Title

Relationship Between Mammographic Density and Breast Cancer Death in the Breast Cancer Surveillance Consortium

Journal

Journal of the National Cancer Institute, 104(16)

ISSN

0027-8874

Authors

Gierach, Gretchen L
Ichikawa, Laura
Kerlikowske, Karla
et al.

Publication Date

2012-08-22

DOI

10.1093/jnci/djs327

Peer reviewed

DOI: 10.1093/jnci/djs327
Advance Access publication on August 20, 2012.

ARTICLE

Relationship Between Mammographic Density and Breast Cancer Death in the Breast Cancer Surveillance Consortium

Gretchen L. Gierach, Laura Ichikawa, Karla Kerlikowske, Louise A. Brinton, Ghada N. Farhat, Pamela M. Vacek, Donald L. Weaver, Catherine Schairer, Stephen H. Taplin, Mark E. Sherman

Manuscript received December 06, 2011; revised June 18, 2012; accepted June 22, 2012.

Correspondence to: Gretchen L. Gierach, PhD, MPH, 6120 Executive Blvd, Ste 550, Rm 5016, Rockville, MD 20852-7234 (e-mail: gierachg@mail.nih.gov).

Background Women with elevated mammographic density have an increased risk of developing breast cancer. However, among women diagnosed with breast cancer, it is unclear whether higher density portends reduced survival, independent of other factors.

Methods We evaluated relationships between mammographic density and risk of death from breast cancer and all causes within the US Breast Cancer Surveillance Consortium. We studied 9232 women diagnosed with primary invasive breast carcinoma during 1996–2005, with a mean follow-up of 6.6 years. Mammographic density was assessed using the Breast Imaging Reporting and Data System (BI-RADS) density classification. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by Cox proportional hazards regression; women with scattered fibroglandular densities (BI-RADS 2) were the referent group. All statistical tests were two-sided.

Results A total of 1795 women died, of whom 889 died of breast cancer. In multivariable analyses (adjusted for site, age at and year of diagnosis, American Joint Committee on Cancer stage, body mass index, mode of detection, treatment, and income), high density (BI-RADS 4) was not related to risk of death from breast cancer (HR = 0.92, 95% CI = 0.71 to 1.19) or death from all causes (HR = 0.83, 95% CI = 0.68 to 1.02). Analyses stratified by stage and other prognostic factors yielded similar results, except for an increased risk of breast cancer death among women with low density (BI-RADS 1) who were either obese (HR = 2.02, 95% CI = 1.37 to 2.97) or had tumors of at least 2.0 cm (HR = 1.55, 95% CI = 1.14 to 2.09).

Conclusions High mammographic breast density was not associated with risk of death from breast cancer or death from any cause after accounting for other patient and tumor characteristics. Thus, risk factors for the development of breast cancer may not necessarily be the same as factors influencing the risk of death after breast cancer has developed.

J Natl Cancer Inst 2012;104:1218–1227

Elevated mammographic density is one of the strongest risk factors for non–familial breast cancer (1). Mammographic density (referred to herein as "density") reflects the tissue composition of the breast as projected on a two-dimensional mammographic image: higher relative adipose content corresponds to lower measured density because adipose tissue is radiolucent. Conversely, breasts composed of a higher proportion of fibroglandular tissue have higher measured density. High density is related to breast cancer risk factors, such as nulliparity, a positive family history of breast cancer, and menopausal hormone therapy use; yet studies consistently demonstrate that, compared with low density, high density confers relative risks (RRs) of four- to fivefold for breast cancer, independent of these and other factors [reviewed in (1)]. Although high density may contribute to delayed detection because of radiologic masking of tumors by dense tissue, reduced mammographic sensitivity alone does not explain the increased breast cancer risk associated with high density (2). In fact, the association between density and risk persists over extended periods and with repeated screening [reviewed in (3)].

Compared with breast cancers associated with low density, cancers arising in dense breasts often demonstrate adverse prognostic features, including larger size, higher histological grade, positive lymph nodes, lymphatic or vascular invasion, and advanced stage (4–10). Neither the reasons underlying the association of high density with increased breast cancer risk nor those accounting for its associations with more aggressive tumor characteristics are completely understood. Microscopic regions of fibroglandular tissue correspond to radiologically dense areas [reviewed in (11)]. However, several studies (12–15) have reported that the absolute amount of radiologically dense area is less predictive of risk than the proportion of the breast composed of dense tissue, suggesting that both dense and nondense radiological components may contribute to the risk associated with mammographic density.

Although data have consistently demonstrated that high density increases risk of breast cancer, it is unclear whether breast cancer patients with high density are at increased risk of death from breast cancer compared with those with low density, after adjusting for

other patient and tumor characteristics. One report did not find a statistically significant difference in breast cancer–specific survival by BI-RADS density (16), whereas another identified a reduction in breast cancer deaths among women with radiologically "mixed/dense" breasts as compared with those with fatty breasts (17). Similarly, it is unclear whether breast cancer patients with higher density have an overall increased risk of death (17–20). Given the hypothesis that high mammographic density reflects cumulative exposure to elevated levels of circulating growth factors (11), high mammographic density may also represent a risk factor for promotion of other types of cancers as well as nonneoplastic diseases. In two studies (18,19), density was not linked to risk of death; in a third study (17), high density was associated with a decreased risk of death, and in a fourth study (20) nested within a Swedish mammography screening trial, high density was related to an increased risk of death of borderline statistical significance. Specifically, the Swedish analysis (20), which was the only one to incorporate adjustments for confounding factors and treatment, found that higher density was related to a relative risk of death of 1.75 (95% confidence interval (CI) = 0.99 to 3.10), after adjusting for age, tumor size, nodal status, grade, and body mass index (BMI). Given that these individual studies included fewer than 1000 breast cancer cases, used different methods to visually assess breast density, and yielded conflicting results, additional analyses are warranted to assess the relationships between density and risk of death due to breast cancer and to all causes.

Accordingly, we undertook an analysis within the US Breast Cancer Surveillance Consortium (BCSC), a population-based registry of breast imaging facilities, to assess the primary hypothesis that elevated breast density is associated with increased risk of breast cancer death among women diagnosed with invasive breast carcinoma, after accounting for other patient and tumor characteristics. As a secondary aim, motivated by prior inconsistent reports, we assessed relationships between density and death from any cause. The BCSC offers several advantages for studying these associations relative to other studies, including the prospective follow-up of a large number of breast cancer patients with detailed information regarding potential confounding factors, including BMI, as well as on screening history, tumor characteristics, and treatment.

Methods

Study Population

The National Cancer Institute–sponsored BCSC was established in 1994 and consists of seven US mammography registries supported by a central statistical coordinating center (SCC), as described elsewhere (21). We restricted our analysis to five BCSC registries that consistently collect data on BMI, which is an adverse prognostic factor for breast cancer (22) that is inversely related to density (11) and, therefore, could potentially confound associations between density and breast cancer death. Thus, our analysis is based on data from the Group Health Cooperative in Washington State, the New Hampshire Mammography Network, the New Mexico Mammography Project, the San Francisco Mammography Registry, and the Vermont Breast Cancer Surveillance System. Each BCSC registry and the SCC have received Institutional Review Board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytical studies. All procedures are Health Insurance Portability and Accountability Act compliant and all registries and the SCC have received a Federal Certificate of Confidentiality for the protection of the identities of women, physicians, and facilities involved with this research.

