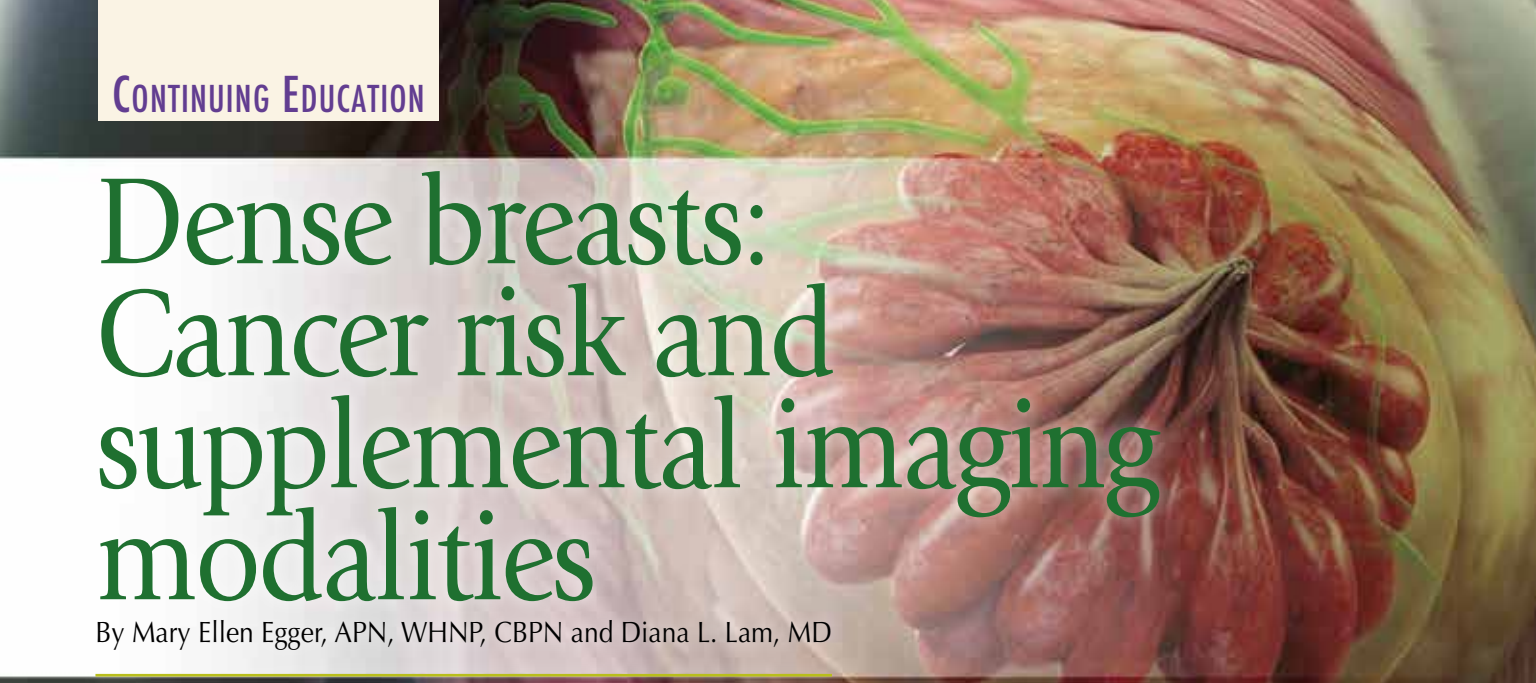

Dense breasts: Cancer risk and supplemental imaging modalities

By Mary Ellen Egger, APN, WHNP, CBPN and Diana L. Lam, MD

To participate in this CE program, click *here*[A].

Faculty:

Mary Ellen Egger, APN, WHNP, CBPN, is a nurse practitioner in the Breast Center at Vanderbilt University in Nashville, Tennessee.

