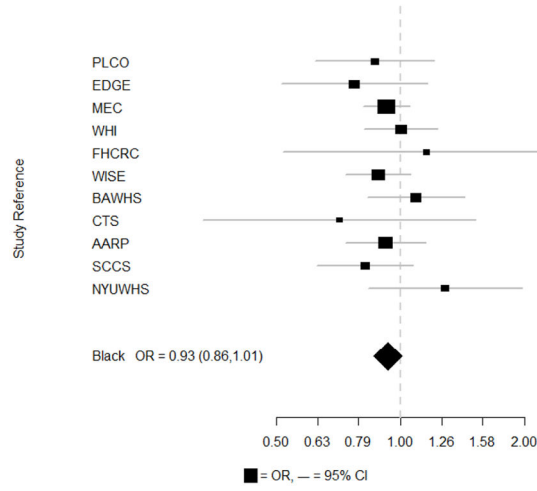
1b: White women
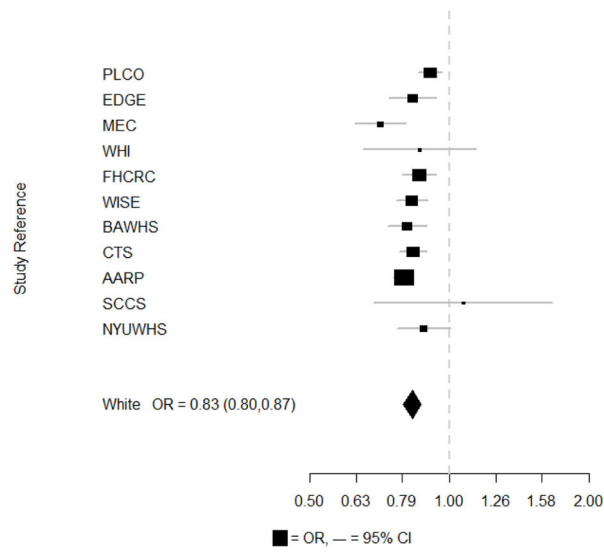
Figure 1.
Forest plot of parity trend by race, a) black women, b) white women

Table 1

Characteristics of the E2C2 studies included in the pooled analysis

Study	Location	Recruitment Period	Last Follow-up	Age Range at Study Entry	Blacks		Whites	
					Cases	Controls	Cases	Controls
Cohort Studies								
American Association of Retired Persons Diet and Health Study	CA, FL, PA, NJ, NC, LA, Atlanta-GA, Detroit-MI	1995–1996		50–71	81	234	1,652	4,525
California Teacher's Study	California	1995–1997		21–90+	12	39	697	2,171
Multiethnic Cohort Study	California, Hawaii	1993–1996		45–75	128	399	171	552
New York University Women's Health Study	New York	1985–1991		34–65	23	76	217	673
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	10 centers across the U.S.	1993–2001		55–74	23	86	654	2,558
Southern Community Cohort Study	12 Southern states, US	2002–2009		40–79	32	111	19	67
Women's Health Initiative	24 US states, DC, and 40 centers	1993–1998		50–79	53	212	53	212
Cohort Studies Total					**352**	**1,157**	**3,463**	**10,758**
Case-control studies								
Bay Area Women's Health Study	California	1996–1999		35–79	44	52	424	411
Estrogen, Diet, Genetics and Endometrial Cancer Study	New Jersey	2001–2005		23–97	39	20	417	422
Fred Hutchinson Cancer Research Center	Washington	1994–2005		50–74	14	18	840	827
Women's Insight and Shared Experience Study	Philadelphia	1999–2002		50–79	67	248	549	1,186
Case-control studies total					**164**	**338**	**2,230**	**2,846**
Total All Studies					**516**	**1,495**	**5,693**	**13,604**

Table 2

Associations between subject characteristics, risk factors, and endometrial cancer, by race.