We restricted this analysis to women aged 30 years and older at the time of their diagnosis with primary incident invasive breast carcinoma. To capture Breast Imaging Reporting and Data System (BI-RADS) breast density assessment from a mammography exam conducted before diagnosis (see details in "Exposure Assessment" below) and to allow for at least three additional years of follow-up for vital status data across registries, we included women diagnosed with cancer between January 1, 1996 and December 31, 2005, with the exception of one registry whose radiology data was complete through August 31, 2005. Of the 26 571 case patients meeting our inclusion criteria, we excluded 5584 who lacked an "index mammogram" (see definition below) and 8382 without BI-RADS density data. We also excluded 281 women with missing American Joint Committee on Cancer (AJCC) stage and one woman with an unqualified AJCC stage of II, because we were unable to distinguish between stage IIA and IIB. We also excluded 2921 women with missing information on BMI and 170 underweight (BMI $<18.5\ kg/m^2$) women, resulting in a final analytic cohort of 9232 women with breast cancer. The BI-RADS density distribution was similar among women with missing BMI compared to those who were included in analyses (data not shown).

Exposure Assessment

Breast density was collected according to the American College of Radiology BI-RADS, a standardized visual assessment metric that is routinely reported by radiologists in the United States. The four BI-RADS breast density categories include: 1) almost entirely fat; 2) scattered fibroglandular densities (referred to in Results as "scattered"); 3) heterogeneously dense ("heterogeneous"); and 4) extremely dense (23). According to BI-RADS, the higher (ie, denser) category should be recorded if density differs between the left and right breasts. We identified an "index mammogram" and used the BI-RADS density score from this exam for analyses. To select the index mammogram, we applied a hierarchical algorithm, first identifying an exam with routine bilateral mammographic views obtained within 5 years before breast cancer diagnosis and selecting the exam that occurred closest in time but before the diagnosis date (89% of case subjects). If an exam with routine bilateral views was not available, then we used the BI-RADS density measurement from the most recent diagnostic exam (10% of case patients). If a prediagnostic mammogram was not available, then we selected the BI-RADS density measurement from the earliest mammographic exam occurring within 30 days after diagnosis (1% of case patients). We used the BI-RADS density and the indication for the index mammogram that was recorded by the radiologist who evaluated the mammogram at the mammography facility.

The BCSC registries collect a standard set of core variables through questionnaires given to women at the time of mammography, including race, ethnicity, ZIP code, height, weight, reproductive history, and exogenous hormone use. Height and weight were

used to calculate BMI (kg/m^2) at the time of the index mammogram. We defined the annual median income as the average for each woman's ZIP code area of residence, based on census information.

We ascertained breast cancer pathology data through the Surveillance, Epidemiology, and End Results (SEER) program and linkage to state cancer registries and/or pathology databases, which included data on tumor characteristics, such as AJCC's Collaborative Stage (5th edition). We collected treatment data from SEER and state cancer registry linkages. The mode of cancer detection was determined by examining mammograms within 365 days before diagnosis and applying the following hierarchy: screen-detected, interval-detected, other screen-detected, clinically detected, or other means of detection. Cancers were considered screen-detected if the diagnosis was preceded by a positive screening mammogram within 12 months and as interval-detected if preceded by a prior negative screening mammogram within 12 months. We used the BCSC definition of a screening mammogram, which requires a recorded designation of screening with routine bilateral views and no record of a mammogram in the prior 9 months, prior cancer diagnosis, or breast implants. A screening mammogram was considered positive if there was a BI-RADS assessment code (23) of 0, 4, 5, or 3 with a recommendation for immediate follow-up. A negative screening mammogram included BI-RADS assessment codes of 1, 2, and 3 with a recommendation for normal or short-interval follow-up. The mode of detection was "other screen" if there was a prior screening mammogram based on the indication for exam but not meeting the BCSC screening definition. A clinically detected cancer had a prior mammogram with an indication for evaluation of a breast problem. Mode of detection was preferentially determined using mammograms within 365 days before cancer diagnosis; otherwise, we used data from mammograms performed within 30 days following diagnosis. If these data were lacking, we coded the mode of detection as "other."

Vital Status

Follow-up information included vital status (alive or dead), follow-up date, and cause of death (if applicable) obtained from cancer registries and state vital records. For three registries, state death information was complete through 2008, and for two through 2009. Cancer registry data were used preferentially when available. Women were presumed to be alive at the date through which the state vital records were complete if they were not identified as deceased in the cancer registry data or state vital records. The SCC performed detailed data quality checks to test for inconsistencies in death dates between cancer registry and state death data sources, and no gross inconsistencies were found.

Statistical Analysis

We examined the distribution of patient and clinical characteristics by BI-RADS density to describe the study population and identify potential covariates of interest with respect to the association between density and risk of breast cancer death. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for breast cancer death and death from all causes associated with BI-RADS density, using years since diagnosis as the time scale. Given the rarity of BI-RADS 1 density, we used BI-RADS 2 density as the referent group to increase the stability of the models. We used the Wald statistic to test for an overall effect of categorical BI-RADS density on risk of death. We also tested for a trend (χ^2 test with 1 degree of freedom) in the relation between density and risk of death. Examination of Kaplan–Meier curves and plots of Schoenfeld residuals did not indicate that the proportional hazards assumption was violated.

Analyses were stratified by AJCC stage at diagnosis (I, IIA, IIB, III, IV). We first examined unadjusted hazard ratios and then conducted "simple" multivariable analyses adjusting for covariates that we had identified a priori as being essential, including registry site (five sites), age at diagnosis (30–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, ≥80 years), and, to account for potential cohort effects, year of diagnosis (1996–1998, 1999–2001, 2002–2003, 2004–2005). We conducted sensitivity analyses to evaluate three different approaches for age adjustment: categorical age (as described above), cubic splines, and risk set stratification (risk sets were defined using the categories noted above for age at diagnosis). The three age adjustment methodologies yielded similar results; we, therefore, used categorical age to facilitate interpretation of results. In addition, we examined hazard ratios from the "simple adjusted" model both without and with BMI (18.5 – <25, 25 – <30, ≥30 kg/m^2). Because BMI attenuated results and statistically significantly contributed to the multivariable models, it was included in all subsequent multivariable models.

We present results from simple multivariable models, without and with BMI adjustment, as well as "fully adjusted" multivariable models. We constructed fully adjusted multivariable models using covariates incorporated in the simple adjusted model, including BMI, and additional potential confounding factors, including mode of detection (screen-detected, interval-detected, other screen, clinically detected, other means of detection), surgery/radiation (no breast surgery, breast conserving therapy without radiation, breast conserving therapy with radiation, other surgery), chemotherapy (yes/no), and annual median income in approximate quartiles (<$42 000, $42 000 – <$52 000, $52 000 – <$66 000, ≥$66 000). We excluded women with any unknown covariate information from multivariable models. In addition, we stratified by breast cancer characteristics potentially related to both BI-RADS density and survival, such as tumor size (<2.0 vs ≥2.0 cm), histology (ductal, lobular, and mixed), grade (low, intermediate, high), lymph node status (negative, positive), and hormone receptor status (estrogen receptor [ER] negative, ER positive, progesterone receptor [PR] negative, PR positive). We also examined whether the relationship between BI-RADS density and breast cancer death differed by BMI (18.5 – <25, 25 – <30, ≥30 kg/m^2). In analyses including all stages, we adjusted for stage at diagnosis. Because of the high proportion of breast cancer deaths (61%) among the small number of women with AJCC stage IV breast carcinoma (n = 257), we further examined associations after excluding these women. Probability values of less than .05 were considered statistically significant. All tests of statistical significance were two-sided. Analyses were performed using SAS software (SAS Institute Inc., Cary, NC).