Diana L. Lam, MD, is an Assistant Professor in the Department of Radiology specializing in Breast Imaging at the University of Washington, Seattle Cancer Care Alliance, in Seattle, Washington.

Intended audience: This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners who provide care for women in any age bracket.

CE approval period: Now through February 28, 2019

Estimated time to complete this activity: 1 hour

CE approval hours: 1.0 contact hour of CE credit

Goal statement: To understand increased breast density as an independent risk factor for breast cancer and to identify supplemental imaging modalities that might be appropriate for each individual woman with dense breasts.

Needs assessment: This activity in *Women's Healthcare* is based on a CE presentation developed by the NPWH Education Committee and presented at the NPWH annual conference held in Seattle, Washington, in October 2017. Within the context of breast cancer, the authors discuss the role of increased breast density, which can mask cancers that present as masses on mammography and which is considered to be an independent risk factor for the disease. Also discussed are supplemental breast imaging modalities that can increase early detection of breast cancer that might otherwise be missed by mammography alone.

Educational objectives: At the conclusion of this educational activity, participants should be able to:

1. Define breast density and describe how it is related to breast cancer risk.
2. Identify the different levels of risk for developing breast cancer and how breast density affects those levels.
3. Discuss recommendations for screening and counseling of women at each level of risk.
4. Review supplemental breast-screening modalities and emerging technology available for breast cancer screening.

Accreditation statement: This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH), and has been approved for 1.0 contact hour of CE credit.

Faculty disclosures: NPWH policy requires all faculty to disclose any affiliation or relationship with a commercial interest that may cause a potential, real, or apparent conflict of interest with the content of a CE program. NPWH does not imply that the affiliation or relationship will affect the content of the CE program. Disclosure provides participants with information that may be important to their evaluation of an activity. Faculty are also asked to identify any unlabeled/unapproved uses of drugs or devices made in their presentation.

Mary Ellen Egger, APN, WHNP, CBPN, has no actual or potential conflicts of interest in relation to this presentation.

Diana L. Lam, MD, has no actual or potential conflicts of interest in relation to this presentation.

Disclosure of unlabeled use: NPWH policy requires authors to disclose to participants when they are presenting information about unlabeled use of a commercial product or device or an investigational use of a drug or device not yet approved for any use.

Disclaimer: Participating faculty members determine the editorial content of the CE activity; this content does not necessarily represent the views of NPWH. This content has undergone a blinded peer review process for validation of clinical content. Although every effort has been made to ensure that the information is accurate, clinicians are responsible for evaluating this information in relation to generally accepted standards in their own communities and integrating the information in this activity with that of established recommendations of other authorities, national guidelines, FDA-approved package inserts, and individual patient characteristics.

Successful completion of the activity: Successful completion of this activity, J-18-01, requires participants to:

1. Log on to **npwh.org/courses/home/details/968** and "Sign In" at the top right-hand corner of the page if you have any NPWH account. You must be signed in to receive credit for this course. If you do not remember your username or password, please follow the "Forgot Password" link and instructions on the sign-in page. If you do not have an account, please click on "Create an Account."*
2. Read the learning objectives, disclosures, and disclaimers on the next page.
3. Study the material in the learning activity during the approval period (now through February 28, 2019).
4. Complete the post-test and evaluation. You must earn a score of 70% or better on the post-test to receive CE credit.
5. Print out the CE certificate if successfully completed.

*If you are an NPWH member, were once a member, or have taken CE activities with NPWH in the past, you have a username and password in our system. Please do not create a new account. Creation of multiple accounts could result in loss of CE credits as well as other NPWH services. If you do not remember your username or password, click on the "Forgot Username" or "Forgot Password" link above or call the NPWH office at (202) 543-9693, ext. 1.

Commercial support: The content for this article was supported by an educational grant from Hologic, Inc.

Before reading the article, click *here*[A] to take the pretest.

