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Statin Use and Breast Cancer Prognosis in Black and White Women

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Abstract

Studies show decreased risk of breast cancer recurrence and improved survival with statin use, but data on racial disparities regarding breast cancer prognosis and statin use are lacking. Our objective was to investigate if racial disparities in breast cancer prognosis can be partially explained by differences in pre-diagnosis statin use. Patients were identified from a prospective, multi-center study examining the effects of metabolic factors on breast cancer prognosis in Black and White women. Statin use, prognosis (as measured by Nottingham Prognostic Index), anthropometric, tumor and socio-demographic characteristics were examined. 587 women (487 White, 100 Black) with newly diagnosed primary invasive breast cancer were recruited. Obesity was more prevalent in Black women than White women (47% vs 19%, $p<0.01$); both groups had

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similar low-density lipoprotein (LDL) cholesterol levels (113 ± 41 vs 113 ± 36 mg/dl, $p=0.90$). More Black women used statins than White women (18% vs 11%; $p=0.06$). Black women had a worse prognosis in an adjusted model than White women (OR 2.13 95% CI 1.23–3.67). Statin use was not associated with prognosis in unadjusted (OR 1.03, 95% CI 0.53–2.0), and adjusted models (OR 1.14, 95% CI 0.56–2.31). In women with newly diagnosed breast cancer, Black women were more likely to be treated with statins than White women, contrary to previous studies. Black women had worse prognosis than White women, but this difference was not explained by differences in pre-diagnosis statin use. Our study suggests that differences in pre-diagnosis statin use do not contribute to racial disparities in breast cancer prognosis.

Keywords

breast cancer; statin; disparities; race/ethnicity; cholesterol

Introduction

While breast cancer mortality is improving overall, the disparity in breast cancer mortality between Black and White women is increasing [1]. Black women are more likely than White women to have breast cancer with poor prognostic features [2]. This disparity cannot be completely explained by differences in established risk factors for breast cancer mortality [2]. Additionally, Black women have higher rates of obesity, insulin resistance, and dyslipidemia when compared with White women [3,4]. Dyslipidemia has been associated with increased cancer risk [5].

Statins (a class of lipid-lowering drugs) are used by approximately 1/4 of women over the age of 40 in the United States [6]. Preclinical studies have demonstrated that statins have an anti-proliferative effect on breast tumor cells [7–9]. Furthermore, five large retrospective cohort studies (which included different types of statins- both lipophilic and hydrophilic) have shown reduced risk of breast cancer recurrence [10–14]. In regards to mortality, some investigations have shown that statin use in women with breast cancer has been associated with improved survival [15–17], while others have shown no significant survival benefit [18–20].

In patients with hypercholesterolemia and coronary artery disease, Black patients are less likely than White patients to use statins [21,22]. Among patients eligible for cholesterol treatment according to the 2013 American College of Cardiology and the American Heart Association (ACC/AHA) guidelines, Black patients were less likely to take cholesterol-lowering medications than White patients [23]. Barriers to taking cholesterol-lowering medications and statins include fewer doctors' visits, decreased awareness of high cholesterol, and decreased adherence [23,24].

As statins have an association with decreased breast cancer recurrence, as well as potentially improved survival, disparities in statin use between Black and White women with breast cancer are important to investigate. Our objective was to elucidate whether or not statin use differs between Black and White women with breast cancer and if racial disparities in breast cancer prognosis can be partially explained by differences in pre-diagnosis statin use.

Materials and Methods

Study population

We prospectively identified 587 women (487 White, 100 Black) with newly diagnosed primary invasive breast cancer. Participants were recruited from multiple medical centers in New York, New Jersey, and Baltimore at the time of their breast cancer surgery. Data were collected primarily for a study investigating the role of insulin resistance in breast cancer prognosis in Black and White Women (National Cancer Institute (NCI) grant 1R01CA171558-01)[25]. Participants were enrolled between March 2013 and March 2017 and recruitment was still ongoing for the insulin resistance study.

Eligibility criteria included age over 21 years, and women self-identifying as White or Black. Hispanic Black women were also included, but Hispanic White were excluded since this group is more likely to have estrogen receptor (ER)/progesterone receptor (PR) negative tumors than non-Hispanic White women, which might influence the association between race and hormone receptor status. This sample excluded women with diabetes treated with oral or injected glucose lowering therapies, as these conditions influence insulin levels, one of the primary endpoints of the main study.

