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Breast Density: Why It Matters

A certified educational program for referring physicians, including family physicians and midlevel providers, and Ob/Gyns, nurses, radiologists, and radiologic technologists

Course Overview

The two greatest risks for developing breast cancer are being female and getting older. But type of breast tissue should also be considered when personalizing a plan for the patient's breast cancer screening exam.

Not only has breast density long been known to mask breast cancer on mammography, but breast density is an independent risk factor for the development of breast cancer. Increasing awareness about the importance of breast density necessitates new conversations between patients and their healthcare providers. Helping prompt these discussions are state laws requiring patients be provided some level of breast density information after undergoing mammography. To date, more than half of the states in the United States have passed legislation requiring at the least general notification about breast density, with some requiring that patients are informed about their breast tissue type.

This comprehensive educational program will inform referrers, including physicians, nurses, midlevel providers, radiologists, and radiologic technologists on educating patients about the implications of dense tissue, including considerations for additional screening for patients who have heterogeneously dense or extremely dense breasts.

This medically-sourced activity includes:

- Discussion and illustrations of the four types of breast tissue
- Explanation of breast cancer risk, including disease-causing genetic mutations
- Recommendations for breast cancer screening, including for those who have dense breast tissue
- Review of factors that can affect breast density
- Assessment of several risk models for patient stratification and approaches for reducing risk
- A Screening Decision Support Tool to help craft an individualized breast cancer screening plan
- Review of breast imaging modalities for supplemental screening, including 3D mammography ("tomosynthesis"), ultrasound, MRI, molecular breast imaging/breast-specific gamma imaging, and contrast-enhanced digital mammography
- An update on breast density inform laws and efforts toward a national standard

Educational Objectives

At the conclusion of this activity, participants should be better able to:

- Describe the BI-RADS® categories of breast density used in mammographic reporting
- Identify the factors that affect breast density
- Discuss risks associated with having dense breasts
- Characterize outcomes from mammography in fatty and dense breasts
- Discuss the benefits and limitations of 3D mammography (digital breast tomosynthesis)
- Explain the benefits and disadvantages of supplemental screening with ultrasound for women with dense breasts
- Describe which women are recommended for screening with MRI and at what ages
- Identify other breast imaging technologies in development
- Review current state breast density inform laws

Jointly Provided by

University of Pittsburgh, International Center for Postgraduate Medical Education, and DenseBreast-info.org.

Accreditation & Credit

ACCME Accreditation Statement
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of University of Pittsburgh and International Center for Postgraduate Medical Education. The University of Pittsburgh is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation

Physicians

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SA-CME: This activity meets the criteria for self-assessment toward the purpose of fulfilling requirements in the American Board of Radiology (ABR) Maintenance of Certification Program.

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Faculty

Wendie A. Berg, MD, PhD, FACR, FSBI, and Chief Scientific Advisor for DenseBreast-info.org, is Professor of Radiology at the University of Pittsburgh School of Medicine and Magee-Womens Hospital of UPMC. Dr. Berg specializes in breast imaging and sees patients at Magee-Womens Hospital in Pittsburgh, PA.

Dr. Berg has been the Principal Investigator of many important research studies in breast imaging, most notably with support of the Avon Foundation and the National Cancer Institute, the ACRIN 6666 protocol, which evaluated screening ultrasound and screening MRI in women with dense breasts. Dr. Berg has led important research evaluating positron emission mammography (PEM) and MRI in women with newly diagnosed cancer and is part of an outstanding team of physicians at UPMC who are evaluating tomosynthesis, fast MRI, contrast-enhanced mammography, and molecular imaging approaches to breast imaging.

Dr. Berg writes and co-edits one of the leading textbooks of breast imaging, *Diagnostic Imaging: Breast* (Amirsys; with 3rd edition release in mid-2019) and has authored or coauthored more than 100 peer-reviewed research publications on breast imaging.

JoAnn Pushkin, Executive Director of DenseBreast-info.org, is a patient/advocate, author, and speaker. She learned of her own breast density's masking effect on her mammogram after finding a palpable lump that went undetected by mammography several years in a row. She is also cofounder of the advocacy group DENSE (Density Education National Survivors' Effort).

Ms. Pushkin's initiative and advocacy served as inspiration for New York State's Breast Density Inform bill, signed into law in July 2012. On the federal level, Ms. Pushkin led the efforts for both the introduction of the Federal Breast Density and Mammography Reporting Act, as well as the FDA's Mammography Quality Standards Act regulatory amendment consideration.

Cindy Henke-Sarmento, RT(R)(M), BA, former Technology Director of DenseBreast-info.org, is an entrepreneur, author, and co-owner of QSUM Biopsy Disposables, LLC. She has 29 years of experience in the mammography field, 22 years of specialized experience in breast care, and holds five patents. Ms. Henke-Sarmento led the initiative for the 2014 introduction of Colorado's breast density reporting bill.

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JoAnn Pushkin has no disclosures to report.

Cindy Henke-Sarmento is co-owner of QSUM Biopsy Disposables, LLC.

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Victoria Phoenix, BS
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About DenseBreast-info.org

DenseBreast-info.org is an educational resource developed to provide breast density information to both patients and health care professionals. This medically-sourced tool is the collaborative effort of world-renowned breast imaging experts and medical reviewers. Dense-Breast-info, Inc. is a 501(c)(3) non-profit charity organized under the laws of New York State. All grants and donations help support the resources and initiatives to provide education about dense breasts to both women and their health care providers. The organization has received corporate unrestricted educational grants from The Avon Foundation for Women, Beekley Medical, CMR Naviscan, Densitas. GE Healthcare, Hologic, iCAD, QSUM Biopsy Disposables, Siemens Healthineers, Volpara Solutions, Wells Fargo.

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Breast Density: Why It Matters

Introduction

Breast cancer is the most common type of cancer, affecting 1 in 8 American women. For 2018, it is estimated that almost 330,080 new breast cancer cases will be diagnosed in the United States, resulting in approximately 40,920 deaths — a staggering statistic.[1]

The two greatest risks for developing breast cancer are being female and getting older. Aside from sex and age, breast density has been found to be the most prevalent of common risk factors for breast cancer.[2] Greater density not only increases the risk of developing cancer but also makes it more difficult to detect cancer on mammography. Approximately 50% of breast cancers are missed on mammography in dense tissue.[3] A *normal*, *negative*, or *benign* mammogram does not exclude cancer in any woman, but this is particularly true in women who have dense breasts.

What is Breast Density?

Breast density is a description of the relative amount of fibrous and glandular tissue versus fat in the breast—the higher the proportion of "fibroglandular" tissue, the denser the breast. Most commonly, breast density is a qualitative determination based on subjective visual assessment of mammographic images by the radiologist.

Breast density can also be assessed on digital mammography or synthetic 2D images created during tomosynthesis using one of several methods by computer software that measures density by either area or volume.

Breast density can also be evaluated on CT and MRI.

Breast Composition

Breast tissue sits on top of the pectoral muscle. All breasts contain glands, ducts, fat, and fibrous connective tissue. "Fibroglandular tissue" refers to glands and fibrous tissue (**Figure 1**). Breast density is determined by the relative amount of fibroglandular tissue (dense) and fat (not dense).

On mammography, dense fibroglandular tissue blocks x-rays and therefore appears white. Cancerous tissue also appears white, making it very difficult or impossible to see – like trying to see a snowman in a blizzard (**Figure 2**).

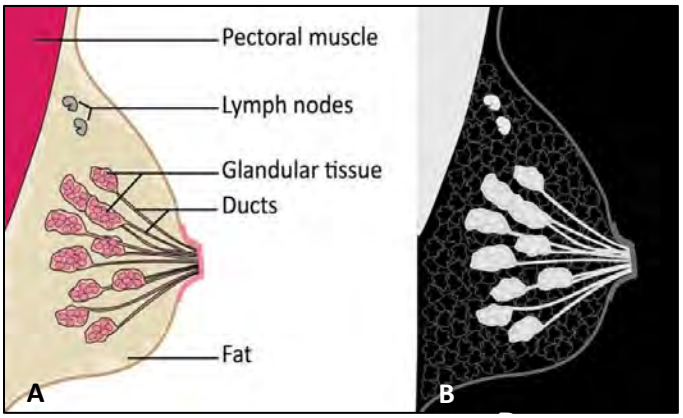

Figure 1. Normal breast. A. The normal breast is composed of milk-producing glands at the ends of ducts leading to the nipple. There is a layer of fat just beneath the skin, and often a few lymph nodes are seen near the underarm (axilla). B. On a mammogram, fat appears dark gray; glandular tissue, fibrous tissue, muscle, and lymph nodes appear light gray or white. Masses due to cancer also appear white.

Courtesy Jeremy M. Berg, PhD

Lymph nodes are normal structures that trap foreign material including bacteria. Lymph nodes can be found in many places in the body, including the breast and especially in the armpits (axillae). When breast cancer is invasive and spreads beyond the breast, the first place it spreads is nearly always to the axillary lymph nodes. In addition to fibroglandular tissue, fat, lymph nodes, arteries, veins, and calcifications are often seen on mammography.

Fatty tissue allows greater x-ray penetration and is seen as dark gray or black (**Figure 3**). Consequently, mammography is far more effective for imaging fatty breasts. Up to 98% of cancers can be visualized against a fatty background.[4] At higher relative breast density, the ability of mammography, whether 2D or 3D (tomosynthesis), to reveal cancers decreases.

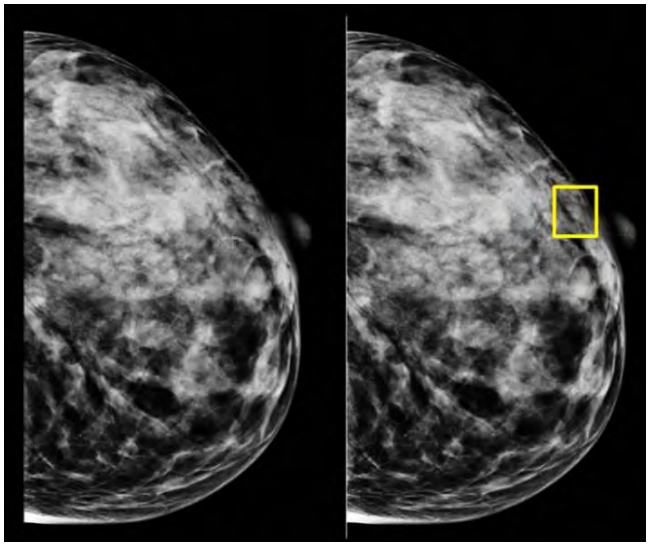

Figure 2. Invasive cancer was not seen in this dense breast on mammography, but was seen on ultrasound.

Courtesy Wendie Berg, MD, PhD

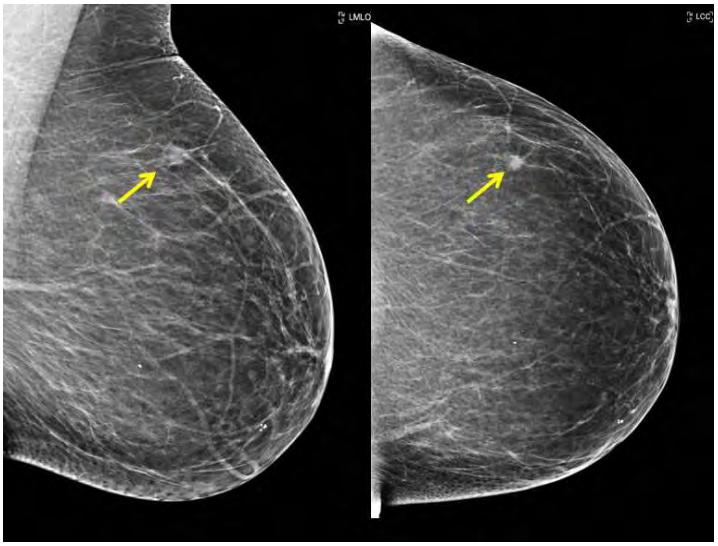

Figure 3. Cancer visualized in fatty breast on mammography.

