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Changes in inflammatory endometrial cancer risk biomarkers in individuals undergoing surgical weight loss

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HIGHLIGHTS

- Endometrial cancer associated biomarker levels decreased after bariatric surgery.
- The change in CRP and IL-1Rα, and SHBG were associated with race.
- After surgery biomarker levels in surgery group were equivalent to healthy controls.

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ABSTRACT

Objective. Obesity has been strongly linked to endometrial cancer (EC) risk. A number of potential EC risk biomarkers have been proposed, including heightened pro-inflammatory cytokines and adipokines. To evaluate if bariatric surgery can serve as a means for altering levels of such EC risk biomarkers, we investigated changes in these biomarkers after weight loss.

Methods. Blood samples were collected pre-operatively and 6 months post-operatively in 107 female bariatric surgery patients aged 18–72 years. Wilcoxon signed-rank tests were used to compare biomarker levels (measured using xMAP immunoassays) pre- and post-surgery. Normative comparisons were implemented to contrast 6-month post-surgery biomarker levels to levels in a sample of 74 age-matched non-obese women. Linear regression was used to evaluate the relationship between biomarker expression at baseline and 6 months post-surgery and the relationship between race and biomarker levels.

Results. On average, participants lost 30.15 kg (SD: 12.26) after the bariatric intervention. Levels of C-peptide, insulin, CRP, leptin, IL-1Rα, and IL-6 significantly decreased, while levels of SHBG, IGFBP1, and adiponectin significantly increased with weight loss. Normative comparisons showed the levels of SHBG, C-peptide, insulin, IGFBP1, adiponectin, CRP, and TNFα after bariatric intervention approached the level of markers in comparison group. Multiple regression analyses revealed significant relationships between changes in BMI and changes in biomarker levels. The changes in IL-1Rα were significantly associated with race.

Conclusions. Our findings demonstrate that normalization of EC risk biomarkers can be achieved with bariatric surgery. Improved understanding of biological mechanisms associated with weight loss may inform preventive strategies for EC.

1. Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy among American women, and has been gradually increasing in incidence in recent years, with approximately 61,380 new diagnoses and 10,920 deaths expected in 2017 [1]. A recent publication from our

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group estimates a 55% increase in the incidence of EC by 2030 [2]. Although multiple factors are involved, increasing rates of obesity are thought to be the primary driver of increasing EC incidence [3–5]. 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 at 42 kg/m^2 [6]. In a recent publication, we indicated that increasing BMI is also associated with a greater risk of endometrial pathology among women with severe obesity (>35 BMI) [7]. As of 2016, no systemic biomarker (or panel of markers) is available to identify women at high risk of precancerous changes, at a time when preventive interventions such as weight loss or hormone therapy may still be possible.

Accumulating evidence from preclinical research, as well as prospective studies exploring associations between biomarker levels in peripheral blood and the development of EC, strongly implicates three basic biological pathways: pro-inflammatory factors, insulin resistance/metabolic factors, and steroid hormones [8–13]. Obesity is associated with a physiological state of chronic, low-grade inflammation, characterized by elevated systemic levels of circulating inflammatory biomarkers mediating, at least in part, the association between obesity and risk of EC [12,14,15]. Increased adipose tissue mass may contribute to the development of cancer via increased secretion of pro-inflammatory cytokines and chemokines [16,17]. A recent study found CRP, an acute-phase reactant protein that can influence production of inflammatory cytokines, to be positively associated with EC risk [13]. CRP, IL-6, and IL-1Rα have been implicated in EC risk in several prospective investigations [11–13,16]. 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 [18]. Insulin, IGFBP2, leptin, adiponectin, and C-peptide have been implicated in EC development in prospective studies [11,13,19,20]. While a very limited number of publications have explored the biomarkers associated with endometrial hyperplasia (EC precursor lesion [21]), it is likely that the development of hyperplasia and EC are associated with abnormal activity of similar inflammatory, hormonal, and metabolic pathways. One such hormone is leptin, which has been found to be elevated in patients with both endometrial cancer and hyperplasia in comparison with pathology free controls [22].