Within the context of breast cancer, the authors discuss the role of increased breast density, which can mask cancers that present as masses on mammography and which is considered to be an independent risk factor for the disease. Also discussed are supplemental breast imaging modalities that can increase early detection of breast cancer that might otherwise be missed by mammography alone.

KEY WORDS: **breast density, breast cancer, mammography, breast MRI, digital breast tomosynthesis, screening whole-breast ultrasound**

One in eight women will be diagnosed with breast cancer in her lifetime.[1] Breast cancer is the second leading cause of cancer deaths among women in the United States, behind lung cancer.[1] At the same time, there are about 3.3 million breast cancer survivors in the U.S. today[2] and the number of deaths due to breast cancer may be declining, a trend ascribed to a combination of early detection and more effective treatments.[1]

Early detection and intervention are possible when breast cancer screening begins at an age when the risk for the disease starts to rise. The National Comprehensive Cancer Network (NCCN) recommends annual mammographic screening for women starting at age 40 and continuing until life expectancy is <5-7 years.[3] Other guidelines, including those of the U.S. Preventive Services Task Force (USPSTF),[4] the American Cancer Society (ACS),[5] and the American Congress of Obstetricians and Gynecologists,[6] are different with respect to when to start mammography, screening interval, and when to stop mammography. However, all of these organizations agree that *annual mammograms beginning at age 40 save the most lives*.[1]

Breast cancer is most frequently diagnosed in women aged 55-64 years.[2] In addition to female sex and older age, non-modifiable risk factors for breast cancer include certain inherited gene mutations, a family history of breast cancer, a personal history of breast cancer, *dense breast tissue*, certain benign breast conditions (e.g., proliferative lesions with atypia), early-onset menarche (before age 12), and late menopause (after age 55).[7] This article focuses on the role of *increased breast density*, which can mask cancers that present as masses on mammography and which is considered to be an independent risk factor for breast cancer.[8] The authors also discuss supplemental breast imaging modalities that can increase early detection of breast cancers that might otherwise be missed by mammography alone.

What is breast density? How common is it?

Breasts are composed primarily of fat and fibroglandular tissue. Fat is non-dense and appears black on a mammogram; fibroglandular tissue is dense and appears white on a mammogram. Breast density is a measure used to describe both the proportion of fibroglandular tissue to fat seen on a mammogram (the greater the amount of fibroglandular tissue, the greater the density) and the masking effect of fibroglandular tissue on non-calcified breast lesions. Factors that affect breast density include:

- age: breast density is generally greater in younger women;
- menstrual cycle changes: breast density is greater during the luteal phase;
- hormones: use of postmeno-

Breast density is a measure used to describe both the proportion of fibroglandular tissue to fat seen on a mammogram and the masking effect of fibroglandular tissue on non-calcified breast lesions.

pausal hormone therapy (HT) can contribute to increased breast density; and
- body habitus: breast density is generally lower in obese women because of a greater amount of fat relative to fibroglandular tissue.

The American College of Radiology's Breast Imaging Reporting and Data System (ACR BI-RADS) places the degree of mammographic breast density into one of four categories: (a) almost entirely fatty, (b) scattered areas of fibroglandular density, (c) heterogeneously dense, and (d) extremely dense.[9] The first two categories are considered *non-dense* and the latter two categories, *dense*. According to a study by Sprague et al,[10] 43.3% of women aged 40-74 years in the U.S.—which translates into 27.6 million women—have heterogeneously dense or extremely dense breasts.

Why is breast density important?

Because dense breast tissue appears white on a mammogram, as do many cancers, it can mask a developing cancer. In addition, as mentioned previously, breast density is an independent risk factor for the development of breast cancer.[8] As of this writing, more than 30 states require that women found to have dense breasts on mammography be notified of this fact.[11]

In one quantitative assessment, the odds ratio (OR) for developing breast cancer for the most dense versus the least dense breast tissue categories ranged from 1.8 to 6.0, with most studies yielding an OR ≥4.0.[12] Three nested case–control studies showed that women with breast density in ≥75% of the mammogram, versus those with breast density in <10% of the mammogram, had an increased risk of breast cancer (OR, 4.7).[13]

How exactly does increased breast density affect breast cancer risk?