Courtesy John Lewin, MD

Dense Tissue Categories

Each woman's breasts are a unique mix of fatty and dense tissue: some are almost all fat, some have very little fat, and most are in-between. Having dense breasts is normal, and breast density tends to decrease with age and menopause. Dense breast tissue is quite common, seen in 43% of all women ages 40-74 years.[5]

Importantly, a woman's breast density status is not determined by how her breast looks or feels.

The Breast Imaging Reporting and Data System

Radiologists working with the American College of Radiology (ACR) established the Breast Imaging Reporting and Data System (BI-RADS®) to standardize description of imaging findings and overall assessments and recommendations for mammography,[6] breast ultrasound,[7] and breast MRI.[8] Screening mammograms are typically assessed as BI-RADS 1, negative, or BI-RADS 2, benign, with recommendation for routine annual screening. BI-RADS 0, incomplete, is used for mammograms when a finding is seen that requires recall for additional imaging such as additional mammographic views or targeted ultrasound. About 10-12% of women undergoing screening will be recalled for additional testing,[9] and about 95% of those women recalled will prove to have normal/benign results.

Diagnostic mammography is monitored by the radiologist during the examination and is performed for women with symptoms such as a lump or nipple discharge or for women recalled for additional testing after screening. On diagnostic mammography, a final assessment is rendered which is commonly BI-RADS 1, negative, or BI-RADS 2, benign, like for screening. Final assessments on diagnostic mammography also include category BI-RADS 3, probably benign, which is used for findings that are more than 98% likely to be benign but for which short interval follow-up imaging is recommended to monitor stability, usually in six months. Findings that are believed to merit biopsy will usually be assessed as BI-RADS 4, suspicious, or BI-RADS 5, highly suggestive of malignancy.

BI-RADS is also used for reporting breast density. While the reporting of breast density directly to patients is not required in all states, it is strongly recommended that breast density be included in all mammography reports that go to physicians.

The four BI-RADS® categories used to describe breast density are:

A. Almost Entirely Fatty – about 10% of women. On mammography, most of the tissue appears dark gray or black, while small amounts of dense, fibroglandular tissue display as light gray or white.

B. Scattered Areas of Fibroglandular Density – about 40% of women. The breast shows scattered areas of fibroglandular tissue mixed with fat. Cancers can be missed if they either appear similar to normal tissue or lie within an area of denser tissue.

C. Heterogeneously Dense – about 40% of women. Large portions of the breast consist of fibroglandular tissue where noncalcified cancers can be hidden.

D. Extremely Dense – about 10% of women. Most of the breast appears to consist of fibroglandular tissue, creating a "white out" and making it extremely difficult to see cancers that lack calcifications.[10]

When we use the term *dense breasts,* we are referring to breast tissue that falls into Categories C and D: heterogeneously and extremely dense. When the density is assessed subjectively, there can be variability in the *visual* assessment of breast density. For instance, the density reported on the mammogram might be described as "scattered" one year and "heterogeneously dense" the next year without any true change in tissue density.

Examples of each density type as visualized on mammography are shown in **Figure 4**, while examples of how cancer appears in each of the four breast density categories are shown in **Figure 5**.

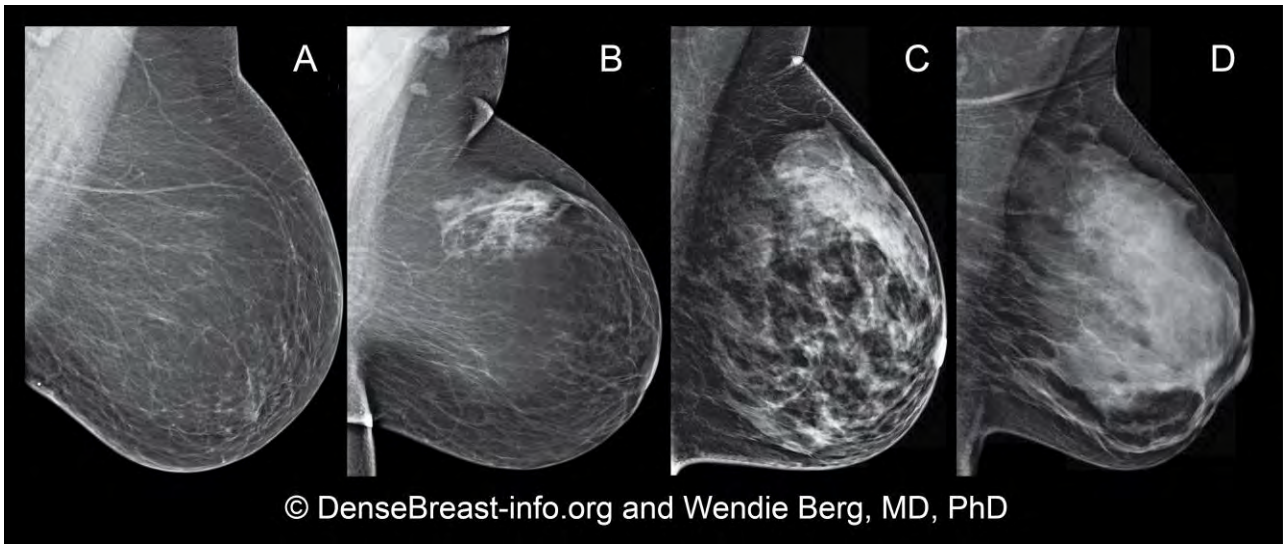

Figure 4. Breast tissue density categories. A. Fatty; B. Scattered fibroglandular density; C. Heterogeneously dense; D. Extremely dense. Breasts that are heterogeneously dense or extremely dense are considered “dense.”

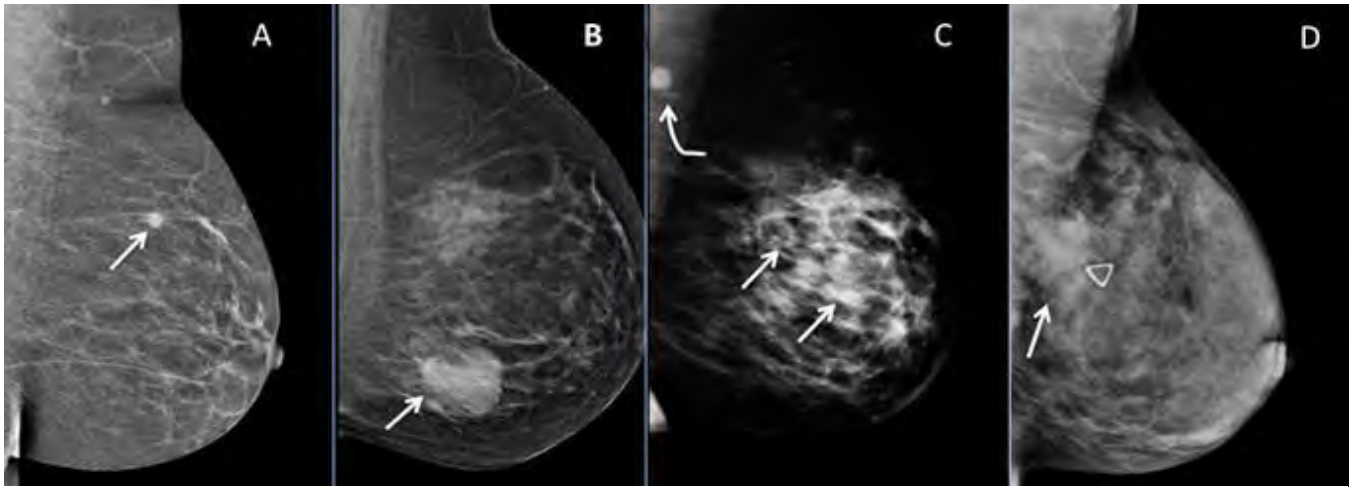

Figure 5. Mammographic images showing how cancer looks in each of the breast density categories. A. A small cancer (arrow) is easily seen in a fatty breast. B. In this breast with scattered fibroglandular density, a large cancer is easily seen (arrow) in the relatively fatty portion of the breast, though a small cancer could have been hidden by areas of normal tissue. C. In this heterogeneously dense breast, a 4-cm cancer (arrows) is hidden by the dense breast tissue. Note the metastatic node in the left axilla (curved arrow). D. In this extremely dense breast, a cancer is seen as part of it is located in the back of the breast where there is a small amount of dark fat, making it easier to see (arrow and triangle marker indicating lump). If this cancer had been located near the nipple and completely surrounded by white (dense) tissue, it probably would not have been seen on mammography.

Courtesy Regina Hooley, MD

Fibrocystic and lumpy breasts

A *fibrocystic* breast is not the same as *fibroglandular* breast tissue. Fibrocystic change is a hormonal condition most pronounced when women are young and usually diminishes after menopause. Fibrocystic breasts can *appear* dense due to cysts or areas of fibrosis. Cysts are common and do not develop into breast cancer. Fibrocystic changes like sclerosing adenosis are proliferative changes that slightly increase the risk for breast cancer (about 1.5X).

Having "lumpy" breasts does not indicate density nor does it mean the breasts are undergoing fibrocystic changes. Fatty breasts can feel lumpy – like soft grapes — in areas where the ligaments that support the breast surround fat lobules.

Breast Cancer Risk

More than half of all women who develop breast cancer have no known risk factors other than being female and aging. The risk for developing breast cancer is influenced by a combination of many factors, and there is currently no reliable means for fully accounting for the interplay of these factors in determining overall risk (click for a Breast Cancer Risk Checklist).

Relative Risk and Prevalence

Relative risk (RR) is the ratio of the observed prevalence of disease in women with a given risk factor to the prevalence in women without that risk factor. **Table 1** and **Figure 6** show the *relative risk* of developing invasive breast cancer by age 80 for a woman with one of these risk factors compared to that of a woman with fatty breasts without that risk factor.[11, 12] Additionally, not captured in **Table 1** or **Figure 6**, women with a personal history of any breast cancer (not just DCIS) have a high risk of second cancer or recurrence.

Table 1. Relative risk of developing invasive breast cancer by age 80.

	Relative Risk
Disease-causing *BRCA1* or *BRCA2* mutation	15x
Prior ductal carcinoma *in situ* (DCIS)	10x
Prior atypical ductal hyperplasia (ADH)	5x
First-degree relative (mother, sister) diagnosed with breast cancer by age 50	2x
Combined estrogen and progesterone therapy after menopause	1.5x
Heterogeneously dense breast tissue	2x
Extremely dense breast tissue	4x

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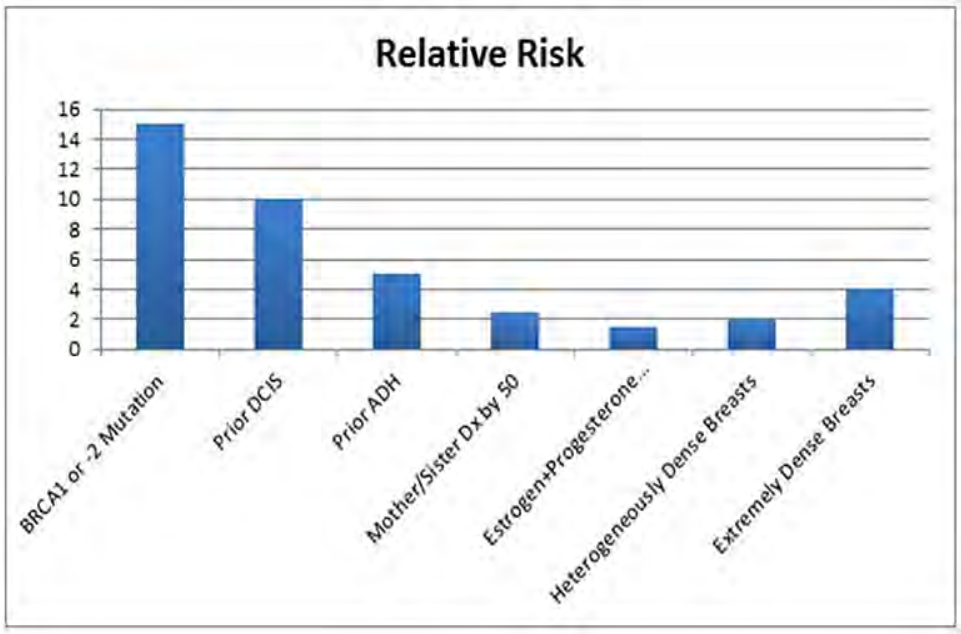

Figure 6. Graphic representation of the relative risk of developing invasive breast cancer by age 80.

