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Endometrial cancer associated biomarkers in bariatric surgery candidates: exploration of racial differences

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Abstract

Background: Obesity is the main risk factor for endometrial cancer (EC), the most common gynecologic malignancy in the United States. A number of potential risk biomarkers have been associated with EC development, including altered proinflammatory cytokines, chemokines, and adipokines.

Objectives: The overarching aim of this research is to investigate racial differences in the expression of EC-associated biomarkers among bariatric surgery candidates.

Setting: Tertiary academic medical center

Methods: Blood samples were collected from 175 women aged 18 to 72 (mean age: 42.93; standard deviation 11.66), before bariatric surgery. Levels of biomarkers associated with obesity and EC risk were measured using xMAP immunoassays. Wilcoxon rank sum and Fisher's exact tests were utilized to compare biomarker and demographic variables between African American and European American women. Linear regression models, adjusted for menopause status and diabetes, were utilized to identify factors associated with biomarker levels.

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Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

Results: When the biomarker levels were compared by race, insulin-like growth factor-binding protein 1 and adiponectin were significantly lower in African American women ($P < .05$), whereas estradiol was significantly higher in African American women ($P < .05$). Linear regression models found that race significantly predicted insulin-like growth factor binding protein 1, adiponectin, resistin, and interleukin-1 receptor alpha expression levels, menopause status and diabetes status were significantly associated with adiponectin and leptin levels, whereas body mass index was significantly associated with leptin, adiponectin, interleukin-1 receptor alpha, and interleukin-6 levels.

Conclusion: As one of the first efforts to explore racial differences in EC-associated biomarkers in a cohort of women with severe obesity, this study found several significant differences that should be further explored in large-scale studies. (*Surg Obes Relat Dis* 2017;13:862–870.) © 2017 American Society for Metabolic and Bariatric Surgery. All rights reserved.

Keywords

Endometrial cancer; Biomarkers; Inflammation; Bariatric surgery; Racial differences

Endometrial cancer (EC) is the most common gynecologic malignancy among American women, and has been gradually increasing in incidence in recent years, with approximately 60,050 new diagnoses and 10,470 deaths expected in 2016 [1]. Although multiple factors are involved, increasing rates of obesity are thought to be the primary driver of increasing EC incidence [2,3]. Prospective studies indicate that EC risk increases 1.6-fold with each additional 5 kg/m² in body mass index (BMI), reaching 9.1-fold higher risk by 42 kg/m² [4]. As of 2015, no systemic biomarker (or panel of markers) was available to identify women at high risk of precancerous endometrial changes, when preventive interventions like weight loss or hormone therapy may be effective. Accumulating evidence from preclinical research, as well as prospective studies exploring associations between biomarker levels in peripheral blood and the development of EC, strongly implicate 3 basic biological pathways associated with EC development: heightened inflammatory factors, insulin resistance and/or metabolic factors, and steroid hormones [5–10]. The focus of this study was to measure these EC-associated biomarkers in a group of bariatric surgery candidates who are at high risk for EC development due to their obesity.

Literature suggests that the incidence of EC may be underestimated in African American (AA) women [11], among whom obesity is more prevalent than in European American (EA) women [12,13]. Several studies have reported that AA women have higher grade and stage tumors, more aggressive histology and recurrence, and lower survival rates, suggesting that exploration of possible mechanisms for EC prevention is especially relevant in AA women [14,15]. In general, EC disproportionately affects AA women, who have a 2-fold higher mortality rate from EC than EA women [16–19]; however, some of the racial differences may be attributed to the fact that AA women may have a higher incidence of nonendometrioid EC [20]. Overall, EC-associated racial differences have rarely been explored for obesity-associated EC. Therefore, identifying racial differences in the expression of EC-associated biomarkers in women with severe obesity is an important venue of investigation.

