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Brief communication

Multiple metabolic risk factors and mammographic breast density

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ABSTRACT

Purpose: We examined whether obesity and a history of diabetes, hypertension, and elevated cholesterol, individually and in combination, are associated with breast density, a strong risk factor for breast cancer.
Methods: We measured percent density and dense area using a computer-assisted method ($n = 191$; age range = 40–61 years). We used linear regression models to examine the associations of each metabolic condition and the number of metabolic conditions (zero, one, two, and three or four conditions) with breast density.
Results: Among individual metabolic conditions, only high blood cholesterol was inversely associated with percent density ($\beta = -5.4$, 95% confidence interval [CI]: −8.5, −2.2) and dense area ($\beta = -6.7$, 95% CI = −11.1, −2.4). Having multiple metabolic conditions was also associated with lower breast density, with two conditions and three or four conditions versus zero conditions associated with 6.4% (95% CI: −11.2, −1.6) and 7.4% (95% CI: −12.9, −1.9) reduction in percent density and with 6.5 cm^2 (95% CI: −13.1, −0.1) and 9.5 cm^2 (95% CI: −17.1, −1.9) decrease in dense area.
Conclusions: A history of high blood cholesterol and multiple metabolic conditions were associated with lower relative and absolute measures of breast density. The positive association between metabolic abnormalities and breast cancer risk may be driven by pathways unrelated to mammographic breast density.

Obesity and diabetes have been associated with an increased risk of postmenopausal breast cancer, but the results for other metabolic risk factors, such as lipid abnormalities and elevated blood pressure, are less consistent (reviewed in [1–3]). More recently, studies have also shown modest positive associations between the presence of multiple metabolic conditions, as frequently defined by the metabolic syndrome (MetS) and breast cancer risk in postmenopausal women (reviewed in [2]).

Although most risk factors for breast cancer are similarly associated with mammographic breast density, a strong intermediate marker of breast cancer, increasing body size has consistently been associated with reduced breast density in both pre- and postmenopausal women [4,5]. Diabetes and high-density lipoprotein cholesterol (HDL-C) have also respectively been associated with breast density in premenopausal women in some [6–9], but not all studies [9–12].

Most research investigating multiple metabolic conditions and breast cancer risk has been conducted among women of European descent [2]. There are race or ethnicity (hereafter racial) differences in the prevalence of specific metabolic conditions; for example, hypertension, high blood glucose, and dyslipidemia are respectively more common among African American, Hispanic, and white people in the United States [13]. Research on metabolic abnormalities and breast cancer risk in racial minorities is further warranted given the disproportionately greater prevalence and earlier age of onset of metabolic disorders in many racial minority people [14,15] and the potentially adverse impact of metabolic disorders on breast cancer mortality [16]. The purpose of this study was to examine whether diagnoses of hypertension, diabetes, and high cholesterol, individually and in combination with each other and with having an obese body size, are associated with breast density in a predominantly African American and Caribbean sample of women.

Conflict of Interest: The authors declare there is no conflict of interest.

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Methods

Study population

The New York City Multiethnic Breast Cancer Project includes epidemiologic risk factors and breast density data for 200 women who were recruited as they presented for screening mammography at a hospital in Brooklyn, NY. As described previously [17], we collected in-person interview data between January 2007 and April 2008 and collected mammograms from the same date as the interview for 84% of the participants; the median time between the dates of mammograms and interviews for the remainder of participants was 14 days. We excluded data from five participants with a previous diagnosis of breast cancer and four participants with poor quality mammograms. The final sample of 191 women were 42% African American, 22% African Caribbean, 22% White, 12% Hispanic, and 2% other ethnicities; 36% were foreign-born.

Metabolic risk factors

Participants reported whether they were ever told by a physician that they had high blood pressure, high blood cholesterol, and type 2 diabetes, and if so reported their age at the first diagnosis for each condition. Data on height and self-reported current weight were used to calculate body mass index (BMI, kilogram per square meter). BMI was categorized into less than 30 and 30 or more, with the latter category signifying obesity. We considered each of the conditions and age at first diagnosis (categorized into ≤ 45 and > 45 years) in relation to breast density. To examine the associations for multiple metabolic conditions, we assessed the number of conditions by summing the presence of each of the three diagnoses and obesity, ranging from 0 to 4. We combined those with three or four conditions into a single category because of small number of participants with four conditions ($n = 7$) and used this measure as a categorical variable in our analysis.