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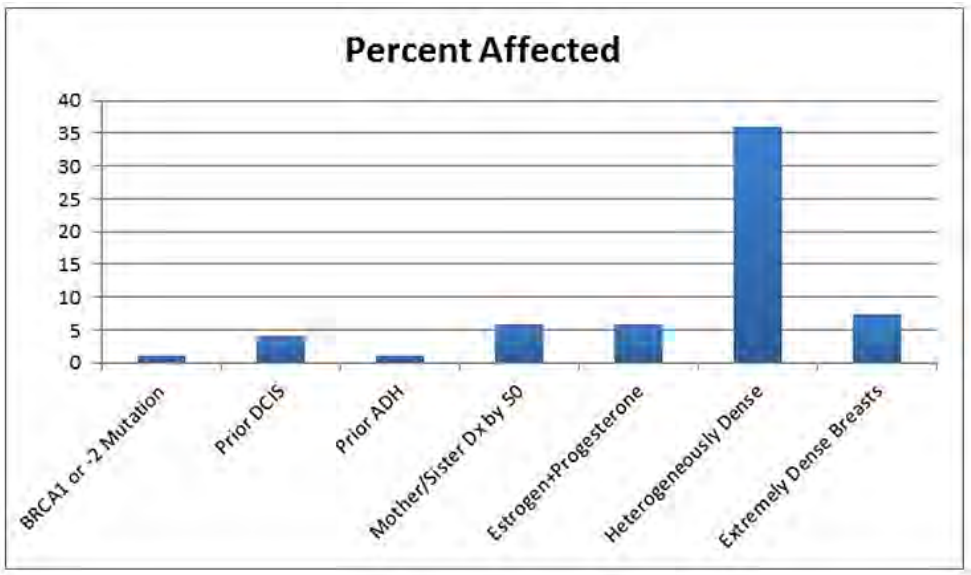

Figure 7. Prevalence of each risk factor in American women ages 40 -74 years (except those on Hormone Replacement Therapy [HRT]).

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The estimated *prevalence* of each risk factor (percent of women affected) for American women ages 40-74 years, except for those taking hormone replacement therapy, is provided in **Figure 7**. While heterogeneously dense breast tissue is common, it produces only a mild increase in risk of developing breast cancer of about 2-fold compared to women with fatty breasts.

Breast Cancer Gene Mutations: *BRCA*

While disease-causing *BRCA* gene mutations and dense breasts are independent risk factors for developing breast cancer, pathogenic *BRCA1* or *BRCA2* mutations are associated with a much higher risk than that of having dense breasts. Women with a known mutation or genetic syndrome that carries increased cancer risk, or an untested woman with a first-degree relative with known *BRCA* or other disease-causing mutation, such as *PTEN*, *CDH1*, or *TP53*, are advised to undergo yearly screening with MRI beginning at age 25-30 years, regardless of their breast density status.[13] A baseline mammogram is suggested when MRI is initiated, with annual screening mammography to begin by age 30. Women with a personal history of radiation therapy to the chest before age 30 and at least 8 years earlier are also at high risk for breast cancer and are recommended for annual screening with MRI and mammography. Compared with other supplemental screening modalities like ultrasound, breast MRI provides greater sensitivity.[14]

Cancers are also more likely to develop at a younger age in women with pathogenic *BRCA* gene mutations. Since breasts are usually denser at younger ages, mammography is especially ineffective as a stand-alone test for this patient population.

Ashkenazi Jewish Heritage

BRCA1/2 mutations are rare in the general population at a prevalence of about 1:400 and 1:800, respectively. Prevalence varies by ethnic group, but among Ashkenazi Jewish women and men, about 1 in 40 carry a disease-causing mutation in *BRCA1/2*. Almost 10% of Ashkenazi Jewish women diagnosed with breast cancer in the United States carry a disease-causing *BRCA1/2* mutation.[15]

Risk Assessment for Ashkenazi Jewish / Black / Hispanic or Asian Women

The American College of Radiology (ACR) recommends all women, and especially black women and those of Ashkenazi Jewish descent, should undergo risk assessment by age 30 so that women at higher risk can be identified and begin earlier and more aggressive screening for breast cancer.[16] In a separate recent analysis from Harvard, black, Hispanic, and Asian women have peak incidence of breast cancer in their 40s and should begin screening at least by age 40.[17]

Breast Density and Cancer Risk

Having dense breasts is an independent risk factor for developing breast cancer and this risk is independent of the risk of tumors being masked by dense tissue. Women with extremely dense breasts are about 4 times (4X) as likely to develop breast cancer as are women with fatty breasts.[18] The breast density for most women falls somewhere in the middle, with cancer risk in-between those with fatty breasts and those with extremely dense breasts. Since the “average” woman has scattered fibroglandular density, some investigators express risk relative to this category: women with heterogeneously dense breasts are about 1.5X as likely to develop breast cancer as are women with scattered fibroglandular density, and women with extremely dense breasts are about twice (2X) as likely.[19]

There are probably several reasons why dense tissue increases risk. One is that the glands tend to be made up of relatively actively dividing cells that can mutate and become cancerous: the more glandular the tissue, the greater the risk. The second is that the local environment around the glands may produce certain growth hormones that stimulate cells to divide, and this seems to be more true for fibrous than fatty tissue.

For breast cancer risk assessment tools, click HERE.

Mortality

The relationship between having dense breasts and an increased chance of dying from breast cancer is not clear. Although there is not extensive research on this topic, Chiu et al. found that because women with dense breasts are at greater risk of developing breast cancer, their risk of dying from breast cancer is about double that of the general population.[20] Some studies have found an increased risk of breast cancer death among women with *fatty* breasts, possibly because the cancers that develop between screening mammograms in women with fatty breasts tend to be particularly aggressive tumors.[21, 22]

Breast Cancer Screening with Mammography

General Recommendations for Breast Cancer Screening

Mammography is the only imaging screening modality that has been studied by multiple randomized controlled trials, and the trials only included women ages 39-74 years. Across those trials, mammography has been shown to reduce deaths due to breast cancer. The randomized trials that have shown a benefit from mammography are those in which mammography increased detection of invasive breast cancers before the cancers spread to lymph nodes.[23, 24] Observational studies of women actually participating in screening have shown even greater benefit to screening mammography.[25, 26] Analysis of the Dutch screening program found that screening mammography reduced breast cancer mortality by 41% in women with fatty breasts and only 13% in women with dense breasts.[27]

No randomized controlled trial examining differences in breast cancer deaths has been performed on any other breast imaging screening modality, and therefore there are no data showing that supplemental screening will or will not decrease mortality, though it is expected that other screening tests that increase detection of lymph node-negative invasive breast cancers beyond mammography should further reduce breast cancer mortality.

Who should be screened?

Mammography is the first step in screening for most women, including those with dense breasts, since there are still cancers and precancerous changes that are better visualized on mammography than on ultrasound or MRI. Additional screening beyond mammography may be recommended for women with dense breasts and/or women who are at high risk for developing breast cancer.

When should screening mammography begin and stop?

Results of randomized trials have shown at least a 15% decrease in deaths due to breast cancer in women who are screened in their 40s, and a 22% reduction in deaths among women screened from ages 50 to 74 years.[28] Based on these findings, the American College of Radiology (ACR), Society for Breast Imaging (SBI), and American Medical Association (AMA) recommend that all women undergo yearly mammograms beginning at age 40, with women at high risk starting earlier. It is especially important for African American and Hispanic women to begin screening by age 40 due to earlier onset of breast cancer, peaking in the 40s.[29] Women should continue to be screened as long as they are in good health.[30, 31]

Because it requires at least 7-9 years to see any benefit from screening[32] in terms of reduced deaths from breast cancer, only women with a life expectancy of at least 10 years are recommended for annual screening (and this applies to any supplemental screening, as well). Even a healthy 85-year-old woman has an average life expectancy of only 10 years,[33] and mammography after age 85 should usually be limited to diagnostic evaluation of women who have breast symptoms. “Some of the greatest harms of screening occur by detecting cancers that would never have become clinically significant. This becomes more likely as life expectancy decreases.”[34]

Breast Cancer Screening Guidelines

While the ACR, SBI, and AMA recommend that all women undergo yearly mammograms beginning at age 40 if they are not at higher-than-average risk for breast cancer, other regulatory bodies and professional societies provide screening guidelines that are slightly different, as shown in **Table 2**.[35, 36, 37, 38, 39, 40, 41, 42, 43]

Ultimately, the decision about when to begin screening is an individual choice based on personal values and preferences that may benefit from input from one’s healthcare provider. Additional resources for patients about the value of screening mammography can be downloaded in both English and Spanish at DenseBreast-info.org and in English at American College of Radiology.

Annual vs. biennial screening

Annual screening is especially important for women in their 40s when cancers tend to be more biologically aggressive. Breast cancer is less common and breast density is greater, and both these factors reduce the benefit of screening mammography for women in their 40s.[44, 45] Biennial screening is nearly as effective as annual screening at reducing deaths due to breast cancer among women who are over the age of 50 or postmenopausal,[46] but the maximum benefit is observed with annual screening.

Table 2. Comparison of breast cancer screening guidelines.

Breast Cancer Screening Guidelines – Comparison

	ACR/SBI	ACS	ACOG	AMA	NCCN	USPSTF
Age to Start Mammography[a]	40	45 Option to start at age 40	Offer at 40, not later than 50	40	40	50
Age to Stop Mammography	No age limit; tailor to individual health status	When life expectancy is < 10 years	Age 75, then shared decision	Not stated	Not stated	74 years
Mammography Interval	Annual	Annual 45-54; Every 1 or 2 years 55 and older	Every 1 or 2 years	Annual	Annual	Every 2 years
View on Tomosynthesis (3D) Mammography	Improves cancer detection, reduces recall rates	Improvement in detection, lower chance of recall	Not stated	Not stated	Improves cancer detection, reduces recall rates	Insufficient evidence to support routine use; grade "I"

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[a] In a 2018 analysis from Harvard*, not considered in the current guidelines, black, Hispanic, and Asian women have peak incidence of breast cancer in their 40s and should begin screening at least by age 40. *Stapleton SM, Oseni TO, Bababekov YJ, Hung Y, Chang DC. Race/Ethnicity and Age Distribution of Breast Cancer Diagnosis in the United States. *JAMA Surg.* Published online March 07, 2018. doi:10.1001/jamasurg.2018.0035

Resources

ACR/SBI Breast Cancer Screening for Average-Risk Women: Recommendations From the ACR Commission on Breast Imaging. 2017
See also: Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR. 2018

ACS Oeffinger KC, Fontham ET, Etzioni R, et al. Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society. JAMA. 2015;314(15):1599-614. https://www.youtube.com/watch?v=6SKh6Tm2HZs&feature=youtu.be

ACOG https://www.acog.org/Resources-And-Publications/Practice-Bulletins/Committee-on-Practice-Bulletins-Gynecology/Breast-Cancer-Risk-Assessment-and-Screening-in-Average-Risk-Women

AMA Action of the AMA House of Delegates 2012 Annual Meeting: Revisions to AMA policy H-525.993 "Mammography Screening in Asymptomatic Women Forty Years and Older". Adopted 06-19-2012. Available at: https://www.ama-assn.org/sites/default/files/media-browser/public/about-ama/councils/Council%20Reports/council-on-science-public-health/a12-csaph6-screeningmammography.pdf

NCCN NCCN Guidelines Breast Cancer Screening and Diagnosis Guidance PDF v.2.107, 6/2/17

USPSTF Siu AL, on behalf of the U.S. Preventive Services Task Force. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164:279-296. doi:10.7326/M15-2886

Screening vs Diagnostic Mammography

A routine annual mammogram for a woman with dense breasts should be scheduled as a *screening* mammogram. If there are signs or symptoms of breast cancer such as a lump, bloody or spontaneous clear nipple discharge, skin or nipple retraction, or constant focal breast pain outside the menstrual cycle, then the appointment should be scheduled as a *diagnostic* mammogram with ultrasound, if needed.

