

UC Davis

UC Davis Previously Published Works

Title

Prevalence of Mammographically Dense Breasts in the United States

Permalink

<https://escholarship.org/uc/item/344994r8>

Journal

Journal of the National Cancer Institute, 106(10)

ISSN

0027-8874

Authors

Sprague, Brian L

Gangnon, Ronald E

Burt, Veronica

et al.

Publication Date

2014-10-01

DOI

10.1093/jnci/dju255

Peer reviewed

Prevalence of Mammographically Dense Breasts in the United States

Brian L. Sprague, Ronald E. Gangnon, Veronica Burt, Amy Trentham-Dietz, John M. Hampton, Robert D. Wellman, Karla Kerlikowske, Diana L. Miglioretti

Manuscript received November 4, 2013; revised February 17, 2014; accepted July 9, 2014.

Correspondence to: Brian L. Sprague, PhD, Office of Health Promotion Research, 1 S. Prospect St, UHC Room 4425, University of Vermont, Burlington, VT 05401 (e-mail: brian.sprague@uvm.edu).

Background National legislation is under consideration that would require women with mammographically dense breasts to be informed of their breast density and encouraged to discuss supplemental breast cancer screening with their health care providers. The number of US women potentially affected by this legislation is unknown.

Methods We determined the mammographic breast density distribution by age and body mass index (BMI) using data from 1 518 599 mammograms conducted from 2007 through 2010 at mammography facilities in the Breast Cancer Surveillance Consortium (BCSC). We applied these breast density distributions to age- and BMI-specific counts of the US female population derived from the 2010 US Census and the National Health and Nutrition Examination Survey (NHANES) to estimate the number of US women with dense breasts.

Results Overall, 43.3% (95% confidence interval [CI] = 43.1% to 43.4%) of women 40 to 74 years of age had heterogeneously or extremely dense breasts, and this proportion was inversely associated with age and BMI. Based on the age and BMI distribution of US women, we estimated that 27.6 million women (95% CI = 27.5 to 27.7 million) aged 40 to 74 years in the United States have heterogeneously or extremely dense breasts. Women aged 40 to 49 years (N = 12.3 million) accounted for 44.3% of this group.

Conclusion The prevalence of dense breasts among US women of common breast cancer screening ages exceeds 25 million. Policymakers and healthcare providers should consider this large prevalence when debating breast density notification legislation and designing strategies to ensure that women who are notified have opportunities to evaluate breast cancer risk and discuss and pursue supplemental screening options if deemed appropriate.

JNCI J Natl Cancer Inst (2014) 106(10): dju255 doi:10.1093/jnci/dju255

Mammographic breast density is a strong risk factor for developing breast cancer (1,2) and also impairs mammography performance (3–6). At least 12 states have recently passed legislation that mandates the disclosure of mammographic breast density information directly to women with dense breasts, along with language communicating that breast density may obscure abnormalities on a mammogram and that these women may benefit from supplemental screening tests (7). Similar legislation is under consideration by many other states and at the national level (8). The number of women potentially affected by this legislation has not been well characterized.

Radiologists qualitatively rate breast tissue density from mammography examinations using four categories defined by the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS): "almost entirely fat," "scattered fibroglandular densities," "heterogeneously dense," and "extremely dense" (9). Legislation defines mammographically

dense breasts as those rated "heterogeneously dense" or "extremely dense."

Breast density declines with increasing age and body mass index (BMI) (10–12). We sought to examine the distribution of mammographic breast density by age and BMI in a geographically diverse sample of women undergoing mammography and estimate the prevalence of US women with dense breasts.

Methods

Study Population

Data on the distribution of mammographic breast density was provided by the Statistical Coordinating Center for the Breast Cancer Surveillance Consortium (BCSC) mammography registries (<http://breastscreening.cancer.gov>). BCSC registries collect patient characteristics and clinical information from a geographically diverse sample of community radiology facilities. The following BCSC

registries contributed data to this analysis: Carolina Mammography Registry, Group Health Cooperative (WA), New Hampshire Mammography Network, New Mexico Mammography Project, San Francisco Mammography Registry, and Vermont Breast Cancer Surveillance System. Registries and the Coordinating Center received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link 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. Analyses of BCSC data included women aged 40 years and older who obtained a mammogram at a BCSC facility from 2007 through 2010. Women with a history of breast cancer, breast augmentation, or breast reconstruction were excluded. For women with multiple mammograms in a single year, a random selection of one observation per woman per year was included. This selection was limited to screening mammograms if at least one was available for the woman in a given year; if not, then diagnostic mammograms were also included.

