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A Case-Control Study of Body Mass Index and Breast Cancer Risk in White and African American Women

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Abstract

Objective—Large body size has been associated with decreased risk of breast cancer in premenopausal, but with increased risk in postmenopausal women. Limited information is available

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about African American women and differences by estrogen- and progesterone-receptor (ERPR) status.

Methods—We analyzed data from the Women's Contraceptive and Reproductive Experiences (CARE) Study among 3,997 white and African American breast cancer case patients diagnosed in 1994-98 and 4,041 control participants aged 35 to 64. We calculated multivariate odds ratios (ORs) as measures of relative risk of breast cancer associated with self-reported body mass index (BMI) at age 18 and 5 years before diagnosis (recent BMI).

Results—Risk tended to decrease with increasing BMI at age 18 in all women ($OR_{BMI \geq 25 \text{ kg/m}^2 \text{ vs } < 20 \text{ kg/m}^2} = 0.76$, 95% CI: 0.63–0.90, $P_{\text{trend}} = 0.005$) and with recent BMI in premenopausal women ($OR_{BMI \geq 35 \text{ kg/m}^2 \text{ vs } < 25 \text{ kg/m}^2} = 0.81$, 95% CI: 0.61–1.06, $P_{\text{trend}} = 0.05$), unmodified by race. Among postmenopausal white but not African American women, there was an inverse relation between recent BMI and risk. High recent BMI was associated with increased risk of ERPR positive tumors among postmenopausal African American women ($OR_{BMI \geq 35 \text{ kg/m}^2 \text{ vs } < 25 \text{ kg/m}^2} = 1.83$, 95% CI: 1.08–3.09, $P_{\text{trend}} = 0.03$).

Conclusion—Among women at age 35-64, BMI at age 18 is inversely associated with risk of breast cancer, but association with recent BMI varies by menopause status, race and hormone receptor status.

Impact—Our findings indicate that studies of BMI and breast cancer should consider breast cancer subtypes.

Keywords

African American; Body Mass Index; Breast cancer; Premenopausal; Postmenopausal

Introduction

An inverse association between body mass index (BMI, kg/m^2) and breast cancer risk in premenopausal women and a positive association between BMI and breast cancer risk has been identified in many studies of postmenopausal women (1-3). In a recent World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report on prevention of cancer (4), body fat percentage was reported as a probable risk reducing factor for premenopausal breast cancer, and as a convincing risk increasing factor for breast cancer in postmenopausal women. Most published data are from studies of predominantly white women.

Obesity during adolescence (5), at age 18 (6), and in adulthood (7) have been inversely associated with premenopausal breast cancer risk in white women. Among African American women, obesity at age 18 has been found to be both not associated (8,9) and inversely associated (10) with breast cancer risk among premenopausal women. Likewise, the established inverse relationship between adult BMI and premenopausal breast cancer in white women has not been as consistently found among African American women (8,9,11,12) and some studies have even suggested a positive association between adult BMI and premenopausal breast cancer risk in African American women (8,9).

The inverse relation between BMI and risk in pre-menopausal women and the positive relation between BMI and risk in post-menopausal women (4) suggest that at some age, there is a “transition” in which BMI ceases to be protective and contributes increased risk. There has been little research on the age at which such a “transition” occurs and it is unknown if there is variation by race. It is possible that the effect is somehow linked to different subtypes of breast cancer having different age-specific incidence rates (13).

Few studies have provided data on the effect of BMI on postmenopausal breast cancer in African American women, and with mixed results (9,10,12,14). The number of studies comparing postmenopausal white women and African American women are limited. One case-control study that included both white women and African American women found no association between adult BMI and postmenopausal breast cancer risk for either race (14).

The Women's Contraceptive and Reproductive Experiences (CARE) Study provided an opportunity to examine the relationship between body size characteristics and risk of breast cancer in a large sample of white women and African American women aged 35 to 64 years.

Methods

Participants

The Women's CARE Study was a population-based case-control study conducted in five metropolitan U.S. areas: Atlanta (Georgia), Seattle (Washington), Detroit (Michigan), Philadelphia (Pennsylvania) and Los Angeles (California). Details of the study methods have been described previously (15). Case patients were identified by SEER cancer registries in Atlanta, Seattle, Detroit, and LA and from hospitals in Philadelphia. Case patients were white women or African American women aged 35 to 64 years with no history of *in situ* or invasive breast cancer who were newly diagnosed with invasive breast cancer between July 1994 and April 1998. Control participants were women without a history of *in situ* or invasive breast cancer who were identified by random-digit dialing. Control participants were matched to case patients within strata of study center, race, and 5-year age group. The participation rate was 76.5% among case patients and 78.6% among control participants. A total of 4,575 case patients (2953 white and 1622 African American women) and 4,682 control participants (3021 white and 1661 African American women) completed interviews. The study protocol was approved by local institutional review boards at each study site. All participants provided a written informed consent.

Data Collection

All participants were interviewed in person using a structured questionnaire that included questions on demographics, reproductive history, medical history including body size and hormone use, family history of breast cancer, lifetime physical activity, and other lifestyle factors.

Body size was recorded in the study questionnaire by asking the women their tallest body height without shoes, and body weight at age 18 and 5 years before the reference date, which was the date of breast cancer diagnosis for case patients and the date when the woman was identified by random-digit dialing for control participants. Women were asked to select their body figure size from nine given picture alternatives at three time points: at the time of their first menstrual period; at 30 years of age; and 5 years before the reference date (16). Bra size (cup size and chest circumference in inches) at 18 years of age and 5 years before the reference date were recorded. We also asked the women to indicate in what area of the body they typically gained weight, selecting from the following responses: didn't gain weight; gained weight around the chest and shoulders, around the waist or stomach, around the hips and thighs, around the buttocks, or equally all over; other (specify); and don't know.

