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

Amanda I. Phipps, PhD^{1,2}, Diana S.M. Buist, PhD^{2,3}, Kathleen E. Malone, PhD^{1,2}, William E. Barlow, PhD^{2,3,4}, Peggy L. Porter, MD^{1,5}, Karla Kerlikowske, MD⁶, Ellen S. O'Meara, PhD³, and Christopher I. Li, MD, PhD^{1,2}

¹Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

²School of Public Health, University of Washington, Seattle, WA

³Group Health Research Institute, Seattle, WA

⁴Cancer Research and Biostatistics, Seattle, WA

⁵School of Medicine, University of Washington, Seattle, WA

⁶Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, CA

Abstract

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 aged 40–84 years receiving mammography, including 13,797 women subsequently diagnosed with breast cancer. Cases were classified into three groups based on expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2: 1) ER-positive (ER+, N=10,026), 2) HER2-overexpressing (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 aged 40–64 years. BMI was positively associated with risks of ER+ and triple-negative breast cancer in women aged 50–84 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-overexpressing and triple-negative breast cancer.

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Corresponding Author: Amanda I. Phipps, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., M4-B402, Seattle, WA 98109, aphipps@fhcrc.org, Telephone: (206) 667-7741, Fax: (206) 667-7850.

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Keywords

breast cancer; triple-negative; breast density; body mass index; estrogen receptor; progesterone receptor; HER2

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. Some studies 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 based on gene expression profile (21, 22); however, there is also considerable heterogeneity among ER– breast cancers. In particular, triple-negative (ER–/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. Demographic data and data on prior 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 over 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 ($<25.0 \text{ kg/m}^2$, $25.0\text{--}29.9 \text{ kg/m}^2$, $\geq 30 \text{ kg/m}^2$).

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 aged <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 (IHC) and/or a negative or borderline result on fluorescence *in situ* hybridization (FISH) testing were interpreted as HER2–; cases who tested 3+ on IHC and/or FISH+ 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; 2,585 cases could not be classified (1,562 missing ER, 1,023 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 evaluate ER+, ER–/PR–/HER2+, and triple-negative breast cancer as model-specific outcomes. Women diagnosed with *in situ* breast cancer ($N=3,689$) or an invasive breast cancer of a subtype other than the model-specific outcome were censored at diagnosis.

Analyses were adjusted for confounders selected *a priori*, including age at study entry (five-year categories), race (white/non-white), history of benign breast biopsy (yes/no), and breast cancer family history (yes/no). Breast density and BMI measures from the start of follow-up were analyzed as categorical variables, as described above. BI-RADS=2 and $\text{BMI} < 25.0 \text{ kg/m}^2$ were used as the referent categories in analyses of breast density and BMI, respectively, as these were the most common groups. Breast density analyses were also adjusted for BMI and HT use at the start of follow-up. To reflect findings from a prior BCSC study indicating the association between breast density and breast cancer risk differs among women aged <65 versus ≥ 65 years (29), we stratified breast density analyses by age (40–64/65–84 years).

Similarly, based on prior evidence of effect modification (14, 30), we stratified BMI analyses by age (40–49/50–84 years) and HT use (yes/no). We evaluated proportional hazards assumptions by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times.

Exposure variables were associated with substantial missingness: 29% of observations were missing breast density, 43% were missing BMI, and 59% were missing one or both variables. To account for missing data, we used multiple-imputation by chained equations (MICE) (31). The imputation model included variables for the two exposures, the outcome, covariates, the log of analysis time, BCSC registry, tumor markers, stage, grade, and histology. Iterative imputations were performed using the *ice* command in STATA SE version 10.1 (College Station, Texas). We also conducted complete-case analyses, wherein observations with missing data were excluded and cases with insufficient tumor marker data were censored at diagnosis.

RESULTS

Distributions of demographic and covariate variables are presented in Table 1. Most women were aged 40–59 years (69%) and non-Hispanic white (74%). Compared to ER+ cases, ER–/PR–/HER2+ and triple-negative cases were less likely to be non-Hispanic white and were younger at study entry.

Distributions of exposure data are presented in Table 2. Breast density was slightly higher among cases than in the overall study population. Within case groups, a lower proportion of triple-negative cases aged 40–49 were normal weight (40% versus 51% overall) and, among women aged 50–84 who were not HT users, a lower proportion of ER–/PR–/HER2+ cases were obese (14% versus 27%). However, these distributions exclude a distinct subset of the study population. Women with unknown breast density were younger, more likely to be non-white, and had lower BMI than women with known breast density. Women with unknown BMI were more likely to be non-white, were older, and had lower breast density than women with known BMI (Table 3).

