Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2020 October ; 29(10): 2048–2056.

doi:10.1158/1055-9965.EPI-20-0358.

Breast Cancer Population Attributable Risk Proportions Associated with Body Mass Index and Breast Density by Race/Ethnicity and Menopausal Status

Michael C. S. Bissell[1], **Karla Kerlikowske**[2], **Brian L. Sprague**[3], **Jeffery A. Tice**[4], **Charlotte C. Gard**[5], **Katherine Y. Tossas**[6], **Garth H. Rauscher**[7], **Amy Trentham-Dietz**[8], **Louise M. Henderson**[9], **Tracy Onega**[10], **Theresa H. M. Keegan**[11], **Diana L. Miglioretti**[1,12], **Breast Cancer Surveillance Consortium**

[1]Division of Biostatistics, Department of Public Health Sciences, University of California Davis School of Medicine, Davis, CA, USA

[2]General Internal Medicine Section, Department of Veteran Affairs and Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA

[3]Department of Surgery, Office of Health Promotion Research, Larner College of Medicine at the University of Vermont and University of Vermont Cancer Center, Burlington, VT, USA

[4]Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

[5]Department of Economics, Applied Statistics, and International Business, New Mexico State University, Las Cruces, NM, USA

[6]Department of Health Behavior and Policy, School of Medicine, Virginia Commonwealth University, Richmond VA, USA

[7]Division of Epidemiology and Biostatistics, University of Illinois at Chicago, Chicago, IL, USA

[8]Department of Population Health Sciences and Carbone Cancer Center, University of Wisconsin, Madison, Madison, WI, USA

[9]Department of Radiology, University of North Carolina at Chapel Hill, Chapel Hill, NC USA

[10]Department of Biomedical Data Science, Dartmouth College, Lebanon, NH, USA

[11]Center for Oncology Hematology Outcomes Research and Training (COHORT) and Division of Hematology and Oncology, University of California Davis School of Medicine, Sacramento, CA

[12]Kaiser Permanente Washington Health Research Institute, Kaiser Permanente Washington, Seattle, WA, USA

Abstract

Correspondence: Michael C. S. Bissell, PhD, University of California, Davis, Department of Public Health Sciences, Division of Biostatistics, One Shields Avenue, Med Sci 1C, Room 182B, Davis, CA 95616, Phone: (530) 752-9744, Fax: (530) 752-3239, mcbissell@ucdavis.edu.

Conflict of Interest Disclosure Statement: The authors declare no potential conflicts of interest.

Background.—Overweight/obesity and dense breasts are strong breast cancer risk factors whose prevalences vary by race/ethnicity. The breast cancer population attributable risk proportions (PARPs) explained by these factors across racial/ethnic groups are unknown.

Methods.—We analyzed data collected from 3,786,802 mammography examinations (1,071,653 women) in the Breast Cancer Surveillance Consortium, associated with 21,253 invasive breast cancers during a median of 5.2 years follow-up. Hazard ratios (HRs) for body mass index (BMI) and breast density, adjusted for age and registry were estimated using separate Cox regression models by race/ethnicity (white, black, Hispanic/Latina, Asian) and menopausal status. HRs were combined with observed risk-factor proportions to calculate PARPs for shifting overweight/obese to normal BMI and shifting heterogeneously/extremely dense to scattered fibroglandular densities.

Results.—The prevalences and HRs for overweight/obesity and heterogeneously/extremely dense breasts varied across races/ethnicities and menopausal status. BMI PARPs were larger for post- vs. premenopausal women (12.0–28.3% vs. 1.0–9.9%) and nearly double among postmenopausal black women (28.3%) than other races/ethnicities (12.0–15.4%). Breast density PARPs were larger for pre- vs. postmenopausal women (23.9–35.0% vs. 13.0–16.7%) and lower among premenopausal black women (23.9%) than other races/ethnicities (30.4–35.0%). Postmenopausal density PARPs were similar across races/ethnicities (13.0–16.7%).

Conclusion.—Overweight/obesity and dense breasts account for large proportions of breast cancers in white, black, Hispanic, and Asian women despite large differences in risk-factor distributions.

Impact.—Risk prediction models should consider how race/ethnicity interacts with BMI and breast density. Efforts to reduce BMI could have a large impact on breast cancer risk reduction, particularly among postmenopausal black women.

Keywords

breast cancer; population attributable risk; race/ethnicity; body mass index (BMI); BI-RADS breast density

Introduction

Body mass index (BMI) and breast density are well-established risk factors for breast cancer.[1–4] Higher breast density is associated with increased risk in both pre- and postmenopausal women.[5,6] Overweight and obesity are associated with increased risk of postmenopausal breast cancer.[3,4] Most large studies and meta-analyses found an inverse association between BMI and a premenopausal diagnosis of breast cancer, including a 2018 study by the Premenopausal Breast Cancer Collaborative Group.[7] However, a 2017 meta-analyses by Chen, et al. showed no association between increased BMI and a premenopausal breast cancer diagnosis[3] and a 2019 systematic literature review and meta-analysis by the World Cancer Research Fund International found an overall inverse association between BMI and a premenopausal breast cancer diagnosis but noted variability across regions; although European studies showed inverse associations, North American studies showed non-significant or inverse associations, and Asian studies showed positive associations.[8] Studies

evaluating the association between premenopausal BMI and future breast cancer (including breast cancers that may occur after the menopausal transition) show mixed results.[8–11]

Distributions of BMI and breast density vary by race/ethnicity and menopausal status. BMI is generally higher among black and Hispanic women,[12] which may be associated with lower breast density.[13,14] Breast density is well studied among Asian women, who have a high prevalence of heterogeneously/extremely dense breasts.[15] However, most studies report results only for specific races/ethnicities or subgroups and for BMI or breast density separately, but not both.[16–18]

Identifying risk factors that are both strongly associated with increased risk and are highly prevalent would help understand potential causes of a large proportion of breast cancers and help develop personalized screening strategies and other interventions to improve early detection and prevention. Studies on breast cancer population attributable risk proportions (PARPs) associated with BMI or breast density by menopausal status found they accounted for large proportions of breast cancers,[19–22] but these studies did not report results by race/ethnicity. We used U.S.-based Breast Cancer Surveillance Consortium (BCSC) data to estimate associations and PARPs of BMI and breast density with invasive breast cancer by race/ethnicity and menopausal status.

Materials and Methods

Study Setting, Data Sources, and Participants

In this cohort study, we selected all screening and diagnostic mammography examinations between January 1, 1994 and December 31, 2016 among women aged 35–84 years at seven U.S.-based BCSC registries (www.bcsc-research.org): Carolina Mammography Registry, New Hampshire Mammography Network, Vermont Breast Cancer Surveillance System, San Francisco Mammography Registry, Kaiser Permanente Washington Registry, Metro Chicago Breast Cancer Registry, and New Mexico Mammography Project. We excluded observations on women with a personal history of invasive breast cancer, ductal carcinoma in situ (DCIS), mastectomy, or breast implants, with invasive breast cancer or DCIS diagnosed within 3 months of the mammogram to remove prevalent cases, or with unknown American College of Radiology Breast Imaging Reporting and Data System (BI-RADS)[23] breast density, menopausal status, or BMI. Observations with multiple self-reported races or race/ethnicity other than the four under study (non-Hispanic white, non-Hispanic black/African American, Asian American, or Hispanic/Latina) were excluded due to small sample sizes. The final study cohort included 3,786,802 observations from 1,071,653 women with a median 5.2 years of follow-up, among whom 66,419 observations were from 21,253 women who were diagnosed with invasive breast cancer. Of these, 1,369,826 observations were from 518,852 premenopausal women who developed 7,337 breast cancers, and 2,416,976 observations were from 679,966 postmenopausal women who developed 15,256 breast cancers. Some women (N=127,165) became postmenopausal during the study, contributing to both cohorts.