Results

Distribution of Patient Characteristics by BI-RADS Breast Density

The mean age at breast cancer diagnosis was 59 years (SD = 13.0; Table 1). Women were predominantly of non–Hispanic white race/

Table 1. Patient characteristics by BI-RADS mammographic density categories*

Characteristic	All categories, N = 9232†	Breast density, N (%) BI-RADS 1, N = 560‡	BI-RADS 2, N = 3735‡	BI-RADS 3, N = 4019‡	BI-RADS 4, N = 918‡
Time of diagnosis					
Diagnosis year					
1996–1998	1744 (18.9)	118 (21.1)	775 (20.7)	670 (16.7)	181 (19.7)
1999–2001	3093 (33.5)	143 (25.5)	1212 (32.4)	1434 (35.7)	304 (33.1)
2002–2003	2309 (25.0)	138 (24.6)	908 (24.3)	1034 (25.7)	229 (24.9)
2004–2005	2086 (22.6)	161 (28.8)	840 (22.5)	881 (21.9)	204 (22.2)
Age at diagnosis, y					
30–34	105 (1.1)	2 (0.4)	25 (0.7)	46 (1.1)	32 (3.5)
35–39	294 (3.2)	4 (0.7)	76 (2.0)	151 (3.8)	63 (6.9)
40–44	762 (8.3)	16 (2.9)	195 (5.2)	395 (9.8)	156 (17.0)
45–49	1139 (12.3)	25 (4.5)	301 (8.1)	608 (15.1)	205 (22.3)
50–54	1332 (14.4)	38 (6.8)	455 (12.2)	668 (16.6)	171 (18.6)
55–59	1284 (13.9)	55 (9.8)	533 (14.3)	579 (14.4)	117 (12.7)
60–64	1070 (11.6)	75 (13.4)	493 (13.2)	435 (10.8)	67 (7.3)
65–69	958 (10.4)	86 (15.4)	459 (12.3)	379 (9.4)	34 (3.7)
70–74	922 (10.0)	87 (15.5)	481 (12.9)	322 (8.0)	32 (3.5)
75–79	680 (7.4)	81 (14.5)	353 (9.5)	228 (5.7)	18 (2.0)
≥80	686 (7.4)	91 (16.3)	364 (9.7)	208 (5.2)	23 (2.5)
Mean (SD) age	59 (13.0)	67 (12.0)	63 (12.6)	57 (12.4)	51 (11.0)
Race/ethnicity					
White, non-Hispanic	7530 (81.6)	439 (78.4)	3067 (82.2)	3308 (82.3)	716 (78.0)
Black, non-Hispanic	141 (1.5)	15 (2.7)	60 (1.6)	55 (1.4)	11 (1.2)
Asian	295 (3.2)	7 (1.3)	87 (2.3)	141 (3.5)	60 (6.5)
American Indian or Alaskan Native	93 (1.0)	12 (2.1)	42 (1.1)	31 (0.8)	8 (0.9)
Hispanic	1025 (11.1)	77 (13.8)	436 (11.7)	401 (10.0)	111 (12.1)
Other/Mixed	146 (1.6)	10 (1.8)	41 (1.1)	83 (2.1)	12 (1.3)
Time of index mammogram					
BMI, kg/m^2					
18.5 – <25	4140 (44.8)	152 (27.1)	1303 (34.9)	2013 (50.1)	672 (73.2)
25 – <30	2838 (30.7)	178 (31.8)	1249 (33.4)	1250 (31.1)	161 (17.5)
≥30	2254 (24.4)	230 (41.1)	1183 (31.7)	756 (18.8)	85 (9.3)
Mean (SD) BMI	26.9 (5.8)	29.8 (6.7)	28.2 (6.1)	26.1 (5.1)	23.9 (4.6)
Annual median income					
<$42 000	1997 (21.8)	163 (29.3)	899 (24.2)	738 (18.5)	197 (21.7)
$42 000 – <$52 000	2709 (29.5)	168 (30.2)	1127 (30.3)	1165 (29.2)	249 (27.5)
$52 000 – <$66 000	2285 (24.9)	128 (23.0)	901 (24.3)	1057 (26.5)	199 (21.9)
≥$66 000	2181 (23.8)	98 (17.6)	788 (21.2)	1033 (25.9)	262 (28.9)
Age at first birth, y					
<30	5599 (69.6)	371 (77.1)	2414 (75.6)	2393 (67.0)	421 (52.9)
≥30 or nulliparous	2446 (30.4)	110 (22.9)	780 (24.4)	1181 (33.0)	375 (47.1)
Menopausal status					
Postmenopausal					
Natural menopause	2919 (32.3)	224 (40.3)	1337 (36.5)	1194 (30.4)	164 (18.4)
Oophorectomy	559 (6.2)	36 (6.5)	266 (7.3)	223 (5.7)	34 (3.8)
Age ≥55 years	2520 (27.9)	235 (42.3)	1223 (33.4)	927 (23.6)	135 (15.2)
Other reason	737 (8.2)	31 (5.6)	252 (6.9)	356 (9.1)	98 (11.0)
Perimenopausal	163 (1.8)	1 (0.2)	56 (1.5)	83 (2.1)	23 (2.6)
Premenopausal	2141 (23.7)	29 (5.2)	533 (14.5)	1144 (29.1)	435 (48.9)
Current HT use§					
No	3995 (63.4)	405 (82.8)	1992 (69.3)	1385 (55.1)	213 (50.0)
Yes	2307 (36.6)	84 (17.2)	883 (30.7)	1127 (44.9)	213 (50.0)

* BI-RADS = Breast Imaging Reporting and Data System; BMI = body mass index; HT = hormone therapy.
† Missing values were excluded from percentage calculations.
‡ BI-RADS 1 = almost entirely fat; BI-RADS 2 = scattered fibroglandular densities; BI-RADS 3 = heterogeneously dense; BI-RADS 4 = extremely dense.
§ Peri- and postmenopausal only.

ethnicity (81.6%), postmenopausal (74.6%), and on average overweight with a mean self-reported BMI of 27 (SD = 5.8) kg/m^2. Approximately 84% of women were classified within the two intermediate breast density categories of BI-RADS 2 or 3. Compared with women with BI-RADS 1 or 2 density, women with BI-RADS 3 or 4 density tended to be younger, premenopausal, leaner, residents of higher income areas, current users of menopausal hormone therapy, and nulliparous or older at first birth.

In 79.6% of case patients, the interval between the index mammogram and cancer diagnosis was less than 1 year, and this interval varied little by BI-RADS density (Table 2). Women with higher BI-RADS density were more likely to have had interval breast cancers (15.7% for BI-RADS 4 vs 4.5% for BI-RADS 1), positive lymph nodes (34.3% for BI-RADS 4 vs 24.7% for BI-RADS 1), and treatment with chemotherapy (51.1% for BI-RADS 4 vs 26.4% for BI-RADS 1); however, women with BI-RADS 1 density were slightly more likely to be diagnosed with AJCC stage IV breast cancer.