Emerging literature suggests that the risk of EC may be particularly responsive to weight loss [3,4,23]. In a large-scale study, Ward et al. recently demonstrated that bariatric surgery is associated with a 71% reduction in risk for uterine malignancy [24]. Similar evidence has been recently published by the Swedish Obese Subject Study, reporting that bariatric surgery lowered the incidence of EC in the bariatric surgery group [25].

The study described in this manuscript was based on the idea that biomarkers in EC risk pathways will be ameliorated by weight loss among women with severe obesity. Our group previously reported that behavioral intervention for weight loss is associated with changes in adiponectin [26]. In this manuscript, we report on the modification of EC risk biomarkers with surgically induced weight loss, an area poorly investigated in existing studies. This study aims to fill an important gap by analyzing biomarkers associated with EC risk in women undergoing weight loss through bariatric surgery and comparing the levels of markers post-bariatric surgery with levels of the same markers in non-obese women.

2. Methods

2.1. Participants and settings

This subanalysis included 107 women aged 18 to 72 (mean age 43.88 years (SD: 11.66 years)) who were participating in the "Effect of weight loss on biomarkers of immunity and inflammation" or Bariatric Marker (BAM) Study at Magee-Womens Hospital which had the goal of determining the extent to which women undergoing bariatric surgery, and its subsequent weight loss, had an overall improvement in inflammatory and endocrine biomarker status. Inclusion criteria for this study included: female, age 18 + years, BMI ≥ 35, approved and scheduled for bariatric surgery (Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, or sleeve gastrectomy), and life expectancy >3 years. Exclusion criteria included: refusal to sign informed consent, unable to attend study visits, plans to become pregnant within one year after surgery, presence of severe inflammatory disease, previous history of cancer (including gynecologic cancer), recent injury or surgery, and plans to move residence within one year.

Seventy-four female non-obese (BMI < 30) comparison participants aged 21 to 75 (mean age 42.04 years (SD: 13.53 years)) were recruited through a general recruitment campaign at the University of Pittsburgh campus. Comparison participants were matched to bariatric surgery patients on the basis of age. The University of Pittsburgh Human Research Protection Office approved this study. All participants signed informed consent documents. Exclusion criteria for comparisons were inability to sign informed consent, obesity, presence of severe inflammatory disease, previous history of cancer (other than non-melanoma skin cancer), and recent injury or surgery.

At each visit (pre- and 6 months post-operatively), participants in the bariatric surgery group completed a set of validated general health questionnaires, and anthropometric measurements and blood samples were obtained. The same procedure was performed at a single time point with participants in the comparison group. Registered research nurses and staff conducted study procedures in the Clinical and Translational Research Center (CTRC) at Magee-Womens Hospital of UPMC.

2.2. Measures

Anthropometric measurements for participants in both groups were obtained in the CTRC by research staff. Height was measured in centimeters using a wall-mounted stadiometer. Waist and hip circumference was 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 Corporation of America) with participants wearing light clothing and no footwear.

Reproductive history, menstrual history, and history of hormone use (hormone therapy, birth control, fertility drugs) were obtained from the Reproductive Health Baseline (RHB) and the Screening Questionnaire for General Health History (SQHH). The RHB was used in the Longitudinal Assessment of Bariatric Surgery-2 Study (LABS) to collect information on the status of the reproductive health of women undergoing bariatric surgery [27]. The SQHH 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 several methods of behavioral weight management [28,29].

2.3. Statistical analysis

Basic descriptive statistics were used to summarize the characteristics of the bariatric surgery population at baseline and the 6-month post-operative visit. Continuous variables are reported as mean (standard deviation) and categorical variables are reported as N (%). Age, BMI, weight, waist circumference (WC), and waist-to-hip ratio (WHR) were analyzed as continuous variables. Race (dichotomized as European American (EA) or African American (AA)) was analyzed as a categorical variable. The time points were categorized as baseline and 6 months post-surgery.

Wilcoxon signed-rank tests were used to compare the mean levels of biomarkers of the participants in the bariatric surgery group at the baseline and 6-month post-operative visits. The Wilcoxon rank-sum test was used to compare mean biomarker levels of the participants in the bariatric surgery group at each time point and in the comparison group to determine if there were significant differences in mean levels between the groups. Fisher's exact test was used to compare categorical variables of participants in the bariatric surgery group at baseline and in

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