Obesity is associated with a physiologic state of chronic, low-grade inflammation characterized by elevated concentrations of circulating inflammatory biomarkers mediating, at least in part, the association between obesity and EC [9,21,22]. Increased adipose tissue mass may contribute to the development of cancer via increased secretion of proinflammatory cytokines and chemokines [23,24]. A recent study found C-reactive protein (CRP), an acute-phase reactant protein that can influence production of inflammatory cytokines, to be positively associated with EC risk [10]. CRP, interleukin-6 (IL-6), and interleukin-1 receptor alpha (IL-1 $R\alpha$) have been implicated in EC risk in several prospective investigations [8–10,24]. Circulating adipokines (small protein molecules produced and secreted by white adipose tissue), such as adiponectin, have systemic immunomodulating effects that also play a major role in the development of several cancers [25]. Insulin, insulin-like growth factor binding protein 2, leptin, adiponectin, and C-peptide have been implicated in EC development in prospective studies [8,10,26,27]. Previously published research suggested that some of these markers may be differentially expressed between AA and EA individuals, including adiponectin [28–30], leptin [31], and insulin [32]. However, little investigation has been done to evaluate if systemically circulating EC-associated biomarkers differ between AA and EA women with obesity. This study aims to fill an important gap by analyzing EC-associated markers in female bariatric surgery candidates.

Also, previously published research raised many interesting questions about which anthropometric measure of adiposity is the most optimal for predicting cancer risk, with BMI and waist circumference (WC) suggested to be equally good measures for predicting EC in postmenopausal women [33]. Thus, the secondary aim of this investigation was to explore which measure of adiposity was the most appropriate in predicting the EC risk biomarker levels in women with severe obesity.

Methods

Patients and settings

This analysis included 175 women aged 18 to 72 (mean age: 42.93 yr; standard deviation [SD]: 11.66 yr) that were consecutively recruited to a study, “Effect of weight loss on biomarkers of immunity and inflammation: implications for endometrial cancer risk observational study” (Barimark (BAM)) at Magee-Womens Hospital of University of Pittsburgh Medical Center. Participants were prospectively recruited from March 2010 through October 2013 from the practices of 4 physicians in the Minimally Invasive Bariatric and General Surgery Program at Magee-Womens Hospital. One participant was recruited out of approximately every 3 women approached. Major reasons for refusal were inability to come for research appointments and no interest in research. Inclusion criteria for this study included the following: female, age 18+ years, approved and scheduled for bariatric surgery (Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, or sleeve gastrectomy), at least 1 ovary, and life expectancy >3 years. Exclusion criteria included refusal to sign informed consent, unable to attend study visits, plans to become pregnant within 1 year after surgery, hysterectomy, endometrial ablation, presence of severe inflammatory disease, recent injury or surgery, and plans to move residences within 1 year. About 20% to 30% of the

women who were approached were not eligible for the study. Of those who were eligible, approximately 40–50% declined to participate because they could not commit to the follow-up appointments. The University of Pittsburgh Human Research Protections Office approved this study. All participants signed informed consents.

Bariatric surgery candidates completed a set of validated general health questionnaires and anthropometric measurements. To reduce participant burden, nonfasting blood samples were obtained at convenient times 2 to 6 weeks before their scheduled surgery. Registered research nurses and staff oversaw study procedures in the Clinical and Translational Research Center (CTRC) at Magee-Womens Hospital of University of Pittsburgh Medical Center.

Measures

Anthropometric measurements for all study participants were obtained in the CTRC by research staff. Height was measured in centimeters using a wall-mounted stadiometer. Waist and hip circumferences were measured in centimeters using a tape measure. Weight (kilograms) and BMI (kg/m^2) were obtained from the Tanita body composition analyzer (Model TBF-310, Tanita Corp. of America (Tanita Corp., Arlington Heights, Illinois)) with participants wearing light clothing and no footwear.

Reproductive history, menstrual history, and history of hormone use (hormone therapy, birth control, fertility drugs), and self-reported diabetes status were obtained from the Reproductive Health Baseline and the Screening Questionnaire for General Health History. The Reproductive Health Baseline was used in the Longitudinal Assessment of Bariatric Surgery-2 Study to collect information on the status of the reproductive health of women undergoing bariatric surgery [34]. The Screening Questionnaire for General Health History has been used in the paving the road to everlasting food and exercise routines (PREFER) and self-monitoring and recording using technology (SMART) studies, which tested modifications of behavioral weight management [35,36].

