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Research Article

Endocrine Disrupting Compounds and Breast Cancer Disparities: Evidence from NHANES (2009-2016)

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Abstract

Purpose: Several studies posit biological and environmental factors are associated with disparities in Breast Cancer (BCa). The purpose of this study was aimed at investigating the association between exposure to Endocrine-Disrupting Compounds (EDCs) and BCa disparities in non-Hispanic Black (AA) and non-Hispanic White (EA) women.

Methods: We performed a retrospective analysis on 348 female participants diagnosed with BCa from a total of 11765 female participants in the National Health and Nutrition Examination Survey (NHANES) from 2009 through 2016.

Results: Wilcoxon rank sum test showed significant and systematic higher levels of Ethylparaben (p= 0.03) and mono-(2-ehyl-5-hydroxyhexyl) phthalate (p= 0.04) association with breast cancer risk. Of the EDCs investigated, Benzophenone-3, Bisphenol-A, Triclosan, Methyl paraben, Ethyl paraben, Propylparaben, mono-ethyl phthalate, mono-benzyl phthalate, and mono-iso-butyl phthalate showed significant ($p<0.05$) differences in AA and EA women without BCa. However, there was no significant difference for the two groups with BCa cases in any of the EDCs investigated. Compared with EA women with BCa, AA women had a higher prevalence of hypertension (22.4% vs. 15.7%), diabetes (11.8% vs. 7.2%) and obesity (47.0% vs. 36.0%) for women >20 years of age. We conclude that exposure to certain EDCs can contribute to certain chronic diseases and exacerbate BCa risk and BCa disparities.

Keywords: Simultaneous kidney pancreas transplantation, Peri-transplant fluid collection, Intramural abscess

Abbreviations: AA: Non-Hispanic Black/African American; BCa: Breast Cancer; EA: Non-Hispanic White/European American; EDCs: Endocrine Disrupting Compounds; NHANES: National Health and Nutrition Examination Survey

Introduction

Breast Cancer (BCa) is the most common cancer among women and the second most common cause of cancer death after lung cancer in the United States [1]. It is estimated that in 2023, 297,790 women (accounting for 15.2% of all newly diagnosed cancers) will be newly diagnosed with BCa and 43,170 women (accounting for 7.1% mortality rates of all cancers) will die from breast cancer, according to the National Cancer Institute, Surveillance, Epidemiology, and End Results Program (SEER database) [2]. Breast cancer does not affect all racial and ethnic groups equally.

Non-Hispanic White (EA) women are more likely to be diagnosed with BCa than any racial group, followed by non-Hispanic Black (AA) women, Asian/Pacific Islander, Hispanic (HA), and American Indian/Alaska Native women with a lower incidence rate. Yet BCa is the leading cause of cancer death among AA and Hispanic women [3,4]. Non-Hispanic Black women have higher mortality rates and are more often first diagnosed at regional or distant stages when compared with EA women (45% versus 35%) [5].

The difference in incidence within populations indicates different biological and environmental factors that cause varying incidence and mortality rates. At the biological level, different subtypes of BCa have been identified. Estrogen-Receptor (ER), Progesterone-Receptor (PR), and Human Epidermal Growth Factor Receptor-2 (HER2) negative BCa (i.e., Triple-Negative Breast Cancer, TNBC) that carries a less favorable prognosis is more common among premenopausal AA women [6,7]. The increased incidence of TNBC among AA women is attributed to a combination of modifiable risk factors including differences in breastfeeding patterns, earlier and higher parity, obesity, as well as non-modifiable factors such as predisposing single nucleotide polymorphisms in the African ancestry [8,9]. While most BCa are sporadic, approximately 5–10% are hereditary [10]. Pathogenic variants in the high penetrance genes BRCA1 and BRCA2 account for approximately 20% of heritable BCa risk [11,12]. In addition to biological factors such as BRCA1 or BRCA2 mutations, family history of BCa, and familial BCa syndromes, a woman's risk of developing BCa is affected significantly by modifiable risk factors, such as alcohol use, smoking, obesity, and physical activity [13,14]. Obesity and physical activity have long been hypothesized to be associated with BCa incidence and mortality [15,16] and their associations may differ by menopausal status and/or by race and ethnicity [16,17]. Physical activity has long been found to be protective against BCa [18,19]. These associations, however, are not as well studied in women who are members of racial and ethnic minority groups as in EA women [16].