If additional targeted imaging or follow-up is needed for an abnormality seen on the most recent prior breast imaging, a diagnostic appointment is also appropriate. Note: Routine mammography for women with a family history of breast cancer, prior benign biopsy, breast implants, cysts, fibrocystic change, or other known benign findings should be scheduled as screening, unless the woman has other indications to be scheduled as diagnostic.

Breast Pain

Breast pain is a very common complaint among women and is most common around the menstrual period. Some women have pain that is not premenstrual and should visit their doctor to find the cause. Usually pain that is related to the menstrual cycle (cyclic breast pain) is intermittent and involves areas of one or both breasts and can be associated with breast swelling and lumpiness. Noncyclic breast pain (not related to the menstrual cycle) can affect pre- and postmenopausal women. It generally affects only one breast or a specific area in the breast and may be constant or occur at different times. Breast pain can also be from muscles of the chest wall outside the breast (especially after vigorous lifting or other exercise), the skin of the breast (cellulitis or burns), joints (especially where the ribs meet the sternum, ie, costochondritis), or heart, and can move toward the breast. Shingles can also cause severe pain in the distribution of nerves.

Causes of Breast Pain

Cyclic breast pain is usually related to reproductive hormones. Some women have pain due to hormone replacement therapy (HRT) such as estrogen and progesterone. It is uncommon for breast cancer to cause breast pain. Breast pain has also been linked to antidepressants like Prozac, Sarafem, and Zoloft. Blood pressure medicines like Aldactone/hydrochlorothiazide can also cause breast pain. Any sort of trauma to the breast, scars, cysts, breast infection, or any infection in the skin of the breast may cause pain as well.

Occasionally a fibroadenoma or a mass due to pseudoangiomatous stromal hyperplasia (PASH), benign masses that are hormonally sensitive, can cause pain. Weight gain can result in breast pain if the (now poorly fitting) brassiere is no longer supporting the breasts well. Unfortunately breast pain can be caused by many things, and sometimes the cause cannot be determined.

Focal breast pain (one fingertip can point to it) that persists in the same area (does not come and go) for more than 6 weeks or that is associated with skin changes or lump(s) should be evaluated. Only
1-2% of women with focal breast pain without a lump or skin change will be found to have breast cancer on imaging.[47, 48] Kushwaha et al recently analyzed 799 women with breast pain and found 1 cancer in the contralateral breast. They suggest routine screening mammography for women with pain over age 40 and no imaging evaluation for younger women with breast pain.[49]

Breast Cancer Screening and Women with Dense Breasts

Recall Rates and False Positives

For every 1,000 women screened with mammography, on average 100 will be recalled for additional testing. Of those 100 women, 60 will be found to have nothing of concern; 20 will be recommended for short interval follow-up of a "probably benign" BI-RADS 3 finding (specific type of mass or calcifications with < 2% risk of malignancy, for which follow-up is a safe alternative to immediate biopsy); and 20 will be recommended for biopsy. On average, five of those women biopsied will be found to have cancer.[50]

Some cancers found by screening mammography are so indolent and slow growing that they might not ever have been detected otherwise in a patient's lifetime (overdiagnosis) and do not require any treatment. While estimates of overdiagnosis vary on average of 11 breast cancers found with screening, 2 will be life-saving, 1 will represent overdiagnosis, and 8 will be found earlier than they would have been without screening (with better prognosis).[51] Some ductal carcinoma *in situ* found on the first screening examination represents overdiagnosis (estimated at 37% of such cases), but new findings on subsequent screens are uncommonly overdiagnosis (estimated at 4% of cancers on annual screens).

Women with dense breasts are more likely to be recalled for additional testing than those who have fatty or scattered fibroglandular breasts.[52, 53] The denser the breast, the more likely a false positive recall will occur, resulting in additional testing when no cancer is present. Women with *extremely* dense breasts are about twice as likely to experience a false positive as are women with fatty breasts.[54]

Calcifications and Non-calcified Masses

Calcifications in the breast are usually crystals of calcium phosphate or calcium oxalate. Arteries can calcify, as can scar tissue, and calcifications are frequently seen in or adjacent to cysts. Calcifications can be formed when cells are rapidly dividing. Calcifications are evaluated based on their size, shape, and distribution. Magnification views provide greater detail than do standard mammographic images and are often required to adequately characterize small "microcalcifications."

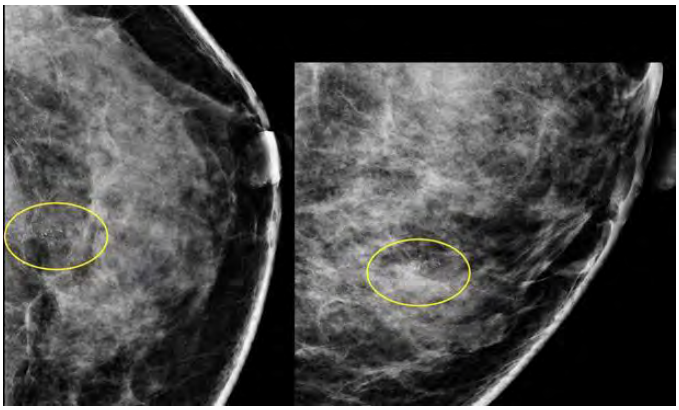


Figure 8. Magnification mammographic images of heterogeneously dense breasts. Note grouped calcifications (circles), which are difficult to see on ultrasound. Most calcifications visualized on mammography are not cancerous, although in this case, biopsy did reveal ductal carcinoma *in situ* which, left untreated, can progress to invasive breast cancer.

Courtesy Wendie Berg, MD, PhD

Microcalcifications are sometimes the only imaging finding of cancer and are much better seen and characterized on mammography than on ultrasound.

About half of cancers seen on mammography will contain calcifications, which can be seen even in dense areas of the breast (**Figure 8**). It is important to note that at least a few calcifications can be seen in nearly all breasts and that the vast majority of calcifications seen on mammography are not due to cancer.

A biopsy may be recommended for calcifications that are new or increasing and/or that have a concerning appearance on magnification views. Even at biopsy, only about one in five lesions manifesting as calcifications are shown to be cancerous.[55, 56]

In the absence of calcifications, some cancerous masses can be seen in dense breasts because they distort or pucker the tissue around them, called *architectural distortion*. Benign causes of architectural distortion may include radial scars; complex sclerosing lesions; fat necrosis; postbiopsy change; and rare spiculated benign lesions, such as granulomatous mastitis, granular cell tumor, and fibromatosis. Architectural distortion is particularly well seen on 3D mammography (tomosynthesis). [57, 58]

Other non-calcified cancerous masses can be visualized in dense breasts tissue because a portion of the mass lies in an area where the breast is fattier (refer to **Figure 5D**).

Interval Cancers and Cancer Recurrence

We know that screening mammography outcomes are different for women with dense breasts than for women with fatty breasts. For women who have dense breasts, cancer is more often found as a lump in the interval between recommended screening mammograms and hence the term “interval cancer.” Interval cancers tend to be more aggressive and have worse outcomes. Having dense breasts also increases the risk of recurrent cancer (if the patient has not had radiation therapy).

Additionally, cancers found in dense breasts are more often larger, of more advanced stage (stages IIb and III),[59] are more often multifocal or multicentric, and mastectomy is more often required to completely remove the cancer.[60]

Table 3 details the increasing odds of interval cancer with increasing breast density. Interval cancer is over 17 times more likely in extremely dense breasts than in fatty breasts.

For breast cancer survivors, there is about a 1.8x increased risk of cancer in the opposite (contralateral) breast when the breasts are dense.[61]

A recent study showed that a 10% decrease of mammographic density or more within the first two years after an original diagnosis, as a result of treatment, is associated with a significantly reduced risk of cancer in the opposite breast, known as contralateral breast cancer.[62] This potential new risk predictor can thus contribute to decision-making in follow-up treatment — particularly the continuation of a chemoprevention drug, like tamoxifen or aromatase inhibitors, which reduce breast density in some women.

Table 3. Interval Cancers and Breast Density.

Visually Estimated Breast Density	Odds Ratio of Interval Cancer (95% Confidence Interval)
< 10%	1.0
10 to 24%	2.1 (0.9 to 5.2)
25 to 49%	3.6 (1.5 to 8.7)
50 to 74%	5.6 (2.1 to 15.3)
≥ 75%	17.8 (4.8 to 65.9)

From *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.*

Factors that Affect Breast Density

Race/Ethnicity

Dense breasts are neither unusual nor abnormal; 40%-50% of American women who undergo screening mammography have either heterogeneously or extremely dense breast tissue. Generally, Asian women tend to have denser breasts than women of other races.[63, 64] There are conflicting data about whether African-American women have denser breasts than women of other races. A 2007 study by del Carmen et al. indicated that they do not,[65] while a more recent study by McCarthy et al. indicated that they do.[66]

Gender

Breast density is not an issue that typically affects men and breast cancer uncommonly affects men. In 2018, it is estimated that about 2,550 new cases of male breast cancer will be diagnosed, resulting in 480 deaths.[67] Normal male breasts are mostly fatty but can become enlarged and develop glandular tissue called *gynecomastia*. Gynecomastia can be caused by a variety of medications, liver failure, some testicular tumors, and marijuana use. The enlargement normally affects one breast more than the other and is usually easy to distinguish from breast cancer on mammography.

Age

Breast tissue typically becomes less dense with age. Glandular tissue, which is a major contributor to breast density, tends to atrophy after menopause and thereby breast density decreases (**Figure 9**).

- More than half of women under age 50 have dense breasts
- About 40% of women in their 50s have dense breasts
- About 25% of women age 60 and older have dense breasts[68, 69]

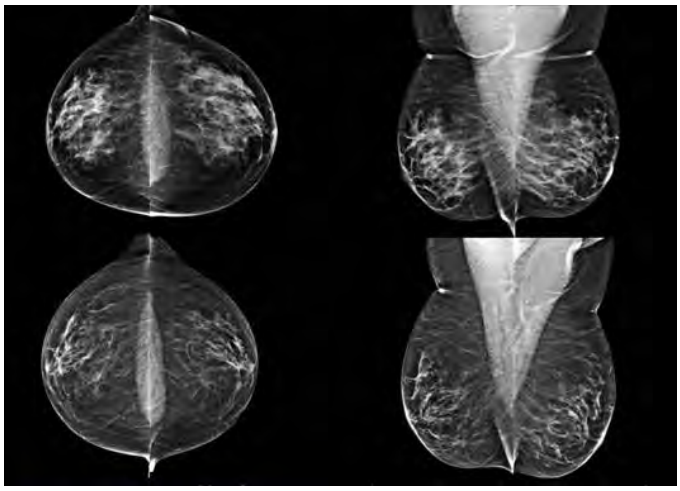


Figure 9. Top: Screening mammogram of a 49-year-old woman shows heterogeneously dense breast tissue. Bottom: Screening mammogram in the same woman at age 52 years, now postmenopausal, shows only scattered fibroglandular density.

Courtesy Wendie Berg, MD, PhD

Family Traits

Breast density is at least partially inherited,[70,71] though it is complex to predict. If a patient's mother or twin sister has dense breast tissue, it is more likely the patient will, too.

Breast Size

Smaller breasts tend to be denser than larger breasts, though there is wide variability.

Pregnancy/Breastfeeding

During pregnancy and breastfeeding, glandular tissue grows, and the breasts become denser and often larger.

Such changes in the breast during pregnancy and lactation reduce the accuracy of screening tests like mammography, ultrasound, and MRI. Unless the patient plans to breastfeed for more than one to two years and is at high risk for developing breast cancer, it is generally recommended to wait a few months after breastfeeding stops before resuming breast screening. Ultrasound is the modality of choice to evaluate breast symptoms while the patient is pregnant or breastfeeding.