	Blacks (n=2,011)				White (n=19,297)			
	Cases (n=516)	Controls (n=1,495)	OR[a]	(95% CI)	Cases (n=5,693)	Controls (n=13,604)	OR[a]	(95% CI)
Age								
mean (std)	64.8 (8.3)	63.4 (7.3)			64.8 (8.3)	64.4 (7.6)		
BMI								
< 18.5	8	31			90	335		
18.5–24.9	76	408	Ref		1950	6786	Ref	
25–29.9	129	485	1.37	(0.97,1.94)	1541	3983	1.43	(1.32,1.56)
30	300	568	2.93	(2.11,4.07)	2107	2498	2.99	(2.74,3.26)
Unknown	3	3	-	-	5	2	-	-
p-trend			<.001				<.001	
Education								
Up to HS graduate	244	654	Ref		1624	3797	Ref	
Post-high school	258	802	0.89	(0.69,1.14)	3993	9635	1.04	(0.96,1.13)
Unknown	14	39	-	-	76	172	-	-
Smoking								
Never	249	614	ref		2867	6482	ref	
Past	156	529	0.72	(0.56,0.93)	1940	5003	0.85	(0.79,0.91)
Current	58	269	0.67	(0.47,0.95)	406	1559	0.63	(0.56,0.72)
Unknown	53	83	-	-	480	560	-	-
Oral Contraception								
Never	292	832	ref		3158	7334	ref	
Ever	211	618	1.09	(0.85,1.40)	2472	6090	1.02	(0.95,1.10)
Unknown	13	45	-	-	63	180	-	-
Never (up to 1 yr)	340	924	ref		3285	7252	ref	
1–4 years	68	228	0.59	(0.37,0.97)	923	2116	1.03	(0.88,1.20)
5–9 years	40	130	0.74	(0.42,1.29)	538	1413	0.95	(0.80,1.13)
10+ years	29	132	0.49	(0.27,0.88)	389	1380	0.69	(0.58,0.83)
Unknown	39	81	-	-	558	1443	-	-

	Blacks (n=2,011)				White (n=19,297)			
	Cases (n=516)	Controls (n=1,495)	OR[a]	(95% CI)	Cases (n=5,693)	Controls (n=13,604)	OR[a]	(95% CI)
p-trend			0.06				<.001	
Nulliparity[b]								
Nulliparous	74	162	1.39	(0.99,1.95)	1249	2088	1.60	(1.46,1.75)
1 or more births	432	1294	ref	-	4386	11390	ref	-
Unknown	10	39	-	-	58	126	-	-
Parity								
Nulliparous	74	162	ref		1249	2088	ref	
1	75	203	0.86	(0.56,1.32)	622	1370	0.75	(0.66,0.85)
2	87	313	0.64	(0.42,0.97)	1641	3745	0.71	(0.64,0.79)
3	101	279	0.80	(0.54,1.20)	1345	3691	0.58	(0.53,0.65)
4	77	186	0.91	(0.59,1.41)	520	1630	0.50	(0.43,0.57)
5+	92	313	0.52	(0.34,0.79)	258	954	0.41	(0.34,0.49)
Unknown	10	39	-	-	58	126	-	-
p trend			0.02				<.001	
Age at first birth[c]								
Never gave birth	74	162	-	-	1249	2088	-	-
Less than 20	189	551	Ref		605	1450	Ref	
20 to 24	142	416	0.92	(0.80,1.24)	2131	5260	0.93	(0.82,1.05)
25 to 29	60	167	1.09	(0.72,1.64)	1178	3231	0.75	(0.66,0.86)
30+ years	30	108	0.77	(0.45,1.31)	483	1447	0.62	(0.53,0.73)
Unknown	21	91	-	-	47	128	-	-
p trend			0.60				<.001	
Age at menarche								
Less than 10	13	24	1.20	(0.86,1.66)	102	116	1.22	(1.11,1.34)
10 to 11	81	196			1047	1856		
12 to 13	242	698	ref		2915	6811	ref	
14 to 15	151	493	0.94	(0.73,1.22)	1462	4377	0.89	(0.82,0.97)
16+ years	21	57	-	-	136	362	-	-
Unknown	8	27	-	-	31	82	-	-
Diabetes								

	Blacks (n=2,011)				White (n=19,297)			
	Cases (n=516)	Controls (n=1,495)	OR[a]	(95% CI)	Cases (n=5,693)	Controls (n=13,604)	OR[a]	(95% CI)
No	349	1189	ref		4416	12099	ref	
Yes	119	240	1.41	(1.07,1.87)	760	881	1.30	(1.15,1.46)
Unknown	48	66	-	-	517	624	-	-
Hypertension								
No	133	413	ref		1937	4752	ref	
Yes	219	614	0.88	(0.66,1.17)	1433	3260	0.99	(0.90,1.08)
Unknown	164	468	-	-	2323	5592	-	-

[a] Adjusted for age, BMI, smoking, OC use, diabetes, study site, age at menarche, and parity as a continuous variable.

[b] Adjusted for age, BMI, smoking, OC use, diabetes, study site, and age at menarche.

[c] Excludes women who never gave birth.