Estrogen and progesterone receptor status of case patients was obtained from the pathology reports and was recorded by each study center as reported earlier (17).

Data Analyses

BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). The body size variables evaluated in this analysis were BMI at age 18 and 5 years before the reference date (recent), weight change from age 18 until the recent measure (as both kg and kg/year), body figure (range from 1 to 9) at menarche, at age 30, and recently, and typical location of weight gain. BMI categories used were ≤ 20 (reference category), 21–24 and 25+ kg/m^2 at age 18 years and ≤ 25 (reference category), 26–29, 30–34 and 35+ kg/m^2 at recent age. Weight change categories were < 5 (reference category), 5–15, 16–25 and > 25 kg . The three bra cup size categories were AA, A and B (reference category), C, CC and CCC, and D +. Analysis of bra cup size were conducted only among women with recent BMI ≤ 25 kg/m^2 to eliminate the effect of overall obesity.

We considered a woman as postmenopausal if she had experienced a final menstrual period more than 12 months before the reference date (and had not used hormonal therapy (HT) before or during the 12 month interval after last menstrual period (i.e., natural menopause), if she had undergone bilateral oophorectomy (surgical menopause), or if her periods stopped because of chemotherapy or radiation therapy at least 12 months before the reference date. Women were considered premenopausal if they were still menstruating and had not taken any HT during the 12 months before the reference date. We were unable to determine menopausal status for women who received a hysterectomy and had at least a portion of an ovary intact or who began HT within 12 months of their last menstrual period.

Because we analyzed the data by menopausal status, we excluded 1,126 participants (534 case patients of which 309 white and 225 African American women, and 592 control participants of which 348 white and 244 African American women) with unknown menopausal status. Additionally, we excluded 25 participants with missing BMI at age 18 (12 case patients and 13 control participants), 30 participants with missing recent BMI (14 case patients and 16 control participants), 5 participants with missing both BMI at age 18 and recent BMI (3 case patients and 2 control participants), 12 participants with missing parity (3 case patients and 9 control participants), 7 participants with missing postmenopausal HT use (3 case patients and 4 control participants), one control participant missing both BMI at age 18 and postmenopausal HT use, and 13 participants with missing physical activity (9 case patients and 4 control participants). The number of participants remaining for analysis was 8,038 (3,997 case patients and 4,041 control participants). In the analysis of body figures, we further excluded 34 participants (16 case patients and 18 control participants) because of missing information on selection of at least one of the body figures. When stratifying for menstrual regularity, we excluded an additional 235 participants (127 case patients and 108 control participants) who lacked data on this variable.

We used unconditional logistic regression analysis to calculate odds ratios (ORs) as relative risk estimates and corresponding 95% confidence intervals (CIs) to examine the relationship between different body size measurements and risk of breast cancer. We included a number of potential confounding variables in our models that were selected *a priori*: age (continuous), race (white / African American), education (less than high school / high school graduate / some college or technical school / college graduate or more), study site (Atlanta / Seattle / Detroit / Philadelphia / Los Angeles), first degree family history of breast cancer defined as breast cancer in mother or sister (yes / no / adopted or unknown), parity (0 / 1 / 2 / 3 / 4 / 5+), postmenopausal HT use (< 1 / 1–4 / 5–9 / 10+ years) and age at menopause (< 35 / 35–39 / 40–44 / 45–49 / 50–54 / 55+ years). We also considered age at menarche and physical activity as potential confounding variables, but dropped both from the final model because they altered the ORs by less than 10%.

We studied possible effect modification of the association between BMI and breast cancer risk by analyzing the data stratified by race, never versus ever use of HT, bra size, regularity of menstrual periods and length of breast feeding. We tested for homogeneity of the BMI effect using a likelihood ratio test comparing the fit of a model with a trend variable for BMI with the fit of a model where the BMI variable was allowed to vary by strata of the other variable (such as race). We also tested for homogeneity of effect by tumor receptor status using a case-case analysis comparing ER+PR+ with ER-PR- cases. Note that a total of 3297 cases (82%) or 1,756 premenopausal and 1,541 postmenopausal cases had ERPR information available. We therefore redid the BMI analyses among cases with ERPR information. The results were essentially identical to the main analyses presented in the tables on all cases, and these results are therefore not shown. We also tested whether only including premenopausal women younger than 55 years or postmenopausal women 40 years or older altered the results, but results were similar to those obtained when all women were included and are not presented.

We used the Statistical Package for Social Sciences for Windows (Release 14.0.2. Chicago, IL: SPSS, Inc.) for all analyses. *P*-values are two-sided and values less than 0.05 were considered statistically significant, while *P*-values of 0.05-0.10 are described as borderline significant.

Results

Women's CARE Study results for several common breast cancer risk factors have been published previously (18-21). Similar results were found in the subset of case patients and control participants in this current study (Table 1). Case patients were more likely than control participants to have a first-degree family history of breast cancer and to be nulliparous. Among parous women, the case patients had higher age for first term pregnancy and lower parity than the control participants.

The effect of BMI in Premenopausal Women

In premenopausal women, both BMI at age 18 and recent BMI were inversely associated with breast cancer risk, although neither trend reached statistical significance (Table 2). Overall, premenopausal women who reported having had a BMI of 25 kg/m² or higher at age 18 were at 24% lower risk of breast cancer than women reporting a BMI of less than 20 kg/m² at that age (95% CI 0.60–0.96, *P*_{trend} = 0.09). Women who reported their recent BMI as 35 kg/m² or higher were at 19% lower risk of breast cancer than women reporting recent BMI of less than 25 kg/m² (95% CI 0.61–1.06, *P*_{trend} = 0.05) (Table 2). Both relative risks were attenuated when the two BMI measures were included in the same model, making it difficult to distinguish the effects of BMI at these two time points (Table 2). The two BMI measures were correlated (Pearson *r*=0.57, *P*<0.001).