Weight, Diet, and Exercise

Dietary fat intake has little to do with breast density. However, the composition of the breast *does* relate to body mass index (BMI). BMI is a measure of body fat based on height and weight, and women with a higher BMI tend to have fattier breast tissue. Higher BMI reduces the percent or proportion of density but may not reduce the total amount of dense tissue, so that if a patient loses a lot of weight, her breasts may *appear* denser due to the loss of fatty tissue.

Thus, BMI and breast density are independent risk factors for breast cancer. Interestingly, before menopause, *low* BMI increases the risk of breast cancer; after menopause, increasing BMI raises the risk for breast cancer, likely due to higher levels of estrogen produced by fatty tissue.[72, 73]

Exercising with weights can increase the amount of pectoral muscle behind the breasts, but the breast tissue itself is not affected by exercise.

Hormone Replacement Therapy

Hormone replacement therapy (HRT), also called hormone therapy, can be prescribed for management of menopausal symptoms or osteoporosis based on a woman's other risk factors.

An increase in mammographic density is much more common among women taking continuous combined (estrogen plus progesterone) hormonal therapy (seen in 21-43% of such women) than for those using oral low-dose estrogen (6%) or transdermal (2%) estrogen treatment. The increase in density is often apparent as soon as the first visit after starting hormone therapy. Risk of breast cancer is also slightly increased in women taking combined hormone therapy.[74, 75, 76, 77] Taking HRT to help manage symptoms of menopause or to help in the prevention of osteoporosis can delay the regression of dense tissue that naturally occurs in women not on HRT, thus increasing the chance for an occult cancer.

Endocrine Therapy for Cancer Treatment

The aim of endocrine therapy is to slow or stop the growth of hormone-sensitive tumors by blocking the body's ability to produce hormones or by interfering with hormone action.[78] Estrogen and progesterone are hormones that stimulate cells to grow when receptors for these molecules are on the surface of the cells.

Tamoxifen

Tamoxifen is one of several selective estrogen receptor modulators (SERMS) and is used to treat breast cancers that express estrogen receptors ("ER-positive" breast cancer).[79] Tamoxifen blocks the estrogen receptors both of normal cells and of breast cancer cells that express the estrogen receptor. Tamoxifen may be recommended for reducing the risk of developing breast cancer in women who have had prior atypical biopsies. Tamoxifen is also prescribed to decrease cancer recurrence for women who have had ER-positive cancer.

In 2012, Cuzick et al. reported that when breast density is carefully measured using computer-aided detection (CAD) software, women whose breasts became at least 10% less dense while taking tamoxifen experienced a 63% reduction in risk of the redevelopment of breast cancer, whereas those women whose breast density did not change did not experience a decrease in risk.[80] Several similar studies in women with a personal history of breast cancer showed that only women whose breast density decreased while on tamoxifen benefitted from a decreased risk of recurrence.[81, 82, 83]

Aromatase Inhibitors

Aromatase inhibitors are drugs that are used to block the activity of the aromatase enzyme that produces estrogen.[84]

Aromatase inhibitors are prescribed for postmenopausal women (once the ovaries are much less active) with a history of ER-positive breast cancer. In 2012, Kim et al. reviewed data of more than 1,000 breast cancer patients who had undergone surgery and received at least two years of anti-estrogen therapy. Breast density was assessed for each patient using CAD. Study results showed that the women who experienced a decrease in breast density while taking tamoxifen or aromatase inhibitors had a lower risk of recurrence than women whose breast density did not decrease.[85]

Medications that block estrogen production or estrogen receptors can produce a decrease in breast density, and women who experience this effect are more likely to benefit from such medications (in terms of reduced breast cancer recurrence risk).

Stratifying Cancer Risk

Several breast cancer risk assessment tools have been developed that combine known major risk factors. Risk models either predict risk of pathogenic mutation in *BRCA1* or *BRCA2*, risk of developing invasive breast cancer, or both. Risk models can be used to stratify patients who may benefit from risk-reducing medications, genetic testing, and/or personalized screening.

Risk Models

Table 4 features details and links to several commonly utilized breast cancer risk assessment models: Gail, Tyrer-Cuzick (IBIS), Penn II, and a link to a paper describing the Claus model.[86] Of these models, only Tyrer-Cuzick (IBIS) includes breast density in risk calculations.

There are risk models that either do or soon will include breast density in risk calculations. Please note, even if density is included in risk calculations, these calculations do not factor in the additional implication of cancers "masked" by dense tissue on mammography:

Breast Cancer Surveillance Consortium (BCSC) model[87] was developed and validated in a large, ethnically diverse, prospective cohort of women undergoing screening mammography. It includes the risk factors with the greatest population attributable risks for breast cancer: age, BI-RADS visually-assessed breast density, family history, history of a breast biopsy, and polygenic risk score (PRS) based on common genetic variations.[88] The updated model is one of only two breast cancer risk assessment models that uses breast density and the only model to include the full range of breast biopsy results, including hyperplasia, atypical hyperplasia, and lobular carcinoma *in situ* (LCIS).[89, 90]

Table 4. Breast cancer Risk Assessment Models.

Gail Model	**Link:** http://www.cancer.gov/bcrisktool/
Provides:	Personal risk; 5-year and lifetime risk (LTR) of developing breast cancer
Includes:	Current age, age at menarche, age at first live birth childbirth, number of first-degree relatives (mother, sisters, daughters) with breast cancer, prior benign biopsies, prior atypical biopsy and race/ethnicity DOES NOT INCLUDE: Age of diagnosis of relatives (used to assess "high-risk" criteria for MRI screening)
When to Use:	When considering tamoxifen or other risk-reducing medications (>1.67% 5-year risk); NOT to be used for risk assessment for purposes of screening MRI nor for genetic testing; NOT to be used for women with a personal history of breast cancer or LCIS or known pathogenic *BRCA1* or *BRCA2* mutation or women younger than 35 years of age
Tyrer-Cuzick (IBIS)	**Link:** http://www.ems-trials.org/riskevaluator/
Provides:	Personal risk and risk of mutation carrier; 5-year, 10-year and LTR of developing breast cancer
Includes:	Version (v8) includes **breast density** (Windows/PC only). Use link above and click on "NEW! v8". Also includes: current age, age at menarche, height, weight, parity, age of first childbirth, age at menopause, HRT use, prior breast biopsy, ovarian cancer, age of dx of breast/ovarian cancer in mother/sister/daughter and, if bilateral, maternal and paternal grandmothers and aunts; and Ashkenazi descent
When to Use:	Risk assessment for genetic testing (10% risk for pathogenic mutations is commonly used as threshold for referral for testing) or MRI screening (20-25% lifetime risk threshold is used)
Penn II	Link: http://www.afcri.upenn.edu/itacc/penn2/
Provides:	Personal risk and risk of mutation carrier; LTR of developing breast cancer
Includes:	Ashkenazi descent, # of women in family diagnosed with both breast and ovarian cancer, # of women in family diagnosed with ovarian or fallopian cancer in absence of breast cancer (BC), # of BC cases in family diagnosed <age 50, age of youngest BC case in family; # of people in family with: presence of mother-daughter dx, w/ bilateral BC, male BC diagnosed, presence of pancreatic cancer or prostate cancer
When to Use:	Risk assessment for genetic testing (10% risk for pathogenic mutations is commonly used as threshold for referral for testing) or MRI screening (20-25% lifetime risk threshold is used)
Claus	**Link:** http://www.ncbi.nlm.nih.gov/pubmed/8299086
Provides:	Personal risk; LTR of developing breast cancer
Includes:	Age at diagnosis of occurrence(s) of breast cancer in first- and second-degree female relative(s)
When to Use:	MRI screening (20-25% lifetime risk threshold is used)
Breast Cancer Surveillance Consortium (BCSC)	**Link:** https://tools.bcsc-scc.org/BC5yearRisk/calculator.htm **App:** *available on Apple iTunes*
Provides:	Personal risk; 5-year and 10-year risk of developing invasive breast cancer
Includes:	Current age, race/ethnicity, BI-RADS visual **breast density**, first-degree relative, prior breast biopsy.
When to Use:	Risk assessment for use of medications for prevention (tamoxifen, raloxifene, aromatase inhibitors)

The latest version (v8) of the Tyrer-Cuzick (IBIS) model, based on input from Dr. Jennifer Harvey at the University of Virginia and Dr. Martin Yaffe at University of Toronto is now available and includes breast density as a risk factor. In the updated model, breast density is one of the top five factors predicting breast cancer risk. The updated version appears to offer better discrimination than the current version of Tyrer-Cuzick, and further validation continues.

How are Risk Models Used?

Women Who May Benefit from Risk-Reducing Medications

The Gail model is used to determine risk for purposes of advising on the use of medications to reduce breast cancer risk. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 study, women at increased risk for breast cancer were defined as: 1) age 35 to 59 years with at least a 1.67% five-year risk for developing breast cancer by the Gail model; 2) personal history of LCIS; or 3) over age 60 years of age. 13,388 such women were randomized to receive tamoxifen or placebo daily for five years. Tamoxifen reduced the risk of *invasive* breast cancer by 49% and the risk of *noninvasive* cancer by 50%.[91]

Only the incidence of subsequent ER-positive breast cancers was reduced and there was also a reduced risk of hip and spine fractures in women using tamoxifen. Unfortunately, there was a 2.5-fold increase in risk of endometrial cancer in women taking tamoxifen and blood clots causing stroke and deep vein thrombosis were also increased in women taking tamoxifen.[92, 93]

Women Who May Carry a Pathogenic Mutation in *BRCA1* or *BRCA2*

The Tyrer-Cuzick (IBIS), Penn II, and two other models, BOADICEA and BRCAPRO, are among the models that predict risk of pathogenic mutation. Women with risk of mutation estimated to be more than 10% are usually recommended for genetic testing, though there has been the recent suggestion to perform genetic testing much more broadly by age 30, as many women who have pathogenic mutations do not have a suggestive family history.[94]

Women Who Meet Criteria for High-Risk Screening MRI

Current American Cancer Society guidelines recommend annual screening MRI beginning by age 25 to 30 in women who have a lifetime risk (LTR) of breast cancer of 20 to 25% or more.[95] Any of the models used to predict risk of a pathogenic mutation, or the Claus model (but NOT the Gail model), can be used to estimate lifetime risk for purposes of screening MRI guidelines. Annual screening MRI is also recommended in women who are known to carry pathogenic (disease-causing) mutations in *BRCA1* or *BRCA2*, unless the woman has had bilateral mastectomy, and in women who are first-degree relatives of known pathogenic mutation carriers but who are themselves untested. Women who are known to carry

or are first-degree untested relatives of individuals with less common disease-causing mutations, such as those associated with Li-Fraumeni, Bannayan-Riley-Ruvalcaba, or Cowden syndrome, are also recommended for annual screening MRI. Based on elevated lifetime risk of at least 20%, the American College of Radiology also recommends annual screening MRI for all women diagnosed with breast cancer by age 50 and for those diagnosed later with dense breasts.[96]

Women with prior chest radiation therapy, for example, for Hodgkin disease, between ages 10 and 30, and at least 8 years earlier, are at high risk for developing breast cancer,[97] similar to *BRCA1/2* carriers, and are also recommended for annual screening MRI. Finally, the National Comprehensive Cancer Network and the American College of Radiology suggest considering supplemental annual screening MRI for women with a history of LCIS or atypical hyperplasia, especially if other risk factors are present.[98, 99]

Risk Models and Diagnostic Considerations

- Risk models may not include all known risk factors, eg, personal history of breast cancer, detailed family history, or breast density
- Estimated absolute risk can vary substantially between models
- Age: As a woman gets older, her 5- and 10-year risk of developing breast cancer increases, but her lifetime risk decreases
- Known risks can change every year, particularly since age is a risk factor. Family history may also change as family members could be diagnosed with breast or ovarian cancer in the interim. As such, it is important to reassess risk every year or two.

Risk Model Limitations

- Adoption, or otherwise unknown family history
- Small family size
- All models underestimate rates of breast cancer. At best they predict about 67% of women who will develop cancer at the population level.
- All models are low in accuracy at identifying the particular individuals who will develop breast cancer, ie, they are low in their "discrimination."