BCSC registries and the Statistical Coordinating Center received Institutional Review Board approval for active or passive consenting processes or a waiver of consent to enroll participants, link and pool data, and perform analysis. All procedures were Health Insurance

Portability and Accountability Act compliant, and registries and the Coordinating Center received a Federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities.

Measures, Definitions, and Outcomes

Our main outcome was a primary, invasive breast carcinoma diagnosis. Diagnoses of invasive breast carcinoma and DCIS were obtained by linkage with pathology databases and regional Surveillance, Epidemiology, and End Results or state and regional tumor registries.

At each mammography examination, self-reported information on age, race/ethnicity, height and weight, and menopausal status was obtained from questionnaires. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and categorized using modified World Health Organization cutoffs[24]: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obesity class I (30.0–34.4 kg/m^2), and obesity class II/III (≥35.0 kg/m^2). Observations were considered premenopausal at the time of examination if the woman reported continued menstrual periods, current use of hormonal birth control, or not knowing if periods had stopped permanently (N=1,286,595); or were <45 years old in the absence of other information (N=83,231).[25] Observations were considered postmenopausal at the time of examination if the woman reported periods that stopped naturally, no period for more than 365 days, hysterectomy with bilateral oophorectomy, or current hormone therapy use (N=2,406,567); or were 55 years or older in the absence of other information (N=10,409).[25] Menopausal status was considered missing otherwise (N=325,220) and these observations were removed from the main analysis.[25] We performed two sensitivity analyses categorizing women with missing menopausal status as pre- or postmenopausal based on two different age cutoffs of 50 and 52 as proxies for age at menopause (Supplementary Tables 1a–1f).[25] Radiologists recorded BI-RADS breast density as almost entirely fat, scattered fibroglandular densities, heterogeneously dense, or extremely dense.[23]

Statistical Analysis

Separate analyses were performed for observations on the pre- and postmenopausal cohorts. Because women may contribute multiple mammograms and the number contributed may be related to overall breast cancer risk, we calculated frequencies, proportions, and hazard ratios (HRs) by inversely weighting each woman's observations by the total number of mammograms she contributed to each of the pre- and postmenopausal cohorts.[26]

We fit separate Cox proportional hazards regression models by race/ethnicity and menopausal status to estimate associations between BMI and breast density with invasive breast cancer. Standard errors were calculated using the robust sandwich variance estimator to account for correlation among multiple observations from the same woman.[26] Follow-up began 3 months after each mammogram to remove prevalent cases. In sensitivity analysis, we found that hazard ratios computed from starting follow-up at 6 months do not differ from hazard ratios computed from starting follow-up at 3 months (Supplementary Table 2). Models adjusted for age as a categorical variable to be consistent with the PARP analysis described below, with age categorized into the following groups: 35–49, 50–59, 60–69, and

70–85 years. Hazard ratio and confidence intervals were similar when adjusting for age as a continuous versus categorical variable. Models were stratified by BCSC registry to allow for separate baseline hazards. The proportional hazards assumption was tested using Schoenfeld residuals in goodness-of-fit tests[27] with all $P>0.10$. In sensitivity analyses, we repeated analyses for Asians using previously suggested lower cutpoints for overweight and obesity (Supplementary Table 3).[28] In sensitivity analyses, we also fit separate Cox models adjusting individually and simultaneously for first-degree family history of breast cancer, history of prior breast biopsy, age at first live birth, or postmenopausal hormone therapy use (Supplementary Tables 4a–4e).

We calculated partial PARPs using a publicly available SAS macro[29] that did not allow use of continuous variables, so age was categorized into the same groups used for estimating the HRs. PARPs for breast density shifted the proportion of women in the heterogeneously or extremely dense categories to scattered fibroglandular densities, while holding the proportion of women in the almost entirely fat category unchanged. PARPs for BMI shifted the proportion of overweight and obese women to normal BMI, while holding the proportion of underweight women unchanged. Observed proportions used to calculate PARPs were computed as total person-time in each combination of age, BMI, and breast density categories to match the analysis used to compute HRs.[29] We calculated Wald-based confidence intervals for pair-wise differences in PARPs using estimates of the standard errors from the macro and assuming unequal variances.

Statistical analyses were performed using SAS/STAT version 14.2 (Cary, NC). Tests of statistical significance used a two-sided alpha=0.05.

Results

Age distributions were similar across racial/ethnic groups among pre- and postmenopausal women, although premenopausal Hispanic women tended to be younger than other races/ethnicities (Table 1). Black women had the highest proportion of premenopausal (82.8%) and postmenopausal (82.7%) overweight or obese women, followed by Hispanic (63.0% premenopausal, 67.6% postmenopausal), white (49.7% premenopausal, 58.3% postmenopausal), and Asian women (29.3% premenopausal, 34.9% postmenopausal). Asian women had the highest proportion of dense breasts among premenopausal (81.2%) and postmenopausal (54.7%) women, followed by white women (61.3% premenopausal, 38.2% postmenopausal), Hispanic women (56.6% premenopausal, 30.9% postmenopausal), and Black women (56.0% premenopausal, 32.1% postmenopausal).

Table 2 shows associations of BMI and breast density with invasive breast cancer stratified by race/ethnicity and menopausal status. Comparing obese II/III to normal BMI among premenopausal women, white women had an increased risk of breast cancer (HR=1.18, 95% confidence interval [CI]=1.09–1.28) with a positive dose-response (P-trend<0.001). Hazard ratios associated with premenopausal BMI among black, Asian, and Hispanic women were not statistically significant.

Postmenopausal overweight/obese BMI showed increased HR estimates for breast cancer across all races/ethnicities studied (*P*-trend for increasing BMI <0.001). Comparing obese II/III to normal BMI, associations were strongest for Asian women (HR=2.21, 95% CI=1.60–3.05) and moderate for black women (HR=1.76, 95% CI=1.47–2.11). Associations were weakest, but still elevated, for white (HR=1.43, 95% CI=1.36–1.50) and Hispanic women (HR=1.37, 95% CI=1.13–1.66).

Pre- and postmenopausal breast density were moderate-to-strong breast cancer risk factors across all races/ethnicities (*P*-trend for increasing breast density <0.001). Comparing extremely dense breasts to scattered fibroglandular densities, Hispanic women had the strongest associations with a premenopausal HR of 2.43 (95% CI=1.94–3.06) and a postmenopausal HR of 2.06 (95% CI=1.67–2.54). Moderate-to-strong risk associated with breast density was observed in white women (premenopausal HR=2.05, 95% CI=1.91–2.19; postmenopausal HR=1.62, 95% CI=1.53–1.72) and black women (premenopausal HR=1.96, 95% CI=1.39–2.76; postmenopausal HR=1.69 95% CI=1.23–2.31). Asian women had the weakest associations with a premenopausal HR of 1.80 (95% CI=1.43–2.26) and a postmenopausal HR of 1.49 (95% CI=1.24–1.78).