Laboratory techniques

Blood samples were obtained at the CTRC at Magee-Womens Hospital using standard blood collection and processing protocols. Samples were obtained from participants who agreed to participate in the BAM study and signed the informed consent. Sera and plasma were separated by centrifugation, immediately aliquoted, frozen, and stored at -80°C . Never thawed 1 mL serum samples were sent on dry ice to the Luminex Core Facility at the University of Pittsburgh Cancer Institute, where they were stored at -80°C until they were assayed. The xMAP bead-based technology (Luminex Corp., Austin, TX) permits multiplexed analyses of several analytes in 1 sample. Twelve xMAP immunoassays were utilized in this study: IL-6, IL-1 Ra , tumor necrosis factor alpha, IGFBP1, insulin-like growth factor binding protein 2, resistin, leptin, insulin, adiponectin, sex hormone binding globulin, C-peptide, and CRP. These markers were chosen because they have been associated with a proinflammatory milieu, as well as with EC development in previous prospective studies [37–40].

Each bead-based assay has been validated in comparison with appropriate standard enzyme-linked immunosorbent assay based on the same antibody pair, and found 89% to 98% correlation. Recovery from serum was 70% to 120% (data presented on Luminex Core Facility website for in house assays; performance of purchased assays was in agreement with that described by the manufacturer). Assays were performed according to manufacturers' protocols as previously described [41]. Samples were analyzed using the Bio-Plex suspension array system (Bio-Rad Laboratories, Hercules, CA). For each analyte, 100 beads were analyzed and means were calculated. Analysis of experimental data was performed using 4-parametric-curve fitting to the standard analyte curves.

Two 1 mL never thawed plasma samples were sent on dry ice to the Biobehavioral Oncology Core Facility at the University of Pittsburgh Cancer Institute for estradiol and testosterone assay analysis in a clinical laboratory. Samples were stored at -80°C until assayed.

Statistical analysis

Basic descriptive statistics were used to summarize the characteristics of the study population. Normally distributed continuous variables are reported as mean (standard deviation) and categorical variables are reported as N (%). Age (yr), BMI (kg/m^2), weight (kg), WC (cm), and waist-to-hip ratio (WHR) were analyzed as continuous variables. Race was dichotomized as EA or AA and analyzed as a categorical variable.

The Wilcoxon rank sum test was used to compare mean biomarker levels of EA and AA women to determine if there were significant differences in the biomarker levels across the racial groups. Fisher's exact test was used for the comparison of categorical variables. Biomarker levels were log transformed, and the mean levels of biomarkers were computed as a continuous average. Linear regression was used to evaluate the relationship between log transformed biomarker expression levels and the various measures of adiposity such as BMI, WC, and WHR, controlling for self-reported age, menopausal status, and diabetes status.

All statistical analyses were done with SAS version 9.4 (SAS Institute Inc., Cary, NC). α level was set at .05 and was 2-sided.

Results

Table 1 lists the demographic and personal characteristics of the study participants. Mean age of the study participants was 42.93 years (SD: 11.66), mean weight was 127.17 kg (SD: 22.63), mean BMI was $46.87 \text{ kg}/\text{m}^2$ (SD: 7.62), mean WC was 127.81 cm (SD: 14.77), and mean WHR was .895 (SD: .085). The racial distribution of the study participants was 77.71% EA and 22.29% AA.

When the biomarker levels were compared by race, IGFBP1 and adiponectin were significantly lower in AA women ($P < .05$), whereas estradiol was significantly higher in AA women ($P < .05$). Table 2 shows the comparison of biomarker levels by race.

Whereas the AA subgroup was slightly younger than the EA subgroup, both groups were similar on most measures of adiposity and factors of reproductive history ($P > .05$). Because

AA women had a significantly larger WHR ($P < .05$) and were less likely to be postmenopausal, our linear regression models controlled for these variables.

