HHS Public Access

Author manuscript

*Breast Cancer Res Treat*. Author manuscript; available in PMC 2023 June 12.

Published in final edited form as:

*Breast Cancer Res Treat*. 2021 July ; 188(1): 283–293. doi:10.1007/s10549-021-06158-y.

# Mediation analysis of racial disparities in triple-negative breast cancer incidence among postmenopausal women

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## Abstract

**Background—**Triple-negative breast cancer (TNBC) is disproportionately higher in Black women relative to White women. The objective of this study was to examine to what extent

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**Author contributions** JL contributed to the study concept and design, acquisition of data, data management, analysis and interpretation of data, and drafting of the manuscript. CHK, MH, and JWW contributed to the study concept and design, interpretation of data, and critical review and revision of the manuscript. XC and FW contributed to analysis of data. All others (AHS, NL, FT, NS, LQ, TDC, RA) contributed to interpretation of data and critical review and revision of the manuscript. JL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10549-021-06158-y.

**Availability of data and materials** Data are available from the Women's Health Initiative upon reasonable request (www.whi.org), and please contact helpdesk@whi.org.

**Conflict of interest** The authors declare no potential conflicts of interest.

the association between race/ethnicity and risk of TNBC is mediated by potentially modifiable factors.

**Methods—**A total of 128,623 Black and White women aged 50–79 years from the Women's Health Initiative were followed for a mean of 15.8 years. 643 incident TNBC cases (92 Black women and 551 White women) were confirmed by medical record review. Mediation analyses were conducted using an approach under a counterfactual framework.

**Results—**Black women had approximately twofold higher risk of TNBC compared with white women (HR = 1.93, 95% CI 1.52–2.45). We observed that 48% of the racial disparity was mediated by metabolic dysfunction defined by having 3 or more cardiometabolic risk factors including elevated waist circumference, having history of diabetes, high cholesterol and hypertension. The racial disparity was not significantly mediated by other factors studied, including socioeconomic, lifestyle or reproductive factors.

**Conclusion—**Our study observed that approximately half of the racial disparity between postmenopausal Black and White women in TNBC incidence was driven by metabolic dysfunction.

### Keywords

Mediation analysis; Triple-negative breast cancer; Racial disparities; Modifiable risk factors

## Background

Triple-negative breast cancer (TNBC), characterized by negative receptors for estrogen, progesterone and human epidermal growth factor receptor-2, is an aggressive subtype of breast cancer, accounting for about 15–20% of all breast cancer cases in the USA [1]. TNBC incidence rates are disproportionately higher in Black women relative to White women [2], which partially contributes to lower breast cancer survival among Black compared with White women, one of the striking racial disparities in oncology. Previous studies have uncovered epidemiological risk factors like premenopausal or younger age at diagnosis, and presence of BRCA1 associated with TNBC [3] indicating genetic influence. However, studies have reported that BRCA1 is less prevalent in Black women relative to White women [4]. Thus, the racial disparity may be unlikely to be primarily driven by the most common cause of hereditary breast cancer.

Studies have suggested that racial disparities in the distribution of breast cancer subtypes may be attributable to psychosocial stress that Black women are more likely to experience [5, 6]. Chronic exposure to social and economic stress can lead to a wide array of health conditions [7]. For example, stress is known to mediate insulin resistance, central fat deposition, hypertension and immune dysfunction in humans [8]. It is also possible that the effects of stress may differ on breast cancer subtypes given the known effects of stress on the endocrine system [6].

Furthermore, stress may also trigger unhealthy behavioral responses such as lack of exercise or poor dietary lifestyle, which leads to obesity and other metabolic disorders [9], and then results in an increased risk of cancer. Studies have shown that both premenopausal

and postmenopausal women with increased waist-to-hip ratio (WHR) had higher risk of developing basal-like TNBC in comparison to women with lower WHR [10, 11]. Notably, elevated abdominal obesity is an integral component of the metabolic syndrome characterized by a cluster of cardiometabolic risk factors (including abdominal obesity, insulin resistance, high blood pressure, and high cholesterol). As both abdominal obesity and metabolic syndrome are more common among Black women than White women, it is possible that metabolic syndrome and its components may be one of the drivers for TNBC in Black women.

