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Genetic predisposition to obesity and inflammation in a tri-racial/ethnic breast cancer population

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Abstract

Aim: Multiple genes and genetic variants may contribute to racial/ethnic disparities in obesity-associated breast cancer diagnosis and prognosis. Therefore, we evaluate whether racial/ethnic differences in polygenic risk score (PRS) contribute to obesity and inflammatory biomarker in breast cancer patients.

Methods: In a tri-racial/ethnic population of 403 breast cancer patients, 21% African American (AA), 65% Hispanic White (HW), and 14% non-Hispanic White (NHW), we evaluated racial/ethnic differences in obesity PRS, the association between PRS and an inflammatory biomarker C-reactive protein (CRP), and its implication in bariatric surgery eligibility. The obesity PRS was constructed via a weighted risk allele model using 35 obesity-related single nucleotide polymorphisms (SNPs). SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA) was used to perform the logistic regression analysis.

Results: About 74% of our study population were overweight or obese. The mean ± SD of obesity PRS was 45.03 ± 10.66 for obese patients and 39.36 ± 8.81 for non-obese patients ($P < 0.0001$). AA patients had a significantly higher obesity PRS than HW and NHW ($P < 0.0001$). The obesity PRS significantly correlated with body mass index and CRP levels ($P < 0.0001$) and was associated with bariatric surgery eligibility (OR = 4.32, 95%CI: 1.89-9.87).

Conclusion: In summary, multiple obesity-associated SNPs contribute to racial/ethnic disparities in obesity of breast cancer patients; the obesity PRS has application in identifying breast cancer patients with higher genetic risk for obesity who may benefit from more aggressive weight management, such as bariatric surgery to improve breast cancer clinical outcomes.

Keywords: Breast cancer, obesity, race, polygenic risk score, c-reactive protein, bariatric surgery

INTRODUCTION

Obesity plays a critical role in the incidence, recurrence, and clinical outcomes of breast cancer[1,2]. High body mass index (BMI) is associated with increased breast cancer incidence[3] and more advanced tumor stage at diagnosis[2,4], particularly in post-menopausal women[1,2,4-8]. This may be due to increased estrogen production from excess adipose tissue[8,9] and elevated insulin levels[4,10]. In addition, multiple studies have shown that women with high BMI experience worse side effects from cancer treatments due to obesity and related comorbidities[3,11]. Obesity may also increase breast cancer mortality rates[1-3,5,12]. The American Cancer Society links 11% of breast cancer deaths to overweight or obese status[13].

Breast cancer is the most common form of cancer among women in the United States and the second leading cause of cancer deaths[2,14,15]. Early detection and improved treatments have led to a remarkable reduction in the mortality rate of breast cancer[16]; however, not all women have benefited equally from such declines. Mortality rates remain highest among African American (AA) women, followed by non-Hispanic White (NHW), Hispanic White (HW), and women of other races[17]. Although NHW women are more likely to be diagnosed with breast cancer, AA women are more likely to die from breast cancer[18].

Obesity is a public health crisis - 42.4% of United States adults are obese, and AA adults are disproportionately affected[19,20]. AA has the highest age-adjusted prevalence of obesity (49.6%) followed by HW (44.8%), NHW (42.2%), and other races[19,20]. Importantly, obesity is heritable. 47%-80% of inter-individual variability in BMI has been attributed to genetic factors[21-23]. The anticipation is that individuals with a genetic predisposition to obesity may require more aggressive treatment methods to achieve a healthy weight, such as bariatric surgery. Recent genome-wide association studies (GWAS) using large samples identified single-nucleotide polymorphisms (SNPs) significantly associated with higher BMI[24]. SNPs refer to single-base pair changes that constitute the majority of inter-individual genetic variability[24]. Over 700 obesity-associated SNPs have been identified[21,25], and these are hypothesized to play a role in the hypothalamic control of energy metabolism, satiety pathways, insulin secretion and action, lipid biology, and adipogenesis[21]. Research surrounding obesity-related SNPs is ongoing, and additional obesity-related loci may be discovered[24].

While single SNPs alone may have insufficient effect sizes to explain inter-individual variability in body composition, multiple large studies have posited that the cumulative effects of multiple SNPs associated with obesity risk factors contribute to an individual's genetic predisposition to obesity[26-31]. The polygenic risk score (PRS) describes an approach to aggregating common polygenic variation in complex traits, like obesity, into a single continuous variable. The PRS for obesity is advantageous in that it accounts for both the amount of inter-individual variation and the likelihood of developing a trait while reducing the statistical burden relating to the multiple comparisons when examining a set of SNPs separately but simultaneously[27,28,32,33].

Inflammation may mediate the association between obesity and breast cancer. C-reactive protein (CRP) is a sensitive, nonspecific biomarker of acute and chronic inflammatory states synthesized in hepatocytes in response to inflammation and tissue damage[34]. Elevated CRP levels have been associated with high cholesterol, blood pressure, fat percentage[35], obesity[36-38], and insulin resistance[39-41]. There is a known association between inflammation and cancer, though studies of CRP and cancer report conflicting findings. A 2009 meta-analysis demonstrated that elevated CRP levels were associated with increased cancer risk[42], and high CRP levels have been shown to correlate with a more advanced disease stage and worse prognosis[43]. However, a more recent review found an association between high CRP and cancer incidence and survival only for ovarian cancer and hepatocellular carcinoma, respectively[44].