Weight change since age 18 was not associated with risk overall. However, among the subgroup of women whose BMI at age 18 was <20 kg/m², we observed a borderline statistically significant increased risk for breast cancer by weight gain (*P*_{trend} = 0.08, results not shown).

The Effect of BMI in Postmenopausal Women

BMI at age 18 was also inversely associated with breast cancer risk among postmenopausal women overall. Those who reported having had a BMI of 25 kg/m² or greater at age 18 were at 25% lower risk of breast cancer than women reporting BMI of less than 20 kg/m² at that age (95% CI 0.58–0.97, *P*_{trend} = 0.02) (Table 2). The BMI measures at age 18 and recently were correlated (Pearson *r*=0.48, *P*<0.001). Recent BMI and weight change since age 18 were not associated with risk in postmenopausal women overall.

Heterogeneity by Race and HT Use

Race did not modify the association between either BMI variable and breast cancer risk among premenopausal women (both $P_{\text{homogeneity white vs. African American}} > 0.20$, Table 3). However, the effect of recent BMI varied by race in postmenopausal women ($P_{\text{homogeneity white vs. African American}} = 0.05$). Recent BMI tended to be inversely associated with risk in white women and positively associated with risk in African American women, although neither trend was statistically significant (Table 3). HT did not modify the effect of either recent BMI or BMI at age 18 (all $P_{\text{homogeneity never vs. ever HT use}} > 0.4$) (Supplemental table 1).

Timing of Menopause by Race

Age at menopause differed between races being lower among African American women than among white women, both among HT users and non-users. In HT users, mean age at menopause was 44.8 in white women and 42.8 in African American women, P for difference < 0.001 . In non-users, mean age at menopause was 48.0 in white women and 46.5 in African American women, P for difference < 0.001 (results not shown). A higher proportion of white women than African American women had unknown menopause status among HT-users (results not shown).

Heterogeneity by Tumor Receptor Status, Premenopausal Women

We did not find any statistically significant heterogeneity of effect by tumor receptor status (ER+PR+/ER-PR-) of the association between BMI and breast cancer risk among premenopausal women within each racial group, although there were stronger inverse associations between BMI at age 18 and ER+PR+ tumors among African American women than among white women. The tests for homogeneity for BMI at age 18 both by ER/PR status and by race were borderline statistical significant ($P_{\text{homogeneity by ERPR}} \leq 0.08$ and $P_{\text{homogeneity white vs. African American}} = 0.07$ (Table 4).

Heterogeneity by Tumor Receptor Status, Postmenopausal Women

Among postmenopausal white women, the effect of recent BMI varied significantly by tumor ERPR status ($P_{\text{homogeneity by ERPR}} = 0.004$) with a significant inverse association only observed for ER-PR- tumors (OR for recent BMI ≥ 35 kg/m² vs. < 25 kg/m² = 0.35, 95% CI 0.15–0.82), $P_{\text{trend}} = 0.03$) (Table 4). Significant modification of the effect of recent BMI was also apparent, although indicating a different relationship, in postmenopausal African American women ($P_{\text{homogeneity by ERPR}} = 0.009$). Among these women, the inverse trend for ER-PR-cancer was not statistically significant; however, recent BMI was positively and significantly associated with risk of ER+PR+ breast cancers ($P_{\text{trend}} = 0.03$). We found a borderline significant modification by race of the association between recent BMI and ER+PR+ breast cancer ($P_{\text{homogeneity white vs. African American}} = 0.08$) (Table 4.). These associations became stronger when the analyses were restricted to never HT users (data not shown). Specifically, the decreasing OR for ER-PR- tumors with increasing BMI at age 18 among white postmenopausal women ($P_{\text{trend}} = 0.04$, Table 4) was significant only among never HT users ($P_{\text{trend}} = 0.002$, $P_{\text{homogeneity never vs. ever HT use}} = 0.02$, results not shown). None of the associations between BMI and ERPR positive or negative tumors were statistically significant among postmenopausal HT users (results not shown).

Heterogeneity by Menstrual Regularity and Race (Not Shown in Table)

We tested whether the effect of BMI differed by whether or not women reported having had regular menstrual cycles during the first year after menarche. A total of 1,691 (21%) of women reported irregular menstrual cycles during the first year. We found no difference in the effect of BMI on breast cancer risk between women reporting regular cycles and women reporting

irregular cycles during the first year neither in premenopausal nor in postmenopausal white or African American women (results not shown).

Body Figure, Location of Weight Gain and Bra Size

Body size figures (16), as reported by the women at menarche, at age 30 years, and recently, were, similar to BMI, inversely associated with the odds for breast cancer, although the results were slightly weaker (Supplemental tables 2-3).

We did not observe statistically significant differences in breast cancer risk by areas on the body where women tended gain weight (Supplemental table 4). Finally, we found no difference in breast cancer risk by bra size measured as bra cup size, analyzed among non-obese women (Supplemental table 5).

Discussion

In this large study of African American and white women aged 35–64, we found that BMI at age 18 was associated with reduced risk of breast cancer. In premenopausal women, recent BMI was associated with reduced risk although the trend was not statistically significant. This association was not significantly modified by race. Among postmenopausal women, for recent BMI, associations in postmenopausal women differed depending on whether the cancer was receptor positive or not. For ER-PR- breast cancers, recent BMI was inversely associated with risk in both AA and white women. For ER+PR+ cancers, recent BMI was positively associated with risk in AA women but there was no association in white women.