Risk Model Indications for Genetic Testing Include

- If appropriate, model estimates pathogenic mutation risk at >10%
- Male breast cancer or family history of male breast cancer: 6% have pathogenic mutation in *BRCA2*
- Personal history of breast cancer and ≤ age 50 at diagnosis; diagnosis at any age and close blood relative diagnosed ≤ age 50; triple negative breast cancer diagnosed ≤ age 60
- Personal history of ovarian cancer[100]

Risk-Reducing Interventions

- Consider tamoxifen or raloxifene, another SERM used to reduce the risk of developing breast cancer in postmenopausal women with at least one of the following:
  - at least 1.67% 5-year risk by Gail model
  - personal history of lobular carcinoma *in situ*
  - age at least 60 years
- For women with disease-causing *BRCA* mutation(s), consider bilateral prophylactic mastectomy, risk-reducing salpingo-oophorectomy if at least 10-year life expectancy

Implementing Increased Surveillance

- Supplemental MRI screening is recommended to begin at age 25 (at least by age 30) in high-risk women:
  - Lifetime risk estimated at 20-25% or more by models that predict mutation carrier status (or the Claus model)
  - Disease-causing *BRCA* or *TP53* or *PTEN* or *CDH1* mutation(s) or first-degree untested relative of disease-causing mutation carrier
  - Prior chest radiation therapy, for example, for Hodgkin's disease, before age 30 and at least 8 years earlier
- In 2018, the American College of Radiology also endorsed annual MRI screening for the following women:
  - Women with a personal history of breast cancer and dense breasts
  - All women diagnosed with breast cancer by age 50
- The American College of Radiology and the National Comprehensive Cancer Network suggest considering supplemental annual screening MRI for women with a history of LCIS or atypical hyperplasia, especially if other risk factors are present.
- Continue annual MRI screening (and mammography) to age 70 (unless bilateral mastectomy) if at least 10-year life expectancy, patient continues to meet high-risk guidelines, and can tolerate MRI (no kidney failure, pacemaker, some other metallic implants, severe claustrophobia).
- MRI screening can be performed at the same time as annual mammography or on an alternating six-month schedule (eg, MRI in January and mammogram in July). Modeling suggests a slight benefit to an alternating six-month schedule[101] with MRI beginning at age 25 and digital mammography beginning at age 30.
- Supplemental ultrasound screening in women at high risk who cannot tolerate MR, and consider in women with dense breasts, especially if other risk factors (personal history of breast cancer, prior atypical biopsy, intermediate family history). Note: Screening ultrasound produces no added benefit in women having screening MRI.

Who Needs More Screening?

The Screening Decision Support Tool developed by clinicians at DenseBreast-info.org at provides a decision-making algorithm to help ensure an individualized screening plan for each patient (**Figure 10**). The strategy presented is relatively aggressive as it is designed to optimize early detection of invasive breast cancer.

All individuals should know how their breasts normally look and feel and report any change promptly to their healthcare provider. Technology can be used in many combinations for breast cancer detection and not every technology is available at every site.

Technology is changing, and guidelines also evolve that influence recommendations. If a patient is recommended for additional US or MRI screening one year, age and other medical conditions may change a patient's personal risk and benefit considerations, and therefore screening recommendations may change from one year to the next.

There is a tendency for a slight decrease in breast density each year, and this tends to be more abrupt in the few years around menopause. One study showed that only 7% of women who were considered not dense one year were classified as "dense" the following year; similarly 6% of women considered "dense" one year were classified as not dense the following year. For 87% of women, there was no change from one year to the next.[102] Any difference that might affect the decision for supplemental screening would be between women considered to have heterogeneously dense or scattered fibroglandular density one year or the other, and radiologists may differ in this assessment even when there is no true change in the breasts.

In a patient with breast density near the threshold, there are likely to be areas in the breast where cancer could be masked: it is not unreasonable to have had supplemental screening even if one's breasts turn out to be slightly less dense this year.[103]

Dense breasts are mostly an issue affecting mammography performance so that a patient under 40 years of age generally does not need to know until they begin having mammograms. For women at normal risk, mammography is often recommended beginning at age 40. If a woman has a family history of breast cancer and has not begun mammography screening, she should speak to her doctor about personal risk factors and when mammography and possibly other screening should begin. As a general guide, if a woman's mother or sister had breast cancer diagnosed before age 50, she may want to begin annual screening 10 years before the relative's age at diagnosis, but not before age 30.

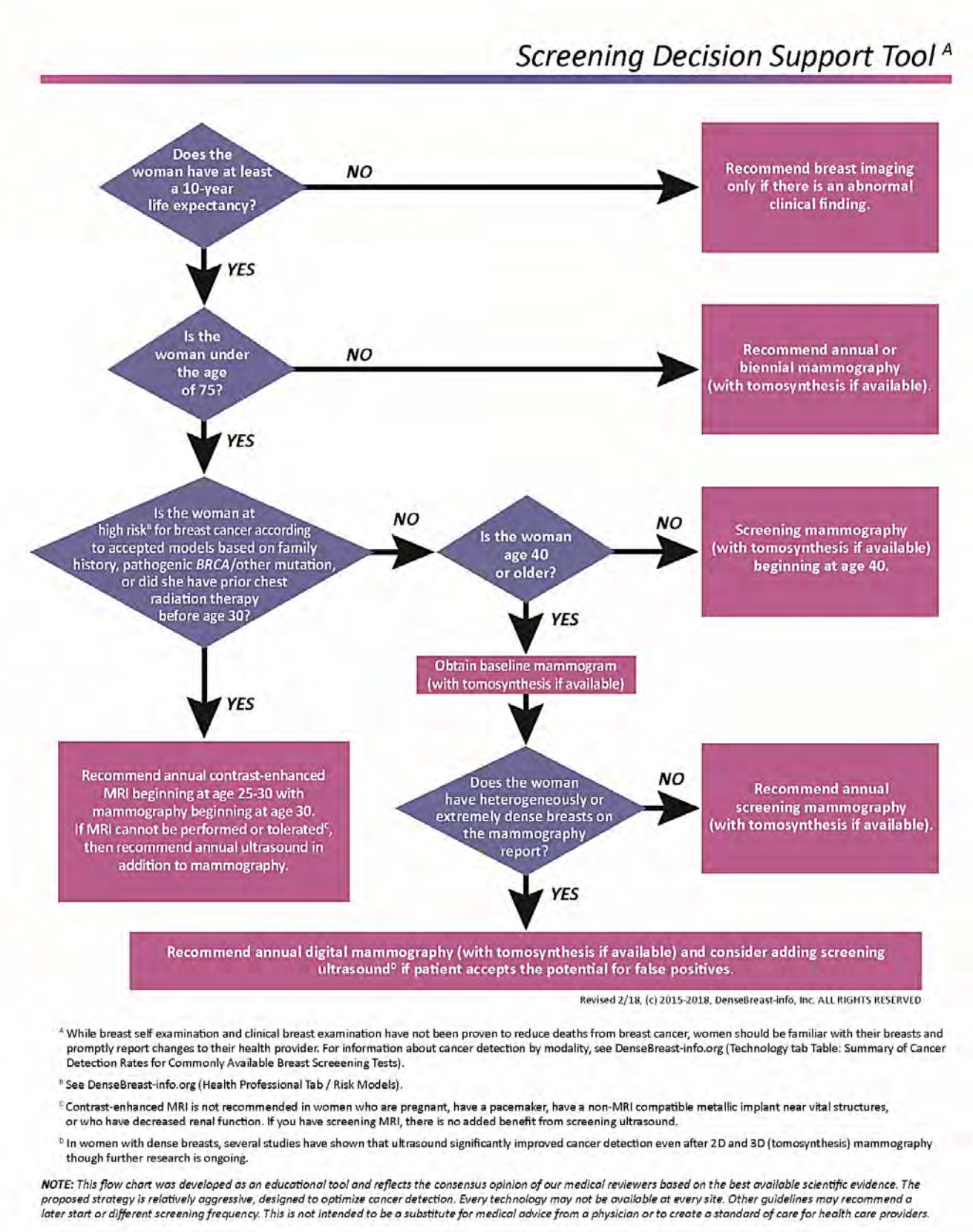


Figure 10. Screening Decision Support Tool developed by clinicians at DenseBreast-info.org.

Breast Imaging Technology: Benefits and Considerations for Supplemental Screening

There are potential benefits as well as known considerations in the form of false positives associated with each type of breast imaging technology and a woman's personal screening plan should always be developed in partnership with her healthcare provider (**Table 5**).

Table 5. Summary of cancer detection and recall rates for commonly available breast screening tests.

If 1,000 Women are Screened with	# Women Found to have Cancer	Type of Technology	# Women Recalled for more Testing
2D-mammogram alone	**2-7 total**	Ionizing radiation	100
2D-mammogram plus 3D-mammogram (tomosynthesis)*	Mammogram 2-7 + Tomosynthesis 1-2 = **3-9 total**	Ionizing radiation	70
Regular 2D-mammogram plus ultrasound (US)*	Mammogram 2-7 + Ultrasound 2-4 = **4-11 total**	Sound waves	170-230
Regular 2D-mammogram plus contrast-enhanced MRI	Mammogram 2-7 + MRI 10 or more = **12-17 or more total**	Magnetic field and intravenous contrast	160-220

* One prospective, multicenter study in Italy (ASTOUND) showed that adding ultrasound significantly improved detection of invasive cancer even after the combination of 2D and 3D mammography.[104, 105, 106, 107]

Courtesy Wendie Berg, MD, PhD

Mammography/3D Mammography

How Mammography Works

The breast is briefly compressed in two different positions — MLO (mediolateral oblique, along the axis of the pectoralis muscle) and CC (craniocaudal, from the head to the foot) — and x-rays are acquired. Compressing the breast reduces the amount of radiation required to penetrate the tissue, and spreading out the breast tissue helps produce excellent image resolution. Compression also reduces motion that can blur the image, potentially resulting in missing clinically significant findings.

Cancers are seen as masses, areas of tissue asymmetry, calcifications, and/or areas of architectural distortion. Most breast masses and asymmetries are similar in density to the breast tissue. Calcifications are denser (whiter) than breast tissue, and areas of distortion are like a puckering of the fabric of the breast and can be seen in any breast density. Many noncancerous conditions also produce masses and calcifications, and normal tissue can appear as areas of asymmetry.

The total mammographic examination is completed in about 10 minutes. Occasionally, additional images are required to ensure full inclusion of all breast tissue.

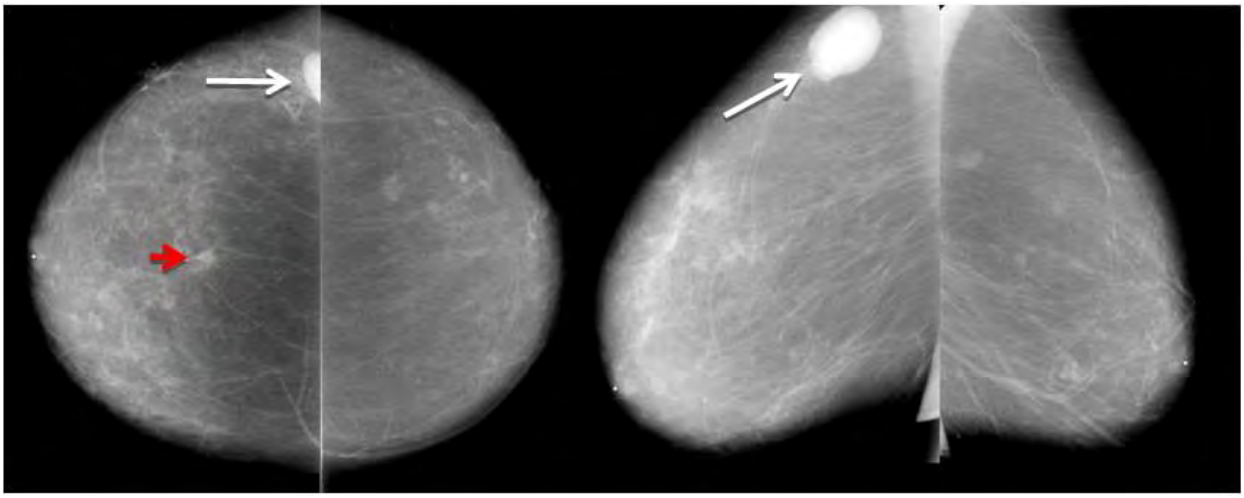


Figure 11. Film (analog) mammograms from a 62-year-old female with a lump felt under the right arm. The breasts are not dense, with only scattered fibroglandular density. CC (left) images and MLO (right) images show a dense mass in the right axilla (white arrow, triangle marker). Ultrasound-guided biopsy showed this mass to be a lymph node involved with cancer spread from the breast, ie, a metastatic lymph node. The primary cancer in the right breast itself was not initially seen on these images but can be seen in retrospect on the CC view only (red arrow).