Several studies report an association between elevated CRP levels and breast cancer risk in postmenopausal women[45-51] and women within the highest quartile of CRP[52,53], linking chronic low-grade inflammation to obesity and breast cancer. High CRP levels have also been associated with reduced disease-free survival and overall survival in women with breast cancer[54-56]. However, multiple studies did not find an association between CRP and breast cancer risk or mortality[57-59]. The mechanism of inflammation in cancer development and progression is complex, and it is unclear whether CRP levels reflect the specific inflammatory pathways involved[44]. Study inconsistencies may also be driven by confounders such as lifestyle factors, differences in population characteristics, or differences in study design[51,59].

In summary, it is necessary to examine the molecular mechanisms of obesity and its impact on racial/ethnic disparities in breast cancer diagnosis and prognosis as well as other health conditions to develop effective, long-term weight management strategies that may improve survival - particularly in high-risk underserved minority populations. This study evaluates genetic predisposition to obesity by first developing a PRS composed of 35 externally-validated SNPs associated with obesity risk. We then assess the association of our PRS with obesity and race/ethnicity in a diverse sample of women with breast cancer to evaluate its utility in identifying a high-risk population who may benefit from aggressive weight-loss interventions, such as bariatric surgery. We also compared the obesity PRS by race/ethnicity as well as the association between the obesity PRS and CRP levels and bariatric surgery eligibility.

METHODS

Study design

We conducted a cross-sectional study using two prospective clinic-based studies of breast cancer patients to evaluate the impact of genomics and exposures on breast cancer radio-sensitivity from 2008 to 2015 at the University of Miami Miller School of Medicine. These studies recruited women diagnosed with breast carcinoma stages 0-III, scheduled to receive adjuvant radiation therapy (RT) on the intact breast or chest wall from the radiation oncology department at the Sylvester Comprehensive Cancer Center and Jackson Memorial Hospital in Miami, FL. Patients were older than 18 years old and self-reported AA or white race, Hispanic or non-Hispanic ethnicity was recruited before RT and followed for up to one year after treatment. Patients with prior radiation or concurrent chemotherapy were excluded from the study.

As of October 2014, 397 post-lumpectomy and 116 post-mastectomy breast cancer patients were enrolled. These two studies were pooled for analysis purposes into a post-surgery RT group of 513 women. Every study participant completed a self-administered study entry questionnaire that included information on demographics, reproductive history, presence of other medical conditions, smoking history, and family history of breast cancer. Whole blood (25-30 mL) was collected from each patient at baseline and at the time of the last RT.

Variables

Race/ethnicity was self-reported. Weight as of June 17, 2015, was also obtained from the patients' electronic medical record (n = 513) and compared to weight at the time of consent. BMI was calculated according to the National Institute of Health (NIH) conversion formula using height and weight at the time of enrollment. Classification of BMI was performed using the World Health Organization index as follows: BMI < 18.50 kg/m^2 as underweight, BMI 18.50-24.99 kg/m^2 as normal weight, BMI 25.0-29.99 kg/m^2 as overweight, BMI 30.00-34.99 kg/m^2 as obese class I, BMI 35.00-39.99 kg/m^2 as obese class II, and BMI ≥ 40.00 kg/m^2 as obese class III. Eligibility criteria for bariatric surgery were defined using NIH guidelines for the management of overweight and obesity (BMI ≥ 40 kg/m^2, or BMI ≥ 35 kg/m^2 with at least one obesity-related comorbidity).

Whole blood was processed within 2 h of phlebotomy and stored at -80 °C. DNA was isolated from whole blood using the Biamp Blood Kit (QIAGEN Inc., Chatsworth, CA). The genomic DNA extracted from whole blood was used for the genotyping performed by the University of Miami Hussmann Institute for Human Genomics using the Illumina Omni 2.5-8 v1 BeadChip and Illumina's Genome Studio Software. Samples with raw call rates < 99%, duplicates, gender mismatches, or relatedness were excluded. SNPs with low calling rates (< 95%) and low minor allele frequencies (MAF < 0.05) were also excluded. Additionally, markers with significant deviations from Hardy-Weinberg Equilibrium ($P < 1 \times 10^{-6}$) were removed.

CRP levels (mg/L) were measured using plasma samples taken before the start of the RT and at the end of RT using the high sensitivity CRP ELISA kit (Cal biotech, Spring Valley, CA) according to the manufacturer's protocol. Briefly, frozen plasma samples were thawed and centrifuged at 10,000 rpm for 3 min. The clarified supernatant was diluted, and 10 μL were added to duplicate CRP-coated wells. 100 μL of enzyme conjugate was then added, and the plate was agitated briefly to mix. Following 1 h of incubation at room temperature, the unbound mixture was removed, and the wells were washed three times with wash buffer. The absorbance at 450 nm was determined using the Synergy HT microplate reader (Biotech Instruments, Winooski, VT). A standard curve with known concentrations of CRP (0.2 to 10 mg/L) was generated and levels of CRP were extrapolated based on the standard curve.