The borderline significant protective effect of increasing adult (recent) BMI on the risk of breast cancer in premenopausal white women is supported by several (7,14,22) but not all (23-30) previous studies. The protective effect of adult overweight and obesity on premenopausal breast cancer risk has been found also in African American women (10), although the findings are not consistent (8,9,12,14).

We observed a borderline significantly reduced risk of premenopausal breast cancer associated with BMI of 25 or greater at age 18 among African American women, a finding consistent with a recent cohort study (10). We further observed an inverse association between increasing BMI at age 18 and risk of ER+PR+ tumors in premenopausal African American women, but not in white women. The Nurses' Health Study reported that the protective effect of obesity at age 18 or 20 years (5,22) was stronger for premenopausal ER+ tumors, although the study population was predominantly white (22). However, in a study of breast cancer subtypes in white and African American women, Millikan et al reported a slight inverse association between BMI and the ER+ breast cancer subtype defined as “luminal A” in premenopausal women (31).

We found no association between recent BMI and postmenopausal breast cancer overall, although there was a non-significant inverse association in white women. Most previous studies (23,26,29,32-34) have found recent BMI to be associated with increased risk of postmenopausal breast cancer; only a few studies have reported no association (25,28) or an inverse association (26,29). In the WCRF/AIRC report, five of 19 cohort studies on postmenopausal women showed decreased risk of breast cancer by BMI, statistically significant in one of them (4). Thus our results appear consistent with a minority of the previous studies. However, the age distribution of the Women's CARE study must be kept in mind. We limited the CARE study to women under age 65 years, resulting in a relatively young group of postmenopausal women. Further, CARE oversampled younger women to get uniform distribution of participants across the 5-year age groups (15). A Dutch cohort study that did not find any association between BMI and postmenopausal breast cancer also included

relatively young postmenopausal women, with median age of 58 years and upper age limit of 73 years at study entry (25). One of the cohort studies that found a positive association between BMI and postmenopausal breast cancer, had mean baseline age less than 60 years, but included women 50-73 years (32). Other studies that find a positive association and present the age of the postmenopausal women, have median age above 60 years (26,33) or have the upper age limit of 79 years (34). Thus, the postmenopausal women in the Women's CARE study were younger than in many of the previous studies. It is not clear exactly where in the menopausal transition BMI shifts from a protective factor to a risk factor for breast cancer, or how many years it takes (35).

Few studies have assessed the effects of BMI on breast cancer risk among postmenopausal African American women, and in general results are more mixed. Two studies found a positive association between recent BMI and postmenopausal breast cancer in African American women (9,12), although two other studies found non-significant inverse associations (10,14). Perhaps the most marked difference between the two racial groups in our analyses was the heterogeneity of effect by ERPR status. Among postmenopausal African American women BMI was associated with increased risk of ER+PR+ tumors. This finding is consistent with prior studies of both white (36-38) and African American women (10). However, among white women in our study, the protective effect of BMI was greater on ER-PR- tumors. Although this latter finding was unexpected, it is consistent with results from a Swedish cohort study, which reported a negative association between BMI and PR- tumors (39). A previous Surveillance, Epidemiology and End Results (SEER) study has reported that the proportion of receptor positive and negative tumors differed between postmenopausal white and African American cases (40). This was also true in our study, with ER+PR+ tumors being more frequent in white cases and ER-PR- tumors more frequent in African American cases. We hypothesize that certain of these molecular subtypes of cancers (even within hormone receptor negative or receptor positive tumors) are more affected by BMI, and these subtypes might differ by race.

On the other hand, the few differences we observed by race and ERPR were not very impressive, and may not be causal differences, but could simply have been due to random fluctuations or chance in our data. Future studies of these associations should include more detail on breast cancer subtypes.

In our study the effects of BMI did not differ significantly by whether women had used HT. Specifically, we did not observe a positive association when limiting the analyses to never or non-current users of HT, as has been found in several other studies (26,29,33).

Previous studies of the association between BMI at age 18 years and postmenopausal breast cancer risk have been predominantly conducted among white women, and have yielded inconsistent results. Most studies have reported no effect of obesity at 15-20 years of age (9, 23,24,29,34), although the Women's Health Initiative observational study (33) and the Black Women's Health Study (10) suggested a protective effect. Our results are consistent with these latter two studies, and suggest that BMI at age 18 might be associated with a reduced risk of postmenopausal breast cancer, with no significant difference between the races.

We did not observe any association between weight change from age 18 years to recently and breast cancer risk in premenopausal women. This is consistent with studies both among white (6,7,24,29,30,41) and African American (9,10) premenopausal women. The only reported effect of weight change on premenopausal breast cancer risk was observed in an Asian population (42). In postmenopausal women, there is strong and consistent evidence that weight gain is associated with breast cancer risk, at least in white women (6,23,24,29,32-34,41,43). Few studies, especially with convincing data, exist on African American women (9,10). Most

of the reported effect has been limited to non-users of HT (6,23,29,33,41,43) or ER+PR+ cancer (6,23,43).

Possible Mechanisms

The mechanisms by which obesity may protect against breast cancer in young women have not been completely elucidated. It has been suggested that any protective effect of high BMI in young women is because of higher prevalence of menstrual irregularities or anovulatory cycles in women with high BMI, and thus lower exposure to ovarian sex steroids (44). One proposed mechanism is that obese premenopausal women have a higher number of anovulatory cycles, resulting in decreased estradiol and progesterone levels (44), which causes reduced risk of breast cancer (45). We found a higher proportion of women with irregular menstrual cycles to be overweight compared with women who had regular cycles. This is consistent with data from earlier studies (46). However, the protective effect of overweight in our study was not restricted to women reporting irregular menstrual periods. We recognize, though, that self-report of irregular menstrual periods 20–40 years ago may not be a good measure of frequency of anovulatory cycles in the post-pubertal period (47).