Collectively, according to the stress-based hypothesis [5, 6], many related risk factors, including socioeconomic status, lifestyle factors, and metabolic dysfunction may influence the racial disparity; however, few studies have performed a formal mediation analysis to quantify the extent to which the disparity may be explained by these potential mediators. We identified only one study examining mediation of racial and ethnic disparities in estrogen/progesterone receptor-negative breast cancer by socioeconomic position and reproductive factors [12]. However, this was a cross-sectional study among breast cancer patients, and outcomes were based on the proportion of ER/PR-negative breast cancer among total breast cancer cases rather than TNBC incidence.

In the current study, we used the Women's Health Initiative, a large and diverse prospective study, to test whether the racial and ethnic disparity in TNBC may be mediated by stress-related factors, including socioeconomic status, lifestyle and metabolic dysfunction (including abdominal obesity, history of diabetes, hypertension and high cholesterol). We also consider reproductive history, since some studies have suggested that the higher incidence of TNBC in Black women may be partially explained by their higher parity and lower prevalence of breastfeeding relative to White women [13-16]. Understanding these relative contributions is essential to understand the higher incidence of TNBC arising in Black women to reduce this disparity.

## Methods

### Women's Health Initiative (WHI)

WHI is a large prospective study among postmenopausal women in the USA [17]. Details of the study's design and recruitment are described elsewhere [18]. Briefly, 161,808 women ages 50–79 were recruited from 40 clinical centers throughout the USA between 1993 and 1998. The WHI includes four clinical trials (CT) and an observational study (OS). All participants in the WHI were followed up annually in the OS, and every 6 months in the CT though 2005 and then annually after 2005. The WHI study was approved by Institutional Review Boards at all 40 clinical centers and at the coordinating center. All participants provided written informed consent.

### Study population

We only included Black and Non-Hispanic White women (we call it White hereafter) from the WHI in the study, because of the small number of TNBC cases in other minority groups. 148,159 women (14,618 Black and 133,541 White) were included. The following

participants were excluded for this analysis: 11,767 women who had a history of cancer (except non-melanoma skin cancer) at baseline; 449 who had no follow-up information; and 5203 women who had missing information on major covariates, including education, alcohol use, smoking, parity, waist circumference, or socioeconomic status, and 2117 women with missing estrogen, progesterone, and HER2 receptor status. After exclusions, 128,623 women (12,345 Black and 116,278 White) remained for further analysis.

## Exposure

**Race/ethnicity—**Self-reported information on race/ethnicity in the WHI was collected at baseline. It was categorized as American Indian or Alaskan Native, Asian or Pacific Islander, Black, Hispanic/Latina, non-Hispanic White, or other. Only Black or White women were considered in this study.

## Outcome

The primary outcome was the (first) incidence of TNBC, defined as estrogen, progesterone, and HER2 receptor-negative newly diagnosed breast cancer occurring after baseline enrollment until March 1, 2019. In the WHI, initial cancer reports were identified by self-administered questionnaires. All self-reported cancer cases were then verified by obtaining medical records and pathology reports. All records were adjudicated centrally by trained physicians and coded with more detailed tumor characteristics based on the Surveillance, Epidemiology and End Results (SEER) coding system.

## Potential confounders or mediators

In addition to age, family history of breast cancer, and participation in different WHI study subcohorts (observational study or clinical trials and different treatment assignments for all 4 clinical trials) we adjusted for other potential confounders and/or mediators measured at baseline including socioeconomic status, health behaviors, metabolic dysfunction and reproductive factors.

**Socioeconomic status (SES)—**Socioeconomic status (SES) was assessed at baseline by a combination of education, annual family income and neighborhood socioeconomic status (NSES). Neighborhood socioeconomic status (NSES) is a previously derived WHI variables measured at the census tract level and obtained from six variables collected in the 2000 Census, including (1) percentage of adults older than 25 with less than a high school education; (2) percentage of males above age 16 who are unemployed; (3) percentage of households with an income below the poverty line; (4) percentage of households receiving public assistance; (5) percentage of female-headed households with children; and (6) the median household income [19]. We assigned 1 point for education being high school degree or lower, 1 point for annual family income < $20,000 (which approximates the federal poverty level for households with one or two persons), and 1 point for NSES lower than 20% of the population, and summed for a total score from 0 to 3. A higher score indicates low SES. Since few women were in the group of 3, we collapsed scores of 2 and 3.