Statistical analysis

After genotyping quality control, 97 samples were excluded. Patients who reported race/ethnicity other than AA, HW, or NHW (n = 11) or who were classified as underweight (n = 2) were also excluded. The final dataset contained 403 patients. Descriptive analyses (mean, standard deviation, median, range, and frequency) were used to identify differences in the participant's characteristics by the study as well as by race/ethnicity. SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA) was used to perform the logistic regression analysis using the PRS to predict obesity status (obese = BMI ≥ 30.00 kg/m^2; not obese = 18.50-29.99 kg/m^2).

Linear regression models were fitted using obesity PRS as a predictor of BMI and CRP levels at baseline. Analysis of variance (ANOVA) was performed on the mean PRS scores among three race/ethnic groups; further Tukey test was performed to find significant differences between each specific group. The obesity PRS was categorized into 4 levels based on quartiles (level 1: PRS ≤ Q1; level 2: Q1 < PRS ≤ Q2; level 3: Q2 < PRS ≤ Q3; and level 4: PRS > Q3). PRS levels were compared by participant's race/ethnicity (AA, HW, NHW), obesity status, and bariatric surgery eligibility using the χ^2 test or fisher's exact test. The significance level was set at alpha = 0.05. Odds ratios (ORs), 95% confidence intervals (95%CI), and P values were calculated.

RESULTS

Constructing the obesity PRS

To build the obesity PRS, SNPs previously found to be associated with BMI and their respective proxies were identified in the literature (n = 700)[21,26,60-76]. After genotyping quality control, 275 BMI-related SNPs were found in our GWAS dataset using PLINK software v1.07c. Minor and major allele frequencies were identified for each SNP using a profile option in the PLINK software.

Obesity risk alleles for each SNP were established using a linear regression model. Regression coefficients and P values were calculated per SNP computing the risk that presenting the minor allele confers to increasing BMI using the Assoc- function in PLINK. Only significantly related SNPs ($P < 0.05$) with low linkage disequilibrium (LD < 0.8) were included in the final dataset of 35 SNPs. The PRS model was then constructed by adding the weighted risk alleles: (1) the number of risk alleles was counted for each SNP and multiplied by its effect size; and (2) weighted risk alleles were summed across all 35 SNPs for each patient. RStudio was used to merge annotations files to find corresponding genes for each SNP in the obesity PRS [Table 1].

Patient characteristics

A total of 403 breast cancer patients were analyzed: 310 were post-lumpectomy, and 93 were post-mastectomy. Patients self-identified as HW (65%), AA (21%), and NHW (14%). The mean age at consent was 55.3 ± 9.4 years (range 27-82), and the mean BMI was 28.9 ± 5.9 kg/m^2 (range 19-63). Overall, 35% of participants were overweight, 27% were obese class I, 8% were obese class II, and 3% were obese class III. BMI differed significantly by race/ethnicity ($P < 0.0001$): AA had the highest mean BMI (30.98 ± 7.88 kg/m^2) , followed by HW (28.79 ± 4.83 kg/m^2), and NHW (26.73 ± 6.33 kg/m^2) [Table 2].

Association between obesity PRS and BMI

Mean obesity PRS was evaluated by BMI category, race/ethnicity, and bariatric surgery eligibility [Table 3]. Overall mean PRS was 41.5 ± 9.93 (range 20.9-74.9; median = 39.8). The mean PRS for obese patients was 45.02 ± 10.6 and 39.3 ± 8.8 for non-obese patients ($P < 0.0001$). There was a significant difference in mean obesity PRS values between each BMI category ($P < 0.0001$), with a corresponding dose-response increase in obesity PRS for each increasing BMI category. When compared by race/ethnicity, the mean PRS was significantly higher in AA (mean ± SD, 55.03 ± 7.99) compared to HW (38.27 ± 6.65) and NHW (35.94 ± 6.90) women ($P < 0.0001$). There was also a significantly greater mean obesity PRS for patients who were eligible for bariatric surgery compared to those who were not ($P < 0.0001$).

The obesity PRS was categorized into 4 levels based on quartiles (level 1; PRS ≤ 34.3; level 2: 34.3 < PRS ≤ 39.8; level 3: 39.8< PRS ≤ 47.18; and level 4: PRS > 47.18).As shown in [Table 4], patients with PRS level 4 had 3.77-fold higher odds of being obese than those with PRS level 1 (95%CI: 2.06-6.89). Conversely, the odds of being obese among those with PRS level 2 (OR = 1.42, 95%CI: 0.76-2.65) was not significantly different from PRS level 1. Together, our data suggest that higher mean PRS scores, particularly PRS scores in the highest two quartiles, are significantly associated with obesity.

As illustrated in [Table 5], the mean CRP value for patients with obesity PRS level 4 (9.03 ± 17.02 mg/L) was higher than for patients with PRS levels 1, 2, or 3, but this difference was not statistically significant.

The results of our linear regression model of the association of PRS with BMI revealed that the PRS improved our BMI prediction by 14% [β = 0.23 (SE = 0.03), $P < 0.0001$] [Figure 1].