An intriguing alternative mechanism for the protective effect of early obesity is that body fat at young age influences the histological constituents of the breast tissue. Evidence from a subset of women in this study suggests that adipose tissue in the breast may be protective. In a study of mammographic density among Los Angeles Women's CARE study participants, women with larger breast size (who tended to also be heavier), had less absolute mammographic density, and both percent and absolute density were weaker risk factors for breast cancer in this group than in women with smaller breasts (48).

The exact age that obesity is most protective against premenopausal breast cancer is not clear. High body fat percentage at age 20 years was observed as a strong protective factor for premenopausal breast cancer among women in the Nurses Health Study II, independent of later BMI (5,22). It has been suggested that body size in early adulthood is inversely associated with premenopausal breast cancer risk only as it predicts adult body size (7). Our results among premenopausal women weakened when we adjusted for recent BMI in the statistical model.

As women pass through menopause, the protective effect of obesity on breast cancer risk is replaced by an increased risk. This change in the effect of obesity is possibly due to peripheral adipose tissue becoming an important source of estrogen, as this is where androstenedione is aromatized and converted to estrogen (49,50).

It is unclear how long it takes for this transition to take place (i.e., for BMI being a protective factor to it being a risk factor for breast cancer). Pike et al. have modeled this effect, and argue that it takes a decade for a BMI of 30 kg/m² in a premenopausal woman (at age 50, relative risk (RR) of 0.75) to become a risk factor (RR of 1.20 at age 62) (35). It is, therefore, possible that the reason that we found no increased risk for postmenopausal breast cancer in white women with high BMI might be partially explained by the relatively young age of the postmenopausal women in our study. One explanation for our findings could be that the timing of the transition might vary between white and African American women. In our study white women had a later age at menopause than African American women; thus, it is possible that this transition took place at a younger age among African American women in general.

Strengths and Limitations of the Study

Our BMI measures were made on the basis of self-reported measures of weight and height. We cannot exclude the possibility that some women might have misreported their weight.

However, we expect any such misclassification to have been non-differential with respect to case status, and therefore, if anything, to have biased the results towards the null.

The interview was conducted after the cases had been diagnosed, but within 18 months after diagnosis. Current weight could have possibly biased recall of previous weight. However, if anything, women with breast cancer tend to gain weight (51), so that any such bias would have resulted in overestimation of weight in cases, not in controls. This implies that the inverse results we observed would be either nonexistent or underestimated. Small sample size of stratified analyses is a limitation in this study. The only positive association we found is for ER+PR+ breast cancer among African American women. Although we cannot exclude the possibility, we find it unlikely that the finding for this specific subtype of cancer was because of such recall bias.

The upper age limit in this study population was 64 years old, and only about one third of the postmenopausal women were above 60 years old. The lack of older women may partly explain why we do not have stronger findings on the risk associated with BMI among postmenopausal women, and why our results are similar to those seen in studies restricted to premenopausal women.

We unfortunately did not have waist and hip circumferences as measurements for central obesity. It has been suggested that central obesity measured as waist-hip ratio might be a risk factor for premenopausal breast cancer, independent of BMI (52,53). However, we observed no differences in breast cancer risk by areas on the body where women tended to gain weight, or by bra size. Therefore, the data collected might not confirm the effect of central obesity among our study population.

Conclusion

In this study we found an inverse association between increasing BMI at age 18 and risk of breast cancer in women aged 35-64 years. We found also an inverse association between increasing recent BMI and risk of premenopausal breast cancer. Effects of recent BMI on premenopausal breast cancer risk were similar in African American and white women. Among postmenopausal women, there was a slight increased risk with recent BMI in African American women, but a slight inverse association in white women. Comparison of our study results with those of others suggests that it might take time before the transition of BMI from a protective factor to a risk factor occurs, and that this change might occur later in white women than in African American women. Our results also suggest that some differences exist in the effect of BMI on ER+PR+ and ER-PR-tumors in both premenopausal and postmenopausal breast cancer, and this effect could also differ between the races. The effects of BMI on various subtypes of breast cancer should be further explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Characteristics of the women with breast cancer and the controls from the Women's CARE study

	Premenopausal women		Postmenopausal women	
	Cases (n = 2,097)	Controls (n = 2,035)	Cases (n = 1,900)	Controls (n = 2,006)
Race (%)				
White	1,365 (65.1)	1,347 (66.2)	1,261 (66.4)	1,294 (64.5)
African American	732 (34.9)	688 (33.8)	639 (33.6)	712 (35.5)
Age at reference date (y)				
35–39	646 (30.8)	605 (29.7)	9 (0.5)	22 (1.1)
40–44	640 (30.5)	673 (33.1)	30 (1.6)	50 (2.5)
45–49	534 (25.5)	528 (25.9)	95 (5.0)	149 (7.4)
50–54	250 (11.9)	208 (10.2)	335 (17.6)	357 (17.8)
55–59	26 (1.2)	17 (0.8)	727 (38.3)	754 (37.6)
60–64	1 (0.0)	4 (0.2)	704 (37.1)	674 (33.6)
Study center (%)				
Atlanta	377 (18.0)	352 (17.3)	358 (18.8)	384 (19.1)
Seattle	453 (21.6)	435 (21.4)	479 (25.2)	447 (22.3)
Detroit	331 (15.8)	356 (17.5)	265 (13.9)	322 (16.1)
Philadelphia	339 (16.2)	318 (15.6)	297 (15.6)	347 (17.3)
Los Angeles	597 (28.5)	574 (28.2)	501 (26.4)	506 (25.2)
First degree family history of breast cancer (%)				
No	1,701 (81.1)	1,811 (89.0)	1,443 (75.9)	1,681 (83.8)
Yes	329 (15.7)	162 (8.0)	363 (19.1)	233 (11.6)
Adopted or unknown	67 (3.2)	62 (3.0)	94 (4.9)	92 (4.6)
Education (%)				
Less than high school	123 (5.9)	106 (5.2)	235 (12.4)	279 (13.9)
High school graduate	529 (25.2)	504 (24.8)	645 (33.9)	673 (33.5)
Technical school or some college	713 (34.0)	686 (33.7)	562 (29.6)	581 (29.0)
College graduate or higher	732 (34.9)	739 (36.3)	458 (24.1)	473 (23.6)
Number of full-term pregnancies				