To answer this question, some background information on lifetime risk (LTR) of breast cancer, and calculation of this risk, is needed first. Based on 2012-2014 data, 12.4% of U.S. women will be diagnosed with breast cancer at some point during their lifetime.[2] A woman, based on her personal and family history, is considered to be at *average risk* if her LTR of developing breast cancer is <12% and at *high risk* if her LTR of developing breast cancer is >20%.[2] *Intermediate risk* is assumed to be between average risk and high risk. The ACS uses the term *moderately high risk* instead, which it defines as a 15%-20% LTR of developing breast cancer.[14] How does having increased breast density affect an individual woman's breast cancer risk level?

A woman's breast cancer risk can be calculated by using an assessment tool based on a risk model. Risk models can be used to identify those women who may benefit from risk-reducing medications, carry a genetic mutation, or benefit from screening magnetic resonance imaging (MRI) of the breasts.[15] Two such assessment tools, the National Cancer Institute's **Breast Cancer Risk Assessment Tool**[B],[16] based on the Gail model, and the Claus model,[17] can be used easily in the office, but *they do not include breast density in their calculation of risk*. The Gail model can be used to identify women who may benefit from chemoprevention, whereas the Claus model calculates LTR for purposes of screening MRI guidelines.

Two assessment tools *do* incorporate breast density into their breast cancer risk calculations. The **IBIS Breast Cancer Risk Evaluation Tool**[C], based on the Tyrer-Cuzick model, provides 5-year and 10-year breast cancer risk values in addition to LTR values.[18] This tool considers a woman's age, BMI, age at menarche, age at first live birth, age at menopause, use of menopausal HT, breast biopsy history, and breast density; history of atypical ductal hyperplasia or lobular carcinoma in situ (LCIS); and family history of breast and ovarian cancer in first- and second-degree relatives. It also estimates risk for presence of a non-*BRCA1/2* breast cancer susceptibility gene mutation. In providing 5- and 10-year risk values (but not LTR values), the **Breast Cancer Surveillance Consortium (BCSC) Risk Calculator**[D] considers age, race/ethnicity, ACR BI-RADS *breast density*, first-degree relative history, and detailed pathology results from prior benign or atypical biopsies.[19]

Having dense breasts alone does not automatically place a woman at

intermediate or high risk for breast cancer. Her risk category depends on her personal/family history, the assessment tool used, and whether or not 5-year risk or LTR is calculated. A study by Kerlikowske et al,[20] which used the BCSC Risk Calculator, found that about half of women with heterogeneously or extremely dense breasts had a low to average 5-year breast cancer risk (0%-1.66%). Rates of *interval cancer*—that is, cancer discovered in between recommended rounds of screening mammography, typically because of a symptom such as a palpable lump, focal pain, or nipple discharge—were highest in women who were already at a high 5-year risk because of other factors such as a positive family history.

What type of management is recommended for a woman with dense breasts but no other risk factors for breast cancer?

As an example, a 54-year-old woman's current mammogram yields negative results but shows that she has dense breasts. An assessment tool shows that she has a 1% 5-year risk and a <12% LTR of developing breast cancer—that is, she is at *average risk*. For her and others like her, management is aimed at early-detection and risk-reduction strategies.

This woman is advised, as per NCCN guidelines, to undergo annual screening mammography, alone or with digital breast tomosynthesis (DBT; see section on supplemental breast imaging modalities) and clinical breast examination (CBE), and to implement breast awareness—that is, to be familiar with her breasts and to report promptly any change to her healthcare provider (HCP).[3] If this woman reports a symptom to her HCP, even if she had a negative screening mammogram result only a few months ago, she should undergo a workup for a possible interval cancer. This workup entails a CBE and diagnostic imaging (e.g., mammography and a targeted ultrasound).