**Health behaviors—**Health behaviors included smoking status (never, former, current), alcohol intake, physical activity and diet quality. According to the “Dietary Guidelines for

Americans 2015–2020" [20], moderate drinking is up to 1 drink per day for women; we categorized women who drank 7 or more drinks per week as heavy drinkers. Physical activity was determined by asking participants how often they were currently participating in different types of physical activity (mild, moderate, and strenuous or very hard exercise) and the frequency and duration of each exercise session. A categorical variable of episodes per week of moderate and strenuous recreational physical activity (≥ 20 min duration) was derived. Four or more episodes per week was defined as physically active. Diet quality was derived from the Food Frequency Questionnaire to obtain the Healthy Eating Index (HEI) score based on the 2015 Dietary Guidelines for Americans [21].

**Metabolic dysfunction—**Metabolic dysfunction was assessed by four cardiometabolic risk factors, including elevated waist circumference (WC), self-reported history of diabetes, high cholesterol, and hypertension. Waist circumference was measured at the natural waist or narrowest part of the torso to the nearest 0.5 cm. High waist circumference was defined as ≥ 88 cm which is the suggested threshold used to define metabolic syndrome for women in the US [22]. History of diabetes was based on validated self-report of physician-diagnosed diabetes. High cholesterol was based on a positive response to a question "has a doctor told you that you have high cholesterol requiring pills?" Hypertension was defined as systolic BP > 130 mg Hg and/or diastolic BP > 85 mm Hg [22] or self-reported use of medications to treat hypertension at baseline. We summed the four components with a total score from 0 to 4. A higher score indicates higher metabolic dysfunction. A same metabolic dysfunction score was used in prior literature [23, 24]. We collapsed scores of 3 and 4 due to a small sample size in the score of 4.

**Reproductive history and hormone use—**Information on parity, breastfeeding, age at first birth and age of menopause was collected at baseline by self-administered questionnaires. Parity was categorized as number of term pregnancies (0, 1, 2, 3, 4, 5 or more). We estimated duration of breastfeeding in months per child using the total months breastfed divided by the number of children. Information on lifetime use of menopausal hormones at baseline was obtained using structured questionnaires and charts displaying colored photographs of various hormone preparations.

## Statistical analysis

Baseline demographic and behavioral characteristics were first compared between Black and White women. Differences were assessed by chi-square tests for categorical covariates and t tests for continuous variables.

Cox proportional hazards regression models were used to evaluate the association of race/ethnicity (Black vs White), SES, lifestyle factors, metabolic dysfunction, and reproductive history with TNBC risk. Survival time was defined from baseline to date of diagnosis of TNBC, date of diagnosis of other types of breast cancer, date of death, loss to follow-up, and March 1, 2019, whichever came first. Events in the study are a diagnosis of TNBC and all other events are were censored. In the multivariable-adjusted models. Different WHI study subcohorts (observational study or clinical trials and different treatment assignments for all

4 clinical trials) was stratified. All exposure and potential mediators were mutually adjusted for each other, in addition to age and family history of breast cancer [25].

A formal mediation analysis was conducted to examine whether and to what extent the association between race/ethnicity and risk of TNBC was mediated by SES, physical activity, metabolic dysfunction, and reproductive factors. The mediation analysis was performed using the approach developed by Valeri and VanderWeele under the counterfactual framework [26, 27]. The counterfactual framework allows for definitions of direct and indirect effects and for decomposition of a total effect into direct and indirect effects even in the presence of exposure-mediator interaction. In the mediation analysis, we adjusted for age, family history of breast cancer, different WHI study subcohorts (observational study or clinical trials and different treatment assignments for all 4 clinical trials), SES, physical activity, metabolic dysfunction, and parity except for the variable being assessed as a mediator. A SAS macro (%mediation) was used to estimate these effects [27]. The 95% CI for the proportion mediated are based on 5000 bootstrap samples (equal tail 95% CI) [28].

The natural direct effect was defined as the hazard ratio of TNBC for Black vs White women when the mediator was kept at the level it would have taken for White women. The natural indirect effect was defined as an effect on average for Black women when the mediator was changed from the level it would take when exposure changed from Black to White. The total effect (TE) was defined as the overall effect comparing Black with White women [26, 27]. All the effects were estimated after adjusting for all potential confounders.