	Premenopausal women		Postmenopausal women	
	Cases (n = 2,097)	Controls (n = 2,035)	Cases (n = 1,900)	Controls (n = 2,006)
0	518 (24.7)	443 (21.8)	265 (13.9)	248 (12.4)
1	408 (19.5)	370 (18.2)	271 (14.3)	239 (11.9)
2	658 (31.4)	634 (31.2)	510 (26.8)	523 (26.1)
3	339 (16.2)	355 (17.4)	400 (21.1)	424 (21.1)
4	112 (5.3)	144 (7.1)	230 (12.1)	260 (13.0)
5+	62 (3.0)	89 (4.4)	224 (11.8)	312 (15.6)
Age at first full-term pregnancy (y)				
≤19	398 (19.0)	395 (19.4)	493 (25.9)	599 (29.9)
20–24	484 (23.1)	496 (24.4)	695 (36.6)	771 (38.4)
25–29	383 (18.3)	371 (18.2)	316 (16.6)	268 (13.4)
30+	314 (15.0)	330 (16.2)	131 (6.9)	120 (6.0)
Nulliparous				
	518 (24.7)	443 (21.8)	265 (13.9)	248 (12.4)
Duration of breast-feeding				
Never breast-fed	1,190 (56.7)	979 (48.1)	1,069 (56.3)	1,054 (52.5)
<6 mo	369 (17.6)	392 (19.3)	430 (22.6)	501 (25.0)
6 mo–<2y	403 (19.2)	452 (22.2)	297 (15.6)	347 (17.3)
2+ y	135 (6.4)	211 (10.4)	103 (5.4)	104 (5.2)
Unknown		1 (0.0)	1 (0.1)	
Age at menopause				
<35			117 (6.2)	180 (9.0)
35–39			147 (7.7)	225 (11.2)
40–44			288 (15.2)	369 (18.4)
45–49			614 (32.3)	581 (29.0)
50–54			605 (31.8)	531 (26.5)
≥55			129 (6.8)	120 (6.0)
			534	592
Undetermined menopause status*				
Oral contraceptive use (%)				
Never or less than 1 year	610 (29.1)	600 (29.5)	1,030 (54.2)	1,015 (50.6)
Ever 1–4 years	656 (31.3)	642 (31.6)	389 (20.5)	454 (22.6)

	Premenopausal women		Postmenopausal women	
	Cases (n = 2,097)	Controls (n = 2,035)	Cases (n = 1,900)	Controls (n = 2,006)
Ever 5-9 years	449 (21.4)	443 (21.8)	278 (14.6)	309 (15.4)
Ever 10+ years	381 (18.2)	348 (17.1)	198 (10.4)	227 (11.3)
Unknown	1 (0.0)	2 (0.1)	5 (0.3)	1 (0.0)
HT pill/patch use (%)				
Never or less than 1 year	2,080 (99.2)	2,019 (99.2)	882 (46.4)	947 (47.2)
1-4y	16 (0.8)	15 (0.7)	341 (17.9)	372 (18.5)
5-9y	0 (0.0)	1 (0.0)	340 (17.9)	296 (14.8)
10+ y	1 (0.0)	0 (0.0)	337 (17.7)	391 (19.5)

* Excluded from the analysis

Table 2
Multivariate odds ratios of invasive breast cancer associated with body mass index (BMI) in pre- and postmenopausal women from the Women's CARE study

	n (case / control)	OR [†] (95% CI)	P _{trend}	OR ^{‡,§} (95% CI)	P _{trend}
All women	3997 / 4041				
BMI at age 18y (kg/m ²)					
<20	2037 / 1971	1.0 (Ref.)		1.0 (Ref.)	
20–24	1685 / 1720	0.94 (0.86–1.04)		0.95 (0.87–1.05)	
25+	275 / 350	0.76 (0.63–0.90)	0.005	0.77 (0.63–0.93)	0.02
Recent* BMI (kg/m ²)					
<25	2260 / 2195	1.0 (Ref.)		1.0 (Ref.)	
25–29	1051 / 1092	0.93 (0.84–1.04)		0.95 (0.85–1.07)	
30–34	422 / 460	0.90 (0.77–1.05)		0.95 (0.81–1.12)	
35+	264 / 294	0.88 (0.73–1.06)	0.07	0.99 (0.81–1.21)	0.62
Weight change 18y until recent (kg)					
≤5	1049 / 1076	1.0 (Ref.)		1.0 (Ref.)	
5.1–15.0	1443 / 1409	1.03 (0.92–1.16)		1.01 (0.89–1.13)	
15.1–25.0	866 / 908	0.98 (0.85–1.12)		0.95 (0.83–1.09)	
25.1+	639 / 648	1.04 (0.89–1.20)	0.89	1.03 (0.89–1.20)	0.97
Premenopausal women	2,097 / 2,035				
BMI at age 18y (kg/m ²)					
<20	1,058 / 1008	1.0 (Ref.)		1.0 (Ref.)	
20–24	882 / 839	0.99 (0.87–1.13)		1.02 (0.89–1.17)	
25+	157 / 188	0.76 (0.60–0.96)	0.09	0.81 (0.62–1.06)	0.40
Recent* BMI (kg/m ²)					
<25	1,342 / 1,266	1.0 (Ref.)		1.0 (Ref.)	
25–29	472 / 466	0.92 (0.79–1.08)		0.93 (0.79–1.10)	
30–34	168 / 175	0.86 (0.68–1.09)		0.89 (0.70–1.14)	
35+	115 / 128	0.81 (0.61–1.06)	0.05	0.89 (0.66–1.21)	0.27
Weight change 18y until recent (kg)					