Non-Hispanic Black women diagnosed with BCa are 42% more likely to die than their EA counterparts due in part to the greater number of comorbid chronic conditions among AA BCa survivors [20]. The SEER database (collected between 1978-2010) showed that the risk of death from Cardiovascular Disease (CVD) among AA BCa survivors is excessively higher than that of their EA counter parts (Hazard Ratio 6.43, CI: 3.61–11.45) [21].

Diabetes affects up to one-third of patients with BCa [22], and evidence shows that women with diabetes have a 40% higher risk of mortality after BCa than women without diabetes [22,23]. Diabetes not only increases non-cancer mortality because of diabetes-related complications but also affects BCa specific mortality [24]. Women with diabetes face poorer BCa prognosis because of estrogenic effects of obesity or metabolic factors such as the growth-promoting influence of hyperinsulinemia and insulin resistance that can lead to more aggressive disease [25-27]. Breast cancer prognosis also may be affected by health care disparities in patients with diabetes. Indeed, studies show that women with diabetes have lower BCa screening rates [28] and present with more advanced diseases than women without diabetes [22,29].

It is estimated that roughly 32.2% of BCa survivors have one or more comorbidities, similar to the national population average of 31.8%; however, the effect of the comorbidity is more significant in BCa survivors and leads to worse quality of life and decreased survival [30]. The higher mortality rates (42%) in AA women compared with EA women could be partly attributed to the disproportionate co-occurrence of chronic diseases, including type 2 diabetes and hypertension [31,32]. Other findings from *Tammemagi, et al*. suggest that comorbidities may account for nearly half of the survival disparities among AA and EA women with BCa [33] whereby hypertension alone is shown to account for 30% of the racial disparity in BCa survival [34]. Furthermore, 30% of BCa cases are attributed to modifiable risk factors, such as excess body weight, physical inactivity, and alcohol intake [35].

There is increasing concern regarding the release of several synthetic chemicals, categorized as potential environmental Endocrine-Disrupting Compounds (EDCs) or pollutant discharges into the environment due to increasing industrial and agricultural activities that can adversely affect human health [36]. Endocrine-disrupting compounds are exogenous compounds that interfere with hormonal action disrupting the endocrine system homeostasis and are recognized as relevant tumorigenic compounds in neoplasia, including BCa [37].

Drinking water is a significant and potential source of EDCs exposure, particularly for populations living near contaminated areas. Spatially, EDCS contamination in drinking water has been widespread at military sites, airports, industrial sites, and wastewater treatment plants, and these facilities are disproportionately located near low-income communities [38]. Additionally, exposure to EDCs from fast food packaging is especially relevant for AA women, as they have reported a higher frequency of fast-food intake than their EA counterparts [39]. One study discusses the importance of understanding the relationship between EDC exposure and breast cancer development, mainly to promote efforts to mitigate exposures and improve breast cancer disparities in socially disadvantaged populations, including AA women [40].

Endocrine-disrupting chemicals, including bisphenols and parabens, are correlated with the development of obesity, hypertension, and diabetes [41]. While the molecular mechanisms of EDCs are not fully elucidated, many EDCs can affect DNA integrity, with accumulating DNA damage, added to spontaneous replication errors if not corrected by the DNA repair system. They can cause

irreversible mutations, leading to the development of tumors and cancer progression. The current study aims to determine if there is an association between EDCs expression and BCa disparities. Using nationally representative data from the National Health and Nutrition Examination Survey (NHANES; 2009-2016), we examined the racial disparity in EDCs status and the prevalence of major comorbidities as related to BCa disparities.

Materials and Methods

Design, Setting, and Participant Selection

Data from the NHANES (2009 – 2016) was used in this study. The NHANES is an annual assessment of the health, functional, and nutritional status of a probability sample of non-institutionalized individuals living in the US [42]. Some subgroups of the US population, such as racial and ethnic minorities and low-income non-Hispanic Whites, are oversampled to ensure the statistics are reliable [42]. All NHANES participants provided signed informed consent. Women between the ages of 20 to 85 years who reported having been diagnosed with BCa were selected for inclusion in this study.

Statistical Analysis

All statistical analyses were performed in R version 3.5.0. Descriptive summaries of patient characteristics are presented as mean ± SD for continuous measures and frequency (%) for categorical measures. The 2-sample T-test was used to compare differences in mean levels of continuous outcomes between groups. When assumptions for normality fails, the Wilcoxon Rank Sum test was used to compare the distribution of Key variable will include patient characteristics, clinicopathological variables, and measures and genomic aberrations and comparison will be between the (i) AA and EA cohorts and (ii) BCa and normal controls. Chi-Square tests were employed for the comparison of difference in prevalence of categorical outcomes. All statistical tests were two-sided, at unadjusted significant levels (p) set at 0.05. Significant levels were adjusted for multiple comparisons using the Bonferroni method.