## Results

Compared with White women, Black women were more likely to be younger, have higher BMI, higher waist circumference, lower family history of breast cancer, be physically inactive, less educated, have low annual family income, low neighborhood SES, smoke more, drink less alcohol, and have lower diet quality. They were more likely to be nulliparous or have 5 or more term pregnancies, have no or lower breastfeeding, have higher history of diabetes, hypertension and high cholesterol, and less likely to use exogenous hormones. For the two derived variables, Black women were more likely to have lower SES and more cardiometabolic risk factors than White women (Table 1).

As of March 1, 2019, 643 TNBC cases (92 Black women and 551 White women) were observed among 128,623 women over a mean follow-up of 15.8 years. Black women had approximately twofold higher risk of TNBC compared with White women (HR = 1.93, 95% CI 1.52–2.45) (Table 2). Family history of breast cancer (HR = 1.56, 95% CI 1.30–1.86), and having 2 or more children were significantly associated with higher risk of TNBC. Among parous women, we did not observe a significant linear trend for number of term pregnancies. Longer duration of breastfeeding appeared to have lower risk of TNBC; however, the p value for the trend test was not significant. Greater amount of physical activity was associated with lower risk of TNBC (HR = 0.79, 95% CI 0.65–0.95). SES was not associated with risk of TNBC. Having more cardiometabolic risk factors appeared to have higher risk of TNBC; however, $p$ value for the trend test did not reach significance

(Table 2). Other factors, including smoking, alcohol consumption, diet quality, and hormone therapy use were not significantly associated with risk of TNBC (Supplemental Table 1). We also examined individual anthropometric measures in relation to TNBC risk, including waist circumference in continuous or in categorical (< 88 cm, ≥ 88), BMI in continuous or in categorical (normal: BMI < 25 kg/m$^2$, overweight: 25– < 30, or obesity: ≥ 30), and WHR in continuous or in categorical (< 0.85, ≥ 0.85). None of them was significantly associated with risk of TNBC. We also examined other reproductive factors, including age at first birth and age of menopause, but did not find that any were associated with risk of TNBC (data not shown).

The association between race/ethnicity and risk of TNBC was significantly mediated by metabolic dysfunction with a mediated proportion of 48% when comparing having 3 or more cardiometabolic risk factors relative to no cardiometabolic risk factor. We did not observe that the racial disparity was significantly mediated by physical activity, or other health behaviors including smoking, alcohol intake or diet quality (data not shown). Although the natural indirect effect by breastfeeding was statistically significant, the proportion mediated by breastfeeding was only 3%. For parity, we observed that the natural direct effect and natural indirect effect were in opposite direction. This was because Black women were more likely to be nulliparous, which was associated with lower risk, and this led to direct and indirect effects that were in opposite directions. When the direct effect and indirect effect are in opposite direction, it is not meaningful to produce the proportion mediated. We also observed a similar pattern for SES, although the natural indirect effect was not significant (Table 3).

## Discussion

Our large prospective study showed that postmenopausal Black women had approximately twofold higher risk of TNBC compared with White women. Other factors significantly associated with risk of TNBC included family history of breast cancer, being parous and low physical activity. 48% of the racial disparity was mediated by metabolic dysfunction. However, we did not observe that the racial disparity was explained by other factors studied, including lifestyle, socioeconomic or reproductive factors.

Our observation of an approximately twofold higher risk of TNBC in Black women relative to White women is consistent with most previous reports [29, 30]. Previous studies have suggested that both genetic and environmental factors may influence the racial disparity [31]. Our data indicate that about half of the racial disparity was attributable to metabolic dysfunction defined by having 3 or more cardiometabolic risk factors. We adjusted for family history of breast cancer as a surrogate variable for genetic predisposition in our analysis but were unable to assess how the racial disparity was explained by genetic predisposition.

Our study was the first to perform a formal mediation analysis of racial disparities for TNBC in a prospective study. It is not surprising that we observed that 48% of the racial disparity in TNBC incidence was mediated by having metabolic dysfunction. The four factors selected to derive metabolic dysfunction were based on components for metabolic

syndrome, which is associated with increased risk of multiple chronic diseases, including cardiovascular disease and cancer. It has been proposed that metabolic syndrome or its components may play a pivotal role in the development of TNBC [32]. One study reported that metabolic syndrome was significantly more prevalent in TNBC patients compared to non-TNBC patients. In the same study, blood glucose, triglyceride and HDL levels also showed significant independent association with TNBC [33]. Several studies also observed that the odds of having a TNBC relative to other subtypes was greater for women with diabetes [34, 35], although the Carolina Breast Cancer Study reported no elevated prior history of diabetes in basal-like breast cancer compared to other breast cancer subtypes [11].