Courtesy Wendie Berg, MD, PhD

Types of Mammography

There are three types of mammography:

1. Film or analog 2D – x-ray beams are captured on film in a cassette
2. Digital 2D or full field digital mammography (FFDM) – a dedicated electronic detector displays the x-ray information
3. Tomosynthesis, also called digital breast tomosynthesis (DBT) or 3D mammography – a dedicated electronic detector system obtains multiple projection images that are "synthesized" by the computer to create thin-slice images of the breast
    a. Some facilities use additional computer software to create a "synthetic" 2D reconstructed image of the breast that mimics a standard digital mammogram.
    b. If a facility only uses the synthetic 2D mammogram instead of a standard mammogram, then the radiation exposure from the 3D examination is about the same as a standard 2D mammogram.

Figures 11, **12**, and **13** provide examples of each type of image.

Digital images can be stored in PACS, a picture archiving and communication system, allowing the radiologist to quickly retrieve previous exams for comparison and to manipulate the images for complete viewing.

Despite the introduction of 2D digital mammography in 2000, there are a small number of breast imaging centers that still rely on film mammography. Women who have dense breasts should undergo digital mammography, with 3D (tomosynthesis) if available, rather than film mammography whenever possible because of slightly improved cancer detection using digital mammography.[108]

Benefits of Mammography

We have learned that 2D mammography allows detection of 2-7 cancers for every thousand women screened (closer to 2 per 1,000 for women in their 40s and 7 per 1,000 for women in their 60s). Screening mammography is the only technology that has been studied by multiple randomized controlled trials, and, across those trials, mammography has been shown to reduce deaths due to breast cancer.[109, 110]

When added to 2D mammography, tomosynthesis is able to detect an additional 1 to 2 cancers per thousand women screened in the first round of screening. [111, 112] The benefits of tomosynthesis appear to persist over subsequent screening rounds though further studies are in progress.[113]

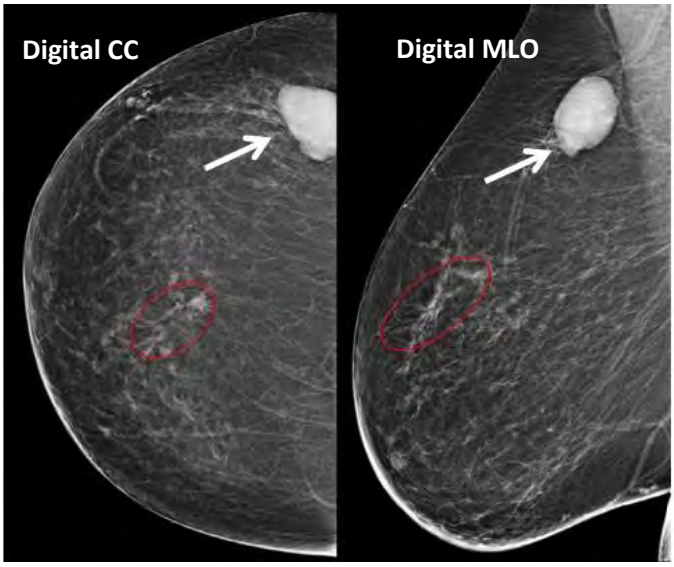


Figure 12. Digital CC and MLO mammograms from same patient as in Figure 8 again show the metastatic cancerous lymph node (arrows). Better seen is a subtle mass with associated distortion (red ovals) in the upper inner right breast. The skin and tissues near the skin are also better seen on digital than on film mammography.

Images courtesy Wendie Berg, MD, PhD

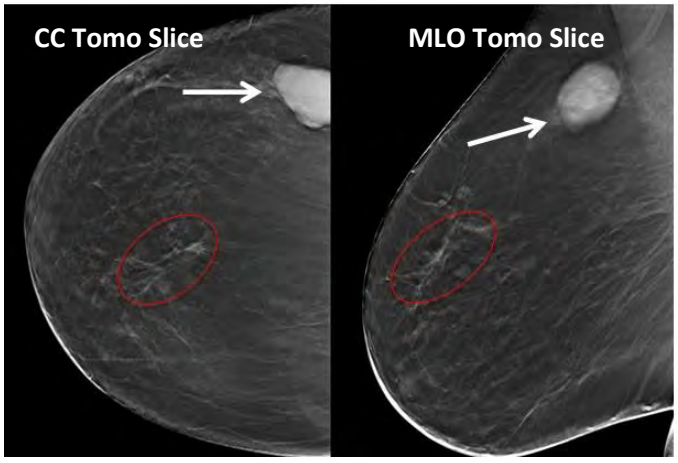


Figure 13. 1-mm slices from CC and MLO tomosynthesis (tomo) from the same patient as in Figures 8 and 9 (done in combination with the standard digital mammogram during the same breast compression). The dense metastatic node (arrows) is again noted. Even better seen on tomosynthesis is the architectural distortion from the primary right breast cancer (red ovals), an invasive ductal cancer associated with DCIS.

3D Mammography

Tomosynthesis — also known as digital breast tomosynthesis, DBT, or "tomo," or 3D mammography — utilizes specially-equipped digital mammography machines and acquires images at multiple angles. Like standard mammography, tomosynthesis utilizes a paddle to compress the breast to minimize the amount of ionizing radiation needed to penetrate the breast tissue and to reduce motion. The images are reconstructed as multiple thin slices to reduce tissue overlap (**Figure 14**). Reconstructed slices can be viewed individually or as a movie or "scrolled through."

Tomosynthesis is often performed in "combination" during the same positioning with a standard 2D mammogram. When a "combo" 2D and 3D mammogram are performed, the study results in a little more than twice the radiation dose as from a 2D mammogram alone — and the dose is greater in thicker breasts. In part to obviate concerns about additional radiation, many centers have the computer software needed to create a synthesized 2D mammogram from the same images used to create the tomosynthesis slices. This synthetic mammogram is being used in some centers instead of the standard 2D mammogram, resulting in a radiation dose from tomosynthesis similar to a standard 2D mammogram.

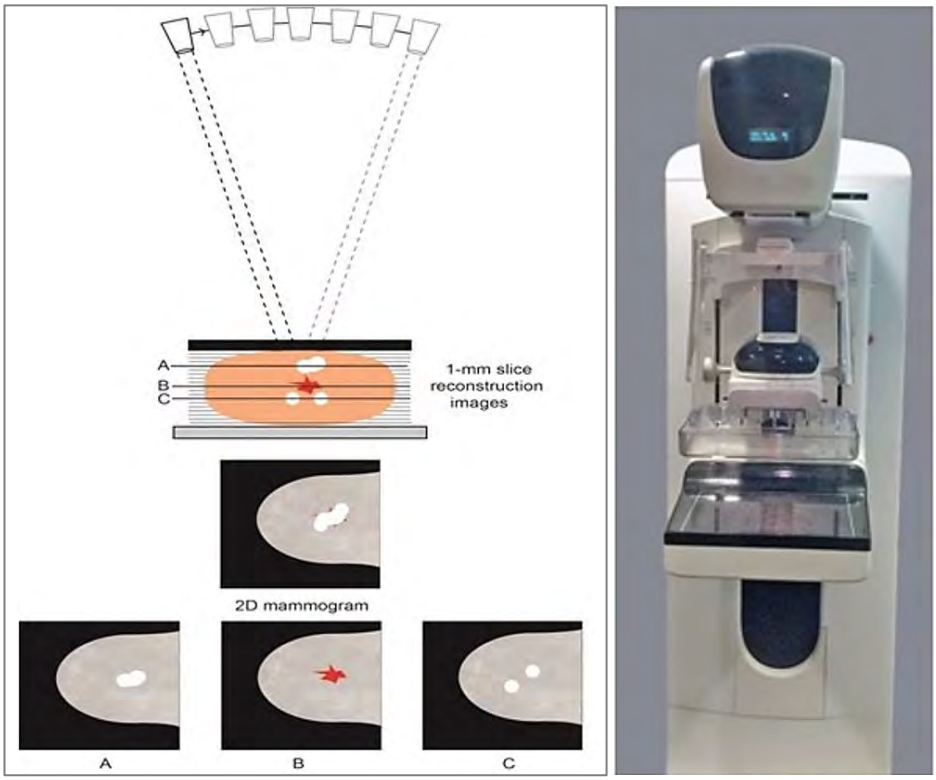


Figure 14. A. For tomosynthesis, the breast is compressed as for a regular 2D mammogram and the x-ray tube moves in an arc over the breast. Multiple short-exposure "projection" images are obtained and used to create thin "slice" images of the breast (A, B and C bottom row), which reduces the overlap of tissues and can help show architectural distortion. B. Image of a tomosynthesis system.

Illustrations courtesy Jeremy Berg, PhD and Wendie Berg, MD, PhD

It is important to note that while the radiation dose from a 2D/3D combo is twice as great as from a 2D mammogram alone, the amount of radiation to the breasts is still within acceptable FDA limits for exposure from mammography.

Tomosynthesis and Dense Breasts

The effectiveness of 3D mammography in dense breasts has not been fully evaluated, and some cancers will still be obscured by dense tissue. A 2016 multicenter analysis by Rafferty et al. of more than 170,000 3D mammograms compared to over 270,000 2D mammograms showed an increase in cancer detection of 1.6 per 1,000 in women with heterogeneously dense breasts — but no improvement in cancer detection in extremely dense breasts.[114] A 2017 study of the diagnostic performance of tomosynthesis and breast ultrasonography as a supplement to digital mammography in women with dense breasts by Kim, et al. showed that tomosynthesis was less sensitive than ultrasound (91.4% vs. 96.4%, p=0.039) but more specific (83.9% vs. 70.4%, p<.001) among 698 women with 140 breast cancers.[115] A 2016 analysis from the University of Pennsylvania showed there is a benefit for undergoing tomosynthesis every year, with fewer cancers presenting as lumps in the interval between screens, though further validation of this approach is needed.[116]

Importantly, compared to standard mammography, tomosynthesis reduces the need for recall for additional testing, such as additional mammographic views, to evaluate areas of overlapping normal tissue. DBT can also reduce the number of examinations for women recalled from screening. When tomosynthesis images show a mass, the spot compression views that are otherwise commonly performed with 2D mammography can often be skipped, and the patient can usually just undergo ultrasound if needed (**Figure 15**).

Considerations

All mammograms utilize x-ray technology and because normal dense tissue and cancerous masses similarly absorb x-rays, tumors can be hidden by overlying dense tissue. So what is the effect of breast density on mammography? A mass or asymmetry due to cancer masked on a 2D mammogram could still be masked on a 3D mammogram unless it is surrounded by fatty tissue. Malignant calcifications can still be seen on mammography in dense tissue, and architectural distortion caused by cancer is especially well seen on tomosynthesis. Standard mammography has been shown to miss about half of cancers present in women with dense breasts.[117] The miss rate of tomosynthesis has not yet been fully established but remains an issue for dense breasts, and especially for extremely dense breasts. Further study is needed on the benefit of having tomosynthesis each year.