Population Attributable Risk Proportions

Table 3 shows breast cancer PARPs associated with BMI and breast density by race/ethnicity and menopausal status. PARPs for BMI were larger for post- vs. premenopausal women (12.0–28.3% vs. 1.0–9.9%). Confidence intervals for PARPs associated with premenopausal BMI among black, Asian, and Hispanic women included zero and did not rule out a protective effect. The PARP associated with premenopausal BMI among white women was statistically significantly greater than zero but small (PARP=3.7%, 95% CI=0.6–6.7%). Postmenopausal BMI accounted for a large proportion of breast cancers among black women (PARP=28.3%, 95% CI=17.4–38.5%), nearly double the PARPs of other races/ethnicities (12.0–15.4%).

PARPs for breast density were larger for pre- vs. postmenopausal women (23.9–35.0% vs. 13.0–16.7%). Premenopausal breast density accounted for roughly one third of breast cancers among Hispanic (PARP=35.0%), Asian (PARP=33.2%) and white (PARP=30.4%) women, and 23.9% of breast cancers among black women (PARP=23.9%, 95% CI=10.6% −36.4%). Postmenopausal breast density accounted for a similar, substantial proportion of breast cancers across all races/ethnicities (13.0–16.7%).

Among premenopausal women, PARPs for reducing both high breast density and high BMI simultaneously were similar across races/ethnicities (31.7%−35.8%). PARPs for reducing both high breast density and high BMI among postmenopausal women were lower than premenopausal women and similar among white, Asian and Hispanic women (23.8% −27.8%), but were larger among black women (PARP=40.9%, 95% CI=28.2%−52.2%) driven by the large PARP associated with postmenopausal BMI among black women.

Pair-wise differences in PARPs across races/ethnicities did not show statistically significant differences except the PARP associated with postmenopausal BMI among black women was significantly higher than for other races/ethnicities (difference in PARPS for black vs.

white=12.9%, 95% CI=1.9%−24.0%; black vs. Asian=13.6%, 95% CI=0.8%−26.3%; black vs. Hispanic=16.3%, 95% CI=2.1%−30.6%).

Sensitivity analyses

Sensitivity analyses showed very little change in in the distributions of BMI and BI-RADS breast density by race/ethnicity and menopausal status when women with missing menopausal status were categorized as pre- or postmenopausal based on two different age cutoffs of 50 years and 52 years as proxies for age at menopause (Supplementary Tables 1a–1f). HRs also showed very little change except for moderate changes in the lowest BMI category of underweight and only among black and Hispanic women where we note that sample sizes are smallest, and the confidence intervals are very wide. PARPs also showed very little change with most changing less than 1% and none more than 3%.

In sensitivity analysis using more conservative BMI cutpoints suggested for Asian women,[28] we did not find meaningful differences in HRs (Supplementary Table 3). However, lower cutpoints shifted 21.3% of premenopausal Asian women from normal BMI to overweight and 6.8% from overweight to obese I and shifted 22.5% of postmenopausal Asian women from normal to overweight and 8.3% from overweight to obese I. Using lower cutpoints for Asian women increased their premenopausal BMI PARP from 3.3% (95% CI=−5.1% −11.7%) to 4.7% (95% CI=−6.7%−16.0%) and postmenopausal BMI PARP from 14.7% (95% CI=8.1%−21.2%) to 18.6% (95% CI=10.0%−27.0%).

Sensitivity analysis showed very limited evidence of confounding (i.e., HRs changed by <10.0%) when adjusting individually for age at first live birth, history of prior breast biopsy, use of hormone replacement therapy, and first-degree family history of breast cancer (Supplementary Tables 4a–4d). When adjusting for all confounders simultaneously, some hazard ratios in the highest BI-RADS breast density categories changed by approximately 10%, but we note that these groups have relatively small sample sizes, particularly among black and Hispanic women, and changes were smaller for white women where sample sizes were largest (Supplementary Table 4e).

Discussion

Our study is the first to directly investigate and report important racial/ethnic differences in PARPs associated with BMI and breast density among pre- and postmenopausal white, black, Hispanic, and Asian women. Across all racial/ethnic groups examined, breast density was a moderate-to-strong risk factor with a clear dose-response for increasing breast density that accounted for statistically and clinically significant proportions of invasive breast cancer among both premenopausal (23.0–35.0%) and postmenopausal (13.0–16.7%) women. Premenopausal BMI was not significantly associated with future breast cancer risk except for a small effect in white women; however, postmenopausal BMI was a strong risk factor with a clear dose-response for increasing BMI for all races examined. If all overweight/obese postmenopausal women achieved a normal BMI, breast cancer incidence could be reduced by 12–15% in white, Asian, and Hispanic women and 28% in black women.

Our findings are consistent with other studies in identifying breast density as a strong and prevalent risk factor for breast cancer and postmenopausal BMI as accounting for a large proportion of breast cancers.[19–22,30,31] Our findings that hazard ratios for premenopausal BMI showed small, but statistically significant, increased risk of future breast cancer among white women, but no significant differences among black, Asian, and Hispanic women, likely differ from most prior studies showing strong, inverse associations between BMI and premenopausal breast cancer[7,8] because our study evaluated premenopausal BMI and future breast cancer, including cancers that may occur after the menopausal transition.

Both pre-and postmenopausal PARPs associated with breast density were generally similar across races/ethnicities. However, the corresponding risk factor prevalences and HRs show important differences across races/ethnicities. Although Hispanic women had lower proportions of dense breasts, Hispanic women had the strongest associations between premenopausal breast density and breast cancer risk. In contrast, Asian women had the largest proportions of dense breasts but modest associations between breast density and breast cancer risk. Screening strategies that consider both breast density and risk may be particularly important for Hispanic and Asian women and risk prediction models should take into account the different prevalences and magnitudes of association with breast density across races/ethnicities when calculating absolute risk.

Postmenopausal BMI was a strong risk factor for all race/ethnicities examined but was a particularly important risk factor among black women. Black women had the highest prevalences of overweight and obesity, and strong associations between postmenopausal BMI and breast cancer risk, leading to almost twice the PARP as other races/ethnicities. Postmenopausal Asian women had the strongest associations between BMI and breast cancer risk, but the lowest prevalences of overweight/obesity resulting in similar PARPs as white and Hispanic women. In contrast, postmenopausal Hispanic women had the second highest prevalences of overweight/obesity but the weakest associations between BMI and breast cancer, resulting in PARPs similar to Asian and white women. By 2030, overall obesity (categories I/II/III) and severe obesity (categories II/III) are projected to rise to 49% and 24%, respectively, with severe obesity becoming the most prevalent BMI category among women and the highest prevalence of obesity projected among black adults followed by Hispanic and white adults.[32] While prevention efforts to avoid and reduce overweight and obesity should be a focus in all women, reducing weight in post-menopausal black women could result in the largest reductions in breast cancer risk.