Results

Demographic and Clinical Characteristics

We studied data from 11765 women, 348 (3.0%) with BCa with mean age of 67.2 years, for which data on environmental phenols and parabens were available. Table 1a show the demographic and clinical characteristics by BCa status. Results showed that 27.0% of the population self-identified as EA, 16.5% were AA, and the rest, 29.8%, reported as other racial category. Most women assessed had income level of <$24,999.00 per annum, had >12th grade education and reported no physical activity. Table 1b compares age, BMI, and lipid profile between the BCa and normal cases. Results showed that women with BCa had significantly higher mean age than normal cases (67.2 versus 49.1 years old, p< 0.05), and a higher mean level of serum total cholesterol (199.8 versus 194.4 mg/dl). There were no significant differences in body weight, serum HDL, serum LDL, or serum triglycerides between the BCa and the normal cases.

Table 1: A. Characteristics of U.S. Women with and without Breast Cancer, National Health and Nutrition Examination Survey, 2009-2016. Reported values are unweighted sample counts-BCa- Breast Cancer Cases and Normal- non-Breast Cancer Cases. B. Age, weight, and lipid profile levels (mg/dl) in the female population ≥20 years of age with and without Breast cancer; NHANES 2009-2016.

Variables	Female Population (n = 11765)	
	BCa	Normal
Total Population (n, %)	(348, 3.0%)	(11417, 97.0%)
Age (years, %)		
20-49	25 (0.2%)	5962 (50.7%)
50-69	149 (1.3%)	3638 (30.9%)
≥70	174 (1.5%)	1817 (15.4%)
BMI (kg/m^2, %)		
≤25	84 (0.7%)	3365 (28.6%)
26 to 30	98 (0.8%)	2981 (25.3%)
≥30	148 (1.3%)	4538 (38.6%)
Race/Ethnicity (*n*, %)		
Non-Hispanic White	132 (1.1%)	3043 (25.9%)
Non-Hispanic Black	41 (0.4%)	1897 (16.1%)
Others	80 (0.7%)	3428 (29.1%)
Income (Annual Family Income) (*n*, %)		
≤$24,999	109 (0.9%)	3857 (32.8%)
$25,000 to $ $54,999	107 (0.9%)	3082 (26.2%)
$55,000 to $74,999	24 (0.2%)	1086 (9.2%)

≥$74,999	72 (0.6%)	2461 (20.9%)
Education (*n*, %)		
<9th grade	37 (0.3%)	1202 (10.2%)
9th to 12th grade	107 (0.9%)	3902 (33.2%)
>12th grade	203 (1.7%)	6296 (53.5%)
Physical Activity (*n*, %)		
Yes	24 (0.2%)	1239 (10.5%)
No	324 (2.8%)	10175 (86.5%)

Variables	Female Population (n = 11765)		
	BCa	Normal	p-Values
Total Population (*n*, %)	(348, 3.0%)	(11417, 97.0%)	
Age (years; mean ± se)	67.2 ± 0.6	49.1 ± 0.2	<0.05
Bodyweight (kg; mean ± se)	76.7 ± 1.1	76.3 ± 0.2	0.74
Serum Total Cholesterol (mg/dL, mean ± se)	199.8 ± 2.3	194.4 ± 0.4	<0.05
Serum HDL (mg/dL, mean ± se)	58.8 ± 1.0	57.3 ± 0.2	0.14
Serum LDL (mg/dL, mean ± se)	116.5 ± 2.8	113.4 ± 0.5	0.29
Serum Triglycerides (mg/dL, mean ± se)	122.8 ± 5.1	113.4 ± 1.4	0.23

Investigating Endocrine Disruptor Compounds and Breast Cancer Disparities

We studied ten environmental endocrine disruptor compounds belonging to the phenols, parabens, and phthalates families from the NHANES laboratory dataset. Given the large range of concentration values, we used the median instead of the mean concentration in the analysis. A Wilcoxon rank-sum test of the median urinary concentrations of the ten metabolites was compared between the BCa cases and normal cases (Table 2a). We further expressed urinary paraben and EP concentrations relative to urinary creatinine concentration to correct for urine dilution, as previously done by *Parada, et al*. [43]. The BCa case exhibited higher median creatinine-corrected urinary concentrations for Ethylparaben and Mono-(2-ethyl-5-hydroxyhexyl) phthalate than the normal case. We did not find a significant difference in the sample ranking between BCa and normal cases for the other eight compounds.

