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Original article

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.

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

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be further explored in large-scale studies. (Surg Obes Relat Dis 2017;▮:00–00.)

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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/m^2 in body mass index (BMI), reaching 9.1-fold higher risk by 42 kg/m^2 [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 Rα) 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