In addition to annual mammograms and CBEs, she should implement these lifestyle modifications as needed[21-23]:

- Decrease alcohol intake: Have no more than one drink (12 oz beer, 5 oz wine, 1.5 oz 80-proof distilled spirits) a day;
- Maintain a healthy weight: Overweight/obese women are at higher risk for postmenopausal breast cancer;
- Reduce dietary fat intake: A high-fat diet in adolescence is associated with a moderate increase in premenopausal breast cancer;
- Limit red meat intake: A higher intake of red meat increases the risk for premenopausal breast cancer; and
- Increase exercise: Exercising strenuously for >4 hours/week is associated with reduced breast cancer risk.

What is recommended for a woman with dense breasts and a moderately high risk for developing breast cancer?

As an example, a 43-year-old woman with dense breasts on mammography has a positive family history: Her mother was diagnosed with breast cancer at age 56. This woman is advised to follow the aforementioned surveillance and lifestyle recommendations for a woman at average risk. For her and others like her, who are considered to be at *moderately high risk* of developing breast cancer, no standard-of-care recommendations for supplemental screening exist. Screening whole-breast ultrasound (WBUS) or a mammogram with DBT can be considered, although coverage of the cost of the additional testing varies from plan to plan.

What is recommended for a woman with dense breasts and a high risk for developing breast cancer?

As an example, a 35-year-old woman has already undergone mammography annually for the past 5 years because she learned that she is a *BRCA1* mutation carrier, which places her in the high-risk category. She knows that she has dense breasts and wants to be as vigilant as possible. She does not want to undergo risk-reducing bilateral mastectomy at this time. According to the ACS, women are at high risk for breast cancer if they[5]:

- have an LTR ≥20%-25%, according to risk assessment tools based mainly on family history;
- have a known *BRCA1/2* gene mutation;
- have a first-degree relative with a *BRCA1/2* gene mutation but have not had genetic testing themselves;
- had radiation therapy to the chest when they were aged 10-30 years; and/or
- have Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or have first-degree relatives with one of these syndromes.

The ACS recommends that women who meet any of these criteria undergo screening mammography and breast MRI every year (these tests can be alternated every 6 months), typically starting at age 30.[24] For women in the high-risk category, breast MRI is generally reimbursed by insurance. Other suggestions for management include

undergoing a CBE every 6 months and initiating a chemoprevention regimen. For a premenopausal woman aged ≥35 years, this may include the selective estrogen receptor modulator (SERM) tamoxifen, whereas a postmenopausal woman can take tamoxifen or raloxifene. If a SERM is contraindicated (e.g., because of a history of thromboembolic events), an aromatase inhibitor can be tried.[25] However, aromatase inhibitors are not FDA approved for this indication.

What should I know about the supplemental breast imaging modalities that are available?

Among available modalities, contrast-enhanced **breast MRI** is the most sensitive for breast cancer detection. In a prospective multicenter cohort study, 687 asymptomatic women at high risk for breast cancer underwent a total of 1,679 annual screening rounds of mammography, WBUS, MRI, and CBE.[26] The cancer yield was 6.0/1,000 screens for WBUS alone and 5.4/1,000 for mammography alone; this rate rose slightly, to 7.7/1,000, when both methods were combined. Cancer yield achieved by MRI alone, 14.9/1,000, was significantly higher—but it was not improved to a significant degree by adding WBUS (14.9/1,000), mammography (16.0/1,000), or both (16.0/1,000). Disadvantages of breast MRI are its high cost, long duration, use of intravenous gadolinium contrast, discomfort for some women, and lack of widespread availability of high-quality scans.[27]

Abbreviated breast MRI, or ABRM, a shorter version of the standard MRI protocol (10 vs. 30 min), is being studied as a lower-cost alternative that is more comfortable for patients. Although use of ABRM is still experimental, preliminary findings have suggested that it works well in identifying breast cancers in a group of women with dense breasts. In a study of 195 asymptomatic women with dense breasts and negative mammography results within the past 11 months, ABMR detected 5 additional cancers.[28] To put these results in perspective, the cancer detection rate of mammography in the average-risk woman is 5/1,000 screens. Extrapolating from these data, the cancer detection rate of ABMR screening would be 25/1,000 screens.