Table 2: A. Endocrine Disruptors Compounds and Breast cancer risk: Wilcoxon rank-sum test for significant difference between BCa vs. Non-BCa urinary biomarker concentrations. Median uncorrected urinary concentrations (ug/l) and median creatine-corrected urinary concentrations for ten environmental endocrine metabolites are shown p<0.05, indicates statistical significance. B: Correlation of endocrine disruptor compounds and cholesterol. Pearson's Correlation Coefficient (r), and P-value for significance in Pearson's correlation.

			Median Uncorrected Urinary Concentrations (µg/l)			Median Creatinine-Corrected Urinary Concentrations (µg/g creatinine)		
Biomarker	LOD	n (%) <LOD	BCa (n=95)	Normal (n=3463)	*p*	BCa (n=95)	Normal (n=3463)	*p*
Benzophenone-3	0.4	108 (3.0)	21	18.4	0.58	23.1	20.3	0.63
Bisphenol A	0.4	466 (13.1)	1.3	1.3	0.81	1.6	1.5	0.65
Triclosan	2.3	1086 (30.5)	6.9	6.3	0.86	7.6	7.8	0.85
Methyl paraben	1	21 (0.6)	92	108.3	0.52	110.4	137.7	0.47
Ethyl paraben	1	1430 (40.2)	1.2	1.9	0.08	1.8	2.8	0.03*
Propyl paraben	0.2	88 (2.5)	15.5	18.7	0.16	16.8	23.7	0.23
Mono-ethyl Phthalate	1.2	9 (0.3)	72.1	49	0.16	68.6	53.7	0.13
Mono-n-butyl phthalate	0.4	96 (2.7)	13.1	11.9	0.6	12.6	12.6	0.32
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	0.4	16 (0.4)	8.6	7.4	0.22	9.3	8.3	0.04*

Mono-isobutyl phthalate	0.8	29 (0.8)	7.1	8	0.47	7.8	8.6	0.16
Creatinine						80	90	0.02

Pearson's correlation was applied to evaluate the relationship between each selected covariate and each compound concentration (Table 2b). A statistically significant negative correlation was found between Bisphenol A concentration and HDL concentration (r= -0.23, p=0.03), and a statistically significant positive correlation was found between creatinine concentration and weight (kg) (r=0.11, p=0.046). Overall, higher Bisphenol A negatively correlated with lower high-density cholesterol levels.

	Age		Weight		Total Cholesterol		HDL		TRYGLY		LDL	
	r	p	r	p	r	p	r	p	r	p	r	p
Analyte												
Benzophenone-3	-0.04	0.71	0.009	0.94	-0.1	0.35	0.04	0.72	-0.21	0.18	-0.14	0.36
Bisphenol A	0.12	0.26	-0.07	0.51	-0.13	0.22	-0.23	*0.03	-0.13	0.43	0.11	0.48
Triclosan	0.13	0.19	0.16	0.12	0.11	0.33	0.04	0.69	0.012	0.94	0.095	0.55
Methyl paraben	-0.11	0.3	0.063	0.55	0.13	0.25	-0.13	0.22	0.026	0.87	-0.03	0.84
Ethylparaben	-0.01	0.95	-0.12	0.23	0.08	0.49	0.16	0.15	0.076	0.63	-0.13	0.41
Propylparaben	-0.1	0.35	0.059	0.57	0.12	0.29	-0.16	0.15	0.059	0.71	-0.03	0.84
MEP	0.12	0.24	0.022	0.83	-0.03	0.79	-0.13	0.22	0.089	0.58	-0.05	0.74
MBP	0.14	0.19	0.044	0.68	-0.11	0.32	-0.12	0.26	-0.15	0.34	0.055	0.73
MEHP	-0.02	0.88	0.019	0.85	-0.08	0.49	0.021	0.85	-0.14	0.36	-0.02	0.91
MIBP	0.1	0.36	-0.02	0.85	-0.11	0.3	0.11	0.32	-0.03	0.85	0.21	0.19
Creatinine	-0.05	0.35	0.11	*0.046	-0.05	0.38	-0.05	0.36	-0.05	0.57	-0.05	0.51

To assess the difference in distribution of EDCs metabolite concentration in AA and EA populations, we carried out Wilcoxon rank-sum test with creatinine-corrected urinary biomarker concentrations, separately for BCa and normal cases (Table 3). Among women without BCa, a statistically significant difference in sample rankings of the urinary phthalate concentrations of AA versus EA individuals was found for all analytes examined except MEHP. However, there was no significant difference in the EDCs metabolites concentrations between the AA and EA BCa cases. This could be attributed to limitations with a small sample size.