Linear regression

As the first step, linear regression models were built to investigate the relationship between various measures of adiposity individually (BMI, WC, and WHR) as predictors of biomarker levels (while controlling for age, menopausal status, and diabetes status) in AA and EA women. BMI was found to be significantly associated with leptin, IL-1 $R\alpha$, and IL-6 levels; WC was significantly associated with resistin, leptin, IL-1 $R\alpha$, and IL-6 levels; menopause status and diabetes status were significantly associated with adiponectin and leptin levels.

We then focused on the contribution of BMI to biomarker expression levels, while controlling for WHR, menopausal status, and diabetes status. With these variables included in the model, BMI was significantly associated with leptin, IL-1 $R\alpha$, and IL-6 (Table 3). We then added an interaction term, race $\times$ BMI, to the model. This interaction term was not significantly associated with biomarker expression ($P > .05$; data not shown).

We observed that race was significantly associated with IGFBP1 and adiponectin levels across all models.

Table 3 shows the linear regression results using the various measures of adiposity while controlling for age, menopause status, diabetes status, and race to predict biomarker expression levels. Included are the beta estimates and their respective P values.

Discussion

This study provided one of the first systemic comparisons between AA and EA women with regard to identification of racial differences in the levels of EC-associated inflammatory biomarkers. Although previously published studies reported racial differences in the levels of some of the EC-associated biomarkers including leptin, adiponectin, and insulin, this is one of the first studies reporting that race was significantly associated with IGFBP1 and adiponectin in women with severe obesity.

We found that BMI was the most reliable measure of adiposity that predicted increased expression levels of leptin, IL-1 $R\alpha$, and IL-6. Previous publication analyzed WHR and WC as measures of EC risk; however, the results were not conclusive [42]. Therefore, it would be particularly interesting for future studies to further explore the role of WHR and WC in EC risk by race in larger data sets. We also found a racial disparity in the expression levels of IGFBP1 and adiponectin, with AA women demonstrating significantly lower expression of these biomarkers. These results are consistent with a recent publication by Morimoto et al. reporting a racial disparity for adiponectin [43] in a large cross-sectional study. Another recent cross-sectional study reported racial differences in the magnitude and the form of adiponectin-BMI association [44]. Although little research has been done on racial disparities in IGFBP1 in adult populations, a study by Wong et al. found racial differences between AA and EA girls in blood concentration of IGFBP1 [45]. Thus, our study fills an

important gap in identifying racial disparities in several important metabolic syndrome/EC-associated biomarkers.

A recent publication from our group estimates a 55% increase in the incidence of EC by 2030 [46]. Because EC in AA women is typically diagnosed in more advanced stage [14,15], results of this research provided initial justification for exploring racial disparities in EC-associated biomarkers. These data have a great potential to open up a new area of prevention research to reduce EC risk and disparities in the EC burden between AA and EA women. AA women have been shown to generally have higher concentrations of inflammatory markers, such as CRP [47] and adipokines that are not entirely explained by BMI [31].

Although our study focused on bariatric surgery candidates, we believe that our findings are potentially generalizable to the general population of women with severe obesity. The mean BMI of bariatric surgery candidates is very similar to typical BMIs of EC patients and comorbidities among these 2 population groups are similar (such as high diabetes incidence), thus this is a good population to explore for EC risk. Since bariatric surgery candidates are typically younger than EC patients, we believe that this population would be especially valuable to target to explore EC preventive interventions in the future. Strengths of this study are adherence to a uniform protocol for the collection of epidemiologic data and blood samples, with all blood samples processed in the same laboratory. Another strength of this study is the careful selection of biological markers based on previous association with EC. Limitations of this study include a relatively modest sample size of AA participants and the inability to evaluate these markers in ethnic groups other than AA or EA women. An additional limitation is that our information on comorbidities, such as diabetes, is self-reported and may not be reliable. Also, recruitment from the practices of only 4 physicians limited our population size. We hope to address these limitations in our future studies targeting larger numbers of participants to accurately evaluate racial differences. Also, our future investigations will evaluate biomarker changes occurring with bariatric surgery-associated weight loss, as literature suggests that intentional weight loss may normalize biomarker levels in severely obese individuals.