However, it is surprising that we did not observe that the racial disparity was significantly mediated by other factors such as SES, obesity alone, or risky behaviors. Among these factors, one common hypothesis is that obesity, especially central obesity, may be one of the drivers for TNBC in Black women [10, 11], as obesity is more common among Black women than White women. However, our data did not support the role of adiposity alone in driving higher TNBC in Black postmenopausal women, despite the finding that Black women were more likely to be obese.

We did not observe that the racial disparity was significantly mediated by other environmental factors, such as socioeconomic, lifestyle or reproductive factors. Although SES contributing to breast cancer survival disparities has been well-recognized, its role in racial disparities for TNBC incidence is unclear. A few studies have suggested that poverty may be associated with higher risk of TNBC [36, 37]; however, a study based on the SEER program reported that socioeconomic status was not associated with hormone receptor-negative tumors or TNBC [38].

Similarly to our study, other studies have shown that smoking and alcohol are not associated with risk of TNBC [39, 40]. We observed that physical activity was associated with lower risk of TNBC, which is in line with two other cohort studies [41, 42]. However, our data did not observe that the racial disparities in TNBC incidence was mediated by physical activity. This may be because the inverse association between physical activity and risk of TNBC was only observed in White women but not in Black women (Supplemental Table 1).

Given that the components of metabolic syndrome did not individually show independent association with the risk of TNBC, it has been suggested that possible synergistic interactions between the various metabolic disorders (such as elevated blood glucose, dyslipidemia and hyperinsulinemia) may play a pivotal role in carcinogenesis [33]. Future studies are needed to understand how the altered intracellular and intercellular signaling in metabolic syndrome impacts the molecular networking of TNBC.

Reproductive factors, such as multiparity, have been shown to protect against ER/PR-positive breast cancer but may be positively associated with ER/PR-negative tumors [11, 43]. Similarly, our data observed that parous women or women who had 2 or more term pregnancies had higher risk of TNBC compared with nulliparous women. However, despite the finding that Black women were more likely to have 5 or more term pregnancies among parous women, they were also more likely to be nulliparous women in our data, which was

associated with lower risk of TNBC. Thus, our data did not support that the racial disparities of TNBC were mediated by parity. Long duration of breastfeeding appeared to be associated with lower risk of TNBC, and Black women were less likely to have long duration of breastfeeding. However, the proportion mediated by breastfeeding was only 3%, although the indirect effect via breastfeeding was significant.

The strengths of this study include the prospective design in a large diverse population with long follow-up, adjudicated outcomes, and availability of comprehensive potential confounders. However, several limitations need to be noted. First, our study only included postmenopausal women. Thus, our findings may not be generalized to premenopausal women. However, TNBC is more likely to be diagnosed among younger age women, especially for Black women. For example, Carey et al. from the Carolina Breast Cancer Study found that 39% of tumors diagnosed in premenopausal African American patients were TNBC [44], compared to only 15% of TNBC among overall breast cancer cases in the USA. Thus, further studies including premenopausal women are needed. Second, we lacked information on direct genetic predisposition. Studies have shown that pathogenic variants in several genes, such as those harboring BRCA mutations, are associated with TNBC, independent of family history [45, 46]. Thus, we are unable to assess the extent of the racial difference in TNBC that may be explained by genetic predisposition. Third, Black or White race/ethnicity was based on self-identification. It may not reflect true ancestral heritage but also an individual's societal and community ties.

In conclusion, our findings illustrate the importance of cardiometabolic risk factors in the disproportionately high risk of TNBC in postmenopausal Black women. Our findings suggest that prevention and efficient management of blood sugar, blood pressure, and dyslipidemia may substantially reduce the disparity.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. A short list of WHI investigators is in a supplemental file.