Relationships Between Breast Density and Risk of Death

The analysis included 9232 case patients (average follow-up of 6.6 years) with 60 759 person-years of follow-up and 1795 deaths, including 889 from breast cancer and 810 from other causes. The remaining 96 women with deaths of uncertain cause were excluded from cause-specific models but included in all cause models. In analyses of all stages combined, BI-RADS density was not statistically significantly related to risk of breast cancer death (P =.09 for overall effect in fully adjusted multivariable model; P for trend = .23; Table 3). In the fully adjusted model, among women with BI-RADS 4 density, the hazard ratio for breast cancer death was 0.92 (95% CI: 0.71 to 1.19) when compared with women with BI-RADS 2 density. Women with BI-RADS 1 density had an elevated risk of breast cancer death (HR = 1.36, 95% CI = 1.04 to 1.77). Repeat analysis excluding stage IV cancers (Table 3) yielded a similar, albeit non-statistically significant, risk estimate for breast cancer death among women with BI-RADS 1 density compared with women with BI-RADS 2 density (HR = 1.22, 95% CI = 0.90 to 1.64). BI-RADS density was not associated with death due to all causes, overall (HR for BI-RADS 4 vs BI-RADS 2 = 0.83, 95% CI = 0.68 to 1.02; P = .22 for overall effect), or in stage-stratified analyses (Supplementary Table 1, available online).

Risk Associations by Tumor Characteristics and BMI

Among women with tumors of at least 2.0 cm, BI-RADS 1 density was associated with an increased risk of breast cancer death (HR = 1.55, 95% CI = 1.14 to 2.09; P = .003 for overall effect of BI-RADS density; Table 4). Women who had both BI-RADS 1 density and high-grade tumors had an increased risk of breast cancer death (HR = 1.45, 95% CI = 1.05 to 2.02; P = .13 for overall effect of density). Although BI-RADS density did not modify risk of breast cancer death in relationship to other pathological factors, women with BI-RADS 1 density tended to have the highest risk, in every stratum.

We also explored whether BMI modified the relationship between density and risk of breast cancer death (Table 5). We found a statistically significant interaction between BMI and BI-RADS density with respect to breast cancer death (P for interaction = .007); specifically, elevated risk associated with having almost entirely fatty breasts was apparent for obese women (BMI ≥30 kg/m^2, HR = 2.02, 95% CI = 1.37 to 2.97) but not overweight (BMI 25 – <30 kg/m^2, HR = 0.70, 95% CI = 0.40 to 1.23) or lean (BMI 18.5 – <25 kg/m^2, HR = 1.27, 95% CI = 0.74 to 2.17) women. To determine whether this association was being driven by a subgroup of women who were morbidly obese (BMI ≥40 kg/m^2), we conducted post hoc analyses after excluding 313 morbidly obese women, of whom 47 died of breast cancer. In BMI-stratified results, the elevated risk associated with having almost entirely fatty breasts remained apparent for obese women (BMI 30 – <40 kg/m^2, HR = 1.68, 95% CI = 1.07 to 2.63), and the interaction between breast density and BMI was still statistically significant (P = .01).

Discussion

This prospective analysis of over 9000 women with invasive breast carcinoma suggests that BI-RADS density is not related to risk of breast cancer death or death from any cause. However, our data suggest that breast cancer patients with low density (BI-RADS 1) who are obese, or diagnosed with large tumors, or possibly have high-grade tumors are at increased risk of breast cancer death. Given that high breast density has been related to breast cancers with adverse prognostic features, we had hypothesized that elevated density might be related to reduced breast cancer survival, although that is not the finding in this analysis. Thus, our results raise additional questions regarding possible interactions between breast density, other patient characteristics, and subsequent treatment in influencing breast cancer prognosis.

The null finding we observed between breast density and breast cancer death is consistent with one (16) of two previous studies to have evaluated this association (16,17). In a British hospital–based study of 759 breast cancer patients, breast cancer–specific survival did not differ by BI-RADS density (the number of breast cancer deaths was not reported) (16). In contrast, an analysis (17) of 989 breast cancer patients identified within the Danish mammography screening program found that having mixed/dense breasts was associated with a reduced risk of breast cancer death compared with having fatty breasts (roughly equivalent to BI-RADS 1 or some BI-RADS 2; age-adjusted RR = 0.53, 95% CI = 0.34 to 0.82, n = 90 breast cancer deaths). The varying results for density and risk of death across these studies could be a result of small numbers of case patients, differences in density assessment and classification, or incomplete adjustment for confounding factors and effect modifiers, including BMI. In addition, international differences in populations or treatments may contribute to differing results.

In contrast to our results, previous studies have not reported an elevated risk of breast cancer death associated with low (BI-RADS 1) density among specific subgroups of breast cancer case patients. One explanation for the increased risks associated with low density among some subgroups is that breasts with a higher percentage of fat may contribute to a tumor microenvironment that facilitates cancer growth and progression. We found that the relation between BI-RADS density and risk of breast cancer death was in fact statistically significantly modified by BMI, an exposure that is directly associated with increased risk of advanced disease at diagnosis (24), worse prognosis (22), and lower breast density (11). In our study, an adverse relationship between low density and risk of breast cancer death was most apparent among obese women. BMI and BI-RADS density are strongly and inversely related; however, only 10% of obese women in this analysis had BI-RADS 1 density. This subgroup constituted 2.5% of our breast cancer study population and included 4.5% of breast cancer deaths. Thus, findings particular to this group might be missed in a smaller study and require replication, particularly in light of the large number of statistical comparisons performed in our analyses. However, our data suggest that breast cancer patients with BI-RADS 1 density are at