Data collection

Eligible patients were identified and consented prior to breast cancer surgery. Participants were surveyed regarding socio-demographic characteristics, medical comorbidities, menstrual history, behavioral characteristics, including physical activity, diet and access to care. Access to care was measured by screening mammography less than 2 years prior to breast cancer diagnosis [26]. Comorbidities were measured via the Charlson Comorbidity Index [27]. Patients were also surveyed about medication use and were categorized as statin users or not statin users. Anthropometric data, including blood pressure, weight, height, waist circumference, were recorded at the initial study visit, or within 1 month of surgery. Fasting lipids, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TGs) were collected at the time of surgery. Fasting glucose was also collected at the time of surgery. Metabolic syndrome was determined for women using waist circumference, fasting glucose, triglycerides, HDL cholesterol, and blood pressure according to the American Heart Association and National Heart, Lung, and Blood Institute guidelines [28]. Additionally, final pathology reports containing ER, PR, human epidermal growth factor receptor 2 (HER2) status, lymph node status, tumor size, and tumor grade were obtained. The pathology data (tumor size, number of positive nodes, and histology grade) were used to calculate the Nottingham prognostic index (NPI). NPI was used rather than tumor stage for prognosis, as NPI is less influenced by health care access than stage and has been validated in multiple countries [29–31]. A study that dichotomized NPI at 4.4 showed significant differences in biomarkers between the good and poor prognosis groups[32], and thus participants were dichotomized into two categories: better prognosis (NPI $\leq$ 4.4) and worse prognosis (NPI $>$ 4.4). Eligibility for statin use was measured according to the 2013 American College of Cardiology /American Heart Association (ACC/AHA) and Adult Treatment Panel III (ATP III) guidelines [33,34]. Both guidelines were included, as patient data collection started in March 2013 spanning the time

when the 2013 ACC/AHA guidelines were published. The study was in accordance with the ethical standards of all institutions' institutional review boards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis

Descriptive analyses were conducted for all baseline characteristics and statin use, including proportions, means and medians, and variability (standard deviations and ranges). Baseline patient characteristics, eligibility for statin use, and statin use if eligible were compared using the Chi-square test for categorical variables and t-test for continuous variables by race.

Multiple logistic regression analysis was used to predict worse prognosis while controlling for potential confounders. Univariate logistic regression analysis was used to determine association between individual variables and worse prognosis. The multivariate models included covariates associated with tumor prognosis, as well as covariates shown in the literature to be strong confounders.

Results

Sociodemographic, behavioral, and health characteristics compared by race are shown in Table 1. Black and White women were similar in age (58.6 ± 13 vs 58.2 ± 12 , $p=0.78$) and proportionally similar in post-menopausal status (46.5% vs 49.3%, $p=0.60$). In regards to socio-demographics, fewer Black women than White women had an income $\leq \$50,000$ (58.5% vs 80%, $p < 0.01$), but were similar in regards to education (education $\geq$ college) (59% vs 64%, $p=0.31$). No statistically significant difference in smoking prevalence was found between Black and White women (15.6% vs 7.1%, $p=0.10$). More Black women had a mammogram within 2 years of breast cancer diagnosis (81.6% vs 76.3%, $p=0.03$).

Furthermore, more Black women had blood pressure $\geq 140/90$ mmHg (71% vs. 45%, $p < 0.01$), had a body mass index (BMI) ≥ 30 kg/m² (47% vs. 19%, $p < 0.01$), had a larger waist circumference (107.8 ± 15 centimeters (cm) vs 94.3 ± 13 cm, $p < 0.01$) and a higher proportion had the metabolic syndrome (40.0% vs. 19.7%, $p < 0.01$) when compared with White women. More Black women had lower HDL (61 ± 16 vs 69 ± 19 mg/dL, $p < 0.01$), lower TGs (86 ± 37 vs 100 ± 91 mg/dL, $p=0.03$), and more triple negative (ER, PR, HER2 negative) breast cancer (14% vs 7%, $p=0.02$) when compared with White women. Similar LDL levels (113 ± 41 vs 113 ± 36 mg/dL, $p=0.90$) were found in both groups. In regards to tumor stage, differences between Black and White women were not statistically significant (Stage I 55.0% vs 64.3%, Stage II 41.0% vs 32.7%, Stage III 4.0% vs 3.1%), $p=0.22$).

A comparison of statin use and eligibility in Black and White women is shown in Table 2. In our sample, more Black women used statins than White women (18% vs 11%; $p=0.06$), but this difference was not statistically significant. Similar proportions of Black women and White women were eligible for statin therapy according to ATP III and 2013 ACC/AHA guidelines (11.0% vs 9.2%; $p=0.60$ and 40.7% vs 33.8%; $p=0.21$, respectively). In general, more women were eligible for statin therapy with the 2013 ACC/AHA criteria compared with ATP III criteria. For women eligible for statin therapy (according to ATP III and 2013 ACC/AHA guidelines), there was no statistically significant difference in statin use between

Black and White women, (30.0% vs 23.8%, $p=0.70$ for ATPIII, and 27.0% vs 24.0%, $p=0.70$ for 2013 ACC/AHA guidelines).