To estimate the US prevalence of BI-RADS breast density categories, we applied the joint age/BMI distribution of breast density from the BCSC to age/BMI-specific counts of the US female population. The distribution of BMI among US women was obtained from the National Health and Nutrition Examination Survey, which includes a series of cross-sectional nationally representative health examination surveys (13). Analyses of NHANES data were limited to nonpregnant women aged 40 years and older participating from 2007 through 2010. Counts of the US female population by age group were obtained from the 2010 US Census.

Measures and Definitions

For the BCSC, women completed a questionnaire at each mammography examination performed at a BCSC facility, which included age, race, personal and family history of breast cancer, height and weight, history of postmenopausal hormone use, menopausal status, hysterectomy status, parity, and education. Radiologists' BI-RADS breast density assessments were recorded using the American College of Radiology's BI-RADS lexicon (9).

For NHANES, body weight and height were measured at a mobile examination center using standardized techniques (14). For both the BCSC and NHANES analyses, BMI was characterized as underweight (<18.5 kg/m²), normal (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (>30 kg/m²), and age was categorized in five-year groups.

Statistical Analysis

Among BCSC records, data on patient age was complete (no missing values) but 18.8% of records were missing BI-RADS breast density, and 46.5% were missing BMI (Supplementary Table 1, available online). Multiple imputation was used to impute five datasets with complete data on breast density and BMI, using a sequential regression approach (15) implemented in IVEWARE software (16). The imputation models included BI-RADS breast density, BMI group, age group, calendar year, BCSC registry, race (non-Hispanic white, non-Hispanic black, Hispanic, Asian, Native Hawaiian/Pacific Islander, American Indian/Alaska native, mixed,

other, unknown), first degree family history of breast cancer (yes, no, unknown), current use of postmenopausal hormones (yes, no, unknown), menopausal status (premenopausal, postmenopausal, other/unknown), hysterectomy status (yes, no, unknown), parity (0, ≥1, unknown), and education (less than high school, high school graduate, some college, college degree, unknown). All variables were categorical and were modeled with either binomial or polytomous logistic regression. Results of the imputation model are provided in Supplementary Table 2 (available online).

All other statistical analyses were performed using SAS Statistical Software (Version 9; SAS Institute, Inc., Cary, NC). To determine the association of breast density with age and BMI in the BCSC, we modeled BI-RADS breast density categories as a function of age group, BMI group, and interaction terms between age and BMI groups using logistic regression. Using the methods of Rubin (17), regression results were combined across the imputed datasets to estimate proportions of women in each density category according to age and BMI groups. The proportions reported by age category are standardized to the age-specific distribution of BMI among US women (from NHANES 2007–2010); the proportions reported by BMI are standardized to the 2010 US Census age distribution of US women.

To estimate the proportion of US women in each BMI category by age group in NHANES, SAS Survey procedures were used to account for the stratified cluster sample, unequal probability of sampling, and nonresponse. The age-specific distribution of BMI categories from NHANES was applied to 2010 US Census counts of women in each age group to estimate the number of US women in each age-by-BMI group.

The age-by-BMI-specific proportion of women in each BI-RADS breast density category from the BCSC was applied to the age-by-BMI-specific counts of US women generated using NHANES and Census data. Counts were summed across BMI groups to obtain breast density category prevalence estimates by age group.

Results

The BCSC study dataset consisted of 1 518 599 mammogram records from 764 507 women aged 40 years and older. The combined proportion of mammograms rated as either heterogeneously or extremely dense declined with age, from 56.6% (95% CI = 56.1% to 57.0%) for women aged 40 to 44 to 28.4% (95% CI = 27.4% to 29.5%) for women aged 85 and older (Figure 1). Overall, 43.3% (95% CI = 43.1% to 43.4%) of women aged 40–74 years had heterogeneously or extremely dense breasts. The frequency of extremely dense breasts declined from 12.5% (95% CI = 12.4% to 12.7%) of women aged 40 to 44 years to 3.1% (95% CI = 2.8% to 3.4%) of women aged 85 and older, with an overall frequency of 7.4% (95% CI = 7.4% to 7.5%) among women aged 40 to 74 years.

The combined proportion of mammograms rated as either heterogeneously or extremely dense declined with increasing body mass index (Figure 2). Among women with normal BMI, 58.9% (95% CI = 58.4% to 59.3%) had heterogeneously or extremely dense breasts, compared with 25.0% (95% CI = 24.8% to 25.3%) of obese women.