Breast density was positively associated with breast cancer risk, regardless of age strata and case group (Table 4). In multiply-imputed analyses within the 40–64 age strata, women with BI-RADS=4 had a 1.77 to 1.80-fold increased risk of ER+, ER–/PR–/HER2+, and triple-negative breast cancer compared to women with BI-RADS=2; complete-case results were similar for ER+ and ER–/PR–/HER2+ case groups, but were attenuated for triple-negative cases. Regardless of age strata or analytic approach, women with BI-RADS=1 had a similarly reduced risk of all three subtypes (HR=0.44 to 0.67 in women aged 40–64 and HR=0.35 to 0.61 in women aged 65–84). The gradient of increasing risk with increasing breast density was less pronounced across subtypes for women aged 65–84 years in analyses reflecting multiple-imputation. The difference between effect estimates from multiple-imputation and complete-case analyses was greater for ER–/PR–/HER2+ and triple-negative than for ER+ breast cancer and was greater in the older age strata.

Associations between BMI and breast cancer risk were inconsistent across subtypes (Table 4). In women aged 40–49 years, there was no association between BMI and risk, regardless of analytic approach or subtype. In women aged 50–84 years, subtype-specific associations with BMI differed by HT use. For ER+ disease, there was a significant increased risk in obese relative to normal weight women, although this association was more pronounced in HT non-users ($HR_{HT\ non-user}=1.37$, 95% CI: 1.24–1.51, $HR_{HT\ user}=1.12$, 95% CI: 1.01–1.25); results were similar for complete-case and multiple-imputation analyses. For triple-negative disease, results based on multiple-imputation indicated associations with obesity by

HT use similar to those for ER+ disease ($HR_{HT \text{ non-user}}=1.32$, 95% CI: 1.06–1.64, $HR_{HT \text{ user}}=1.09$, 95% CI: 0.79–1.49), although no associations were evident in complete-case analyses. BMI was not associated with risk of ER–/PR–/HER2+ breast cancer, regardless of age, HT use, or analytic approach.

DISCUSSION

In this cohort of women undergoing mammography, we found that breast density was similarly positively associated with risk of ER+, ER–/PR–/HER2+, and triple-negative breast cancers. BMI was modestly positively associated with risk of ER+ and triple-negative breast cancer in women aged 50–84 years who were not users of HT.

Certain limitations must be considered in interpreting these results. In particular, there was considerable missing data in exposure and tumor marker variables. Differences between results from complete-case and multiple-imputation analyses illustrate that these missing data impact observed associations. Because breast density is known to vary with age (32), race/ethnicity (33), and BMI (4, 10), differences in the distribution of these factors in observations with known versus unknown breast density indicate that missingness was not completely random; the same was true for BMI. We used multiple-imputation to account for missing data (31). Simulation studies comparing multiple-imputation to complete-case analyses suggest that excluding observations with missing data can lead to considerable bias in regression coefficients if missingness is not completely random, and that such bias can be reduced via multiple-imputation (34). HRs based on a complete-case approach may be unbiased if data are missing completely at random; however, excluding those observations with missing data still contributes to a loss in power. Thus, while there is no way to validate our imputation models, imputation offers a gain in statistical efficiency by making use of observations that would otherwise be discarded (35). Despite differences in point estimates from multiple-imputation and complete-case analyses, both approaches indicate a positive association between breast density and breast cancer risk for all subtypes, and more modest, less consistent positive associations with BMI.

A number of cases were diagnosed in the days immediately following their first mammogram during the study period: 25% of ER+, 18% of ER–/PR–/HER2+, and 12% of triple-negative cases were diagnosed within the first 3 months of follow-up. Because breast density and BMI could change with time and/or as a consequence of breast cancer development, measured exposure values in these cases may not reflect values prior to cancer development. Cases diagnosed in the first 3 months of follow-up had lower breast density (53.4% with BI-RADS=1–2 versus 43.8% in other cases) and higher BMI (30.4% versus 25.8% with BMI ≥ 30 kg/m²). Results changed only slightly when excluding these cases, with no change to the conclusions presented here.