Table 2. Clinical characteristics by BI-RADS mammographic density categories*

Characteristic	All categories, N = 9232†	Breast density, N (%) BI-RADS 1, N = 560‡	BI-RADS 2, N = 3735‡	BI-RADS 3, N = 4019‡	BI-RADS 4, N = 918‡
Characteristics of index mammogram					
Interval between index mammogram and cancer diagnosis					
0–7 d before diagnosis	2299 (24.9)	142 (25.4)	888 (23.8)	1050 (26.1)	219 (23.9)
8–30 d before diagnosis	2786 (30.2)	177 (31.6)	1199 (32.1)	1167 (29.0)	243 (26.5)
31–365 d before diagnosis	2264 (24.5)	129 (23.0)	928 (24.8)	989 (24.6)	218 (23.7)
>365 d before diagnosis	1584 (17.2)	90 (16.1)	625 (16.7)	676 (16.8)	193 (21.0)
30 d after diagnosis	299 (3.2)	22 (3.9)	95 (2.5)	137 (3.4)	45 (4.9)
Time since last mammogram, y					
No previous mammogram	1021 (11.7)	65 (12.9)	408 (11.6)	429 (11.2)	119 (13.8)
<1	1207 (13.8)	50 (9.9)	466 (13.2)	554 (14.4)	137 (15.9)
1–2	5065 (58.0)	245 (48.6)	2017 (57.2)	2300 (60.0)	503 (58.4)
3–4	741 (8.5)	68 (13.5)	312 (8.8)	299 (7.8)	62 (7.2)
≥5	696 (8.0)	76 (15.1)	326 (9.2)	253 (6.6)	41 (4.8)
Indication for index mammogram					
Screening	6153 (66.9)	380 (67.9)	2624 (70.5)	2618 (65.4)	531 (57.8)
Additional evaluation	176 (1.9)	8 (1.4)	80 (2.2)	76 (1.9)	12 (1.3)
Short interval follow-up	208 (2.3)	7 (1.3)	89 (2.4)	93 (2.3)	19 (2.1)
Breast problem	2660 (28.9)	165 (29.5)	927 (24.9)	1213 (30.3)	355 (38.7)
Other	2 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.1)
Film or digital mammogram					
Film	7537 (95.7)	420 (95.2)	3032 (96.3)	3311 (94.8)	774 (97.7)
Digital	335 (4.3)	21 (4.8)	116 (3.7)	180 (5.2)	18 (2.3)
Mammogram views/indication					
Bilateral, routine views	8272 (89.6)	477 (85.2)	3370 (90.2)	3619 (90.0)	806 (87.8)
Diagnostic indication	960 (10.4)	83 (14.8)	365 (9.8)	400 (10.0)	112 (12.2)
Mode of detection					
Screen-detected	3742 (40.5)	231 (41.3)	1690 (45.2)	1575 (39.2)	246 (26.8)
Interval-detected	886 (9.6)	25 (4.5)	294 (7.9)	423 (10.5)	144 (15.7)
Other screen	730 (7.9)	66 (11.8)	316 (8.5)	296 (7.4)	52 (5.7)
Clinically detected	2784 (30.2)	175 (31.3)	963 (25.8)	1272 (31.6)	374 (40.7)
Other	1090 (11.8)	63 (11.3)	472 (12.6)	453 (11.3)	102 (11.1)
Tumor characteristics and treatment					
Tumor size, cm					
No size given	193 (2.1)	4 (0.7)	83 (2.3)	82 (2.1)	24 (2.7)
<1	1754 (19.4)	119 (21.8)	807 (22.1)	670 (17.0)	158 (17.7)
1 – <2	3630 (40.2)	212 (38.9)	1466 (40.2)	1598 (40.6)	354 (39.6)
≥2	3448 (38.2)	210 (38.5)	1295 (35.5)	1585 (40.3)	358 (40.0)
Positive lymph node(s)					
No	4142 (45.0)	262 (46.9)	1633 (43.8)	1829 (45.6)	418 (45.7)
Yes	2698 (29.3)	138 (24.7)	1005 (27.0)	1241 (30.9)	314 (34.3)
Not examined	2374 (25.8)	159 (28.4)	1090 (29.2)	942 (23.5)	183 (20.0)
AJCC stage, 5th edition					
I	4861 (52.7)	300 (53.6)	2101 (56.3)	2017 (50.2)	443 (48.3)
IIA	2274 (24.6)	139 (24.8)	875 (23.4)	1023 (25.5)	237 (25.8)
IIB	1150 (12.5)	61 (10.9)	432 (11.6)	539 (13.4)	118 (12.9)
III	690 (7.5)	37 (6.6)	235 (6.3)	322 (8.0)	96 (10.5)
IV	257 (2.8)	23 (4.1)	92 (2.5)	118 (2.9)	24 (2.6)
Grade					
1	1904 (22.3)	108 (21.2)	787 (22.8)	825 (22.1)	184 (21.4)
2	3613 (42.3)	191 (37.5)	1481 (42.9)	1586 (42.5)	355 (41.4)
3/4	3029 (35.4)	210 (41.3)	1181 (34.2)	1319 (35.4)	319 (37.2)
Histology type					
Ductal	6833 (76.4)	434 (79.8)	2807 (77.7)	2902 (74.6)	690 (76.9)
Lobular	782 (8.7)	43 (7.9)	298 (8.3)	368 (9.5)	73 (8.1)
Mixed	779 (8.7)	29 (5.3)	265 (7.3)	397 (10.2)	88 (9.8)
Other	550 (6.1)	38 (7.0)	242 (6.7)	224 (5.8)	46 (5.1)
ER/PR status§					
Test(s) not done	305 (3.7)	27 (5.4)	137 (4.1)	117 (3.2)	24 (2.9)
ER–/PR–	1397 (16.8)	107 (21.6)	539 (16.2)	615 (16.8)	136 (16.3)
ER–/PR+	146 (1.8)	9 (1.8)	54 (1.6)	71 (1.9)	12 (1.4)
ER+/PR–	947 (11.4)	63 (12.7)	400 (12.0)	387 (10.6)	97 (11.6)
ER+/PR+	5526 (66.4)	290 (58.5)	2197 (66.0)	2475 (67.5)	564 (67.7)
Surgery/radiation					
No breast surgery	286 (3.1)	26 (4.7)	118 (3.2)	118 (3.0)	24 (2.6)
BCT w/o radiation	1353 (14.8)	104 (18.7)	604 (16.4)	521 (13.0)	124 (13.6)
BCT w/ radiation	4253 (46.5)	234 (42.2)	1765 (47.9)	1865 (46.6)	389 (42.5)
Other surgery	3263 (35.6)	191 (34.4)	1200 (32.5)	1494 (37.4)	378 (41.3)

(Table continues)

Table 2. (Continued)

Characteristic	All categories, N = 9232†	Breast density, N (%) BI-RADS 1, N = 560‡	BI-RADS 2, N = 3735‡	BI-RADS 3, N = 4019‡	BI-RADS 4, N = 918‡
Chemotherapy					
No	5681 (62.4)	409 (73.6)	2513 (68.3)	2317 (58.5)	442 (48.9)
Yes	3417 (37.6)	147 (26.4)	1167 (31.7)	1642 (41.5)	461 (51.1)

* AJCC = American Joint Committee on Cancer; BCT = breast conserving therapy; BI-RADS = Breast Imaging Reporting and Data System; ER = estrogen receptor; PR = progesterone receptor.
† Missing values were excluded from percentage calculations.
‡ BI-RADS 1 = almost entirely fat; BI-RADS 2 = scattered fibroglandular densities; BI-RADS 3 = heterogeneously dense; BI-RADS 4 = extremely dense.
§ Borderline included as "positive."

Table 3. Survival model results for the relation between mammographic density and risk of breast cancer death, overall and by AJCC stage*