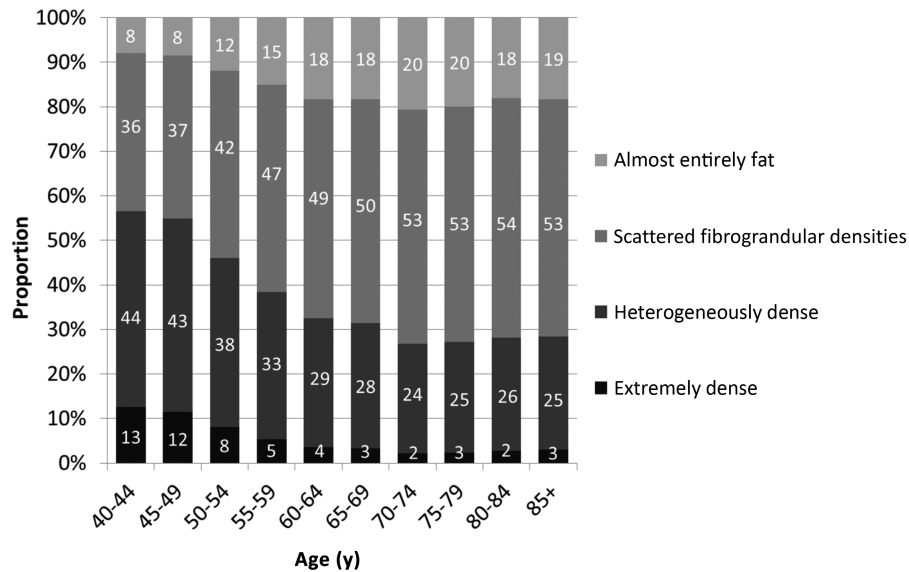


Figure 1. Distribution of BI-RADS breast density categories by age, Breast Cancer Surveillance Consortium, 2007–2010. Proportions are standardized to the NHANES 2007–2010 age-specific distribution of body mass index among US women. BI-RADS = American College of Radiology’s Breast Imaging Reporting and Data System.

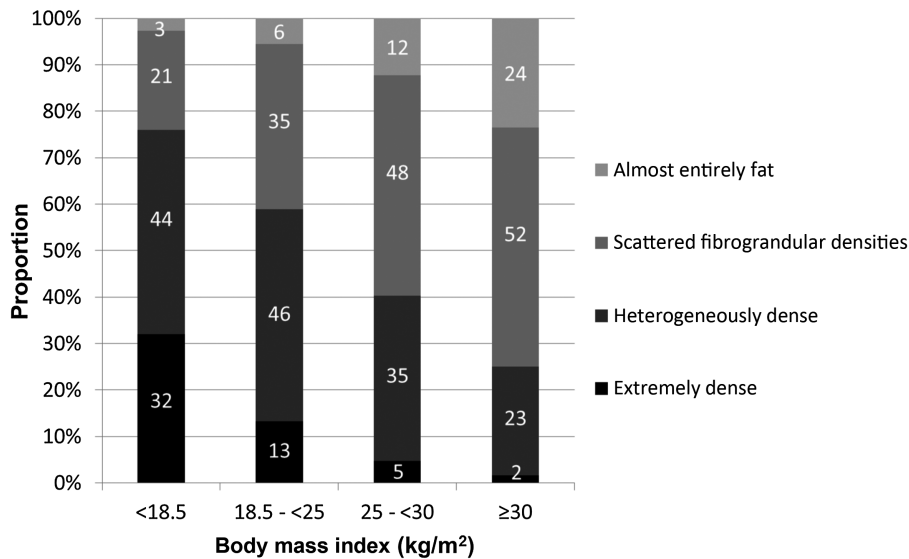


Figure 2. Distribution of BI-RADS breast density categories by body mass index, Breast Cancer Surveillance Consortium, 2007–2010. Proportions are standardized to the 2010 US Census age distribution among US women aged 40 years and older. BI-RADS = American College of Radiology’s Breast Imaging Reporting and Data System.

We estimated that 27.6 million women (95% CI = 27.5 to 27.7 million) aged 40 to 74 years in the United States have heterogeneously or extremely dense breasts (Table 1). Women aged 40 to 49 years (N = 12.3 million) accounted for 44.3% of this group. The inclusion of women aged 75 years and older adds a relatively small number of women (N = 3.1 million), yielding a total prevalence of 30.8 million women (95% CI = 30.6 to 30.9 million) aged 40 years and older with dense breasts.