Screening WBUS can be performed with a hand-held device or a semi-automated device with a large ultrasound paddle. WBUS is the most widely available supplemental imaging modality for women with dense breasts and a negative mammography screen.[27] Advantages of WBUS are that it is practical, requires no ionizing radiation or intravenous contrast, and is relatively inexpensive.[27] A literature review of studies assessing the efficacy of supplemental WBUS in women with dense breasts showed that, overall, it detected a median of 4.2 additional cancers/1,000 exams; however, it was associated with a median of 52.2 additional biopsies/1,000 exams.[29] Results of a study by Sprague et al[30] demonstrated another downside of WBUS besides a high rate of false-positive results (345/1,000 women): The cost-effectiveness ratio was $325,000 per quality-adjusted life-year (QALY) gained. Any value >$100,000 is considered excessive.

Digital breast tomosynthesis, also known as 3D mammography, uses a rotating x-ray tube that travels in an arc over the compressed breast, which provides multiple thin-sliced images through the breast that a radiologist can scroll through (similar to a CT scan). Six large studies of the use of supplemental DBT in the general population have shown that it increases cancer yield by an average of 1.25/1,000 screenings—an increase of 20%—and it reduces the recall rate, by an average of 16%.[31-36]

In a study that took breast density into account, supplemental DBT led to an increase in the cancer detection rate and a reduction in the recall rate for women with dense *or* non-dense breasts.[37] Combined gains were largest for women with heterogeneously dense breasts—potentially addressing limitations in cancer detection seen with mammography alone in this group—but were not significant for women with extremely dense breasts. Using a breast cancer simulation model that included U.S. women aged 50-74 years with dense breasts, Lee et al[38] found that supplemental DBT increased breast cancer detection by 6 cases/1,000 women, decreased the number of false-positives by 405, and averted 0.5 deaths. Compared with the high cost of adding WBUS, that of adding DBT was $53,983/QALY gained.[38]

How do these supplemental imaging modalities compare with each other in terms of detecting cancer in women with dense breasts?

WBUS vs. breast MRI: Berg et al[39] compared supplemental cancer detection yield of WBUS and breast MRI in women with dense breasts and at least one additional risk factor for breast cancer. Supplemental screening with WBUS, done annually for 3 years in more than 2,300 women, and breast MRI, done once in a subset of 612 participants who completed the 3 years of supplemental screening with WBUS, increased the breast cancer detection yield by 4.3/1,000 screens and 14.7/1,000 screens, respectively. The biopsy rate

resulting from positive findings seen only on WBUS was high—5%—with only 7.4% of those women found to have cancer. An additional 7% of women underwent biopsy because of their breast MRI results; 19% were found to have cancer.

WBUS vs. DBT: Tagliafico et al[40] conducted a prospective multicenter study of 3,231 asymptomatic women aged 44-78 with mammography-negative screens and dense breasts to compare WBUS and DBT with regard to incremental breast cancer detection and the number of false-positive recalls. Of the 24 additional breast cancers detected, 13 were found by DBT (4.0/1,000 screens) and 23 by WBUS (7.1/1,000 screens), a significant difference favoring WBUS. Incremental false-positive recall occurred in 107 women (3.33%) and did not differ between DBT and WBUS. Of note, this study was performed in a system where supplemental WBUS was routinely performed and where DBT was recently instituted. It is possible that, over time, the false-positive recall rate with DBT would decline.