As a potentially modifiable risk factor, BMI is an attractive target for intervention and risk reduction. Sustained weight loss in women aged 50 and older has been shown to reduce breast cancer risk.[33] In addition, changes in lifestyle factors such as increased vigorous physical activity and exercise, maintaining health body weight and body composition, breast feeding, reduced alcohol consumption, and increased consumption of fruits and vegetables are all associated with BMI[24,34] and all are associated with reduced breast cancer risk.[35] As an extreme example, dramatic weight loss associated with bariatric surgery among severely obese women has been shown to reduce overall and estrogen receptor-positive breast cancer risk.[36,37]

Breast density reduction is also associated with reduced risk of breast cancer.[38] Reduced breast cancer risk following weight loss or bariatric surgery may be due, in part, to reductions in total volume of dense breast tissue, although results for other breast density measures are conflicting.[39–41] Alcohol consumption increases breast cancer risk[35] but the effects on breast density remains unclear.[42] Preventive tamoxifen reduces breast density with the largest reductions in women under 45 years, in whom density is highest,[43] and reduces breast cancer risk in clinical trials by approximately one-third[44] among women who experienced at least a 10% density reduction.[45] Studies on aromatase inhibitors (AIs) and breast density reduction have mixed results.[46–48] One recent study found that AIs were associated with larger volumetric percent density reductions among postmenopausal women than tamoxifen, whereas tamoxifen was associated with larger density reductions among premenopausal women than AIs.[49] Studies of gonadotropin-releasing hormone agonist (GnRHA) show promise in chemoprevention and treatment through ovarian hormone suppression and may be associated with reduced breast density.[50–52] However, preventative tamoxifen, AIs, and GnRHA use are generally not prescribed for women of average risk and use is low among high-risk women due to side effects.[51,52] BMI is inversely associated with qualitative measures of breast density, such as BI-RADS breast density, but is not cross-sectionally associated with some quantitative measures such as dense tissue volume.[15] Weight loss impacts breast density by decreasing overall breast volume and volume of fibroglandular tissue, which leads to percent fibroglandular tissue remaining unchanged or in some cases increasing.[39] As a result, BI-RADS or other qualitative measures of density may not show the impact of weight loss on decreased volume of dense tissue.[39,53] Given limited strategies to reduce breast density in otherwise average risk women, secondary prevention efforts for women with dense breasts should focus on identifying those at high risk of advanced breast cancer who might benefit from supplemental screening.[54]

Some studies show that Asians are at higher risk of weight-related diseases than whites at similar BMI or weight-gain levels,[55] perhaps due to higher percent body fat at similar BMI levels.[56] Using more conservative BMI cutpoints suggested for Asians[28] did not meaningfully change the HRs for breast cancer but increased the proportion of overweight/obese women which slightly increased the PARPS.

Strengths and Limitations

Study limitations include inability to evaluate differential effects of BMI and breast density by country of ancestry, place of birth, or acculturation, which may modify breast cancer risk in subgroups of races/ethnicities.[57–61] Even with very large study cohorts and multiple observations per woman, some estimated CIs were wide due to small samples, for example in the highest obesity categories among Asian women and the highest breast density categories among black and Hispanic women. We were unable to evaluate quantitative measures of breast density; however, BI-RADS breast density is the most collected density measure in clinical practice in the U.S. and used in breast cancer risk prediction models.[62–64] We did not evaluate potential interactions between BMI and BI-RADS breast density due to the added complexity given results are subdivided by menopausal status and race/ethnicity (8 separate subgroups) and concerns about lack of power for detecting interactions due to relatively small sample sizes for all but white women. However, a prior study found

no significant interactions between BMI and BI-RADS breast density among premenopausal nor postmenopausal women, suggesting any interactions may be small.[65] Although BMI is not a perfect measure of adiposity, it was readily available in the medical record. We were not able to analyze other measures such central adiposity, waist-to-hip ratios, or visceral versus subcutaneous fat distribution because these measures were not available in the medical record.

Study strengths include the prospective BCSC cohort, which is broadly representative of the U.S. population, has larger sample sizes than other studies for the four largest U.S. races/ethnicities, links women to state and/or regional tumor registries for near complete capture of breast cancer diagnoses, and covers the spectrum of breast imaging facilities from mobile vans to university hospitals. We were able to include women receiving either screening or diagnostic mammograms to improve the generalizability of our population. The large BCSC cohort allowed evaluation of both breast density and BMI by race/ethnicity and menopausal status.

Conclusions

We found that overweight/obesity and dense breasts accounted for a large proportion of breast cancers in white, black, Hispanic, and Asian women despite large differences in risk-factor distributions and variation in associations with breast cancer. Breast density was a strong and important risk factor for breast cancer in both pre- and postmenopausal women of all races/ethnicities examined, with larger effects in premenopausal women. BMI was a strong risk factor among postmenopausal women, especially in black women, but not among premenopausal women. Primary and secondary prevention efforts and risk prediction models should consider racial/ethnic differences in risk associations and PARPs for breast density and BMI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was funded by the National Cancer Institute and the National Institutes of Health Office of Research on Women's Health (3P01CA154292-07S1). Data collection for this work was supported by funding from the National Cancer Institute (P01CA154292, U54CA163303); the Patient-Centered Outcomes Research Institute (PCS-1504-30370); and the Agency for Healthcare Research and Quality (R01 HS018366-01A1). Additional resources were funded by the UC Davis Comprehensive Cancer Center Support Grant awarded by the National Cancer Institute (P30CA093373). 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.bcsc-research.org/work/acknowledgement.html.

The funding agencies had no role in the study's design; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health Office of Research on Women's Health, the National Cancer Institute, the National Institutes of Health, or the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee. We thank Chris Tachibana, PhD, who provided scientific editing, and Deborah Seger, who provided data management, as part of their positions at Kaiser Permanente Washington Health Research Institute and did not receive additional compensation besides their salary. We also thank the participating women, mammography facilities, and radiologists for the data they have provided the Breast Cancer Surveillance Consortium (BCSC) for this study. You can learn more about the BCSC at: http://www.bcsc-research.org/.

Funding:

National Cancer Institute (NCI) and Office of Research on Women's Health (ORWH) 3P01CA154292-07S1: Michael C. S. Bissell, Karla Kerlikowske, Diana L. Miglioretti

National Cancer Institute (NCI) P01CA154292: Karla Kerlikowske, Brian L. Sprague, Jeffrey A Tice, Charlotte C. Gard, Garth Rauscher, Amy Trentham-Dietz, Louise M Henderson, Tracy L. Onega, Diana L. Miglioretti

Patient-Centered Outcomes Research Institute (PCORI) PCS-1504-30370: Karla Kerlikowske, Brian L. Sprague, Garth Rauscher, Amy Trentham-Dietz, Louise M Henderson, Tracy L. Onega, Diana L. Miglioretti

Agency for Healthcare Research and Quality (AHRQ) R01 HS018366-01A1: Garth Rauscher