Conclusion

This study was the first systemic comparison between AA and EA women with regard to levels of EC-associated biomarker profiles, and found that race was significantly associated with levels of some of the biomarkers of interest. Because increasing obesity is associated with an increased risk of harboring subclinical endometrial pathology [48], bariatric surgery candidates are an ideal group to investigate in this context. Future studies must carefully evaluate the link between obesity, racial disparities, measures of adiposity, and endometrial pathology in a longitudinal manner.

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Comparison of demographic and personal characteristics by race in a cohort of women with severe obesity at the prebariatric surgery visit

Table 1

	Overall Mean (standard deviation)	European American Mean (standard deviation)	African American Mean (standard deviation)	P value
Age, yr; n = 175	42.93 (11.66)	43.62 (11.97)	40.54 (10.30)	.08 [*]
Weight, kg; n = 175	127.17 (22.63)	127.49 (23.82)	126.03 (18.13)	.45 [*]
Body mass index, kg/m ² ; n = 175	46.87 (7.62)	47.02 (7.79)	46.35 (7.08)	.73 [*]
Waist circumference, cm; n = 165	127.81 (14.77)	127.80 (14.50)	127.84 (15.97)	.45 [*]
Waist-to-hip ratio; n = 165	.895 (.085)	.889 (.086)	.917 (.076)	.02 [*]
Smoking history, n = 170	Overall N (%)	European American N (%)	African American N (%)	P value
Never smoker	98 (57.65)	76 (57.14)	22 (59.46)	.08 [†]
Former smoker	72 (42.35)	57 (42.86)	15 (40.54)	
Postmenopause, n = 165				.01 [†]
Yes	53 (32.12)	48 (37.50)	5 (13.51)	
No	112 (67.88)	80 (62.50)	32 (86.49)	.23 [†]
Polycystic ovary syndrome, n = 164				
Yes	31 (18.90)	27 (21.26)	4 (10.81)	
No	133 (81.10)	100 (78.74)	33 (89.19)	.23 [†]
Hormone use, n = 163				
Yes	31 (19.02)	27 (21.43)	4 (10.81)	
No	132 (80.98)	99 (78.57)	33 (89.19)	.07 [†]
Irregular periods, n = 164				
Yes	58 (35.37)	40 (31.50)	18 (48.65)	
No	106 (64.63)	87 (68.50)	19 (51.35)	.23 [†]
Spotting, n = 165				
Yes	56 (33.94)	40 (31.25)	16 (43.24)	
No	109 (66.06)	88 (68.75)	21 (56.76)	

	Overall Mean (standard deviation)	European American Mean (standard deviation)	African American Mean (standard deviation)	<i>P</i> value
Pregnancy history, n = 165				.52 [†]
Yes	121 (73.33)	92 (71.88)	29 (78.38)	
No	44 (26.67)	36 (28.13)	8 (21.62)	
Diabetes, n = 164				.11 [†]
Yes	38 (23.17)	26 (20.31)	12 (33.33)	
No	126 (76.83)	102 (79.69)	24 (66.67)	

^{*} *P* values from Wilcoxon rank sum tests.

[†] *P* values from Fisher's exact tests.

Comparison of systemic biomarker levels by race obtained from a cohort of women with severe obesity at the prebiatric surgery visit.