AJCC stage	BI-RADS breast density	No. of breast cancer deaths	Simple adjusted without BMI† HR (95% CI)	*P*§	Simple adjusted with BMI† HR (95% CI)	*P*§	Fully adjusted‡ HR (95% CI)	*P*§
All stages, I–IV¶	Almost entirely fat	72	1.38 (1.06 to 1.79)	.02	1.34 (1.03 to 1.74)	.12	1.36 (1.04 to 1.77)	.09
	Scattered	346	1 (referent)		1 (referent)		1 (referent)	
	Heterogeneous	387	0.96 (0.83 to 1.12)		1.01 (0.87 to 1.18)		1.07 (0.92 to 1.25)	
	Extremely dense	84	0.83 (0.65 to 1.07)		0.91 (0.71 to 1.18)		0.92 (0.71 to 1.19)	
Sensitivity analysis, excluding AJCC stage IV								
AJCC stages, I–III¶	Almost entirely fat	56	1.26 (0.94 to 1.69)	.07	1.23 (0.92 to 1.65)	.34	1.22 (0.90 to 1.64)	.33
	Scattered	291	1 (referent)		1 (referent)		1 (referent)	
	Heterogeneous	315	0.93 (0.79 to 1.09)		0.98 (0.83 to 1.16)		0.99 (0.83 to 1.17)	
	Extremely dense	70	0.78 (0.59 to 1.02)		0.87 (0.66 to 1.14)		0.84 (0.63 to 1.12)	
Stratified by AJCC stage								
I	Almost entirely fat	10	1.13 (0.58 to 2.22)	.70	1.09 (0.55 to 2.13)	.88	1.08 (0.55 to 2.13)	.62
	Scattered	68	1 (referent)		1 (referent)		1 (referent)	
	Heterogeneous	57	0.96 (0.67 to 1.39)		1.02 (0.70 to 1.47)		1.00 (0.68 to 1.46)	
	Extremely dense	9	0.66 (0.32 to 1.37)		0.76 (0.36 to 1.60)		0.61 (0.28 to 1.34)	
IIA	Almost entirely fat	16	1.25 (0.72 to 2.17)	.49	1.17 (0.67 to 2.03)	.75	1.12 (0.63 to 2.00)	.63
	Scattered	78	1 (referent)		1 (referent)		1 (referent)	
	Heterogeneous	81	0.93 (0.68 to 1.28)		0.99 (0.71 to 1.36)		0.95 (0.68 to 1.33)	
	Extremely dense	13	0.69 (0.38 to 1.27)		0.76 (0.41 to 1.40)		0.69 (0.37 to 1.27)	
IIB	Almost entirely fat	16	1.41 (0.81 to 2.45)	.47	1.39 (0.80 to 2.42)	.60	1.34 (0.76 to 2.36)	.63
	Scattered	78	1 (referent)		1 (referent)		1 (referent)	
	Heterogeneous	90	0.94 (0.68 to 1.28)		0.97 (0.71 to 1.34)		0.99 (0.71 to 1.37)	
	Extremely dense	20	0.82 (0.50 to 1.37)		0.87 (0.52 to 1.46)		0.83 (0.48 to 1.42)	
III	Almost entirely fat	14	1.29 (0.70 to 2.39)	.67	1.27 (0.68 to 2.34)	.88	1.25 (0.67 to 2.35)	.89
	Scattered	67	1 (referent)		1 (referent)		1 (referent)	
	Heterogeneous	87	0.93 (0.67 to 1.30)		1.01 (0.72 to 1.41)		1.04 (0.73 to 1.48)	
	Extremely dense	28	0.84 (0.53 to 1.33)		0.95 (0.59 to 1.53)		0.95 (0.58 to 1.55)	
IV	Almost entirely fat	16	1.68 (0.91 to 3.12)	.42	1.65 (0.89 to 3.08)	.45	1.87 (0.99 to 3.55)	.22
	Scattered	55	1 (referent)		1 (referent)		1 (referent)	
	Heterogeneous	72	1.08 (0.73 to 1.59)		1.06 (0.72 to 1.58)		1.40 (0.89 to 2.18)	
	Extremely dense	14	1.07 (0.56 to 2.05)		1.09 (0.57 to 2.08)		1.32 (0.64 to 2.73)	

P for covariates in fully adjusted model with all stages I–IV combined	
AJCC stage	<.001
Registry	.13
Age at diagnosis	<.001
Year of diagnosis	<.001
BMI	<.001
Mode of detection	<.001
Surgery/radiation	<.001
Chemotherapy	.009
Annual median income	.83

* AJCC = American Joint Committee on Cancer; BI-RADS = Breast Imaging Reporting and Data System; BMI = body mass index; CI = confidence interval; HR = hazard ratio. N = 96 women excluded from the cause-specific models.
† Without and with adjustment for BMI. Simple adjusted includes covariates for registry site (five sites), age at diagnosis (30–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, ≥80 years), year of diagnosis (1996–1998, 1999–2001, 2002–2003, 2004–2005), with and without BMI (18.5 – <25, 25 – <30, ≥30 kg/m^2).
‡ Fully adjusted model includes covariates for registry (five sites), age at diagnosis (30–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, ≥80 years), year of diagnosis (1996–1998, 1999–2001, 2002–2003, 2004–2005), BMI (18.5 – <25, 25 – <30, ≥30 kg/m^2), mode of detection (screen-detected, interval-detected, other screen, clinically detected, other), surgery/radiation (no breast surgery, breast conserving therapy without radiation, breast conserving therapy with radiation, other surgery), chemotherapy (yes/no), and annual median income (<$42 000, $42 000 – <$52 000, $52 000 – <$66 000, ≥$66 000). Women with missing covariate information were excluded.
§ *P* value from Wald statistic to test for an overall effect of categorical BI-RADS density. All statistical tests were two-sided.
¶ AJCC stage is included as a categorical covariate in models with all stages combined, with and without stage IV.

Table 4. Survival model results for the relation between mammographic density and risk of breast cancer death, stratified by tumor characteristics, AJCC stages I–IV combined*

Tumor characteristic	BI-RADS breast density	No. of breast cancer deaths	HR (95% CI)	*P*†
Tumor size, cm				
<2.0	Almost entirely fat	13	1.05 (0.56 to 1.95)	.99
	Scattered	90	1 (referent)	
	Heterogeneous	77	1.04 (0.75 to 1.45)	
	Extremely dense	18	1.01 (0.58 to 1.76)	
≥2.0	Almost entirely fat	56	1.55 (1.14 to 2.09)	.003
	Scattered	224	1 (referent)	
	Heterogeneous	272	1.07 (0.88 to 1.29)	
	Extremely dense	51	0.73 (0.52 to 1.02)	
Nodal status				
Negative	Almost entirely fat	12	1.20 (0.63 to 2.28)	.57
	Scattered	61	1 (referent)	
	Heterogeneous	82	1.09 (0.76 to 1.56)	
	Extremely dense	11	0.71 (0.36 to 1.41)	
Positive	Almost entirely fat	36	1.31 (0.89 to 1.92)	.45
	Scattered	175	1 (referent)	
	Heterogeneous	198	0.96 (0.78 to 1.19)	
	Extremely dense	57	1.07 (0.77 to 1.48)	
Grade				
Low (I)	Almost entirely fat	3	0.81 (0.20 to 3.33)	.46
	Scattered	19	1 (referent)	
	Heterogeneous	24	1.26 (0.61 to 2.58)	
	Extremely dense	1	0.27 (0.03 to 2.19)	
Intermediate (II)	Almost entirely fat	16	1.14 (0.63 to 2.04)	.44
	Scattered	85	1 (referent)	
	Heterogeneous	87	1.26 (0.91 to 1.75)	
	Extremely dense	17	0.91 (0.49 to 1.67)	
High (III/IV)	Almost entirely fat	48	1.45 (1.05 to 2.02)	.13
	Scattered	195	1 (referent)	
	Heterogeneous	226	1.03 (0.84 to 1.26)	
	Extremely dense	59	1.15 (0.84 to 1.58)	
Histology				
Ductal	Almost entirely fat	58	1.35 (1.00 to 1.82)	.23
	Scattered	260	1 (referent)	
	Heterogeneous	264	1.09 (0.90 to 1.31)	
	Extremely dense	69	0.99 (0.74 to 1.33)	
Lobular	Almost entirely fat	3	0.99 (0.28 to 3.48)	.98
	Scattered	27	1 (referent)	
	Heterogeneous	38	0.89 (0.50 to 1.57)	
	Extremely dense	0	No breast cancer deaths	
Mixed	Almost entirely fat	2	1.43 (0.27 to 7.57)	.98
	Scattered	16	1 (referent)	
	Heterogeneous	29	0.99 (0.49 to 2.01)	
	Extremely dense	6	0.98 (0.32 to 2.98)	
Hormone receptor status				
ER−/PR−	Almost entirely fat	28	1.57 (1.01 to 2.45)	.18
	Scattered	105	1 (referent)	
	Heterogeneous	125	0.98 (0.74 to 1.31)	
	Extremely dense	30	1.16 (0.73 to 1.82)	
ER−/PR+‡	Almost entirely fat	3	8.26 (0.49 to 139.19)	.48
	Scattered	8	1 (referent)	
	Heterogeneous	18	1.99 (0.45 to 8.85)	
	Extremely dense	3	1.39 (0.20 to 9.56)	
ER+/PR−‡	Almost entirely fat	11	1.75 (0.83 to 3.67)	.24
	Scattered	43	1 (referent)	
	Heterogeneous	40	0.96 (0.59 to 1.58)	
	Extremely dense	10	0.62 (0.28 to 1.38)	
ER+/PR+‡	Almost entirely fat	21	1.28 (0.78 to 2.09)	.10
	Scattered	134	1 (referent)	
	Heterogeneous	151	1.25 (0.97 to 1.61)	
	Extremely dense	27	0.80 (0.51 to 1.27)	