Table 3: Relative expression of endocrine disruptor compounds in normal and Breast cancer cases comparing non-Hispanic Blacks (AA) versus non-Hispanic Whites (EA). Wilcoxon rank-sum test for significance difference between AA versus EA. Creatinine-corrected urinary biomarker concentrations for BCa and Non-BCa groups. p<0.05 indicates statistical significance.

	BCa			Normal		
	AA	EA		AA	EA	
Total Population	**(n=11)**	**(n=27)**		**(n=633)**	**(n=984)**	
Analyte (g/mL)	**median**		**p**	**median**		**p**
Benzophenone-3	15.3	40	0.22	8.59	30.92	<0.05
Bisphenol-A	1.02	1.56	0.57	1.29	1.43	<0.05
Triclosan	3.33	9.56	0.34	4.53	7.6	<0.05
Methyl paraben	89.8	59.66	0.31	177.06	102.91	<0.05
Ethyl paraben	1.45	2.09	0.95	2.08	3.36	<0.05
Propylparaben	9.94	5.13	0.78	23.98	19.77	<0.05
MEP	117.76	32.87	0.07	64.64	34.95	<0.05
MBP	7.72	11.67	0.49	11.17	10.12	<0.05
MEHP	5	8.2	0.28	6.78	7.03	0.25
MIBP	7.5	6.89	0.47	8.62	7.34	<0.05
Creatinine	91.50 (n=38)	70.50 (n=122)		126.0 (n=1783)	81.00 (n=2860)	

Investigating Co-Morbidities and Breast Cancer Disparities

Comorbidities lead to worse quality of life and decreased survival in patients with BCa. We examined the racial disparity in the prevalence of major comorbidities as a proxy for health status. In Figure 1, we assessed the prevalence of hypertension, diabetes, and obesity risk for women ≥20 years of age with breast cancer in the NHANES dataset 2009-2016. We observed that compared with EA women with BCa, AA women had a higher prevalence of hypertension (stage 1= 21%, stage 2= 21.4%) versus (stage 1= 20.7%, stage 2= 15.7%, respectively). On the other hand, a higher proportion of EA women than AA women had normal blood pressure (40.1% versus 33.1%) whereas the prevalence of elevated blood pressure was slightly higher in EA women than AA women (16.8% vs. 15.7%, respectively). Similarly, a higher incidence of pre-diabetes and diabetes were observed in AA women than EA women (pre-diabetes = 32.0%, diabetes = 11.8%) versus (pre-diabetes= 21.7%, diabetes= 7.2%), respectively. The prevalence of women without diabetes was higher in EA women than AA women (68.2% vs. 48.9%, respectively). Finally, the prevalence of obesity was higher in AA women than EA women (47.0% vs. 36.0%, respectively). Whereas the prevalence of overweight women was higher in EA than AA (33.4% vs. 27.8%, respectively) and prevalence of women with normal body weight was higher in EA than AA (28.2% vs. 22.3%, respectively).

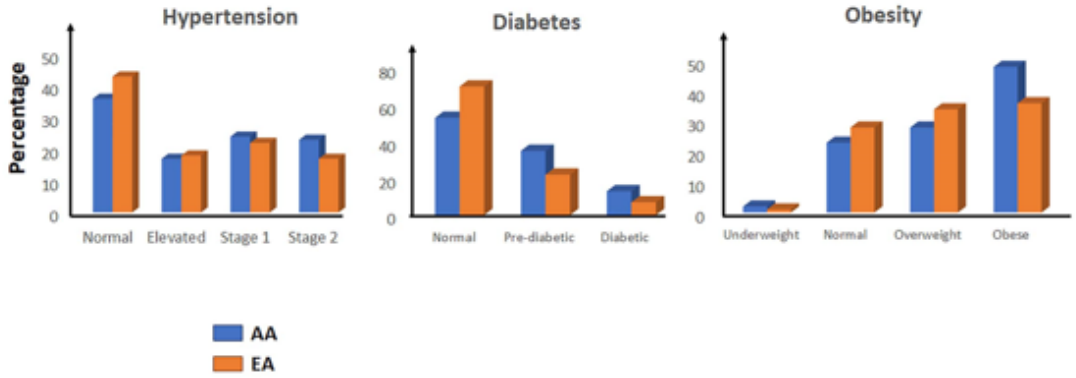

Figure 1: Investigating co-morbidities and breast cancer disparities in the NHANES 2009-2016 in African American (AA) and European American (EA) women ≥20 years of age. Incidence of Hypertension, diabetes and obesity are shown as weighted total of the estimated population in NHANES 2009-2016.