National Cancer Institute (NCI) U54CA163303: Brian L. Sprague

References

1. Wolfe JN. Risk for breast cancer development determined by mammographic parenchymal pattern. Cancer. 1976;37(5):2486–92. [PubMed: 1260729]
2. Huo CW, Chew GL, Britt KL, Ingman WV, Henderson MA, Hopper JL, Thompson EW. Mammographic density-a review on the current understanding of its association with breast cancer. Breast Cancer Res Treat. 2014;144(3):479–502. [PubMed: 24615497]
3. Chen Y, Liu L, Zhou Q, Imam MU, Cai J, Wang Y, Qi M, Sun P, Ping Z, Fu X. Body mass index had different effects on premenopausal and postmenopausal breast cancer risks: a dose-response meta-analysis with 3,318,796 subjects from 31 cohort studies. BMC Public Health. 2017;17(1):936. [PubMed: 29216920]
4. Liu K, Zhang W, Dai Z, Wang M, Tian T, Liu X, Kang H, Guan H, Zhang S, Dai Z. Association between body mass index and breast cancer risk: evidence based on a dose-response meta-analysis. Cancer Manag Res. 2018;10:143–51. [PubMed: 29403312]
5. Kerlikowske K, Cook AJ, Buist DS, Cummings SR, Vachon C, Vacek P, Miglioretti DL. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. J Clin Oncol. 2010;28(24):3830–7. [PubMed: 20644098]
6. 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):1159–69. [PubMed: 16775176]
7. Premenopausal Breast Cancer Collaborative G, Schoemaker MJ, Nichols HB, Wright LB, Brook MN, Jones ME, O'Brien KM, Adami HO, Baglietto L, Bernstein L, Bertrand KA, Boutron-Ruault MC, Braaten T, Chen Y, Connor AE, Dorronsoro M, Dossus L, Eliassen AH, Giles GG, Hankinson SE, Kaaks R, Key TJ, Kirsh VA, Kitahara CM, Koh WP, Larsson SC, Linet MS, Ma H, Masala G, Merritt MA, Milne RL, Overvad K, Ozasa K, Palmer JR, Peeters PH, Riboli E, Rohan TE, Sadakane A, Sund M, Tamimi RM, Trichopoulou A, Ursin G, Vatten L, Visvanathan K, Weiderpass E, Willett WC, Wolk A, Yuan JM, Zeleniuch-Jacquotte A, Sandler DP, Swerdlow AJ. Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women. JAMA Oncol. 2018:e181771. [PubMed: 29931120]
8. Chan DSM, Abar L, Cariolou M, Nanu N, Greenwood DC, Bandera EV, McTiernan A, Norat T. World Cancer Research Fund International: Continuous Update Project-systematic literature review and meta-analysis of observational cohort studies on physical activity, sedentary behavior, adiposity, and weight change and breast cancer risk. Cancer Causes Control. 2019;30(11):1183–200. [PubMed: 31471762]
9. Kerlikowske K, Gard CC, Tice JA, Ziv E, Cummings SR, Miglioretti DL, Breast Cancer Surveillance C. Risk Factors That Increase Risk of Estrogen Receptor-Positive and -Negative Breast Cancer. J Natl Cancer Inst. 2017;109(5).
10. Noh H, Charvat H, Freisling H, Olafsdottir GH, Olafsdottir EJ, Tryggvadottir L, Arnold M, Soerjomataram I. Cumulative exposure to premenopausal obesity and risk of postmenopausal cancer: A population-based study in Icelandic women. Int J Cancer. 2019.
11. Shieh Y, Scott CG, Jensen MR, Norman AD, Bertrand KA, Pankratz VS, Brandt KR, Visscher DW, Shepherd JA, Tamimi RM, Vachon CM, Kerlikowske K. Body mass index, mammographic

density, and breast cancer risk by estrogen receptor subtype. Breast Cancer Res. 2019;21(1):48. [PubMed: 30944014]

12. Centers for Disease Control and Prevention. Adult Obesity Facts. 2018 Available from: https://www.cdc.gov/obesity/data/adult.html.
13. Conroy SM, Woolcott CG, Koga KR, Byrne C, Nagata C, Ursin G, Vachon CM, Yaffe MJ, Pagano I, Maskarinec G. Mammographic density and risk of breast cancer by adiposity: an analysis of four case-control studies. Int J Cancer. 2012;130(8):1915–24. [PubMed: 21630258]
14. Reeves KW, Stone RA, Modugno F, Ness RB, Vogel VG, Weissfeld JL, Habel LA, Sternfeld B, Cauley JA. Longitudinal association of anthropometry with mammographic breast density in the Study of Women's Health Across the Nation. Int J Cancer. 2009;124(5):1169–77. [PubMed: 19065651]
15. Brandt KR, Scott CG, Ma L, Mahmoudzadeh AP, Jensen MR, Whaley DH, Wu FF, Malkov S, Hruska CB, Norman AD, Heine J, Shepherd J, Pankratz VS, Kerlikowske K, Vachon CM. Comparison of Clinical and Automated Breast Density Measurements: Implications for Risk Prediction and Supplemental Screening. Radiology. 2016;279(3):710–9. [PubMed: 26694052]
16. Maskarinec G, Jacobs S, Park SY, Haiman CA, Setiawan VW, Wilkens LR, Le Marchand L. Type II Diabetes, Obesity, and Breast Cancer Risk: The Multiethnic Cohort. Cancer Epidemiol Biomarkers Prev. 2017;26(6):854–61. [PubMed: 28087607]
17. McCarthy AM, Keller BM, Pantalone LM, Hsieh MK, Synnestvedt M, Conant EF, Armstrong K, Kontos D. Racial Differences in Quantitative Measures of Area and Volumetric Breast Density. J Natl Cancer Inst. 2016;108(10).
18. Oppong BA, Dash C, O'Neill S, Li Y, Makambi K, Pien E, Makariou E, Coleman T, Adams-Campbell LL. Breast density in multiethnic women presenting for screening mammography. Breast J. 2018;24(3):334–8. [PubMed: 29063662]
19. Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K, Breast Cancer Surveillance C. Population-Attributable Risk Proportion of Clinical Risk Factors for Breast Cancer. JAMA Oncol. 2017;3(9):1228–36. [PubMed: 28152151]
20. Sprague BL, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Hampton JM, Newcomb PA. Proportion of invasive breast cancer attributable to risk factors modifiable after menopause. Am J Epidemiol. 2008;168(4):404–11. [PubMed: 18552361]
21. Tamimi RM, Spiegelman D, Smith-Warner SA, Wang M, Pazaris M, Willett WC, Eliassen AH, Hunter DJ. Population Attributable Risk of Modifiable and Nonmodifiable Breast Cancer Risk Factors in Postmenopausal Breast Cancer. Am J Epidemiol. 2016;184(12):884–93. [PubMed: 27923781]
22. Ho PJ, Lau HSH, Ho WK, Wong FY, Yang Q, Tan KW, Tan MH, Chay WY, Chia KS, Hartman M, Li J. Incidence of breast cancer attributable to breast density, modifiable and non-modifiable breast cancer risk factors in Singapore. Sci Rep. 2020;10(1):503. [PubMed: 31949192]
23. D'Orsi CJ SE, Mendelson EB, Morris EA, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology; 2013.
24. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1–253.
25. Phipps AI, Ichikawa L, Bowles EJ, Carney PA, Kerlikowske K, Miglioretti DL, Buist DS. Defining menopausal status in epidemiologic studies: A comparison of multiple approaches and their effects on breast cancer rates. Maturitas. 2010;67(1):60–6. [PubMed: 20494530]
26. Williamson JM, Kim HY, Manatunga A, Addiss DG. Modeling survival data with informative cluster size. Stat Med. 2008;27(4):543–55. [PubMed: 17640035]
27. Kleinbaum DGK M Survival Analysis: A Self-Learning Text. Third ed: Springer; 2012.
28. Hsu WC, Araneta MR, Kanaya AM, Chiang JL, Fujimoto W. BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. Diabetes Care. 2015;38(1):150–8. [PubMed: 25538311]
29. Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. Cancer Causes Control. 2007;18(5):571–9. [PubMed: 17387622]

30. Maas P, Barrdahl M, Joshi AD, Auer PL, Gaudet MM, Milne RL, Schumacher FR, Anderson WF, Check D, Chattopadhyay S, Baglietto L, Berg CD, Chanock SJ, Cox DG, Figueroa JD, Gail MH, Graubard BI, Haiman CA, Hankinson SE, Hoover RN, Isaacs C, Kolonel LN, Le Marchand L, Lee IM, Lindstrom S, Overvad K, Romieu I, Sanchez MJ, Southey MC, Stram DO, Tumino R, VanderWeele TJ, Willett WC, Zhang S, Buring JE, Canzian F, Gapstur SM, Henderson BE, Hunter DJ, Giles GG, Prentice RL, Ziegler RG, Kraft P, Garcia-Closas M, Chatterjee N. Breast Cancer Risk From Modifiable and Nonmodifiable Risk Factors Among White Women in the United States. JAMA Oncol. 2016;2(10):1295–302. [PubMed: 27228256]

31. Mezzetti M, La Vecchia C, Decarli A, Boyle P, Talamini R, Franceschi S. Population attributable risk for breast cancer: diet, nutrition, and physical exercise. J Natl Cancer Inst. 1998;90(5):389–94. [PubMed: 9498489]

32. Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, Long MW, Gortmaker SL. Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity. N Engl J Med. 2019;381(25):2440–50. [PubMed: 31851800]

33. Teras LR, Patel AV, Wang M, Yaun SS, Anderson K, Brathwaite R, Caan BJ, Chen Y, Connor AE, Eliassen AH, Gapstur SM, Gaudet MM, Genkinger JM, Giles GG, Lee IM, Milne RL, Robien K, Sawada N, Sesso HD, Stampfer MJ, Tamimi RM, Thomson CA, Tsugane S, Visvanathan K, Willett WC, Zeleniuch-Jacquotte A, Smith-Warner SA. Sustained weight loss and risk of breast cancer in women >/=50 years: a pooled analysis of prospective data. J Natl Cancer Inst. 2019.