* N = 96 women excluded from cause-specific models. Fully adjusted model includes covariates for AJCC stage (I, IIA, IIB, III, IV), registry (five sites), age at diagnosis (30–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, ≥80 years), year of diagnosis (1996–1998, 1999–2001, 2002–2003, 2004–2005), body mass index (18.5 – <25, 25 – <30, ≥30 kg/m^2), mode of detection (screen-detected, interval-detected, other screen, clinically detected, other), surgery/radiation (no breast surgery, breast conserving therapy without radiation, breast conserving therapy with radiation, other surgery), chemotherapy (yes/no), and annual median income (<$42 000, $42 000 – <$52 000, $52 000 – <$66 000, ≥$66 000). Women with missing covariate information were excluded. AJCC = American Joint Committee on Cancer; BI-RADS = Breast Imaging Reporting and Data System; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; PR = progesterone receptor.

† *P*-value from Wald statistic to test for an overall effect of categorical BI-RADS density. All statistical tests were two-sided.

‡ Borderline included as "positive."

Table 5. Survival model results for the relation between mammographic density and risk of breast cancer death, stratified by BMI*

BMI, kg/m²	BI-RADS breast density	No. of breast cancer deaths	HR (95% CI)†	*P*‡
18.5 – <25	Almost entirely fat	16	1.27 (0.74 to 2.17)	.24
	Scattered	107	1 (referent)	
	Heterogeneous	166	1.05 (0.80 to 1.38)	
	Extremely dense	43	0.75 (0.50 to 1.12)	
25 – <30	Almost entirely fat	16	0.70 (0.40 to 1.23)	.24
	Scattered	104	1 (referent)	
	Heterogeneous	122	1.04 (0.79 to 1.37)	
	Extremely dense	28	1.39 (0.89 to 2.17)	
≥30	Almost entirely fat	40	2.02 (1.37 to 2.97)	.003
	Scattered	135	1 (referent)	
	Heterogeneous	99	1.05 (0.79 to 1.38)	
	Extremely dense	13	0.87 (0.48 to 1.58)	

* BI-RADS, Breast Imaging Reporting and Data System; BMI, body mass index; CI, confidence interval; HR, hazard ratio. N = 96 women excluded from cause-specific models. All tumors: BMI × density interaction, $P = .007$.

† Fully adjusted model includes covariates for American Joint Committee on Cancer stage (I, IIA, IIB, III, IV), registry (five sites), age at diagnosis (30–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, ≥80 years), year of diagnosis (1996–1998, 1999–2001, 2002–2003, 2004–2005), mode of detection (screen-detected, interval-detected, other screen, clinically detected, other), surgery/radiation (no breast surgery, breast conserving therapy without radiation, breast conserving therapy with radiation, other surgery), chemotherapy (yes/no), and annual median income (<$42 000, $42 000 – <$52 000, $52 000 – <$66 000, ≥$66 000). Women with missing covariate information were excluded.

‡ *P* value from Wald statistic to test for an overall effect of categorical BI-RADS density. All statistical tests were two-sided.

increased risk of breast cancer death irrespective of tumor characteristics, supporting the robustness of the finding. Given the rising prevalence of obesity worldwide, it is likely that the number of women who are obese and have low breast density will also likely rise, and therefore this group may benefit from modified treatment and increased surveillance efforts.

Proposed explanations for the poorer survival among obese breast cancer patients have included treatment with insufficient doses of chemotherapy, increased levels of factors produced in adipose tissue, such as estrogens and adipokines, and indirect effects resulting in higher concentrations of insulin-like growth factors and elevated bioavailability of hormones [reviewed in (22)]. However, our data suggest that only a subset of obese women with fatty breasts (ie, 10% with low breast density) is at elevated risk of fatal cancers, thereby implicating the breast microenvironment in aggressive tumor biology. In support of this proposal, emerging data suggest that there are differences in metabolic and endocrine properties of adipose tissue between lean and a subset of obese women (25,26). In postmenopausal women with cancer, BMI and testosterone levels in breast adipose tissue are directly associated (25), and aromatase activity is increased in these patients (26), suggesting that local aromatization of androgens to estrogens may provide stimulus for tumor growth.

Both animal models and studies of human breast tissues have suggested that there are relationships between elevated BMI, larger adipocyte size, inflammation in the breast (26,27), and markers of increased cell proliferation (28). Furthermore, laboratory studies have suggested that adipocytes interact with breast cancer cells to create a microenvironment conducive to invasion and metastasis [reviewed in (29)]. It has been postulated that obesity-associated and cancer-associated adipocytes may share procarcinogenic attributes (30). Therefore, it is biologically plausible to propose that increased fat content within the breast (ie, among obese women with low breast density) may enhance or complement obesity-related mechanisms that heighten tumor aggressiveness.

Our findings are consistent with the idea that both the fibroglandular and adipose tissue components, which are reflected radiologically in mammographic breast density, play a role in breast carcinogenesis. However, we were unable to quantify dense and nondense areas in this analysis. BI-RADS density assessment has moderate interobserver reliability (31,32); any misclassification in this exposure would most likely have attenuated our findings, pointing to a need to replicate these findings using quantitative, reliable, and precise measurements of breast density. Furthermore, the growing evidence that the local tumor microenvironment is important in breast carcinogenesis points to the need for improved measures of breast density that account for its spatial distribution in localized regions in the breast.

In addition to the limitations of the BI-RADS density measure, our analysis was limited in that we lacked detailed, cumulative information on treatment, comorbidities, and changes in weight after diagnosis. Although we assessed numerous potential confounding factors, we cannot exclude the possibility of unmeasured confounding in our analysis. Nevertheless, we were able to account for mode of detection and many established prognostic factors collected in the BCSC.

Risk factors for the development of breast cancer may not necessarily be the same as factors influencing the risk of death from breast cancer once it has developed. It is reassuring that elevated breast density, a prevalent and strong breast cancer risk factor, was not associated with risk of breast cancer death or death from any cause in this large, prospective study. However, we identified subsets of women with breast cancer for whom low density was associated with adverse prognoses, highlighting the possibility of integrating breast density with epidemiological data and other measurements to understand mechanisms of breast carcinogenesis and to identify women who are likely to develop aggressive cancers, which might be preventable or detectable through specific interventions. Our findings underscore the need for an improved understanding of the biological characteristics of and the relationships between the breast tissue components that are responsible for the inter-individual variations in breast density. In future studies, evaluating targeted treatment and prevention strategies (such as use of aromatase inhibitors, metformin, weight

control or exercise), assessment of breast density, epidemiological characteristics, and collection of tissues for bioassays may aid in the identification of patients most likely to benefit from these agents and enhance our understanding of breast carcinogenesis.