Discussion

This study utilized a risk assessment approach to demonstrate the association of environmental exposures, particularly phthalate of the EDCs in urine samples, along with BCa disparities in US women (NHANES data 2009- 2016). Two of the 10 EDCs examined, Ethylparaben and Mono-(2-ethyl-5-hydroxyhexyl) phthalate, showed significant differences in expression between BCa cases compared with normal cases after correcting for urinary creatinine concentration suggesting a potential role of these EDCs with BCa risk. However, we did not observe significant racial differences in the median concentration of these 10 EDCs in the BCa cases from AA compared with EA; this could be due to the small population sizes analyzed. On the other hand, 9 out of the 10 EDCs showed significant differences in the median expression levels between the normal cases from AA compared with EA women. Several reports indicate a positive association of higher urinary expression of EDCs, including MEP and parabens, with precocious puberty in girls [44,45]. While there are few studies on the association of EDCS, precocious puberty, and BCa disparities, one report suggests that metabolic disruption concomitants of abdominal-type obesity could play a role in promoting mammary carcinogenesis at a young age, mainly if genetic predisposition is present [46]. The potential role of EDCs in BCa disparities is further supported by our analysis of three types of co-morbidities as proxies for health status among BCa survivors: diabetes, irrespective of type 1 or type 2, hypertension, and obesity. Non-Hispanic Blacks, compared with EA women with BCa, showed a higher prevalence of all three co-morbidities and may contribute to BCa disparities. Our observation is consistent with previous reports that have observed disparities in paraben exposure between different racial/ethnic groups. For example, urinary levels of methyl and propyl paraben are higher in AA and Mexican American women than in EA women [47]. Furthermore, concentrations of parabens (and other EDCs) are higher in AA women and Hispanic/Latinx women before age 11 compared to age-matched EA women [48]. In a recent study, parabens were shown to have disproportionate exposure in AA women and BCa-associated activity at biologically relevant doses [49]. Our study is the first to investigate the role of EDCS and co-morbidities and BCa disparities in USA African American versus European American women. Our findings contribute to the growing body of literature regarding the intersection of endocrine disruptors, co-morbidities factors, and BCa risk and potentially BCa disparities.

Strengths

The current study provides numerous strengths to previous literature and the application of national US-based analyses. By building on the continuous NHANES cycles (2009-2016) and combining several processes, the current study allows for increased sample size, and statistical power, as well as generalizability to adult female cancer survivor populations within the US for those racial/ethnic minorities.

Limitations

These findings should be interpreted considering their limitations. Some variables utilized were self-reported (via the interview portion of NHANES cycles), allowing for misclassification and recall bias. The current findings should also be interpreted with consideration that our stratification of comorbidity reduced subgroup sample sizes.

Declaration

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Availability of Data and Materials

The NHANES (2009-2016) dataset is publicly available. The NHANES protocol was reviewed and approved by the National Center for Health Statistics Research Ethics Review Board (42). All NHANES participants provided signed informed consent. Non-Hispanic Black and non-Hispanic White women between the ages of 18 to 85 who reported having been diagnosed with breast cancer were selected for inclusion in this study.

Code Availability

Not applicable.

Author's Contributions

Nuha Mohammad, David Kwabi-Addo, and Kwasi Yeboah-Afihene carried out the data science portion of the studies. Qingguo Wang carried out a biostatistical and bioinformatics analysis of the project. John Kwagyan and Kwasi Yeboah-Afihene contributed to the conceptualization of the project. Bernard Kwabi-Addo contributed to the manuscript's conceptualization, study design, and writing.

Ethics Approval and Consent to Participate

We used publicly available NHANES dataset. The NHANES Institutional Review Board collected patient samples and data in accordance with the guidelines of the Declaration of Helsinki approved protocols.

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Conflict of Interest/Competing interests

The authors declare no conflict of interest or any relevant competing financial interests.

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