Based on their NPI scores, 17% of the women had worse prognosis breast cancer (NPI > 4.4). More Black women than White women had worse prognosis breast cancer (27% vs 15%, $p=0.009$) (Table 1). Unadjusted and adjusted analyses of the association of statin use, race, and other variables with prognosis are shown in Table 3. Statin use was not associated with prognosis in unadjusted (OR 1.03, 95% CI 0.53–2.0) or adjusted (OR 1.14, 95% CI 0.56–2.31) models. Black race was associated with poor prognosis in the multivariate model (OR 2.13 95% CI 1.23–3.67) adjusting for age, LDL, menopausal status, metabolic syndrome, and mammography 2 years before breast cancer diagnosis (a measure of access to care).

Discussion

In this study of women with primary invasive breast cancer, a higher proportion of Black women used statins than White women and statin use was not associated with breast cancer prognosis. We also found that Black race was associated with worse breast cancer prognosis. To our knowledge, this study is the first to investigate racial disparities in statin use and its relationship with breast cancer prognosis.

In our investigation, we observed that a higher proportion of Black women used statins than White women, though this difference was not statistically significant. In regards to dyslipidemia, our study found similar LDL levels in Black and White women and lower HDL and TGs in Black women than White women, which is consistent with prior population-based studies[3,4]. Additionally, we found that there was no significant racial difference in treatment eligibility for statin use. There was also no racial difference in statin use if eligible according to ATP III and ACC/AHA guidelines. Our findings contrast with prior population studies that reported that Black patients with coronary artery disease and high cholesterol were less likely to take statins than White patients [21,22]. Our results also contrast with a study that showed that treatment eligibility for lipid lowering drugs was similar in White and Black patients, yet Black patients were less likely to take lipid lowering drugs even when eligible [23]. Our study population includes only women diagnosed with breast cancer, and perhaps reflects a patient cohort who is more engaged with the health care system and more likely to be prescribed medications as indicated than other cohorts. Our study also excludes women being medically treated for diabetes, which excludes many women in the population who would be treated with statins and might explain the lower rate of statin use in our patient population when compared with the general population. Interestingly, in studies investigating statin use and breast cancer outcomes that included race data, only one showed decreased post-diagnosis statin use in Black women compared with White women, while two other studies reported similar rates of statin use in both groups [10,12,17].

Preclinical studies have strongly demonstrated that statins have an anti-proliferative effect on breast cancer cells [7–9], but epidemiologic studies examining statins and breast cancer outcomes have had inconsistent results. Our finding that statin use is not associated with

breast cancer prognosis is consistent with several previous investigations that did not demonstrate a significant relationship between statin use and breast cancer mortality[18,19] and recurrence.[10,13,14] However, there are several studies that have found that both pre- and post-diagnosis statin use improves breast cancer recurrence rates[12,11], as well as mortality[15–17]. These studies did not investigate if outcomes differed by race.

In our study, Black women had worse prognosis than White women in a non-adjusted model and a model that adjusted for metabolic syndrome, LDL, menopausal status, breast cancer screening patterns and triple negative breast cancer. The difference in prognosis could not be explained by differences in statin use. This is consistent with previous studies showing that Black women are more likely to present initially with breast cancer with aggressive features and have worse breast cancer prognosis [2,35]. Black women were more likely than White women to have the metabolic syndrome, poor diet, lower HDL, higher number of comorbidities, and triple-negative disease, which could have a multifactorial impact on breast cancer prognosis [5,36,37].

Our analysis has several limitations. Some major limitations are the cross-sectional nature of our data analysis and that determination of statin use was based upon self-reported medication lists. Data regarding statin treatment duration and treatment were not collected, so we were not able to analyze any dose-dependent effects. Additionally, our population size and the proportion of recruited Black women were too small to assess the differences between lipophilic and hydrophilic statins.

In summary, in a population of women with newly diagnosed breast cancer, our study shows that Black women have a worse prognosis than White women, which could not be explained by differences in statin use. Black women were more likely than White women to be obese, have metabolic syndrome, and low HDL cholesterol, yet few studies have specifically investigated how these differences are associated with racial disparities in breast cancer outcomes. Further studies with larger populations and longer follow-up should investigate the differential effects of dyslipidemia and statin use on breast cancer tumor characteristics, prognostic features, and outcomes in Black and White women.