Additional limitations are inherent to the design of the BCSC. Misclassification of BMI is possible; this variable is based on self-report and women may under-report their weight (36). However, any such misclassification is unlikely to be related to the outcomes evaluated here. Misclassification of breast density is possible since BI-RADS classification is somewhat subjective and was based on reports from multiple radiologists across BCSC registries; however, prior studies have noted general agreement between BI-RADS classification and quantitative breast density (37). Also, because tumor marker data were taken from multiple laboratories, and because assays and practices for interpreting tumor marker test results vary across institutions, some misclassification of case subtypes is possible. However, it is reasonable to assume this misclassification is non-differential with respect to exposures.

To our knowledge, this is the first study to evaluate breast density as a risk factor for ER-/PR-/HER2+ breast cancer. Consistent with reports that the association between breast density and breast cancer risk is similar across ER/PR (17, 18) and HER2 status (18), we found breast density was strongly positively associated with risk of ER-/PR-/HER2+ breast cancer, with a magnitude of association similar to that for other subtypes. This is the second study to examine the association between breast density and triple-negative breast cancer (18). Ma et al. previously reported no difference in the association between breast density and breast cancer risk for luminal A (i.e., ER+ and/or PR+, HER2-) versus triple-negative breast cancer (18): women with a breast density $\geq 60\%$ experienced a 2.22-fold (95% CI: 1.04–4.78) increased risk of luminal A and a 2.96-fold (95% CI: 1.21–7.23) increased risk of triple-negative breast cancer, relative to women with a breast density $<10\%$.

This study is the largest to date of the association between BMI and breast cancer risk by joint ER/PR/HER2 status. In a prior study within the BCSC it was reported that, in postmenopausal women not using HT, rates of ER+ but not ER- breast cancer were higher in obese or overweight women than normal-weight women (16); our findings for ER+ breast cancer are consistent with that result. Our results for ER+ breast cancer are also consistent with prior reports of effect modification by HT use and age/menopausal status (14, 30), indicating a positive association between BMI and ER+ breast cancer that was largely restricted to women aged 50–84 not using HT. Similarly, there was a modest positive association between BMI and triple-negative breast cancer risk in women aged 50–84 that was restricted to non-users of HT; however, this association was evident only in imputed analyses. There was no evidence of an association with BMI for ER-/PR-/HER2+ breast cancer. Consistent with these findings, prior studies in postmenopausal women have indicated a positive association between BMI and risk of ER+ and triple-negative breast cancer in women who were not using HT (38, 39). Two other studies have reported non-significant inverse associations between postmenopausal BMI and risk of basal-like breast cancer (i.e., triple-negative and cytokeratin 5/6+ and/or EGFR+), although neither study stratified estimates by HT use (40, 41). Some (40, 42, 43), but not all (41) previous studies in younger women have reported a modest positive association between BMI and triple-negative breast cancer, which is also not consistent with results presented here. Differences between our findings and prior studies may reflect small numbers, differences in subtype definitions, study demographics, and stratification by HT use.

Breast cancer subtypes defined by joint ER/PR/HER2 status exhibit distinct biologies that may reflect distinct alterations in cellular pathways. Thus, it is plausible that risk factors for breast cancer overall would differ in their associations with specific breast cancer subtypes. The hormone receptor-negativity that defines ER-/PR-/HER2+ and triple-negative breast cancers implies a lack of hormone-responsiveness which, in turn, implies a role of non-hormonal mechanisms in the etiology of these tumors. Better characterization of subtype-specific risk factor associations can inform the etiologies of these tumor subtypes.

Although an extensive literature has implicated breast density and BMI as risk factors for breast cancer overall, the mechanisms behind these associations remain unclear. Consistent with patterns of effect modification by age/menopausal status and HT use, and consistent with the fact that adipose tissue is the primary source of endogenous estrogen in postmenopausal women (11), it has been suggested that the association between BMI and breast cancer reflects hormonal pathways. However, the modest association between BMI and triple-negative breast cancer suggests that BMI may also influence risk through non-hormonal mechanisms: obesity is associated with increased levels of insulin (11), leptin (44), and markers of inflammation (e.g., tumor necrosis factor, interleukin 6) (45), which may plausibly influence breast cancer risk. The association between breast density and breast cancer risk may also reflect multiple mechanisms. Evidence that HT use (3, 28) and

reproductive factors (2, 4) are mediators of breast density suggests a role of hormonal mechanisms. However, prior studies of the association between breast density and breast cancer risk by ER/PR status have been inconsistent (46), noting either no difference by hormone receptor status (17, 18), a stronger association with ER+ breast cancer (47, 48), or a stronger association with ER– breast cancer (49); most case-only analyses have reported no association between breast density and ER status (19, 20, 50). We found that the association with breast density was comparable across ER+, ER–/PR–/HER2+, and triple-negative subtypes, implying that non-hormonal mechanisms may be important to the association between breast density and breast cancer risk. In particular, some previous studies have noted positive associations between levels of circulating IGF-1 (51–53) and prolactin (52, 54) and breast density, suggesting that breast density could reflect cumulative exposure to growth factor stimuli promoting cell division in the breast.