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**Table 1**

Baseline characteristics of participants between Black and non-Hispanic White participants

| Variable label | Overall *N* = 116,278 | Non-Hispanic White *N* = 116,278 | Black *N* = 12,345 |
|---|---|---|---|
| Age at screening | 63.2 ± 7.2 | 63.4 ± 7.2 | 61.4 ± 7.1 |
| Body-mass Index, kg/m$^2$ | 28.0 ± 5.9 | 27.6 ± 5.7 | 31.2 ± 6.7 |
| Waist, cm | 86.6 ± 13.8 | 86.0 ± 13.7 | 91.9 ± 14.1 |
| Family history of breast cancer | | | |
| No | 105,969 (82.4%) | 95,318 (82.0%) | 10,651 (86.3%) |
| Yes | 22,654 (17.6%) | 20,960 (18.0%) | 1694 (13.7%) |
| Physical activity | | | |
| 3 or less episodes/week | 96,233 (74.8%) | 85,911 (73.9%) | 10,322 (83.6%) |
| 4 or more episodes/week | 32,390 (25.2%) | 30,367 (26.1%) | 2023 (16.4%) |
| Education | | | |
| Below college degree | 76,528 (59.5%) | 68,614 (59.0%) | 7914 (64.1%) |
| College or higher | 52,095 (40.5%) | 47,664 (41.0%) | 4431 (35.9%) |
| Annual family income | | | |
| < $20,000 | 18,770 (15.5%) | 15,314 (14.0%) | 3456 (29.8%) |
| $20,000– < $50,000 | 54,799 (45.2%) | 49,872 (45.5%) | 4927 (42.5%) |
| $50,000– < $100,000 | 35,704 (29.5%) | 32,997 (30.1%) | 2707 (23.3%) |
| $100,000 or more | 11,950 (9.9%) | 11,434 (10.4%) | 516 (4.4%) |
| Neighborhood socioeconomic status (quintile) | | | |
| 0 | 23,342 (20.0%) | 16,127 (15.2%) | 7215 (69.2%) |
| 1 | 23,341 (20.0%) | 21,920 (20.6%) | 1421 (13.6%) |
| 2 | 23,342 (20.0%) | 22,629 (21.3%) | 713 (6.8%) |
| 3 | 23,341 (20.0%) | 22,733 (21.4%) | 608 (5.8%) |
| 4 | 23,341 (20.0%) | 22,865 (21.5%) | 476 (4.6%) |
| Smoking | | | |
| Never or former | 119,626 (93.0%) | 108,684 (93.5%) | 10,942 (88.6%) |
| Current | 8997 (7.0%) | 7594 (6.5%) | 1403 (11.4%) |
| Alcohol drink | | | |
| 6 or less drinks/week | 112,880 (87.8%) | 101,063 (86.9%) | 11,817 (95.7%) |

| Variable label | Overall *N* = 116,278 | Non-Hispanic White *N* = 116,278 | Black *N* = 12,345 |
|---|---|---|---|
| 7 or more drinks/week | 15,743 (12.2%) | 15,215 (13.1%) | 528 (4.3%) |
| Diet quality | 65.2 ± 10.4 | 65.5 ± 10.3 | 62.6 ± 10.8 |
| Reproductive factors | | | |
| Nulliparous women | 14,979 (11.6%) | 13,308 (11.4%) | 1671 (13.5%) |
| Parous women | 113,644 (88.4%) | 102,970 (88.6%) | 10,674 (86.5%) |
| Number of term pregnancies | | | |
| 1 | 11,136 (8.7%) | 9270 (8.0%) | 1866 (15.1%) |
| 2 | 32,356 (25.2%) | 29,500 (25.4%) | 2856 (23.1%) |
| 3 | 31,500 (24.5%) | 29,248 (25.2%) | 2252 (18.2%) |
| 4 | 19,786 (15.4%) | 18,290 (15.7%) | 1496 (12.1%) |
| 5 or more | 18,866 (14.7%) | 16,662 (14.3%) | 2204 (17.9%) |
| Breastfeeding per child | | | |
| No breastfeeding | 49,120 (38.2%) | 44,170 (38.0%) | 4950 (40.1%) |
| 1–3 months | 35,869 (27.9%) | 32,316 (27.8%) | 3553 (28.8%) |
| 4–6 months | 14,653 (11.4%) | 13,465 (11.6%) | 1188 (9.6%) |
| 6 months or more | 14,002 (10.9%) | 13,019 (11.2%) | 983 (8.0%) |
| History of diabetes | | | |
| No | 121,551 (94.6%) | 110,886 (95.4%) | 10,665 (86.5%) |
| Yes | 7002 (5.4%) | 5337 (4.6%) | 1665 (13.5%) |
| History of hypertension | | | |
| No | 85,767 (66.7%) | 80,121 (68.9%) | 5646 (45.7%) |
| Yes | 42,856 (33.3%) | 36,157 (31.1%) | 6699 (54.3%) |
| High cholesterol | | | |
| No | 104,515 (86.4%) | 94,662 (86.6%) | 9853 (84.5%) |
| Yes | 16,484 (13.6%) | 14,675 (13.4%) | 1809 (15.5%) |
| History of hormone therapy use | | | |
| None | 55,397 (43.1%) | 48,101 (41.4%) | 7296 (59.1%) |
| Estrogen alone | 38,589 (30.0%) | 34,948 (30.1%) | 3641 (29.5%) |
| Estrogen and progestin | 27,265 (21.2%) | 26,147 (22.5%) | 1118 (9.1%) |
| Mixed | 7372 (5.7%) | 7082 (6.1%) | 290 (2.3%) |
| Low socioeconomic status (SES)[a] | | | |