Table 2

	Total n = 175 Mean (standard deviation)	European American n = 136 Mean (standard deviation)	African American n = 39 Mean (standard deviation)	P value [*]
Inflammatory factors				
C-reactive protein, µg/mL	2.77 (1.26)	2.78 (1.26)	2.74 (1.26)	.81
Interleukin-1 receptor alpha, ng/mL	2.51 (1.54)	2.66 (1.64)	2.08 (.96)	.07
Interleukin-6, pg/mL	2.67 (1.76)	2.64 (1.75)	2.78 (1.82)	.54
Tumor necrosis factor-alpha, pg/mL	10.36 (5.26)	10.62 (5.51)	9.48 (4.24)	.58
Metabolic factors				
C-peptide, ng/mL	3.28 (1.21)	3.37 (1.19)	2.99 (1.26)	.23
Insulin, ng/mL	1.52 (1.37)	1.54 (1.41)	1.44 (1.24)	.94
Insulin-like growth factor binding protein 1, ng/mL	1.46 (2.34)	1.66 (2.59)	.77 (.79)	.0002
Insulin-like growth factor binding protein 2, ng/mL	4.52 (3.47)	4.38 (1.61)	5.01 (6.74)	.08
Adiponectin, µg/mL	6.76 (2.38)	7.04 (2.37)	5.75 (2.18)	.0004
Resistin, ng/mL	10.99 (3.63)	11.21 (3.68)	10.25 (3.40)	.44
Leptin, ng/mL	83.06 (59.55)	83.28 (58.26)	82.28 (64.67)	.95
Hormones				
Estradiol, pg/mL	80.89 (77.94)	74.79 (72.45)	101.61 (92.32)	.03
Testosterone, nmol/L	2.64 (1.24)	2.63 (1.34)	2.65 (.80)	.45
Sex hormone binding globulin, pM	49,246 (29,507)	48,241 (29,528)	52,754 (29,542)	.38

^{*} P-values from Wilcoxon rank sum tests.

Table 3

Beta coefficients and *P* values from linear regression models, adjusted for menopause status and diabetes, utilized to identify factors associated with biomarker levels in a cohort of women with severe obesity assessed at the prebariatric surgery visit: Biomarker level = $\beta_0 + \beta_1 \text{ BMI} + \beta_2 \text{ WHR} + \beta_3 \text{ age} + \beta_4 \text{ menopause status} + \beta_5 \text{ diabetes} + \beta_6 \text{ race}$

Model 1	β_1 Body mass index	<i>P</i> value	β_2 Waist-to-hip ratio	<i>P</i> value	β_3 Age	<i>P</i> value	β_4 Menopause status	<i>P</i> value	β_5 Diabetes	<i>P</i> value	β_6 Race	<i>P</i> value
C-reactive protein	.008	.16	-.53	.28	.006	.18	-.04	.71	.07	.48	-.03	.80
Interleukin-1 receptor alpha	.02	<.0001	.26	.56	.002	.66	-.07	.49	.17	.07	-.23	.02
Interleukin-6	.03	<.0001	.52	.36	.003	.56	.14	.31	.16	.18	.11	.37
Tumor necrosis factor-alpha	.007	.25	.66	.21	.01	.02	.05	.70	.09	.42	-.02	.88
C-peptide	.004	.45	.24	.60	-.006	.20	.14	.20	-.09	.30	-.65	.50
Insulin	.005	.53	.52	.48	-.007	.27	.06	.73	0.24	.11	-.05	.73
Insulin-like growth factor	.008	.48	-1.32	.14	.02	.03	-.01	.96	.30	.11	-.72	.0002
binding protein 1												
Insulin-like growth factor	.005	.23	.07	.83	.005	.13	-.05	.47	-.004	.95	-.01	.85
binding protein 2												
Adiponectin	.006	.12	-.60	.05	.003	.23	.16	.02	-.20	.002	-.16	.01
Resistin	.005	.24	.22	.51	-4.4 E-5	.58	-.05	.49	.006	.93	-.16	.03
Leptin	.03	<.0001	-.12	.77	-.007	.10	.43	<.0001	-.32	.004	.07	.43
Estradiol	-.007	.47	-1.33	.10	-.04	<.0001	-.24	.22	-.12	.48	.25	.15
Testosterone	.005	.20	.38	.24	-.002	.49	-.02	.83	-.005	.95	.05	.47
Sex hormone binding globulin	-.002	.77	-.07	.89	.01	.04	.06	.64	-.17	.14	.16	.15