34. Baker JL, Gamborg M, Heitmann BL, Lissner L, Sorensen TI, Rasmussen KM. Breastfeeding reduces postpartum weight retention. Am J Clin Nutr. 2008;88(6):1543–51. [PubMed: 19064514]

35. Breast cancer: How diet, nutrition and physical activity affect breast cancer risk: World Cancer Research Fund International; 2017 [20200205]. Available from: https://www.wcrf.org/dietandcancer/breast-cancer.

36. Feigelson HS, Caan B, Weinmann S, Leonard AC, Powers JD, Yenumula PR, Arterburn DE, Koebnick C, Altaye M, Schauer DP. Bariatric Surgery is Associated With Reduced Risk of Breast Cancer in Both Premenopausal and Postmenopausal Women. Ann Surg. 2019.

37. Hassinger TE, Mehaffey JH, Hawkins RB, Schirmer BD, Hallowell PT, Schroen AT, Showalter SL. Overall and Estrogen Receptor-Positive Breast Cancer Incidences Are Decreased Following Bariatric Surgery. Obes Surg. 2018.

38. Kerlikowske K, Ichikawa L, Miglioretti DL, Buist DS, Vacek PM, Smith-Bindman R, Yankaskas B, Carney PA, Ballard-Barbash R, National Institutes of Health Breast Cancer Surveillance C. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. J Natl Cancer Inst. 2007;99(5):386–95. [PubMed: 17341730]

39. Hassinger TE, Mehaffey JH, Knisely AT, Contrella BN, Brenin DR, Schroen AT, Schirmer BD, Hallowell PT, Harvey JA, Showalter SL. The impact of bariatric surgery on qualitative and quantitative breast density. Breast J. 2019.

40. Hosseini A, Khoury AL, Varghese F, Carter J, Wong JM, Mukhtar RA. Changes in mammographic density following bariatric surgery. Surg Obes Relat Dis. 2019.

41. Williams AD, So A, Synnestvedt M, Tewksbury CM, Kontos D, Hsiehm MK, Pantalone L, Conant EF, Schnall M, Dumon K, Williams N, Tchou J. Mammographic breast density decreases after bariatric surgery. Breast Cancer Res Treat. 2017;165(3):565–72. [PubMed: 28660430]

42. Ziembicki S, Zhu J, Tse E, Martin LJ, Minkin S, Boyd NF. The Association between Alcohol Consumption and Breast Density: A Systematic Review and Meta-analysis. Cancer Epidemiol Biomarkers Prev. 2017;26(2):170–8. [PubMed: 27672053]

43. Cuzick J, Warwick J, Pinney E, Warren RM, Duffy SW. Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst. 2004;96(8):621–8. [PubMed: 15100340]

44. Cuzick J, Forbes J, Edwards R, Baum M, Cawthorn S, Coates A, Hamed A, Howell A, Powles T, investigators I. First results from the International Breast Cancer Intervention Study (IBIS-I): a randomised prevention trial. Lancet. 2002;360(9336):817–24. [PubMed: 12243915]

45. Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthorn S, Howell A, Forbes JF, Warren RM. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. J Natl Cancer Inst. 2011;103(9):744–52. [PubMed: 21483019]

46. Cigler T, Richardson H, Yaffe MJ, Fabian CJ, Johnston D, Ingle JN, Nassif E, Brunner RL, Wood ME, Pater JL, Hu H, Qi S, Tu D, Goss PE. A randomized, placebo-controlled trial (NCIC CTG MAP.2) examining the effects of exemestane on mammographic breast density, bone density, markers of bone metabolism and serum lipid levels in postmenopausal women. Breast Cancer Res Treat. 2011;126(2):453–61. [PubMed: 21221773]
47. Vachon CM, Suman VJ, Brandt KR, Kosel ML, Buzdar AU, Olson JE, Wu FF, Flickinger LM, Ursin G, Elliott CR, Shepherd L, Weinshilboum RM, Goss PE, Ingle JN. Mammographic breast density response to aromatase inhibition. Clin Cancer Res. 2013;19(8):2144–53. [PubMed: 23468058]
48. Prowell TM, Blackford AL, Byrne C, Khouri NF, Dowsett M, Folkerd E, Tarpinian KS, Powers PP, Wright LA, Donehower MG, Jeter SC, Armstrong DK, Emens LA, Fetting JH, Wolff AC, Garrett-Mayer E, Skaar TC, Davidson NE, Stearns V. Changes in breast density and circulating estrogens in postmenopausal women receiving adjuvant anastrozole. Cancer Prev Res (Phila). 2011;4(12):1993–2001. [PubMed: 21885816]
49. Engmann NJ, Scott CG, Jensen MR, Ma L, Brandt KR, Mahmoudzadeh AP, Malkov S, Whaley DH, Hruska CB, Wu FF, Winham SJ, Miglioretti DL, Norman AD, Heine JJ, Shepherd J, Pankratz VS, Vachon CM, Kerlikowske K. Longitudinal Changes in Volumetric Breast Density with Tamoxifen and Aromatase Inhibitors. Cancer Epidemiol Biomarkers Prev. 2017;26(6):930–7. [PubMed: 28148596]
50. Gram IT, Ursin G, Spicer DV, Pike MC. Reversal of gonadotropin-releasing hormone agonist induced reductions in mammographic densities on stopping treatment. Cancer Epidemiol Biomarkers Prev. 2001;10(11):1117–20. [PubMed: 11700258]
51. Weitzel JN, Buys SS, Sherman WH, Daniels A, Ursin G, Daniels JR, MacDonald DJ, Blazer KR, Pike MC, Spicer DV. Reduced mammographic density with use of a gonadotropin-releasing hormone agonist-based chemoprevention regimen in BRCA1 carriers. Clin Cancer Res. 2007;13(2 Pt 1):654–8. [PubMed: 17255289]
52. Yang H, Zong X, Yu Y, Shao G, Zhang L, Qian C, Bian Y, Xu X, Sun W, Meng X, Ding X, Chen D, Zou D, Xie S, Zheng Y, Zhang J, He X, Sun C, Yu X, Ni J. Combined effects of goserelin and tamoxifen on estradiol level, breast density, and endometrial thickness in premenopausal and perimenopausal women with early-stage hormone receptor-positive breast cancer: a randomised controlled clinical trial. Br J Cancer. 2013;109(3):582–8. [PubMed: 23860520]
53. Vohra NA, Kachare SD, Vos P, Schroeder BF, Schuth O, Suttle D, Fitzgerald TL, Wong JH, Verbanac KM. The Short-Term Effect of Weight Loss Surgery on Volumetric Breast Density and Fibroglandular Volume. Obes Surg. 2017;27(4):1013–23. [PubMed: 27783370]
54. Kerlikowske K, Sprague BL, Tosteson ANA, Wernli KJ, Rauscher GH, Johnson D, Buist DSM, Onega T, Henderson LM, O'Meara ES, Miglioretti DL. Strategies to Identify Women at High Risk of Advanced Breast Cancer During Routine Screening for Discussion of Supplemental Imaging. JAMA Intern Med. 2019.
55. Wen CP, David Cheng TY, Tsai SP, Chan HT, Hsu HL, Hsu CC, Eriksen MP. Are Asians at greater mortality risks for being overweight than Caucasians? Redefining obesity for Asians. Public Health Nutr 2009;12(4):497–506. [PubMed: 18547457]
56. Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P. The paradox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. Int J Obes Relat Metab Disord. 2000;24(8):1011–7. [PubMed: 10951540]
57. Banegas MP, John EM, Slattery ML, Gomez SL, Yu M, LaCroix AZ, Pee D, Chlebowski RT, Hines LM, Thompson CA, Gail MH. Projecting Individualized Absolute Invasive Breast Cancer Risk in US Hispanic Women. J Natl Cancer Inst. 2017;109(2).
58. Keegan TH, John EM, Fish KM, Alfaro-Velcamp T, Clarke CA, Gomez SL. Breast cancer incidence patterns among California Hispanic women: differences by nativity and residence in an enclave. Cancer Epidemiol Biomarkers Prev. 2010;19(5):1208–18. [PubMed: 20447917]
59. Gomez SL, Quach T, Horn-Ross PL, Pham JT, Cockburn M, Chang ET, Keegan TH, Glaser SL, Clarke CA. Hidden breast cancer disparities in Asian women: disaggregating incidence rates by ethnicity and migrant status. Am J Public Health. 2010;100 Suppl 1:S125–31. [PubMed: 20147696]