| Variable label | Overall *N* = 116,278 | Non-Hispanic White *N* = 116,278 | Black *N* = 12,345 |
|---|---|---|---|
| 0 | 78,074 (60.7%) | 74,345 (63.9%) | 3729 (30.2%) |
| 1 | 36,015 (28.0%) | 31,227 (26.9%) | 4788 (38.8%) |
| 2 | 14,534 (11.3%) | 10,706 (9.2%) | 3828 (31.0%) |
| Cardiometabolic risk factors[b] | | | |
| 0 | 51,335 (39.9%) | 48,849 (42.0%) | 2486 (20.1%) |
| 1 | 44,078 (34.3%) | 39,798 (34.2%) | 4280 (34.7%) |
| 2 | 24,831 (19.3%) | 20,972 (18.0%) | 3859 (31.3%) |
| 3 | 8379 (6.5%) | 6659 (5.7%) | 1720 (13.9%) |

Values expressed as *n*(%) for categorical variables, mean ± standard deviation for continuous variables. Difference tests between Black and White women were based on Chi-square test for categorical variables and *T*-test for continuous variables. All comparisons were significant with all *p*-values < 0.0001

[a]We assigned 1 point for education being high school degree or lower, 1 point for annual family income < $20,000, and 1 point for NSES lower than 20% of the population, and summed for a total score from 0 to 3; scores of 2 and 3 were collapsed. A higher score indicates low SES

[b]Metabolic dysfunction was assessed by four cardiometabolic risk factors, including elevated WC, self-reported history of diabetes, high cholesterol, and hypertension. We summed the four components with a total score from 0 to 4. A higher score indicates higher metabolic dysfunction. We collapsed scores of 3 and 4 due to a small sample size in the score of 4

## Table 2

Associations between race/ethnicity, socioeconomic status, anthropometrics, reproductive history and risk of TNBC

| | Cases | Multivariable-adjusted model[a] |
|---|---|---|
| Race/ethnicity | | |
| Non-Hispanic White | 551 | 1 |
| Black | 92 | 1.93 (1.52–2.45) |
| Family history of breast cancer | | |
| No | 489 | 1 |
| Yes | 159 | 1.56 (1.30–1.86) |
| Physical activity[b] | | |
| Exercises 3 or less episodes per week | 502 | 1 |
| Exercises 4 or more episodes per week | 141 | 0.79 (0.65–0.96) |
| Reproductive history | | |
| Parity | | |
| 0 | 53 | 1 |
| 1 | 47 | 1.18 (0.79–1.76) |
| 2 | 184 | 1.59 (1.16–2.18) |
| 3 | 157 | 1.44 (1.04–1.99) |
| 4 | 97 | 1.41 (0.99–2.00) |
| 5 or more | 105 | 1.63 (1.15–2.32) |
| P for trends among parous women | 590 | 0.38 |
| Breastfeeding per child among parous women | | |
| No breastfeeding | 252 | 1 |
| 1–3 months | 199 | 1.07 (0.88–1.29) |
| 4–6 months | 77 | 0.99 (0.77–1.28) |
| 6 months or more | 62 | 0.82 (0.62–1.09) |
| *P* value for trends | 590 | 0.26 |
| Low socioeconomic status (SES)[c] | | |
| 0 | 393 | 1 |
| 1 | 193 | 1.06 (0.89–1.27) |
| 2 | 57 | 0.80 (0.60–1.07) |
| *P* value for trend | | 0.35 |
| Cardiometabolic risk factors[d] | | |
| 0 | 270 | 1 |
| 1 | 192 | 0.85 (0.71–1.03) |
| 2 | 133 | 1.08 (0.87–1.34) |
| 3 | 48 | 1.27 (0.93–1.74) |
| *P* value for trend | | 0.25 |