The results presented here indicate that breast density is an important risk factor across breast cancer subtypes, and that BMI is modestly associated with risk of ER+ and triple-negative breast cancer among older women not using HT. These results suggest the biological and clinical distinctions between ER+, ER–/PR–/HER2+ and triple-negative breast cancers do not translate to differences in risk factor associations with BMI and breast density.

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Abbreviations and acronyms

ER	estrogen receptor
PR	progesterone receptor
BMI	body mass index
HT	hormone therapy
HR	hazard ratio
CI	confidence interval
BCSC	Breast Cancer Surveillance Consortium
SCC	Statistical Coordinating Center
BI-RADS	breast imaging reporting and data system
IHC	immunohistochemistry
FISH	fluorescence in situ hybridization

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Table 1

Demographic and covariate characteristics in the overall study population and within case groups at the start of follow-up^a

	OVERALL STUDY POPULATION (N=1,054,466) N (%)	All Cases (N=13,797) N (%)	ER+ Cases (N=10,026) N (%)	ER-/PR-/HER2+ Cases (N=308) N (%)	Triple-Negative Cases (N=705) N (%)
Age (years)					
40–44	228,378 (22)	1,486 (11)	1,071 (11)	38 (12)	94 (13)
45–49	178,433 (17)	1,794 (13)	1,291 (13)	49 (16)	115 (16)
50–54	177,434 (17)	2,052 (15)	1,494 (15)	69 (22)	90 (13)
55–59	138,755 (13)	2,082 (15)	1,481 (15)	48 (16)	110 (16)
60–64	102,071 (10)	1,766 (13)	1,286 (13)	35 (11)	102 (14)
65–69	84,344 (8)	1,498 (11)	1,103 (11)	27 (9)	67 (10)
70–74	66,683 (6)	1,423 (10)	1,064 (11)	18 (6)	50 (7)
75–79	50,375 (5)	1,097 (8)	800 (8)	17 (6)	55 (8)
80–84	27,993 (3)	599 (4)	436 (4)	7 (2)	22 (3)
Race/ethnicity					
White non-Hispanic	701,715 (74)	10,306 (79)	7,583 (80)	191 (68)	501 (76)
Hispanic white	61,230 (6)	529 (4)	352 (4)	3 (1)	3 (1)
African-American	65,761 (7)	723 (6)	438 (5)	14 (5)	47 (7)
Asian/Pacific Islander	88,276 (9)	1,084 (8)	838 (9)	63 (22)	75 (11)
Other	34,072 (4)	382 (3)	272 (3)	10 (4)	29 (4)
Missing	103,412	773	543	27	50
Prior breast biopsy or surgery					
No	813,309 (82)	9,677 (73)	6,989 (73)	209 (74)	520 (77)
Yes	183,349 (18)	3,535 (26)	2,591 (27)	75 (26)	154 (23)
Missing	57,808	585	446	24	31
Family history of breast cancer					
No	827,338 (87)	9,914 (79)	7,115 (79)	217 (81)	520 (79)
Yes	122,336 (13)	2,570 (21)	1,906 (21)	52 (19)	135 (21)
Missing	104,792	1,313	1,005	39	50
Current hormone therapy use					
No	720,396 (81)	8,579 (73)	6,100 (78)	174 (70)	427 (73)

	OVERALL STUDY POPULATION (N=1,054,466) N (%)	All Cases (N=13,797) N (%)	ER+ Cases (N=10,026) N (%)	ER-/PR-/HER2+ Cases (N=308) N (%)	Triple-Negative Cases (N=705) N (%)
Yes	173,461 (19)	3,168 (23)	2,358 (22)	74 (30)	159 (27)
Missing	160,609	2,050	1,568	60	119

^aCounts reflect raw demographic and covariate data for study participants at the start of follow-up and do not reflect multiple imputation.