	n (case / control)	OR [†] (95% CI)	P _{trend}	OR ^{‡,§} (95% CI)	P _{trend}
≤5	686 / 672	1.0 (Ref.)		1.0 (Ref.)	
5.1–15.0	802 / 782	0.98 (0.84–1.14)		0.96 (0.82–1.11)	
15.1–25.0	359 / 363	0.93 (0.77–1.12)		0.91 (0.76–1.11)	
25.1+	250 / 218	1.09 (0.87–1.37)	0.79	1.11 (0.89–1.39)	0.75
Postmenopausal women					
1,900 / 2,006					
BMI at age 18y (kg/m ²)					
<20	979 / 963	1.0 (Ref.)		1.0 (Ref.)	
20–24	803 / 881	0.89 (0.78–1.03)		0.89 (0.78–1.02)	
25+	118 / 162	0.75 (0.58–0.97)	0.02	0.72 (0.55–0.96)	0.02
Recent [*] BMI (kg/m ²)					
<25	918 / 929	1.0 (Ref.)		1.0 (Ref.)	
25–29	579 / 626	0.95 (0.82–1.11)		0.98 (0.84–1.14)	
30–34	254 / 285	0.95 (0.77–1.16)		1.02 (0.82–1.26)	
35+	149 / 166	0.96 (0.75–1.24)	0.59	1.09 (0.83–1.43)	0.67
Weight change 18y until recent (kg)					
≤5	363 / 404	1.0 (Ref.)		1.0 (Ref.)	
5.1–15.0	641 / 627	1.13 (0.94–1.36)		1.10 (0.91–1.32)	
15.1–25.0	507 / 545	1.05 (0.87–1.28)		1.01 (0.83–1.23)	
25.1+	389 / 430	1.06 (0.86–1.31)	0.87	1.03 (0.84–1.27)	0.92

Abbreviations: BMI: body mass index (kg/m²); OR: Odds Ratio; CI: Confidence Interval

^{*} Five years before the reference date

[†] Adjusted for age (continuous), race (white/African American), education (less than high school/high school graduate/some college or technical school/college graduate or more), study site (Atlanta/Seattle/Detroit/Philadelphia/Los Angeles), 1st degree family history of breast cancer (yes/no/unknown), parity (0/1/2/3/4/5+), age at menopause (<35/35–40/41–45/46–50/51–54/55+ years), HT use (<1 / 1–4/5–9/10+ years).

[‡] Additionally adjusted for BMI at the other time point (age 18 or recent BMI).

[§] OR by weight change also adjusted for BMI at age 18.

Table 3
Multivariate odds ratios of invasive breast cancer associated with body mass index in pre- and postmenopausal women from the Women's CARE study stratified by race

BMI categories (kg/m ²)	n (case / control)	OR [†] (95% CI)	P _{trend}	n (case / control)	OR [†] (95% CI)	P _{trend}	P _{homogeneity white vs AA}
Premenopausal women							
White							
At age 18	1,365 / 1,347			African American	733 / 688		
<20	721 / 710	1.0 (Ref.)		337 / 298	1.0 (Ref.)		
20–24	562 / 544	1.02 (0.87–1.19)		320 / 295	0.94 (0.75–1.18)		
25+	82 / 93	0.84 (0.61–1.15)	0.58	76 / 95	0.67 (0.47–0.96)	0.06	0.27
Recent*							
<25	993 / 942	1.0 (Ref.)		349 / 324	1.0 (Ref.)		
25–29	240 / 258	0.87 (0.71–1.06)		232 / 208	1.02 (0.79–1.30)		
30–34	82 / 92	0.80 (0.59–1.10)		86 / 83	0.94 (0.66–1.33)		
35+	50 / 55	0.86 (0.57–1.29)	0.09	66 / 73	0.81 (0.56–1.19)	0.34	0.52
Postmenopausal women							
White							
At age 18	1,261 / 1,294			African American	639 / 712		
<20	682 / 648	1.0 (Ref.)		297 / 315	1.0 (Ref.)		
20–24	517 / 559	0.89 (0.75–1.05)		286 / 322	0.91 (0.72–1.14)		
25+	62 / 87	0.70 (0.49–1.00)	0.03	56 / 75	0.80 (0.54–1.19)	0.22	0.58
Recent*							
<25	733 / 713	1.0 (Ref.)		185 / 216	1.0 (Ref.)		
25–29	333 / 355	0.93 (0.77–1.12)		246 / 271	1.05 (0.80–1.37)		
30–34	127 / 137	0.94 (0.72–1.24)		127 / 148	0.98 (0.71–1.35)		
35+	68 / 89	0.75 (0.53–1.06)	0.13	81 / 77	1.26 (0.85–1.85)	0.44	0.05

Abbreviations: BMI: body mass index (kg/m²); OR: Odds Ratio; CI: Confidence Interval

* Five years before the reference date.