Table 1. List of 35 SNPs included in the obesity PRS and linear regression coefficients

CHR	SNP ID	Gene	SNP Type	B	SE	*P*-value	Ref.
1	rs11583200	*ELAVL4*	INTRON	-1.289	0.4045	0.00155	[21]
2	rs17476669	*NRXN1*	INTRON	-1.172	0.4213	0.005666	[26,71]
2	rs7586879	*ADCY3*	INTRON	0.9862	0.4007	0.01427	[76]
2	rs10195252	*GRB14 COBLL1*	INTERGENIC	0.9306	0.4006	0.02068	[21]
2	rs7599312	*ERBB4 LOC646249*	INTERGENIC	0.9962	0.4669	0.03348	[21]
2	rs6732471	*LOC727944 TMEM18*	INTERGENIC	-1.239	0.5838	0.03441	[26,71]
2	rs11688816	*EHBP1*	INTRON	-0.8245	0.41	0.04501	[21]
3	rs1435703	*RARB*	INTRON	2.007	0.5238	0.0001484	[26,69]
3	rs12635698	*RFTN1*	INTRON	1.421	0.4552	0.001927	[26,69]
5	rs4704220	*COL4A3BP*	INTRON	-1.248	0.3874	0.001381	[21]
5	rs7715806	*C5orf37 LOC391798*	INTERGENIC	-1.238	0.3911	0.00167	[26,71]
6	rs2223662	*BMP5 COL21A1*	INTERGENIC	-1.228	0.4466	0.006235	[26,62]
6	rs2275215	*LAMA2 ARHGAP18*	INTERGENIC	1.101	0.4314	0.01108	[26,65]
8	rs4471028	*GDAP1 PI15*	INTERGENIC	-1.381	0.4315	0.001481	[26,62]
8	rs7824886	*YTHDF3 LOC100130155*	INTERGENIC	1.487	0.7113	0.03718	[26,71]
8	rs2922763	*HNF4G LOC100192378*	INTERGENIC	-1.005	0.4976	0.04419	[26,75]
10	rs6602024	*PFKP*	INTRON	1.416	0.6082	0.02044	[26,61]
10	rs7903146	*TCF7L2*	INTRON	-0.9969	0.4832	0.03975	[21]
11	rs12271537	*CYB5R2 | OVCH2*	INTERGENIC	1.166	0.4371	0.007929	[26,71]
11	rs10838774	*NUP160*	INTRON	-1.1	0.4231	0.009695	[60]
11	rs4752856	*MTCH2*	INTRON	-1.135	0.447	0.0115	[26,67]
13	rs4771122	*MTIF3*	INTRON	-1.057	0.5086	0.03826	[21,26,75]
15	rs2245715	*MAP1A*	CODING	1.085	0.4187	0.0099	[26,67]
16	rs3751813	*FTO*	INTRON	-1.554	0.4058	0.0001492	[26,71]
16	rs1121980	*FTO*	INTRON	1.378	0.4086	0.0008176	[21,26,61,63,64,71]
16	rs9936385	*FTO*	INTRON	1.275	0.4183	0.002459	[26,71]
16	rs8050136	*FTO*	INTRON	1.273	0.4212	0.002664	[26,61,63,66,71]
16	rs7190492	*FTO*	INTRON	-0.9862	0.4054	0.01542	[26,66,71]
17	rs12940622	*KIAA1303*	INTRON	0.8537	0.4108	0.03834	[21]
17	rs3764400	*LOC100288682*	UTR	-1.371	0.6641	0.03961	[26,75]
18	rs1840440	*ZNF521|LOC100287386*	INTERGENIC	1.498	0.401	0.0002144	[26,72]
18	rs1805081	*NPC1*	CODING	-1.351	0.4425	0.002411	[21,68]
18	rs1380100	*LOC100130297|SEC11C*	INTERGENIC	1.028	0.5199	0.04875	[21]
19	rs17724992	*PGPEP1*	INTRON	-1.179	0.4367	0.007226	[21]
19	rs3810291	*ZC3H4*	UTR	-0.9234	0.3852	0.01699	[21,75]

SNPs: Single nucleotide polymorphisms; PRS: polygenic risk score.

Correlation between obesity PRS and CRP

Using the linear regression model, CRP = 2.49 + PRS (0.09), PRS was significantly correlated with CRP values at baseline; this knowledge aided in prediction of CRP by 1% [β = 0.09 (SE = 0.04), P = 0.0279] [Figure 2].

On the other hand, patients with the highest PRS quartile had a 1.94-fold higher odds of having above-median CRP values (CRP > 3.57) than patients with PRS level 1 (95%CI: 1.11-3.40, P = 0.0790) [Table 6].

Bariatric surgery eligibility

About 74% of the study participants were overweight or obese, with 11% being obese class II or III, and 58%

Table 2. Patient characteristics by race/ethnicity

Variable	All (*n* = 403)		Race/Ethnicity[1]						*P*-value[4]
			AA (*n* = 86, 21%)		HW (*n* = 262, 65%)		NHW (*n* = 55, 14%)		
	n	%	*n*	%	*n*	%	*n*	%	
Study									
Post-lumpectomy	310	77	66	77	193	74	51	93	< 0.0001
Post-mastectomy	93	23	20	23	69	26	4	7	
Age (years)									
Mean (SD)	55.39 (9.43)		54.86 (10.45)		55.47 (9.28)		55.82 (8.54)		0.8187
Median, Q1, Q3	52.29, 48.94, 62.20		57.07, 48.91, 61.10		55.47, 49.14, 62.25		55.79, 48.66, 61.33		
Min, Max	27.56, 82.54		27.56, 81.16		28.31, 82.49		43.53, 79.90		
Age (years)									
< 50	111	28	23	27	72	27	16	29	0.7328
50-59	153	38	37	43	94	36	22	40	
> 60	139	34	26	30	96	37	17	31	
BMI (kg/m^2)									
Mean (SD)	28.98 (5.94)		30.98 (7.88)		28.79 (4.84)		26.73 (6.33)		0.0001
Median, Q1, Q3	28.29, 24.89, 32.19		30.14, 25.68, 33.83		28.43, 25.06, 32.09		25.68, 22.31, 27.69		
Min, Max	19.05, 68.56		19.69, 63.56		19.05, 48.45		19.53, 49.77		
BMI (kg/m^2)[2]									
Normal weight	106	26	17	20	64	24	25	45	< 0.0001
Overweight	143	35	25	29	100	38	18	33	
Obese class I	108	27	26	30	74	28	8	15	
Obese class II	32	8	11	13	19	7	2	4	
Obese class III	14	3	7	8	5	2	2	4	
Number of obesity comorbidities[3]									
0	170	42	25	29	118	45	27	49	0.0547
1	152	38	38	44	96	37	18	33	
2	58	14	19	22	34	13	5	9	
3	23	6	4	5	14	5	5	9	

