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Breast Density, Body Mass Index, and Risk of Tumor Marker-Defined Subtypes of Breast Cancer

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PURPOSE: Breast density and body mass index (BMI) are correlated attributes and are both potentially modifiable risk factors for breast cancer. However, relationships between these factors and risk of molecularly-defined subtypes of breast cancer have not been established.
METHODS: We used breast density and BMI data collected by the Breast Cancer Surveillance Consortium from 1,054,466 women ages 40 to 84 years receiving mammography, including 13,797 women subsequently diagnosed with breast cancer. Cases were classified into three groups on the basis of expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2:1) ER-positive (ER+, n = 10,026), 2) HER2-expressing (ER-negative/PR-negative/HER2-positive, n = 308), or triple-negative (ER-negative/PR-negative/HER2-negative, n = 705). Using Cox regression, we evaluated subtype-specific associations with breast density and BMI.
RESULTS: Breast density was similarly positively associated with risk of all subtypes, especially among women ages 40 to 64 years. BMI was positively associated with risks of ER+ and triple-negative breast cancer in women ages 50 to 84 who were not users of hormone therapy.
CONCLUSIONS: Breast density is positively associated with breast cancer risk, regardless of disease subtype. Associations with BMI appear to vary more by breast cancer subtype. Additional studies are needed to confirm and further characterize risk factors for HER2-expressing and triple-negative breast cancer.
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KEY WORDS: Body Mass Index, Breast Cancer, Breast Density, Estrogen Receptor, HER2, Progesterone Receptor, Triple-Negative.

INTRODUCTION

Breast density is one of the strongest and most consistent risk factors for breast cancer (1). Observations that reproductive history (2–6) and hormone therapy (HT) use (2, 3, 6) are predictors of breast density suggest that hormonal mechanisms underlie this association, although associations between breast density and endogenous hormone levels are inconsistent (7–9). Body mass index (BMI), an inverse predictor of breast density (4, 10), is also hypothesized to impact postmenopausal breast cancer risk through hormonal mechanisms (11). If hormonal mechanisms are involved, it is plausible that breast density and BMI would be most strongly associated with risk of estrogen receptor-positive (ER+) breast cancer. In some studies authors have noted that the association between postmenopausal BMI and breast cancer risk is most pronounced for ER+ breast cancer (12–16). However, most previous studies assessing the association between breast density and breast cancer risk suggest that high breast density is a risk factor for ER+ and ER-negative (ER−) disease (17, 18) and that breast density is not associated with ER status in women with breast cancer (19, 20).

Biological evidence indicates that breast cancer is a heterogeneous disease. Distinctions between breast cancer subtypes by ER status are consistent with the highest-level subtype distinctions on the basis of gene expression profile

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Selected Abbreviations and Acronyms

HT = hormone therapy
BMI = body mass index
ER = estrogen receptor
PR = progesterone receptor
BCSC = Breast Cancer Surveillance Consortium
BI-RADS = Breast Imaging Reporting And Data System
SCC = statistical coordinating center
HR = hazard ratio
CI = confidence interval

(21, 22); however, there is also considerable heterogeneity among ER− breast cancers. In particular, triple-negative (ER−/progesterone receptor [PR]−/HER2−) breast cancer is associated with a gene-expression profile distinct from ER−/PR−/HER2+ breast cancer (22). Both subtypes are distinct from ER+ disease. Biological distinctions between triple-negative, ER−/PR−/HER2+, and ER+ breast cancers may imply important differences in tumor etiology (23). Thus, assessing associations between breast density, BMI, and breast cancer risk by tumor subtype may better elucidate the relationship between these factors and breast cancer risk. We used data from the Breast Cancer Surveillance Consortium (BCSC) to examine the association between breast density, BMI, and risk of ER+, triple-negative, and ER−/PR−/HER2+ subtypes of breast cancer.

METHODS

Details of the BCSC have been provided elsewhere (24). The present analysis includes data from six BCSC registries: the Carolina Mammography Registry, Group Health (Western Washington State), the New Hampshire Mammography Network, the New Mexico Mammography Project, the San Francisco Mammography Registry, and the Vermont Breast Cancer Surveillance System. BCSC registries collect risk factor information through self-administered questionnaires completed at the time of mammography (25). Demographic data and data on previous breast biopsies and breast cancer family history were collected by all registries for the duration of the study period. Breast density and BMI data were also collected by all registries, although not all registries collected these data during the full study period. Breast density, collected from clinical radiology reports, was categorized by radiologists using Breast Imaging-Reporting and Data System (BI-RADS) classifications (26): 1 = almost entirely fat, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, or 4 = extremely dense. BMI was calculated from self-reported height and weight and categorized into a three-level variable (<25.0 kg/m^2, 25.0–29.9 kg/m^2, ≥ 30 kg/m^2).

Each BCSC registry and the statistical coordinating center (SCC) have received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant, and all registries and the SCC have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities who are subjects of this research.

Study Population

The study population included women who received a screening mammogram within the BCSC during the study period. Women with a history of invasive or in situ breast cancer at the time of screening and women ages <40 or >84 years were excluded. The timing and duration of the study period varied between registries, reflecting differences in the earliest diagnosis date for which registries submitted HER2 data to the SCC and the date up to which cancer ascertainment was complete. Registry-specific study period start-dates ranged from January 1, 1999, to January 1, 2003; end-dates ranged from May 31, 2007, to October 31, 2008.

In total, 1,054,466 women (2,599,946 mammograms) were included. The average duration of follow-up, from the time of the first mammogram in the study period until the end of the study or breast cancer diagnosis, was 3.7 years (range, 0–9.0 years).

Case Population

BCSC registries linked with cancer registries and/or pathology databases to ascertain breast cancers diagnoses and associated tumor characteristics. HER2 testing results of 0, 1+, or 2+ on immunohistochemistry and/or a negative or borderline result on fluorescence in situ hybridization testing were interpreted as HER2−; cases who tested 3+ on immunohistochemistry and/or positive on fluorescence in situ hybridization were considered HER2+. Among 13,797 women diagnosed with invasive breast cancer during follow-up, 10,026 were ER+, 308 were ER−/PR−/HER2+, and 705 were triple-negative; 2585 cases could not be classified (1562 missing ER, 1023 ER−/PR− with missing HER2 status), and 173 were ER− and either PR+ or missing PR status.

Statistical Analyses

We evaluated the association between breast density, BMI, and breast cancer risk using Cox proportional hazards regression, using time since a woman's first screening mammogram during the study period as the time axis. We constructed three separate regression models for each exposure to