References

1. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(6):1159–1169.
2. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007;356(3):227–236.
3. Vachon C, van Gils C, Sellers T, et al. Mammographic density, breast cancer risk and risk prediction. *Breast Cancer Res.* 2007;9(6):217.
4. Sala E, Warren R, McCann J, et al. Mammographic parenchymal patterns and mode of detection: implications for the breast screening programme. *J Med Screen*. 1998;5(4):207–212.
5. Sala E, Solomon L, Warren R, et al. Size, node status and grade of breast tumours: association with mammographic parenchymal patterns. *Eur Radiol*. 2000;10(1):157–161.
6. Harrison DA, Duffy SW, Sala E, et al. Deterministic models for breast cancer progression: application to the association between mammographic parenchymal pattern and histologic grade of breast cancers. *J Clin Epidemiol.* 2002;55(11):1113–1118.
7. Aiello EJ, Buist DSM, White E, et al. Association between mammographic breast density and breast cancer tumor characteristics. *Cancer Epidemiol Biomarkers Prev*. 2005;14(3):662–668.
8. Roubidoux MA, Bailey JE, Wray LA, et al. Invasive cancers detected after breast cancer screening yielded a negative result: relationship of mammographic density to tumor prognostic factors. *Radiology*. 2004;230(1):42–48.
9. Yaghjyan L, Colditz GA, Collins LC, et al. Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. *J Natl Cancer Inst.* 2011;103(15):1179–1189.
10. Kerlikowske K, Cook AJ, Buist DSM, et al. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. *J Clin Oncol.* 2010;28(24):3830–3837.
11. Martin LJ, Boyd NF. Mammographic density. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. *Breast Cancer Res*. 2008;10(1):201.
12. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst*. 1995;87(21):1622–1629.
13. Ursin G, Ma H, Wu AH, et al. Mammographic density and breast cancer in three ethnic groups. *Cancer Epidemiol Biomarkers Prev*. 2003;12(4):332–338.
14. Vachon CM, Brandt KR, Ghosh K, et al. Mammographic breast density as a general marker of breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2007;16(1):43–49.
15. Torres-Mejía G, De Stavola B, Allen DS, et al. Mammographic features and subsequent risk of breast cancer: a comparison of qualitative and quantitative evaluations in the Guernsey prospective studies. *Cancer Epidemiol Biomarkers Prev*. 2005;14(5):1052–1059.
16. Porter GJ, Evans AJ, Cornford EJ, et al. Influence of mammographic parenchymal pattern in screening-detected and interval invasive breast cancers on pathologic features, mammographic features, and patient survival. *Am J Roentgenol*. 2007;188(3):676–683.
17. Olsen AH, Bihrmann K, Jensen MB, et al. Breast density and outcome of mammography screening: a cohort study. *Br J Cancer* 2009;100:1205–1212.
18. van Gils CH, Otten JD, Verbeek AL, et al. Effect of mammographic breast density on breast cancer screening performance: a study in Nijmegen, The Netherlands. *J Epidemiol Community Health*. 1998;52(4):267–271.
19. Cil T, Fishell E, Hanna W, et al. Mammographic density and the risk of breast cancer recurrence after breast-conserving surgery. *Cancer*. 2009;115(24):5780–5787.
20. Chiu SY, Duffy S, Yen AM-F, et al. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. *Cancer Epidemiol Biomarkers Prev*. 2010;19:1219–1228.
21. Ballard-Barbash R, Taplin SH, Yankaskas BC, et al. Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. *Am J Roentgenol*. 1997;169(4):1001–1008.
22. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2010;123(3):627–635.
23. D'Orsi CJ, Bassett LW, Berg WA, et al. *Breast Imaging Reporting and Data System: ACR BI-RADS-Mammography*. 4th ed. Reston, VA: American College of Radiology; 2003.
24. Kerlikowske K, Walker R, Miglioretti DL, et al. Obesity, mammography use and accuracy, and advanced breast cancer risk. *J Natl Cancer Inst*. 2008;100(23):1724–1733.
25. Falk RT, Gentzschein E, Stanczyk FZ, et al. Sex steroid hormone levels in breast adipose tissue and serum in postmenopausal women. *Breast Cancer Res Treat*. 2012;131(1):287–294.
26. Morris PG, Hudis CA, Giri D, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. *Cancer Prev Res (Phila)*. 2011;4(7):1021–1029.
27. Sun X, Casbas-Hernandez P, Bigelow C, et al. Normal breast tissue of obese women is enriched for macrophage markers and macrophage-associated gene expression. *Breast Cancer Res Treat.* 2012;131(3):1003–1012.
28. Daling JR, Malone KE, Doody DR, et al. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. *Cancer*. 2001;92(4):720–729.
29. Tan J, Buache E, Chenard MP, et al. Adipocyte is a non-trivial, dynamic partner of breast cancer cells. *Int J Dev Biol*. 2011;55(7-9):851–859.
30. Dirat B, Bochet L, Escourrou G, Valet P, Muller C. Unraveling the obesity and breast cancer links: a role for cancer-associated adipocytes? *Endocr Dev*. 2010;19:45–52.
31. Ciatto S, Houssami N, Apruzzese A, et al. Categorizing breast mammographic density: intra- and interobserver reproducibility of BI-RADS density categories. *Breast*. 2005;14(4):269–275.
32. Kerlikowske K, Grady D, Barclay J, et al. Variability and accuracy in mammographic interpretation using the American College of Radiology Breast Imaging Reporting and Data System. *J Natl Cancer Inst*. 1998;90:1801–1809.

Funding

This work was supported (in part) by the Intramural Research Program of the National Institutes of Health, National Cancer Institute (NCI), and the NCI-funded Breast Cancer Surveillance Consortium (U01CA63740 to KK, U01CA86076 to DM, U01CA86082 to TO, U01CA63736 to GC, U01CA70013 to BG, U01CA69976 to RR, U01CA63731 to DB, U01CA70040 to BY, and HHSN261201100031C to DM).

Notes

The collection of cancer and vital status data used in this study was supported in part by several state public health departments and cancer registries throughout the United States. For a full description of these sources, please see http://www.breastscreening.cancer.gov/work/acknowledgement.html. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study. A list of the BCSC investigators and procedures for requesting BCSC data for research purposes are provided at http://breastscreening.cancer.gov/.

Affiliations of authors: Hormonal and Reproductive Epidemiology Branch (GLG, LAB, MES), Biostatistics Branch, Division of Cancer Epidemiology and Genetics (CS), Process of Care Research Branch, Behavioral Research Program, Division of Cancer Control and Population Sciences (SHT), National Cancer Institute, National Institutes of Health, Rockville, MD; Group Health Research Institute, Seattle, WA (LI); General Internal Medicine Section, San Francisco Veterans Affairs Medical Center, University of California San Francisco, San Francisco, CA (KK); University of Balamand, Beirut, Lebanon (GNF); Department of Medical Biostatistics, University of Vermont College of Medicine, Burlington, VT (PMV); Department of Pathology, University of Vermont College of Medicine and Vermont Cancer Center, Burlington, VT (DLW).