[1]AA: African American; HW: Hispanic white; NHW: non-Hispanic white. [2]Normal weight: BMI < 25; overweight: 25 ≤ BMI < 30; obese class I: 30 ≤ BMI < 35; obese class II: 35 ≤ BMI < 40; obese class III: BMI ≥ 40 (kg/m^2). [3]Sum of 9 patient-reported comorbidity conditions diabetes, hypertension, sleep apnea, gastroesophageal reflux disease (GERD), hyperlipidemia, osteoarthritis, coronary artery disease, heart disease, or fatty liver disease. [4]*P*-value from chi-square, Fisher's exact test, or ANOVA comparing AA, HW, and NHW. ANOVA: Analysis of variance.

of participants had obesity-related comorbidities. Six percent (n = 25) of patients met the NIH criteria for bariatric surgery. Significant differences in bariatric surgery eligibility were evident among race/ethnicities: 12% of AA women were eligible for bariatric surgery, followed by 5% HW, and 2% NHW (P < 0.0504). As shown in [Table 7], significant differences in patient eligibility were observed across PRS levels; 14% of patients with PRS level 4 were eligible for bariatric surgery, whereas no patients with PRS level 1 were eligible, 2% of patients with PRS level 2 were eligible, and 9% of patients with PRS level 3 were eligible (P < 0.0001).

As shown in [Table 8], there was a strong association between the above-median PRS and bariatric surgery eligibility (OR = 12.92, 95%CI: 3.00-55.58, P < 0.0001). We also showed that the highest quartile PRS was significantly associated with bariatric surgery eligibility (OR = 4.32, 95%CI: 1.89-9.87, P < 0.0002). PRS: Polygenic risk score.

Table 3. Obesity PRS values by BMI, race/ethnicity, and bariatric surgery eligibility

Variable	PRS			
	n	Mean	SD	*P*-value[3]
Total	403	41.50	9.93	NA
BMI (kg/m^2)[1]				
Normal weight	106	38.4	9.13	< 0.0001
Overweight	143	40.07	8.53	
Obese class I	108	42.61	9.96	
Obese class II	32	48.53	8.54	
Obese class III	14	55.67	12.14	
Race/Ethnicity[2]				
AA	86	55.03	7.99	< 0.0001*
HW	262	38.27	6.65	
NHW	55	35.94	6.90	
Eligible for bariatric surgery				
Yes	25	50.08	8.68	< 0.0001
No	378	40.96	9.77	

[1]Normal weight: BMI < 25; overweight: 25 ≤ BMI < 30; obese class I: 30 ≤ BMI < 35; obese class II: 35 ≤ BMI < 40; obese class III: BMI ≥ 40 (kg/m^2). [2]AA: African American; HW: Hispanic White; NHW: non-Hispanic White. [3]*P*-value from *t*-test or ANOVA. *Mean PRS was significantly different ($P < 0.0001$) for AA *vs.* HW and AA *vs.* NHW. ANOVA: Analysis of variance.

Table 4. Association between obesity and RPS levels

PRS level[2]	Obese[1]		Not obese[1]		*P*-value[3]	OR (95%CI)
	n	%	*n*	%		
1	24	16	77	31	< 0.0001	Reference
2	31	20	70	28		1.42 (0.76-2.65)
3	45	29	56	22		2.58 (1.41-4.71)
4	54	35	46	18		3.77 (2.06-6.89)

[1]Obese: BMI ≥ 30; not obese: BMI < 30. [2]PRS level 1: PRS ≤ 34.3; level 2: 34.3 < PRS ≤ 39.8; level 3: 39.8 < PRS ≤ 47.18; level 4: PRS > 47.18. [3]*P*-value from chi-square test. BMI: Body mass index; PRS: polygenic risk score.

Table 5. Baseline CRP level by obesity PRS level

Obesity PRS level[1]	CRP at baseline (mg/L)					*P*-value[2]
	n	Mean	SD	Minimum	Maximum	
1	100	5.07	6.97	0.1	34.89	0.0808
2	101	6.23	7.51	0.1	39.5	
3	100	6.57	9.58	0.11	50.84	
4	97	9.03	17.02	0.08	149.09	

[1]PRS level 1: PRS ≤ 34.3; level 2: 34.3 < PRS ≤ 39.8; level 3: 39.8 < PRS ≤ 47.18; level 4: PRS > 47.18. [2]*P*-value from ANOVA. ANOVA: Analysis of variance.