60. Jemal A, Fedewa SA. Is the prevalence of ER-negative breast cancer in the US higher among Africa-born than US-born black women? Breast Cancer Res Treat. 2012;135(3):867–73. [PubMed: 22915073]

61. Sung H, DeSantis CE, Fedewa SA, Kantelhardt EJ, Jemal A. Breast cancer subtypes among Eastern-African-born black women and other black women in the United States. Cancer. 2019;125(19):3401–11. [PubMed: 31190337]

62. Tice JA, Miglioretti DL, Li CS, Vachon CM, Gard CC, Kerlikowske K. Breast Density and Benign Breast Disease: Risk Assessment to Identify Women at High Risk of Breast Cancer. J Clin Oncol. 2015;33(28):3137–43. [PubMed: 26282663]

63. Lee A, Mavaddat N, Wilcox AN, Cunningham AP, Carver T, Hartley S, Babb de Villiers C, Izquierdo A, Simard J, Schmidt MK, Walter FM, Chatterjee N, Garcia-Closas M, Tischkowitz M, Pharoah P, Easton DF, Antoniou AC. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med. 2019;21(8):1708–18. [PubMed: 30643217]

64. Brentnall AR, Cuzick J, Buist DSM, Bowles EJA. Long-term Accuracy of Breast Cancer Risk Assessment Combining Classic Risk Factors and Breast Density. JAMA Oncol. 2018;4(9):e180174. [PubMed: 29621362]

65. Engmann NJ, Scott CG, Jensen MR, Winham S, Miglioretti DL, Ma L, Brandt K, Mahmoudzadeh A, Whaley DH, Hruska C, Wu F, Norman AD, Hiatt RA, Heine J, Shepherd J, Pankratz VS, Vachon CM, Kerlikowske K. Combined effect of volumetric breast density and body mass index on breast cancer risk. Breast Cancer Res Treat. 2019;177(1):165–73. [PubMed: 31129803]

Table 1.

Characteristics of the 1,071,653 women with 21,253 breast cancers in the study cohort by race/ethnicity and menopausal status.[a]

	White		Black		Asian		Hispanic	
	N	(%)	N	(%)	N	(%)	N	(%)
Premenopausal								
Breast Cancer Status								
No Breast Cancer	371,515	(98.6)	33,712	(99.1)	50,835	(98.9)	55,902	(99.1)
Breast Cancer	5,462	(1.4)	314	(0.9)	576	(1.1)	535	(0.9)
Age Group, Years								
35–39	40,833	(10.8)	3,336	(9.8)	3,599	(7.0)	6,959	(12.3)
40–44	148,762	(39.5)	13,114	(38.5)	20,284	(39.5)	26,699	(47.3)
45–49	110,847	(29.4)	10,011	(29.4)	17,222	(33.5)	14,743	(26.1)
50–54	76,536	(20.3)	7,565	(22.2)	10,306	(20.0)	8,036	(14.2)
Body Mass Index (kg/m^2)								
Underweight (<18.5)	6,437	(1.7)	208	(0.6)	2,044	(4.0)	527	(0.9)
Normal (18.5–24.9)	183,137	(48.6)	5,642	(16.6)	34,326	(66.8)	20,351	(36.1)
Overweight (25.0–29.9)	97,807	(25.9)	9,680	(28.4)	11,307	(22.0)	18,606	(33.0)
Obese I (30.0–34.9)	49,443	(13.1)	8,368	(24.6)	2,776	(5.4)	10,372	(18.4)
Obese II/III (≥35.0)	40,154	(10.7)	10,128	(29.8)	958	(1.9)	6,582	(11.7)
BI-RADS Breast Density								
Almost Entirely Fat	19,185	(5.1)	2,220	(6.5)	782	(1.5)	3,886	(6.9)
Scattered Fibroglandular	126,541	(33.6)	12,749	(37.5)	8,866	(17.2)	20,634	(36.6)
Heterogeneously Dense	176,850	(46.9)	15,711	(46.2)	27,616	(53.7)	25,648	(45.4)
Extremely Dense	54,402	(14.4)	3,346	(9.8)	14,148	(27.5)	6,268	(11.1)
Observations per Woman								
1	150,927	(40.0)	14,260	(41.9)	23,196	(45.1)	29,964	(53.1)
2	79,456	(21.1)	7,519	(22.1)	11,713	(22.8)	12,370	(21.9)
3	48,726	(12.9)	4,563	(13.4)	6,712	(13.1)	6,285	(11.1)
4	31,161	(8.3)	2,829	(8.3)	3,862	(7.5)	3,333	(5.9)
5 or more	66,708	(17.7)	4,856	(14.3)	5,930	(11.5)	4,485	(7.9)
Postmenopausal								
Total Women								
No Breast Cancer	492,441	(97.6)	48,479	(98.5)	65,048	(98.7)	59,640	(98.5)
Breast Cancer	11,854	(2.4)	756	(1.5)	866	(1.3)	881	(1.5)
Age Group, Years								
5–44	6,432	(1.3)	402	(0.8)	362	(0.5)	1,029	(1.7)
45–54	79,894	(15.8)	6,020	(12.2)	9,881	(15.0)	8,663	(14.3)
55–64	231,259	(45.9)	23,747	(48.2)	35,474	(53.8)	30,435	(50.3)
65–74	126,740	(25.1)	13,766	(28.0)	15,159	(23.0)	14,846	(24.5)
75–84	59,971	(11.9)	5,300	(10.8)	5,039	(7.6)	5,548	(9.2)
Body Mass Index (kg/m^2)								