WBUS vs. breast MRI vs. DBT: The USPSTF conducted a systematic review of reproducibility of ACR BI-RADS density categorization, test performance, and clinical outcomes of supplemental screening with hand-held, WBUS, automated WBUS, breast MRI, and DBT in women with dense breasts and negative mammography results.[41] Supplemental screening with any of the four modalities consistently detected additional cases of breast cancer. With the possible exception of DBT, supplemental testing led to many additional recalls and biopsies.

ABMR vs DBT: The ECOG-ACRIN Research Group is undertaking a study to compare the efficacy of ABMR and DBT in detecting cancer in women with dense breasts.[42] The estimated primary completion date of the trial is December 31, 2018.

What are the general cancer screening recommendations for women with dense breasts?

Women with dense breasts should undergo screening mammography once a year until their life expectancy is <5-7 years. The risks of supplemental WBUS may outweigh the benefits, although this modality may be useful in women with extremely dense breasts who can accept the risk of false-positive findings. DBT may be the best additional test for detecting cancer *without* producing an excess of false-positives. Women with a high LTR for breast cancer, regardless of breast density, should have the option of undergoing an annual breast MRI, the most sensitive test for breast cancer detection.

References

1. American Cancer Society (ACS). Cancer Facts & Figures 2016. cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2016.html
2. SEER Cancer Stat Facts: Female Breast Cancer. National Cancer Institute. Bethesda, MD. seer.cancer.gov/statfacts/html/breast.html
3. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis. Version 1.2017. June 2, 2017. nccn.org/professionals/physician_gls/pdf/breast-screening.pdf
4. United States Preventive Services Task Force (USPSTF). Final Recommendation Statement. Breast Cancer Screening. January 2016. uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-screening1
5. American Cancer Society (ACS) Recommendations for the Early Detection of Breast Cancer. Last revised October 9, 2017. cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/american-cancer-society-recommendations-for-the-early-detection-of-breast-cancer.html
6. American Congress of Obstetricians and Gynecologists (ACOG). ACOG Revises Breast Cancer Screening Guidance: Ob-Gyns Promote Shared Decision Making. June 22, 2017. acog.org/About-ACOG/News-Room/News-Releases/2017/ACOG-Revises-Breast-Cancer-Screening-Guidance-ObGyns-Promote-Shared-Decision-Making
7. American Cancer Society (ACS). Breast Cancer Risk Factors You Cannot Change. Last revised September 6, 2017. cancer.org/cancer/breast-cancer/risk-and-prevention/breast-cancer-risk-factors-you-cannot-change.html
8. National Cancer Institute (NCI). Breast Cancer Treatment (PDQ®)–Health Professional Version. General Information About Breast Cancer. Risk Factors. cancer.gov/types/breast/hp/breast-treatment-pdq#link/_627_toc
9. D'Orsi CJ, Sickles EA, Mendelson EB, Morris EA. *ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System*. 5th ed. Reston, VA: American College of Radiology; 2013.
10. Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst*. 2014;106(10).
11. Are You Dense website. State Density Reporting Bills Spread Across the Country/Federal Bill Introduced. areyoudense.org/news-events/state-density-reporting-bills-spread-across-countryfederal-bill-introduced/
12. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. *Radiology*. 2004;230(1):29-41.
13. 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.
14. American Cancer Society (ACS). Breast Cancer Facts & Figures, 2017-2018. cancer.org/content/dam/cancer-org/research/can-