Table 2
Distribution of breast density and BMI in the overall study population and within case groups^a

		OVERALL STUDY POPULATION (N=1,054,466) N (%)	All Cases (N=13,797) N (%)	ER+ Cases (N=10,026) N (%)	ER-/PR-/HER2+ Cases (N=308) N (%)	Triple-Negative Cases (N=705) N (%)
Breast density (BI-RADS)						
<i>Age 40–64:</i>	1	38,673 (7)	183 (3)	130 (3)	3 (2)	9 (3)
	2	247,405 (42)	2,283 (37)	1,557 (36)	44 (33)	112 (36)
	3	252,452 (43)	3,074 (49)	2,169 (50)	65 (49)	157 (51)
	4	53,992 (9)	683 (11)	477 (11)	20 (15)	32 (10)
	Unknown	232,549	2,957	2,290	107	201
<i>Age 65–84:</i>	1	20,269 (12)	221 (7)	163 (7)	1 (3)	9 (7)
	2	94,022 (56)	1,737 (53)	1,243 (53)	13 (33)	65 (53)
	3	49,990 (30)	1,182 (36)	853 (36)	24 (60)	41 (33)
	4	4,849 (3)	119 (4)	84 (4)	2 (5)	8 (7)
	Unknown	60,265	1,358	1,060	29	71
BMI (kg/m²)						
<i>Age 40–49:</i>	<25	118,736 (51)	955 (52)	698 (53)	26 (58)	42 (40)
	25–29	61,586 (26)	499 (27)	348 (26)	10 (22)	38 (36)
	30+	53,506 (23)	379 (21)	273 (21)	9 (20)	26 (25)
<i>Age 50–84, HT non-user:</i>	Unknown	172,983	1,447	1,043	42	103
	<25	90,370 (41)	1,192 (36)	836 (35)	28 (44)	61 (41)
	25–29	70,383 (32)	1,095 (33)	792 (33)	26 (41)	44 (30)
<i>Age 50–84, HT user:</i>	30+	59,758 (27)	1,029 (31)	763 (32)	9 (14)	44 (30)
	Unknown	176,212	2,625	1,820	41	110
	<25	43,945 (46)	822 (44)	614 (43)	16 (47)	33 (45)
	25–29	30,148 (32)	588 (32)	445 (31)	11 (32)	24 (33)
	30+	20,859 (22)	449 (24)	356 (25)	7 (21)	16 (22)
	Unknown	50,994	1,093	801	31	74

^aCounts reflect raw demographic and covariate data for study participants at the start of follow-up and do not reflect multiple imputation.

Table 3

Distribution of mammogram-level characteristics according to missingness in breast density and BMI at the start of follow-up

	Breast Density		BMI	
	Non-Missing N (%)	Missing N (%)	Non-Missing N (%)	Missing N (%)
Age at start of follow-up				
40–49	641,629 (35)	305,910 (40)	527,201 (38)	420,338 (35)
50–64	744,552 (42)	307,117 (40)	597,566 (43)	484,103 (41)
65–84	417,457 (23)	153,281 (20)	280,596 (20)	290,142 (24)
Race/ethnicity				
White non-Hispanic	1,375,632 (81)	454,721 (63)	1,101,497 (80)	728,856 (70)
Hispanic white	67,387 (4)	35,050 (5)	90,149 (7)	12,288 (1)
African-American	115,948 (7)	28,538 (4)	33,328 (2)	111,158 (11)
Other	138,233 (8)	196,130 (27)	143,691 (11)	190,672 (18)
Missing	136,438	51,869	36,698	151,609
Prior breast biopsy or surgery				
No	1,413,417 (78)	580,208 (81)	1,097,035 (79)	896,590 (80)
Yes	389,044 (22)	136,229 (19)	295,340 (21)	229,993 (20)
Missing	31,177	49,871	12,988	68,060
Family history of breast cancer				
No	1,492,227 (85)	578,028 (85)	1,126,422 (84)	943,833 (87)
Yes	262,131 (15)	98,469 (15)	217,065 (16)	143,535 (13)
Missing	79,280	89,811	61,876	107,215
Current hormone therapy use				
No	1,280,353 (76)	418,439 (76)	979,382 (75)	719,410 (78)
Yes	393,523 (24)	130,139 (24)	323,242 (25)	200,420 (22)
Missing	159,762	217,730	102,739	274,753
BMI (kg/m²)				
<25	469,044 (44)	178,201 (52)	N/A	N/A
25–29	323,302 (30)	97,390 (29)		
30	272,037 (26)	65,389 (19)		
Missing	769,255	425,328		

	Breast Density		BMI	
	Non-Missing N (%)	Missing N (%)	Non-Missing N (%)	Missing N (%)
Breast density (BI-RADS)^a				
1	N/A	N/A	76,849 (7)	55,486 (7)
2			454,584 (43)	364,338 (47)
3			446,160 (42)	296,766 (39)
4			86,790 (8)	52,665 (7)
Missing			340,980	425,328

^aBI-RADS categories: 1 = almost entirely fat, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, 4 = extremely dense.