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Table 1

Comparison of characteristics between White and Black Women

Socio-demographic characteristics			
	White (N=487)	Black (N=100)	P-value *
	N (%)	N (%)	
Age (mean, SD)	58.2 (12.4)	58.6 (12.5)	0.78
Education college	295 (64.4)	56 (59.0)	0.31
Income \$50,000	132 (80.5)	24 (58.5)	<0.01
Insurance type			0.02
Medicaid	20 (4.3)	12 (12.1)	
Medicare	21 (4.5)	3 (3.0)	
None	2 (0.43)	0 (0)	
Private Commercial	425 (90.8)	84 (84.7)	
Behavioral characteristics			
	White (N=487)	Black (N=100)	P-value *
	N (%)	N (%)	
Smoking	16 (7.1)	5 (15.6)	0.10
Pap smear within 3 years	379 (85.6)	69 (81.2)	0.28
Screening mammogram within 2 years prior to diagnosis	376 (76.3)	82 (81.6)	0.03
Colonoscopy within 10 years	300 (64.3)	56 (58.3)	0.26
Clinical Characteristics			
	White (N=487)	Black (N=100)	P-value *
	N (%)	N (%)	
Statin use	55 (11.3)	18 (18)	0.06
Post-menopausal	241 (49.3)	47 (46.5)	0.60
Obesity (BMI ≥30)	90 (19.0)	47 (47.0)	<0.01
Waist (cm) (mean, SD)	94.3 (13.2)	107.8 (15.0)	<0.01
BP ≥140/90mmHg	219 (45.0)	71 (71.0)	<0.01
LDL cholesterol (mean, SD)	113.4 (36)	112.9 (41)	0.90
HDL cholesterol (mean, SD)	69.0 (19.4)	61.4 (15.8)	<0.01
Triglycerides (mean, SD)	100.2 (90.9)	86.1 (36.5)	<0.01
Fasting glucose ≥100	89 (20.3)	33 (36.7)	<0.01
Metabolic syndrome	96 (19.7)	40 (40.0)	<0.01
Charlson Comorbidity Index ≥1	252 (51.8)	69 (69)	<0.01
Family history of BC	143 (30.0)	19 (19.0)	0.03
Hormone receptor status			
ER+	420 (90.3)	73 (79.4)	<0.01
PR+	390 (84)	68 (74.7)	0.03
ER/PR negative	75 (16)	24 (26)	0.02

HER2			0.77
Negative 1+	364 (79.1)	69 (76.7)	
Border 2+	68 (14.8)	16 (17.8)	
Positive 3+	28 (6.1)	5 (5.6)	
Triple negative	31 (6.8)	13 (14.6)	0.01
Stage			0.22
I	313 (64.3)	55 (55.0)	
II	159 (32.7)	41 (41.0)	
III	15 (3.1)	4 (4.0)	
NPI >4.4	75 (15.4)	27 (27.0)	<0.01
Tumor size, cm (mean, SD)	1.56 (1.19)	1.78 (1.45)	0.10

* Chi-square for categorical variables, t-test for continuous variables

BC=breast cancer; LDL= low density lipoprotein; HDL=high density lipoprotein; BMI = body mass index; ER=estrogen receptor; PR= progesterone receptor; Her2= human epidermal growth factor 2; NPI = Nottingham Prognostic Index

Table 2

Statin use, eligibility for statin use, and statin use if eligible according to ACC/JHA 2013 and ATP III guidelines in White and Black women

	White N (%)	Black N (%)	P-value *
Statin use	N=487	N=100	
	55 (11.3)	18 (18)	0.06
Eligible for statin use according to guidelines	N= 456	N=91	
2013 ACC/JHA	154 (33.8%)	37 (40.7%)	0.21
ATP III	42 (9.2%)	10 (11.0%)	0.60
Statin use if eligible according to guidelines	N = 154	N = 37	
2013 ACC/JHA	37 (24.0%)	10 (27.0%)	0.70
ATP III	10 (23.8%)	3 (30.0%)	0.68

*
Chi-square test

ACC/JHA: American College of Cardiology and the American Heart Association; ATP III: Adult Treatment Panel III

Table 3

Logistic Regression: Odds Ratios (95% Confidence Interval) from models predicting worse cancer prognosis (NPI > 4.4)

Variables	OR Unadjusted	OR Adjusted
Race		
White		REF
Black		2.13 (1.23–3.67)
Statin use		
No	REF	REF
Yes	1.03 (0.53–2.00)	1.14 (0.56–2.31)
Age		1.00 (0.97–1.02)
LDL		
130		REF
>130		0.75 (0.44–1.27)
Mammography		
2 years		REF
> 2 years		1.50 (0.89–2.50)
Metabolic syndrome		
No		REF
Yes		0.99 (0.57–1.43)
Menopausal Status		
Pre		REF
Post		0.68 (0.40–1.12)

OR= odds ratio; CI=confidence interval; REF= reference

* Model including all variables listed in table. The C-statistic for the model is 0.65. The p-value=0.03.