† Adjusted for age (continuous), education (less than high school/high school graduate/some college or technical school/college graduate or more), study site (Atlanta/Seattle/Detroit/Philadelphia/Los Angeles), 1st degree family history of breast cancer (yes/no/adopted or partly unknown), parity (0/1/2/3/4/5+), age at menopause (<35/35–40/41–45/46–50/51–54/55+ years), HT use (<1 /1–4/5–9/10+ years).

Table 4
Multivariate odds ratios of invasive breast cancer associated with body mass index in pre- and postmenopausal women from the Women's CARE study stratified by race and tumor estrogen and progesterone receptor status

Pre-menopausal women									
BMI categories (kg/m ²)	n (case / control)	OR [†] (95% CI)	P _{trend}	P _{homogeneity by ERPR[‡]}	n (case / control)	OR [†] (95% CI)	P _{trend}	P _{homogeneity by ERPR[‡]}	P _{homogeneity white vs AA}
ER+PR+ cases vs. controls									
White									
	718 / 1,347								
At age 18									
<20	377 / 710	1.0 (Ref.)			123 / 298	1.0 (Ref.)			
20–24	291 / 544	1.00 (0.82–1.21)			113 / 295	0.88 (0.64–1.20)			
25+	50 / 93	0.99 (0.68–1.45)	0.95	0.92	21 / 95	0.50 (0.30–0.87)	0.02	0.08	0.07
Recent*									
<25	527 / 942	1.0 (Ref.)			126 / 324	1.0 (Ref.)			
25–29	118 / 258	0.80 (0.62–1.03)			82 / 208	0.96 (0.68–1.35)			
30–34	49 / 92	0.88 (0.60–1.28)			29 / 83	0.83 (0.51–1.35)			
35+	24 / 55	0.75 (0.45–1.25)	0.09	0.33	20 / 73	0.63 (0.36–1.11)	0.12	0.07	0.90
ER-PR- cases vs. controls									
White									
	329 / 1,347								
At age 18									
<20	173 / 710	1.0 (Ref.)			99 / 298	1.0 (Ref.)			
20–24	139 / 544	1.08 (0.84–1.39)			102 / 295	1.10 (0.79–1.52)			
25+	17 / 93	0.76 (0.44–1.33)	0.82		29 / 95	0.96 (0.59–1.57)	0.93		0.83
Recent*									
<25	227 / 942	1.0 (Ref.)			103 / 324	1.0 (Ref.)			
25–29	71 / 258	1.15 (0.85–1.57)			79 / 208	1.24 (0.87–1.77)			
30–34	20 / 92	0.91 (0.55–1.53)			24 / 83	1.03 (0.61–1.74)			
35+	11 / 55	0.88 (0.45–1.74)	0.92		24 / 73	1.12 (0.66–1.91)	0.62		0.66

Premenopausal women									
BMI categories (kg/m ²)	n (case / control)	OR [†] (95% CI)	P _{trend}	P _{homogeneity by ERPR[‡]}	n (case / control)	OR [†] (95% CI)	P _{trend}	P _{homogeneity by ERPR[‡]}	P _{homogeneity white vs AA}
ER+PR+ cases vs. controls									
White									
	679 / 1,294				African American				
At age 18					225 / 712				
<20	365 / 648	1.0 (Ref.)			111 / 315	1.0 (Ref.)			
20–24	277 / 559	0.89 (0.73–1.09)			94 / 322	0.80 (0.57–1.11)			
25+	37 / 87	0.80 (0.52–1.22)	0.17	0.37	20 / 75	0.80 (0.46–1.41)	0.21	0.80	0.88
Recent *									
<25	379 / 713	1.0 (Ref.)			63 / 216	1.0 (Ref.)			
25–29	180 / 355	0.99 (0.79–1.25)			77 / 271	1.04 (0.70–1.54)			
30–34	72 / 137	1.07 (0.77–1.50)			49 / 148	1.20 (0.76–1.88)			
35+	48 / 89	1.12 (0.76–1.66)	0.55	0.004	36 / 77	1.83 (1.08–3.09)	0.03	0.009	0.08
ER-PR- cases vs. controls									
White									
	214 / 1,294				African American				
At age 18					158 / 712				
<20	122 / 648	1.0 (Ref.)			79 / 315	1.0 (Ref.)			
20–24	82 / 559	0.76 (0.56–1.04)			69 / 322	0.91 (0.63–1.33)			
25+	10 / 87	0.60 (0.30–1.21)	0.04		10 / 75	0.55 (0.27–1.14)	0.16		0.83
Recent *									
<25	129 / 713	1.0 (Ref.)			50 / 216	1.0 (Ref.)			
25–29	57 / 355	0.89 (0.63–1.26)			72 / 271	1.15 (0.76–1.76)			
30–34	22 / 137	0.86 (0.52–1.42)			26 / 148	0.77 (0.45–1.34)			
35+	6 / 89	0.35 (0.15–0.82)	0.03		10 / 77	0.58 (0.27–1.24)	0.12		0.89

Abbreviations: BMI: body mass index (kg/m²); OR: Odds Ratio; CI: Confidence Interval, ER: estrogen receptor; PR: progesterone receptor

* Five years before the reference date.

† Adjusted for age (continuous), education (less than high school/high school graduate/some college or technical school/college graduate or more), study site (Atlanta/Seattle/Detroit/Philadelphia/Los Angeles), 1st degree family history of breast cancer (yes/no/adopted or partly unknown), parity (0/1/2/3/4/5+), age at menopause (<35/35-40/41-45/46-50/51-54/55+ years), HT use (<1 /1-4/5-9/10+ years).

‡ Test for homogeneity by tumor receptor status (ER+PR+ vs. ER-PR-, from case-case analysis).