[a]All the variables listed in the table were mutually adjusted for each other in addition to adjustment for age and stratification on different WHI study subcohorts (observational study or clinical trials and different treatment assignments for all 4 clinical trials)

[b] Physical active was defined as having exercises 4 or more episodes per week

[c] We assigned 1 point for education being high school degree or lower, 1 point for annual family income < $20,000, and 1 point for NSES lower than 20% of the population, and summed for a total score from 0 to 3; scores of 2 and 3 were collapsed. A higher score indicates low SES

[d] Metabolic dysfunction was assessed by four cardiometabolic risk factors, including elevated WC, self-reported history of diabetes, high cholesterol, and hypertension. We summed the four components with a total score from 0 to 4. A higher score indicates higher metabolic dysfunction. We collapsed scores of 3 and 4 due to a small sample size in the score of 4

**Table 3**

Mediation analysis of racial disparities for TNBC by socioeconomic status, family history, physical activity, anthropometrics and reproductive history

| | Estimate | 95% CI lower limit | 95% CI upper limit | Proportion mediated (95% CI) |
|---|---|---|---|---|
| Cardiometabolic risk factors[a] (3 vs 0) | | | | 0.48 (0.17–1.25) |
| Natural direct effect | 1.40 | 0.89 | 2.19 | |
| Natural indirect effect | 1.26 | 1.01 | 1.58 | |
| Total effect | 1.76 | 1.19 | 2.59 | |
| Physical activity | | | | |
| Natural direct effect | 1.94 | 1.53 | 2.46 | _*c* |
| Natural indirect effect | 1.00 | 0.98 | 1.02 | |
| Total effect | 1.94 | 1.53 | 2.45 | _*c* |
| Parity | | | | |
| Natural direct effect | 1.99 | 1.56 | 2.54 | |
| Natural indirect effect | 0.95 | 0.92 | 0.98 | |
| Total effect | 1.89 | 1.48 | 2.42 | |
| Breastfeeding among parous women (≥ 6 months per child) | | | | 0.03 (0.01–0.04) |
| Natural direct effect | 1.97 | 1.55 | 2.52 | |
| Natural indirect effect | 1.01 | 1.00 | 1.02 | |
| Total effect | 2.00 | 1.57 | 2.55 | _*c* |
| Low socioeconomic status (SES) (2 vs 0)[b] | | | | |
| Natural direct effect | 2.25 | 1.62 | 3.12 | |
| Natural indirect effect | 0.88 | 0.75 | 1.03 | |
| Total effect | 1.98 | 1.48 | 2.63 | |

In the mediation analysis, we adjusted for age, family history of breast cancer, different WHI study subcohorts (observational study or clinical trials and different treatment assignments for all 4 clinical trials), cardiometabolic risk factors, physical activity, parity, breastfeeding, and socioeconomic status except for the variable being assessed as a mediator

[a]Metabolic dysfunction was assessed by four cardiometabolic risk factors, including elevated WC, self-reported history of diabetes, high cholesterol, and hypertension. We summed the four components with a total score from 0 to 4. A higher score indicates higher metabolic dysfunction. We collapsed scores of 3 and 4 due to a small sample size in the score of 4

[b]We assigned 1 point for education being high school degree or lower, 1 point for annual family income < $20,000, and 1 point for NSES lower than 20% of the population, and summed for a total score from 0 to 3; scores of 2 and 3 were collapsed. A higher score indicates low SES

[c] Since the natural direct effect and natural indirect effect are in opposite direction, it is not meaningful to estimate the proportion mediated