Table 4

Breast density, BMI, and subtype-specific breast cancer risk, by age and current HT use at start of follow-up^a

	ER+		ER-/PR-/HER2+		Triple-Negative		
	HR _{CC} (95% CI) ^b	HR _{MI} (95% CI) ^b	HR _{CC} (95% CI) ^b	HR _{MI} (95% CI) ^b	HR _{CC} (95% CI) ^b	HR _{MI} (95% CI) ^b	
Breast density (BI-RADS) ^{c,d}							
Age 40-64:	1	0.45 (0.35-0.58)	0.51 (0.43-0.61)	0.53 (0.12-2.23)	0.44 (0.19-1.05)	0.67 (0.29-1.55)	0.50 (0.35-0.71)
	2	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	3	1.63 (1.48-1.78)	1.47 (1.35-1.59)	0.87 (0.52-1.46)	1.37 (0.98-1.91)	1.48 (1.07-2.07)	1.50 (1.24-1.81)
	4	2.04 (1.77-2.35)	1.80 (1.63-1.98)	1.80 (0.93-3.48)	1.79 (1.10-2.93)	1.17 (0.64-2.12)	1.77 (1.34-2.33)
Age 65:	1	0.61 (0.49-0.77)	0.60 (0.50-0.73)	--	0.47 (0.15-1.49)	0.35 (0.08-1.50)	0.59 (0.35-0.99)
	2	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	3	1.31 (1.16-1.48)	1.27 (1.17-1.38)	3.78 (1.27-11.24)	1.37 (0.95-1.99)	0.99 (0.55-1.79)	1.12 (0.87-1.44)
	4	1.51 (1.13-2.03)	1.30 (1.06-1.59)	4.01 (0.45-36.09)	1.39 (0.53-3.65)	3.29 (1.31-8.21)	1.43 (0.80-2.54)
BMI (kg/m ²)							
Age 40-49:	<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	25-29	0.99 (0.87-1.14)	0.97 (0.87-1.09)	0.74 (0.36-1.52)	0.94 (0.57-1.55)	1.87 (1.19-2.95)	1.19 (0.87-1.62)
	30+	0.87 (0.75-1.01)	0.88 (0.74-1.04)	0.83 (0.40-1.74)	0.94 (0.61-1.44)	1.14 (0.66-1.96)	1.05 (0.81-1.36)
Age 50, HT non-user:	<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	25-29	1.17 (1.06-1.29)	1.20 (1.08-1.33)	1.30 (0.75-2.24)	1.23 (0.90-1.69)	0.96 (0.63-1.44)	1.08 (0.88-1.33)
	30+	1.37 (1.24-1.52)	1.37 (1.24-1.51)	0.60 (0.29-1.24)	1.11 (0.82-1.51)	1.09 (0.72-1.64)	1.32 (1.06-1.64)
Age 50, HT user:	<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
	25-29	1.00 (0.88-1.13)	1.03 (0.94-1.13)	0.72 (0.30-1.68)	1.00 (0.62-1.60)	1.00 (0.59-1.71)	1.17 (0.90-1.52)
	30+	1.11 (0.97-1.27)	1.12 (1.01-1.25)	0.79 (0.32-1.97)	1.03 (0.58-1.84)	0.90 (0.50-1.65)	1.09 (0.79-1.49)

^aHRCC = hazard ratio from analysis including only observations with complete exposure, covariate, and outcome data (i.e., complete case); HRMI = hazard ratio from analysis using multiple imputation to account for missing data.

^bAdjusted for age at start of follow-up interval (5-year categories), white race, family history, prior breast procedure, and BCSC registry.

^cAdditionally adjusted for BMI (categorical, at start of follow-up), and current HT use (at start of follow-up).

^dBI-RADS categories: 1 = almost entirely fat, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, 4 = extremely dense.