DISCUSSION

Obesity is a public health threat that continues to disproportionately affect AA woman. Our data corroborate this observation, as AA women had significantly higher BMI than HW and NHW women. Moreover, obesity has been associated with increased breast cancer risk, recurrence, and worse outcomes among postmenopausal women[2,3,8,77-81]. Racial/ethnic trends in obesity may contribute to the higher rates of mortality observed among AA women with breast cancer compared to NHW women[18].

Table 6. Association between CPR and obesity PRS

Obesity PRS levels[2]	CRP (mg/L)				OR (95%CI)
	Below median[1]		Above median[1]		
	n	%	*n*	%	
1	60	59%	41	41%	Reference
2	50	50%	51	50%	1.49 (0.86 - 2.60)
3	51	50%	50	50%	1.44 (0.82 - 2.50)
4	43	43%	57	57%	1.94 (1.11 - 3.40)

[1]Below median CRP ≤ 3.57, above median CRP > 3.57. [2]PRS level 1: PRS ≤ 34.3; level 2: 34.3 < PRS ≤ 39.8; level 3: 39.8 < PRS ≤ 47.18; level 4: PRS > 47.18. CRP: C-reactive protein; PRS: polygenic risk score.

Table 7. Bariatric surgery eligibility by PRS level and race/ethnicity

Variable	Bariatric surgery eligibility				*P*-value[3]
	Eligible		Not eligible		
	n	%	*n*	%	
Total	25	6	378	94	
PRS level[1]					
1	0	0	101	100	< 0.0001
2	2	2	99	98	
3	9	9	92	91	
4	14	14	86	86	
Race/ethnicity[2]					
AA	10	12	76	88	0.0504
HW	14	5	248	95	
NHW	1	2	54	98	

[1]PRS level 1: PRS ≤ 34.3; level 2: 34.3 < PRS ≤ 39.8; level 3: 39.8 < PRS ≤ 47.18; level 4: PRS > 47.18. [2]AA: African American; HW: Hispanic White; NHW: non-Hispanic White. [3]*P*-value from chi-square or Fisher's exact test. As shown in Table 8, there was a strong association between the above-median PRS and bariatric surgery eligibility (OR = 12.92, 95%CI: 3.00-55.58, $P < 0.0001$). We also showed that the highest quartile PRS was significantly associated with bariatric surgery eligibility (OR = 4.32, 95%CI: 1.89-9.87, $P < 0.0002$). PRS: Polygenic risk score.

Table 8. Association between obesity PRS and bariatric surgery eligibility

Eligible for bariatric surgery	Obesity PRS groups			
	Above median[1] (Q3 + Q4)	Below median[1] (Q1 + Q2)	The highest quartile[1] (Q4)	Other quartiles[1] (Q1 + Q2 + Q3)
Yes	23	2	14	11
No	178	200	86	292
OR (95%CI)	12.92 (95%CI: 3.00-55.58)		4.32 (95%CI: 1.89-9.87)	
***P*-value[2]**	< 0.0001		< 0.0002	

[1]PRS Q1: ≤ 34.3; Q2: 34.4-39.8; Q3: 39.9-47.18; Q4 > 47.18. [2]*P*-value from logistic regression.

Accumulating evidence suggests that obesity is highly heritable[21,23]. Here, we modeled individual genetic predisposition to obesity by utilizing a PRS to aggregate multiple externally-validated obesity-associated SNPs into a continuous variable. Through the review of large GWAS studies of obesity-related phenotypes, we identified 700 SNPs associated with BMI. The 35 SNPs included were selected due to their significant association ($P < 0.05$) and low LD linkage disequilibrium (LD < 0.8), as aligned with previous studies[25-27]. Polygenic obesity risk is an area of ongoing study. Obesity-related SNPs continue to be discovered through population GWAS, and many obesity-related SNPs likely remain to be discovered. Our obesity PRS model