	White		Black		Asian		Hispanic	
	N	(%)	N	(%)	N	(%)	N	(%)
Underweight (<18.5)	8,612	(1.7)	404	(0.8)	2,589	(3.9)	634	(1.0)
Normal (18.5–24.9)	201,912	(40.0)	8,125	(16.5)	40,343	(61.2)	18,966	(31.3)
Overweight (25.0–29.9)	154,865	(30.7)	15,194	(30.9)	17,732	(26.9)	22,181	(36.6)
Obese I (30.0–34.9)	81,520	(16.2)	12,757	(25.9)	3,929	(6.0)	12,123	(20.0)
Obese II/III (≥35.0)	57,386	(11.4)	12,755	(25.9)	1,321	(2.0)	6,618	(10.9)
BI-RADS Breast Density								
Almost Entirely Fat	65,350	(13.0)	6,417	(13.0)	4,628	(7.0)	10,418	(17.2)
Scattered Fibroglandular	246,077	(48.8)	26,992	(54.8)	25,202	(38.2)	31,400	(51.9)
Heterogeneously Dense	167,016	(33.1)	14,349	(29.1)	29,448	(44.7)	16,471	(27.2)
Extremely Dense	25,852	(5.1)	1,478	(3.0)	6,637	(10.1)	2,232	(3.7)
Observations per Woman								
1	151,927	(30.1)	14,988	(30.4)	24,382	(37.0)	23,798	(39.3)
2	97,612	(19.4)	10,160	(20.6)	15,371	(23.3)	13,348	(22.1)
3	65,227	(12.9)	7,035	(14.3)	8,948	(13.6)	8,178	(13.5)
4	45,859	(9.1)	4,553	(9.2)	5,668	(8.6)	5,588	(9.2)
5 or more	143,670	(28.5)	12,499	(25.4)	11,547	(17.5)	9,609	(15.9)

[a]Frequencies differ from the text due to inverse weighting by the number of observations per woman, rounding, and transitioning of 127,165 women from pre- to postmenopausal status during the study who contributed observations to both cohorts.

Abbreviations: kg, kilograms; m, meters; BI-RADS, Breast Imaging Reporting and Data System.

Table 2.

Hazard ratios (95% confidence intervals) of invasive breast cancer associated with body mass index and BI-RADS breast density stratified by race/ethnicity and menopausal status[a]

Risk factor	White	Black	Asian	Hispanic
Premenopausal				
Body Mass Index (kg/m^2)				
Underweight (<18.5)	0.94 (0.80, 1.10)	1.53 (0.55, 4.29)	0.96 (0.69, 1.35)	0.65 (0.28, 1.54)
Normal (18.5–24.9)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Overweight (25.0–29.9)	1.11 (1.05, 1.16)	1.05 (0.79, 1.39)	1.07 (0.91, 1.26)	0.83 (0.70, 0.99)
Obese I (30.0–34.9)	1.11 (1.04, 1.19)	1.25 (0.93, 1.70)	1.24 (0.89, 1.73)	0.96 (0.78, 1.19)
Obese II/III (≥35.0)	1.18 (1.09, 1.28)	1.14 (0.81, 1.59)	1.62 (0.96, 2.73)	1.12 (0.86, 1.46)
BI-RADS Breast Density				
Almost entirely fat	0.45 (0.38, 0.53)	0.58 (0.35, 0.96)	0.55 (0.24, 1.28)	0.34 (0.19, 0.59)
Scattered fibroglandular densities	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Heterogeneously dense	1.66 (1.57, 1.74)	1.45 (1.16, 1.83)	1.56 (1.25, 1.93)	1.80 (1.51, 2.14)
Extremely dense	2.05 (1.91, 2.19)	1.96 (1.39, 2.76)	1.80 (1.43, 2.26)	2.43 (1.94, 3.06)
Postmenopausal				
Body Mass Index (kg/m^2)				
Underweight (<18.5)	0.77 (0.68, 0.87)	0.55 (0.23, 1.30)	0.67 (0.48, 0.94)	0.57 (0.29, 1.13)
Normal (18.5–24.9)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Overweight (25.0–29.9)	1.26 (1.22, 1.30)	1.25 (1.05, 1.48)	1.45 (1.29, 1.63)	1.13 (0.99, 1.28)
Obese I (30.0–34.9)	1.41 (1.35, 1.46)	1.56 (1.31, 1.86)	1.51 (1.23, 1.85)	1.31 (1.14, 1.51)
Obese II/III (≥35.0)	1.43 (1.36, 1.50)	1.76 (1.47, 2.11)	2.21 (1.60, 3.05)	1.37 (1.13, 1.66)
BI-RADS Breast Density				
Almost entirely fat	0.56 (0.53, 0.59)	0.65 (0.53, 0.80)	0.60 (0.47, 0.76)	0.54 (0.45, 0.65)
Scattered fibroglandular densities	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Heterogeneously dense	1.39 (1.35, 1.43)	1.58 (1.41, 1.77)	1.26 (1.12, 1.42)	1.36 (1.21, 1.52)
Extremely dense	1.62 (1.53, 1.72)	1.69 (1.23, 2.31)	1.49 (1.24, 1.78)	2.06 (1.67, 2.54)

[a]All models adjust for age, BMI, and BI-RADS breast density.

Abbreviations: kg, kilograms; m, meters; BI-RADS, Breast Imaging Reporting and Data System.

Table 3.

Population attributable risk proportions (percent and 95% confidence interval) associated with body mass index and BI-RADS breast density and observed proportions of women in high risk categories of body mass index and BI-RADS breast density by race/ethnicity and menopausal status.[a]

	White		Black		Asian		Hispanic	
	PARP (95% CI)	**% High Risk**	**PARP (95% CI)**	**% High Risk**	**PARP (95% CI)**	**% High Risk**	**PARP (95% CI)**	**% High Risk**
Premenopausal								
Body Mass Index[b]	3.7 (0.6, 6.7)	49.7	9.9 (−12.4, 31.2)	82.8	3.3 (−5.1, 11.7)	29.3	1.0 (−1.4, 3.4)	63.0
BI-RADS Breast Density[c]	30.4 (27.5, 33.1)	61.3	23.9 (10.6, 36.4)	56.0	33.2 (20.1, 45.2)	81.2	35.0 (26.0, 43.4)	56.6
BMI and BI-RADS Breast Density[bc]	33.2 (28.5, 37.7)	87.4	31.7 (3.2, 55.5)	96.1	35.7 (17.9, 51.3)	91.1	35.8 (25.6, 45.2)	88.6
Postmenopausal								
Body Mass Index[b]	15.4 (13.4, 17.4)	58.3	28.3 (17.4, 38.5)	82.7	14.7 (8.1, 21.2)	34.9	12.0 (2.8, 21.0)	67.6
BI-RADS Breast Density[c]	14.1 (12.7, 15.5)	38.2	16.7 (11.1, 22.3)	32.1	13.5 (6.6, 20.3)	54.7	13.0 (8.1, 17.9)	30.9
BMI and BI-RADS Breast Density[bc]	27.8 (25.0, 30.6)	79.2	40.9 (28.2, 52.2)	90.7	26.7 (15.8, 37.0)	74.2	23.8 (11.7, 35.2)	80.9

[a] All models adjust for age, body mass index and BI-RADS breast density.

[b] PARP calculated for shifting BMI categories overweight and obese I/II/III to normal BMI and holding underweight constant.

[c] PARP calculated for shifting BI-RADS categories heterogeneously dense and extremely dense to scattered fibroglandular densities and holding almost entirely fat constant.

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; BMI, body mass index (kilograms/meters^2); PARP, population attributable risk proportion.