Among women aged 40 to 74 years, we estimated that 7.4% (95% CI = 7.4% to 7.5%) have extremely dense breasts. Thus, women with extremely dense breasts make up approximately 17.1% (N = 4.7 million) of the total number of women considered to have dense breasts according to the definition used

in breast density notification legislation (heterogeneously or extremely dense).

Discussion

We estimated that approximately 43% of women aged 40 to 74 years have heterogeneously or extremely dense breasts, corresponding to approximately 27.6 million US women who are potentially affected by pending national legislation to mandate reporting of mammographically dense breasts. In light of the ongoing controversies regarding mammography screening for women before age 50 (18,19), it is notable that nearly 45% of women aged 40 to 74 years with dense breasts are younger than age 50 years.

Table 1. Estimated prevalence of BI-RADS breast density categories for the US female population aged 40 years and older, 2007–2010*

Age group, y	BI-RADS breast density category				
	Almost entirely fat	Scattered fibroglandular densities	Heterogeneously dense	Extremely dense	Heterogeneously dense or extremely dense
Count in millions (95% confidence interval)					
40–44	0.83 (0.81 to 0.85)	3.73 (3.69 to 3.76)	4.62 (4.59 to 4.66)	1.32 (1.30 to 1.33)	5.94 (5.89 to 5.99)
5–49	0.98 (0.96 to 0.99)	4.21 (4.17 to 4.26)	4.98 (4.93 to 5.03)	1.33 (1.31 to 1.35)	6.31 (6.24 to 6.38)
50–54	1.35 (1.34 to 1.37)	4.78 (4.74 to 4.81)	4.32 (4.28 to 4.35)	0.92 (0.91 to 0.93)	5.24 (5.19 to 5.28)
55–59	1.52 (1.51 to 1.54)	4.72 (4.69 to 4.75)	3.36 (3.33 to 3.38)	0.54 (0.53 to 0.55)	3.90 (3.87 to 3.93)
60–64	1.60 (1.58 to 1.62)	4.30 (4.27 to 4.33)	2.53 (2.51 to 2.56)	0.31 (0.30 to 0.32)	2.84 (2.81 to 2.87)
65–69	1.20 (1.19 to 1.22)	3.31 (3.29 to 3.34)	1.85 (1.83 to 1.87)	0.22 (0.21 to 0.22)	2.07 (2.04 to 2.09)
70–74	1.04 (1.02 to 1.06)	2.65 (2.62 to 2.68)	1.24 (1.22 to 1.26)	0.11 (0.10 to 0.11)	1.35 (1.32 to 1.37)
75–79	0.82 (0.81 to 0.84)	2.19 (2.17 to 2.21)	1.03 (1.01 to 1.04)	0.09 (0.09 to 0.10)	1.12 (1.10 to 1.14)
80–84	0.62 (0.61 to 0.64)	1.86 (1.83 to 1.88)	0.88 (0.86 to 0.90)	0.09 (0.09 to 0.10)	0.97 (0.95 to 0.99)
≥85	0.68 (0.66 to 0.71)	1.97 (1.93 to 2.01)	0.94 (0.91 to 0.96)	0.11 (0.10 to 0.13)	1.05 (1.01 to 1.09)
40–74	8.52 (8.48 to 8.57)	27.70 (27.59 to 27.82)	22.90 (22.79 to 23.00)	4.73 (4.70 to 4.77)	27.64 (27.54 to 27.73)

* BI-RADS = American College of Radiology's Breast Imaging Reporting and Data System.

The results can also be used to project the potential impact of modifications to breast density notification requirements. Restricting mandated notification to women with extremely dense breasts would substantially reduce the count of US women potentially affected, with 4.7 million women aged 40 to 74 years having extremely dense breasts. The majority (56%) of these women are between ages 40 and 49 years.

Notably, these results reflect the underlying prevalence of dense breasts among the entire US female population aged 40 years and older irrespective of screening adherence rates. The number of US women with dense breasts actually screened in a given year would be somewhat smaller in magnitude. Since screening adherence varies by region, patient characteristics, and over time, our analyses were intended to provide estimates of the underlying prevalence of mammographically dense breasts that could be applied across any number of hypothetical scenarios. For example, the National Health Interview Survey indicates that in 2010 approximately 70% of women aged 40 years and older had been screened in the past two years (20). This could be applied to our estimate of 30.8 million women aged 40 years and older in the United States with dense breasts to arrive at an estimate of 21.6 million women with dense breasts screened in the past two years. Estimates for specific populations (eg, within a given US state or health care system) could be created by applying our age- and BMI-specific density distribution estimates to utilization rates within those populations.