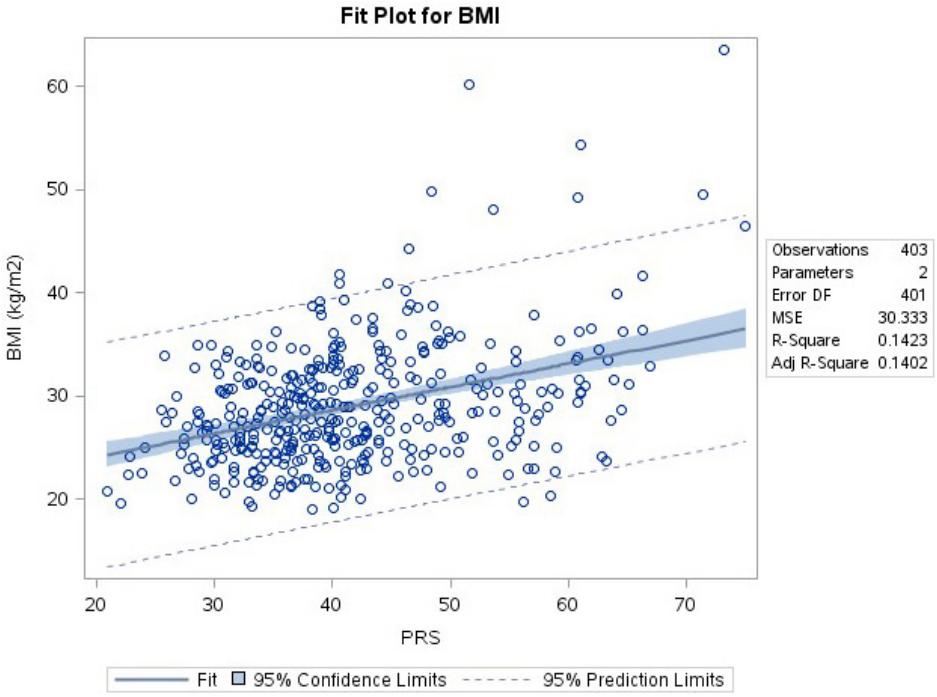

Figure 1. Results of linear regression analysis of body mass index (BMI, kg/m^2) and polygenic risk score (PRS). [BMI = 19.620 + PRS (0.23)].

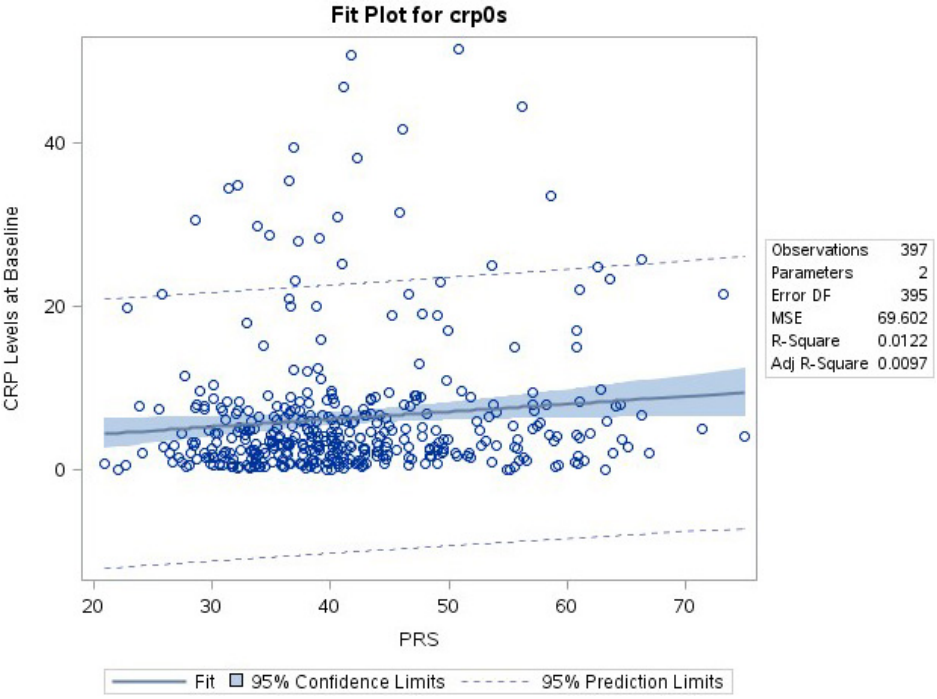

Figure 2. Linear regression analysis of CRP and PRS [CRP = 2.49 + PRS (0.09)]. As illustrated in Table 5, the mean CRP value for patients with obesity PRS level 4 (9.03 ± 17.02 mg/L) was higher than for patients with PRS levels 1, 2, or 3, but this difference was not statistically significant.

is limited in that it may not encompass the full scope of genetic variability in obesity. Future studies using

large, diverse populations are necessary to refine our understanding of how SNPs contribute to genetic obesity risk.

Consistent with previous studies, our data demonstrate that the PRS is strongly associated with BMI[82,83]. Indeed, there was a dose-response increase in PRS for each increasing BMI category, and women with a PRS level 4 had 3.77-fold higher odds of being obese. Comparison of PRS by race/ethnicity aligned with known racial/ethnic trends in obesity, as PRS for AA women, was found to be significantly greater than HW and NHW women. Genetic predisposition to obesity varies significantly by race/ethnicity.

The mechanism by which obesity leads to carcinogenesis is multifactorial and not entirely understood; however, many propose that one causal link may be inflammation. Obesity represents a chronic low-grade inflammatory state, and there is a known bidirectional link between chronic inflammation and carcinogenesis[84-87]. Chronic inflammation creates an inflammatory microenvironment that promotes tumorigenesis[86,88]; tumor cells, in turn, attract immune cells that produce cytokines and chemokines that induce carcinogenic DNA mutations in nearby cells[84-87,89]. This inflammatory tumor microenvironment facilitates the progression of the disease and contributes to poor outcomes[81,84-86,88,90].

We demonstrate that the PRS is closely associated with blood levels of CRP. CRP is an inflammatory biomarker that differs by BMI[36-38,91], making it a suitable biomarker for studying inflammation in this study. Excess adipose tissue in overweight and obese individuals can release cytokines, stimulate CRP synthesis, and induce low-grade systemic inflammation[34,91]. Elevated CRP levels may also contribute to leptin resistance in obese individuals[32]; high leptin and CRP levels have been shown to exacerbate pre-existing systemic inflammation in breast cancer patients and survivors, increasing susceptibility to recurrence and/or metastasis[34,92]. In our cohort, women with PRS level 4 had 3.77-fold increased odds of being obese and had exceptionally high CRP levels. These findings support the hypothesis that inflammation links obesity and breast cancer and additionally suggest that CRP may be implicated.