Breast density assessment

We measured mammographic density using left craniocaudal view mammograms; right craniocaudal views were used for four participants for whom left views were not available. We digitized all films using a Kodak Lumisys Film Digitizer (Kodak LS85) and used Cumulus software [18] to measure breast density. A single trained reader, blinded to exposure data, outlined the total areas of the breast and dense tissue, and the computer software measured the number of pixels in these areas. Percent density was calculated as dense area divided by total breast area (in percentage), and the number of pixels for the dense area was converted into square meter to capture the amount of dense tissue. We assessed density from one film per participant in batches of approximately 50 films. We reread a 10% randomly selected sample of films, obtaining Pearson correlation coefficients of 0.99 for breast area and 0.88 for dense area for the repeated readings [17].

Statistical analyses

We performed linear regression models to examine the associations of each metabolic risk factor, age at first diagnosis, and the number of metabolic risk factors with breast density, adjusting for continuous measures of age at mammogram and BMI. We examined whether menstrual and reproductive factors substantially affected these associations. Only age at menarche and menopausal status altered most of the estimates of associations for the metabolic conditions by at least 10% and were included in the final multivariable models. We also explored whether the associations between the number of metabolic conditions and breast density differed by obesity and menopausal statuses, through inclusion of cross-product terms between these factors in the multivariable models and through stratification across levels of obesity and menopausal status.

Results

The study participants had an average BMI of 29.8 kg/m^2 and a mean age of 50.0 years (range: 40–61); 35% were postmenopausal (Table 1). More than one-third of the participants had a history of high blood pressure or cholesterol, and 8% had a history of diabetes (Table 2). The average ages at first diagnosis of these conditions were 42.0 (SD = 10.3), 47.8 (SD = 6.8), and 46.8 (SD = 7.4) years for hypertension, elevated cholesterol, and diabetes, respectively. Obesity, hypertension, and elevated cholesterol level had a similar prevalence among participants with a single condition. Among those with multiple metabolic risk factors, diabetes always co-occurred with other conditions, and hypertension was reported by all participants with three or four conditions. African Americans had a higher prevalence of hypertension (48%) than other racial groups (e.g., 26% in African Caribbean and 24% in whites), but there were no other significant racial differences in the prevalence or age at onset for other conditions (data not shown).

Table 2 displays the regression coefficient estimates and corresponding 95% confidence interval (CI) for age and BMI adjusted associations of each metabolic condition, age at each diagnosis, and the number of multiple conditions with percent density and dense area. Obesity, hypertension, and diabetes were not associated with dense area in any of the models. Obesity and hypertension had inverse age-adjusted associations with percent density, but these associations were no longer statistically significant after further adjustment for BMI. High blood cholesterol was associated with significantly lower percent density ($\beta = -5.35$, 95% CI: -8.51, -2.18) and dense area ($\beta = -6.74$, 95% CI = -11.09, -2.38) in models that adjusted for age and BMI. The associations between high cholesterol diagnosis and breast density were similar for age at diagnosis (e.g., age at diagnosis 45 or less and more than 45 years for percent

Table 1
Sample characteristics of New York City Multiethnic Breast Cancer Project ($n = 191$)

Participant Characteristics	Mean (SD) or percent (n)
Age at interview (y)	50.0 (5.7)
Educational attainment	
≤high school	29.1 (55)
Some college/associate degree	33.9 (64)
≥College degree	37.0 (70)
Race/ethnicity	
Non-Hispanic African American	42.4 (81)
Non-Hispanic African Caribbean	22.0 (42)
Non-Hispanic white	21.5 (41)
Hispanic	12.5 (24)
Non-Hispanic other	1.6 (3)
Age at menarche (y)	12.4 (1.8)
BMI (kg/m^2)	29.8 (6.7)
Positive family history of breast cancer	13.2 (25)
Parity	1.6 (1.5)
Age at first full-term pregnancy (in parous women, y)	23.0 (7.0)
Lifetime history of breast feeding	39.5 (75)
Menopausal status*	
Premenopausal	64.9 (124)
Postmenopausal	35.1 (67)

* Postmenopausal women did not have a menstrual period within the last 12 months or had bilateral oophorectomy. Premenopausal women had a period within the last 12 months and did not have bilateral oophorectomy. If data on last menstrual cycle and gynecological surgery were missing, women younger than 54 (90th percentile of age of natural menopause among postmenopausal women in this study population) were considered premenopausal and women 54 years or older were considered postmenopausal.