Our results are consistent with prior studies demonstrating strong inverse associations of age and BMI with mammographic breast density (10–12). Notably, our sample size with 1.5 million mammograms is by far the largest to date and our results reflect recent practices of community radiologists from a large catchment area that is similar in demographics to the US population (21). We are not aware of any prior studies estimating national counts of women with dense breasts. We used US Census and NHANES data to project the breast density distribution observed in the BCSC sample to nationally representative counts of the US female population based on age and BMI, which are the strongest predictors of breast density.

Some limitations should be considered while interpreting our results. In our extrapolation to the US population, we did not consider other factors that are correlated with breast density, such as a family history of breast cancer, race/ethnicity, or the use of postmenopausal hormones. These factors have very modest associations with mammographic breast density after adjusting for age and BMI, and their associations are dwarfed by the effects of age and BMI. However, caution should be used in extrapolating the results of this study to populations that vary markedly in such characteristics. The time period of this study coincided with the widespread transition from film to digital mammography in the United States (22). However, we have previously shown that BI-RADS breast density assessment by radiologists is similar for film and digital mammography (23). The majority of mammography exams (64%) included in our study were digital.

Data on mammographic breast density and BMI were missing for substantial fractions of the BCSC mammography exams. The vast majority of missing data are “missing at random” because some facilities do not collect this information. We used multiple imputation to create the most statistically efficient estimates of the breast density distribution and to avoid bias that would have been introduced by exclusion of exams with incomplete data (24). Notably, the study population included a large number of records with complete data on age, BMI, and breast density (N = 632 685), such that the imputation model was well informed. The estimates for the percentage of women with dense breasts by age and BMI in the BCSC dataset were similar in analyses using the imputation approach and analyses that were restricted to records with complete age, BMI, and breast density data (Supplementary Table 3, available online).

Our results are based on radiologists' classifications of breast density using the four BI-RADS density categories, which remain the clinical standard. The new version of the BI-RADS Atlas includes revisions to the descriptions of these density categories which could influence the prevalence of breast density as measured (25). Concerns with the limited precision and interobserver reliability of the BI-RADS density categories (26) have motivated the development of automated density measurement algorithms (27). These may be increasingly utilized in clinical practice and may permit the refinement of cutpoints for characterizing dense breasts.

Our results indicate that the prevalence of mammographically dense breasts in the United States among women of common breast cancer screening ages exceeds 25 million. Currently, the optimal clinical management of women with dense breasts is unclear given the very limited evidence regarding the effectiveness of supplemental screening approaches in this population (7). Clinical trials and observational studies suggest that the addition of screening ultrasound to mammography screening for women with dense breasts provides an increase in cancer detection rates, but also substantially increases the number of false positives (28,29). Notably, these studies have been conducted predominantly among high-risk populations; a recent Cochrane review was unable to find any controlled studies on the use of supplemental ultrasound screening in women at average risk for breast cancer (30). Additionally, the cost-effectiveness of supplemental screening for women with dense breasts has yet to be evaluated (7). The potential impact of supplemental screening on overdiagnosis, an increasingly recognized concern in breast cancer screening (31,32), is also unknown.

Policymakers should consider the large prevalence of women with dense breasts when debating breast density notification legislation. Healthcare providers need to carefully consider strategies to ensure that women who are notified have opportunities to discuss available evidence, evaluate breast cancer risk, and pursue supplemental screening options if deemed appropriate.