Considering our understanding of the association between obesity and breast cancer risk, recurrence, and poor outcomes, weight loss interventions among obese women may represent an effective strategy for breast cancer prevention and improving outcomes. Initial weight loss recommendations include lifestyle modifications focused on diet and exercise. Although evidence indicates that multidisciplinary programs reliably produce and sustain a 5%-10% weight loss, this may not be sufficient to mitigate health risks in obese class II and III women, especially among those with a high genetic predisposition to obesity[93]. These women may instead benefit from more aggressive approaches, like bariatric surgery, to achieve a greater weight loss than possible with lifestyle modifications alone[94,95]. In our cohort, a high PRS was significantly associated with bariatric surgery eligibility. Bariatric surgery may be recommended in women who meet NIH criteria and have a high genetic predisposition to obesity (indicated by above-median PRS) to improve both breast cancer outcomes and other obesity-associated comorbidities.

In addition to improved quality of life, the known benefits of bariatric surgery include improved glucose homeostasis, insulin responsiveness, and reduced inflammation - all of which are believed to be protective against the development of cancer[96]. In addition, the Swedish Obese Subjects study found that bariatric surgery significantly decreased cancer incidence among women[94]. Although literature exploring bariatric surgery outcomes in breast cancer patients is limited, one large retrospective cohort study demonstrated a reduced risk of postmenopausal breast cancer in women who underwent bariatric surgery compared to BMI-matched subjects who did not[97].

Despite the evident benefits of bariatric surgery in obese class II and III women with breast cancer, when and how to integrate bariatric surgery into the breast cancer care continuum has not been explored. There is some evidence to suggest that bariatric surgery may be well-tolerated in breast cancer survivors after completing all treatments[98], but very few studies have examined the outcomes of bariatric surgery in this population. Additionally, little is known about the impact of bariatric surgery on breast cancer recurrence rates, metastasis, or mortality. Future studies should explore the optimal time to undergo bariatric surgery after mastectomy, lumpectomy, chemotherapy, and/or radiotherapy. Longitudinal studies of the effects of bariatric surgery on progression-free and overall survival are also warranted.

Our study has several limitations. First, study reliability is limited by the small sample size (n = 403) that was highly enriched for HW women (65%). Findings may therefore not be generalizable to all populations. In addition, our study focused solely on women with breast cancer and did not include a healthy control group. Results must only be interpreted in the context of breast cancer patients. It is not clear how obesity PRS and CRP levels in this sample compare to healthy women, and future case-control studies comparing breast cancer populations to healthy populations will be essential to corroborate findings. Second, BMI may be an oversimplified measure of adiposity, as it neither accounts for fat distribution nor distinguishes fat from muscle[99,100]. Waist circumference may be a better reflection of obesity and associated breast cancer risk[99,100]; however, this is not routinely collected in the clinical setting, and our analysis was limited by the data available in the electronic medical record. Third, CRP is a nonspecific marker of inflammation[101]. Although some studies suggest an association between high CRP and obesity or breast cancer, our results must be interpreted cautiously, as spurious elevations in CRP may contribute to the observed trends. CRP was the sole biomarker evaluated in the current study due to its known association with inflammation and the economic feasibility of collection; however, oxidative stress is also known to play a critical role in the pathogenesis of obesity and breast cancer[102]. Future studies are warranted to evaluate whether our obesity PRS may also be associated with biomarkers of oxidative stress. Lastly, nutritional intake, physical activities, and other environmental factors may modify the genetic effects on obesity. However, we did not collect such information; it is not possible to adjust for these variables in our regression analysis. Future studies should collect such information for adjustment.

Our findings validate previous studies suggesting that aggregating polygenic risk into a PRS helps predict obesity risk. In particular, our obesity PRS can identify breast cancer patients with a high genetic predisposition to obesity who may benefit from aggressive weight-loss strategies, such as bariatric surgery. Our study also highlights that obesity-associated SNPs may be related to racial and ethnic disparities in obesity and subsequently, breast cancer outcomes. Together, racial/ethnic variation in obesity rates and high obesity PRS may contribute to worse breast cancer outcomes observed in minority women, highlighting the importance of intervention in this high-risk population. Additionally, we demonstrate an association between genetic risk of obesity and inflammation that highlights one possible mechanism by which obesity promotes carcinogenesis. Future studies utilizing larger sample sizes will be necessary to validate these findings. Finally, we carefully propose that bariatric surgery may be considered as a prevention strategy for breast cancer incidence and/or recurrence, and to improve the quality of life and overall survival in eligible women. Additional studies should target racial/ethnic disparities in outcomes to examine the potential benefits of introducing bariatric surgery into the breast cancer continuum of care.

DECLARATIONS

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Authors' contributions

Conceived and designed study: Puyana C, Hu JJ
Data analysis and interpretation: Puyana C, Schindler E, Lee E, Hu JJ
Drafted and revised the manuscript: Puyana C, Schindler E, Lee E, Hu JJ
All authors read and approved the manuscript.

Availability of data and materials

The data that support the findings of this manuscript are available from the corresponding author upon request.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Study protocols were approved by the Institutional Review Board at the University of Miami. Informed consent was obtained from all study participants at the time of enrollment.

Consent for publication

Not applicable.

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