cer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf

15. DenseBreast-info website. Risk Models for Breast Cancer: A Primer. densebreast-info.org/explanation-of-dense-breast-risk-models.aspx
16. National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool. cancer.gov/bcrisktool/
17. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early onset breast cancer. *Cancer*. 1994;73(3):643-651.
18. IBIS Breast Cancer Risk Evaluation Tool. ems-trials.org/riskevaluator/
19. Breast Cancer Surveillance Consortium Risk Calculator. tools.bcsc-scc.org/BC5yearRisk/calculator.htm
20. Kerlikowske K, Zhu W, Tosteson AN, et al; Breast Cancer Surveillance Consortium. Identifying women with dense breasts at high risk for interval cancer: a cohort study. *Ann Intern Med*. 2015;162(10):673-681.
21. CDC. What Can I Do to Reduce My Risk of Breast Cancer? Page last updated September 27, 2017. cdc.gov/cancer/breast/basic_info/prevention.htm
22. American Cancer Society (ACS). Can I Lower My Risk of Breast Cancer? Page last updated September 6, 2017. cancer.org/cancer/breast-cancer/risk-and-prevention/can-i-lower-my-risk.html
23. Key Research Findings from the Nurses' Health Studies. nurseshealthstudy.org/sites/default/files/pdfs/table%20v2.pdf
24. Saslow D, Boetes C, Burke W, et al; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57(2):75-89.
25. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Risk Reduction. Version 1.2017. December 16, 2016. nccn.org/professionals/physician_gls/pdf/breast_risk.pdf
26. Kuhl C, Weigel S, Schrading S, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. *J Clin Oncol*. 2010;28(9):1450-1457.
27. Hooley RJ. Breast density legislation and clinical evidence. *Radiol Clin North Am*. 2017;55(3):513-526.
28. Weinstein S, Schnall MD, McDonald ES, et al. Abbreviated Breast MRI May Be Additional Screening Option for Dense Breasts. Presented at: Radiological Society of North America meeting; November 2017; Chicago, IL. pennmedicine.org/news/news-releases/2017/november/abbreviated-breast-mri-may-be-additional-screening-option-for-dense-breasts
29. Scheel JR, Lee JM, Sprague BL, et al. Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts. *Am J Obstet Gynecol*. 2015;212(1):9-17.
30. Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med*. 2015;162(3):157-166.
31. Rose SL, Tidwell AL, Bujnoch LJ, et al. Implementation of breast tomosynthesis in a routine screening practice: an observational study. *AJR Am J Roentgenol*. 2013;200(6):1401-1408.
32. Ciatto S, Houssami N, Bernardi D, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. *Lancet Oncol*. 2013;14(7):583-589.
33. Skaane P, Bandos AI, Gullien R, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. *Radiology*. 2013;267(1):47-56.
34. Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. *JAMA*. 2014;311(24):2499-2507.
35. McDonald ES, McCarthy AM, Akhtar AL, et al. Baseline screening mammography: performance of full-field digital mammography versus digital breast tomosynthesis. *AJR Am J Roentgenol*. 2015;205(5):1143-1148.
36. Sharpe RE Jr, Venkataraman S, Phillips J, et al. Increased cancer detection rate and variations in the recall rate resulting from implementation of 3D digital breast tomosynthesis into a population-based screening program. *Radiology*. 2016;278(3):698-706.
37. Rafferty EA, Durand MA, Conant E, et al. Breast cancer screening using tomosynthesis and digital mammography in dense and nondense breasts. *JAMA*. 2016;315(16):1784-1786.
38. Lee CI, Cevik M, Alagoz O, et al. Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. *Radiology*. 2015;274(3):772-780.
39. Berg WA, Zhang Z, Lehrer D, et al; ACRIN 6666 Investigators. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography with elevated breast cancer risk. *JAMA*. 2012;307(13):1394-1404.
40. Tagliafico AS, Calabrese M, Mariscotti G, et al. Adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts: interim report of a prospective comparative trial. *J Clin Oncol*. 2016 Mar 9. Epub ahead of print.
41. Melnikow J, Fenton JJ, Whitlock EP, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164(4):268-278.
42. ECOG-ACRIN Research Group. EA1141–Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women with Dense Breasts. ecog-acrin.org/clinical-trials/ea1141-educational-materials

Web resources

A. npwh.org/courses/home/details/968
B. cancer.gov/bcrisktool/
C. ems-trials.org/riskevaluator/
D. tools.bcsc-scc.org/BC5yearRisk/calculator.htm