References

- 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.
- Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann Intern Med*. 2008;148(5):337–347.
- Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. *JAMA*. 1996;276(1):33–38.
- Buist DS, Porter PL, Lehman C, Taplin SH, White E. Factors contributing to mammography failure in women aged 40–49 years. *J Natl Cancer Inst*. 2004;96(19):1432–1440.
- Carney PA, Miglioretti DL, Yankaskas BC, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med*. 2003;138(3):168–175.
- Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med*. 2005;353(17):1773–1783.
- Lee CI, Bassett LW, Lehman CD. Breast density legislation and opportunities for patient-centered outcomes research. *Radiology*. 2012;264(3):632–636.
- U.S. Congress. H.R. 3404 Breast Density and Mammography Reporting Act of 2013. U.S. Congress; 2013.
- American College of Radiology. *ACR BI-RADS® - Mammography*. 4th Edition. ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas. Reston, VA: American College of Radiology; 2003.
- Brisson J, Morrison AS, Kopans DB, et al. Height and weight, mammographic features of breast tissue, and breast cancer risk. *Am J Epidemiol*. 1984;119(3):371–381.
- Boyd NF, Lockwood GA, Byng JW, Little LE, Yaffe MJ, Tritchler DL. The relationship of anthropometric measures to radiological features of the breast in premenopausal women. *Br J Cancer*. 1998;78(9):1233–1238.
- Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control*. 2000;11(7):653–662.
- Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.
- Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey Anthropometry Procedures Manual (http://www.cdc.gov/nchs/data/nhanes/nhanes_09_10/BodyMeasures_09.pdf). Atlanta, GA; 2009.
- Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Survey Methodology*. 2001;27(1):85–95.
- Survey Methodology Program. IVEWARE. Survey Research Center, Institute for Social Research, University of Michigan.
- Rubin DB. *Multiple imputation for nonresponse in surveys*. New York: John Wiley & Sons; 1987.
- DeAngelis CD, Fontanarosa PB. US Preventive Services Task Force and breast cancer screening. *JAMA*. 2010;303(2):172–173.
- Quanstrum KH, Hayward RA. Lessons from the mammography wars. *N Engl J Med*. 2010;363(11):1076–1079.
- National Center for Health Statistics. Health, United States, 2011: With Special Feature on Socioeconomic Status and Health. Hyattsville, MD; 2012.
- Sickles EA, Miglioretti DL, Ballard-Barbash R, et al. Performance benchmarks for diagnostic mammography. *Radiology*. 2005;235(3):775–790.
- U.S. Food and Drug Administration. Mammography Quality Standards Act and Program Document Archives. 2013.
- Harvey JA, Gard CC, Miglioretti DL, et al. Reported mammographic density: film-screen versus digital acquisition. *Radiology*. 2013;266(3):752–758.
- Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol*. 1995;142(12):1255–1264.
- American College of Radiology. *ACR BI-RADS® - Mammography*. 5th Edition. ACR BI-RADS Atlas: Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology; 2013.
- Spayne MC, Gard CC, Skelly J, Miglioretti DL, Vacek PM, Geller BM. Reproducibility of BI-RADS breast density measures among community radiologists: a prospective cohort study. *Breast J*. 2012;18(4):326–333.
- Wang J, Azziz A, Fan B, et al. Agreement of mammographic measures of volumetric breast density to MRI. *PLoS One*. 2013;8(12):e81653.
- Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA*. 2008;299(18):2151–2163.
- Hoooley RJ, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. *Radiology*. 2012;265(1):59–69.
- Gartlehner G, Thaler K, Chapman A, et al. Mammography in combination with breast ultrasonography versus mammography for breast cancer screening in women at average risk. *Cochrane Database Syst Rev*. 2013;4:CD009632.
- Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med*. 2012;367(21):1998–2005.
- Esserman LJ, Thompson IM Jr, Reid B. Overdiagnosis and overtreatment in cancer: an opportunity for improvement. *JAMA*. 2013;310(8):797–798.

Funding

This work was supported by the National Cancer Institute–funded Breast Cancer Surveillance Consortium (P01 CA154292, HHSN261201100031C), the National Cancer Institute–funded grants U01 CA152958, U54 CA163303, P30 CA014520, and T15 HL097789, and the Department of Biostatistics and Medical Informatics at the University of Wisconsin.

Notes

The authors are solely responsible for the study design, data generation, analysis and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication.

We thank the BCSC investigators, 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 is provided at: <http://breastscreening.cancer.gov/>. We also thank Jue Wang for assistance with data management.

Affiliations of authors: Department of Surgery, Office of Health Promotion Research and Vermont Cancer Center, University of Vermont, Burlington, VT (BLS); Department of Population Health Sciences, University of Wisconsin,

Madison, WI (REG, VB, ATD); University of Wisconsin Carbone Cancer Center, Madison, WI (REG, ATD, JMH); Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI (REG); Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, CA (KK); Division of Biostatistics, Department of Public Health Sciences, University of California Davis School of Medicine, Davis, CA (DLM); Group Health Research Institute, Group Health Cooperative, Seattle, WA (RDW, DLM).