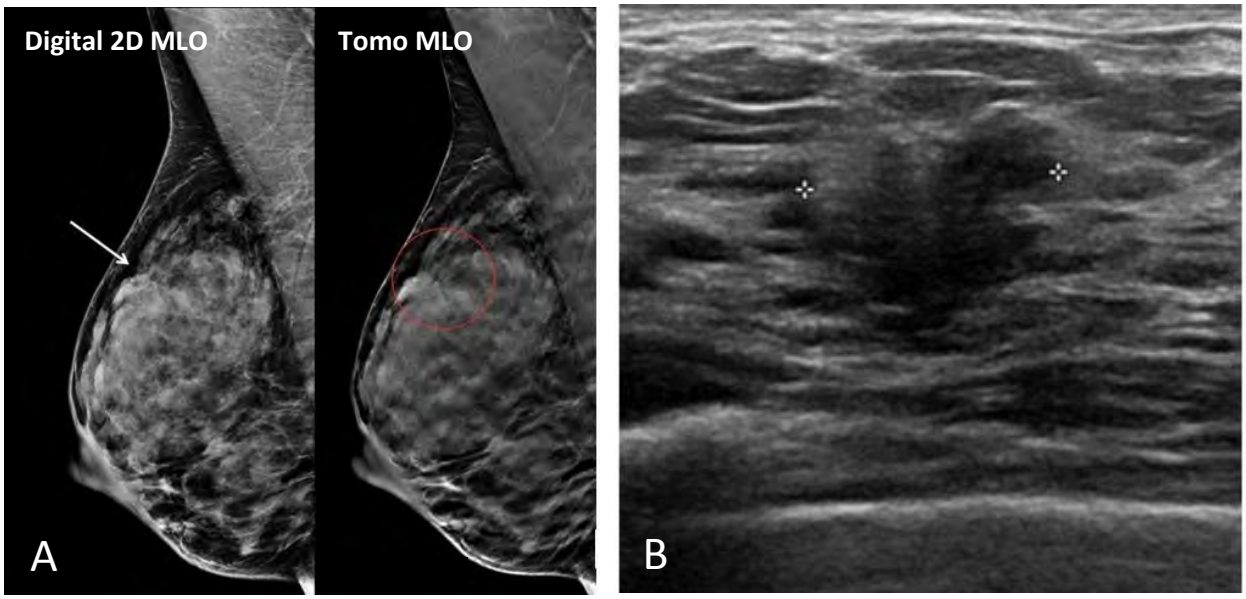


Figure 15. (A) Standard digital 2D mammogram, MLO view and MLO tomosynthesis 1mm slice of a 48-year-old woman with heterogeneously dense breasts shows very subtle possible distortion (arrow) in the upper right breast on standard mammogram. On tomosynthesis, the distortion is better seen, as is the underlying irregular mass (circle). (B) Ultrasound was performed directed to the mass seen on tomosynthesis and shows an irregular hypoechoic (dark gray) mass (marked by calipers) compatible with cancer. US-guided core needle biopsy showed grade 2-3 invasive ductal cancer with associated DCIS.

Courtesy Wendie Berg, MD, PhD

It is important not to ignore a lump just because the recent mammogram was normal, especially if the breasts are dense. While cysts and areas of normal tissue can present as lumps, malignant masses, especially those lacking calcifications, are frequently masked by dense breast tissue and a "normal," "negative," or "benign" mammogram does not mean that there is no cancer present.

Tomosynthesis can help show some cancers not found with 2D mammography, but **ultrasound** is the test of choice for evaluating palpable lumps and allows direct correlation of the area being felt with findings on ultrasound. If there is a mass suspicious for cancer, the radiologist/technologist may also include ultrasound of the tissue in the axilla because the first place cancer will spread is to lymph nodes in the axilla. As discussed earlier, cancers presenting because of symptoms prior to the next annual mammogram are called "interval cancers", and interval cancers are increasingly common with increasing breast density.

Breast Ultrasound

Breast ultrasound – also known as sonography – uses high-frequency sound waves that cannot be heard by humans. Screening ultrasound (US) examinations emit no ionizing radiation and can be performed by a trained radiologists or radiologic technologist.

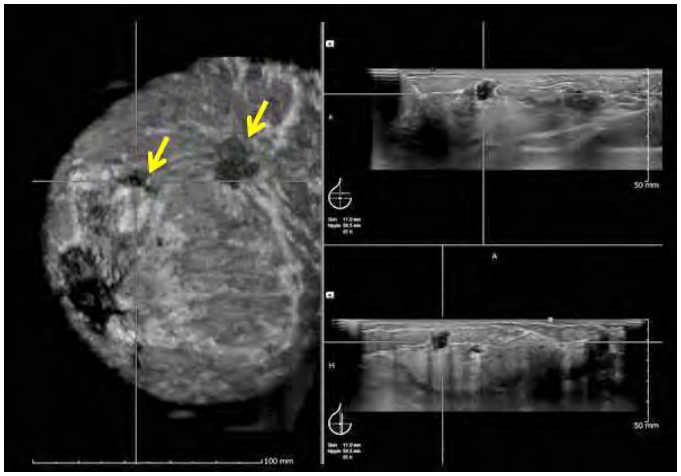


Figure 16. Automated breast ultrasound images. Coronal view (left), transverse view (top right), and sagittal view (bottom right) images from automated US show two irregular hypoechoic (dark gray) masses (yellow arrows and crosshairs) due to grade 2-3 invasive ductal carcinoma.

Courtesy Ellen Mendelson, MD

Figure 17. Automated breast ultrasound (top) and semi-automated ultrasound (bottom).

Hand-held ultrasound is performed by moving the transducer over the breast to acquire the needed images. Hand-held screening ultrasound requires skill on the part of the person performing the test since an abnormality must be seen while scanning in order to be reported by the radiologist. It is also necessary to perform real-time adjustments of technique while performing hand-held breast ultrasound. On average, handheld screening ultrasound takes about 15 minutes to perform, though it can take longer if there are multiple findings requiring documentation. As performed in ACRIN 6666,[118] the minimum standard documentation is one image in each quadrant and one behind the nipple for a negative examination. Results with technologists performing this examination are similar to those with physicians performing the examination.[119]

Automated breast ultrasound typically uses a special wide transducer (usually 15-cm) to document the entire breast, usually in three separate acquisitions which generate hundreds of images. A *semi-automated approach* adapts a motorized arm to a standard 3.8 to 5-cm transducer that moves across the breast in overlapping segments. Both automated and semi-automated approaches create hundreds of images that are reviewed later by a radiologist. An example of images obtained using an automated approach is seen in **Figure 16**. Examples of both automated and semi-automated technologies are shown in **Figure 17**.

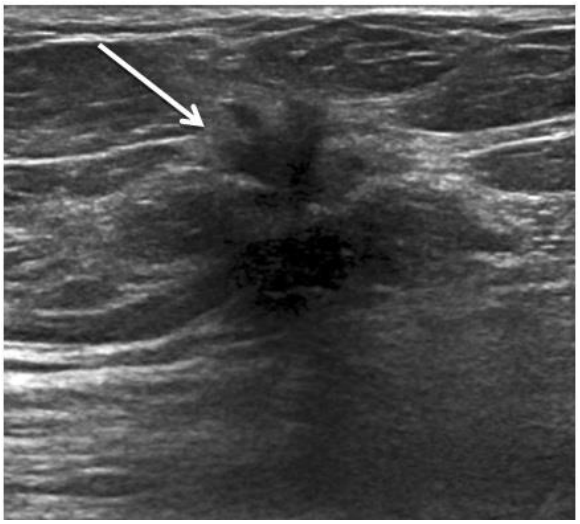


Figure 18. Ultrasound of breast cancer. This 60-year-old woman was noted to have an irregular mass on screening mammography. Ultrasound shows an irregular, hypoechoic (dark gray) spiculated mass (arrow), highly suspicious for cancer. US-guided biopsy and subsequent surgery showed invasive lobular cancer.

Images courtesy Wendie Berg, MD, PhD

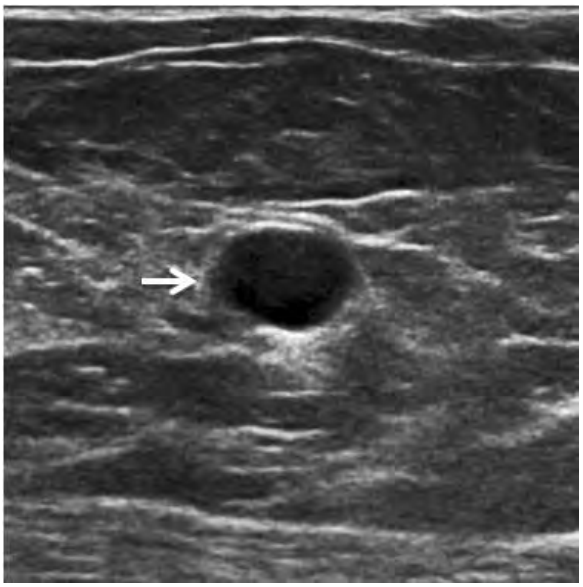


Figure 19. Ultrasound of a simple cyst. This 73-year-old woman uses estrogen cream, and a new mass was seen on her screening mammogram. On ultrasound targeted to the mammographic mass, a circumscribed (well-defined) oval anechoic (black) mass is seen, with increased echoes (whiter) deep to the mass (posterior enhancement), ie, a simple cyst, a benign finding. Cysts do not require follow-up or biopsy. When very large, a cyst can be aspirated if causing pain.

Several other approaches to whole breast ultrasound are in development, including return to use of prone positioning. Since automated ultrasound is less dependent on the operator performing the screening, it may require less training on the part of the operator.

Preliminary studies show similar or slightly lower cancer detection rates for fully automated ultrasound[120] compared to hand-held ultrasound,[121] and recall for additional targeted ultrasound is needed more often with automated approaches, though further comparison studies are warranted. Results with semi-automated ultrasound showed cancer detection rates at least as high as with handheld ultrasound, with fewer benign biopsies.[122]

How it Works

Ultrasound uses high-frequency sound waves to form a sonogram. The sound waves pass through the breast and bounce back or “echo” from various tissues to form a picture of the internal structures of the breast. Gentle pressure is applied to the breasts and rarely causes discomfort. A water-soluble gel or lotion is placed on the skin of the breast, acting as a coupling agent and allowing transmission of the sound waves to the tissues that require imaging. Cancers are usually seen as masses that are slightly darker than the normal lighter gray fat or white (fibrous) breast tissue (**Figures 18** and **19**). Sometimes distortion of the tissue or bright (white) echogenic dots due to calcifications can be seen. Often seen on ultrasound, cysts are round or oval black fluid-filled sacs and are a normal finding (**Figure 20**).

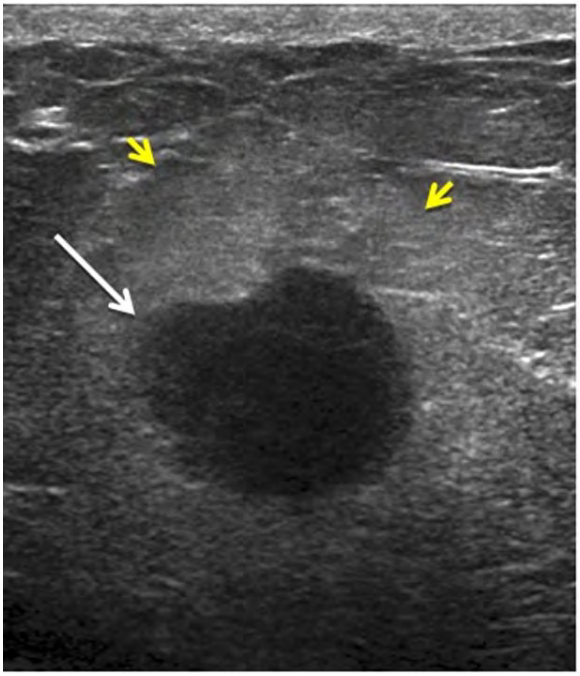


Figure 20. Ultrasound of triple negative breast cancer. This 32-year-old woman was 10 weeks pregnant and noted a lump in her left breast. US showed an oval hypoechoic (dark gray) mass (white arrow) with surrounding hyperechoic (whiter) rim (short yellow arrows). Possibilities included abscess and cancer. US-guided fine needle aspiration did not show pus, so core biopsy was performed, showing grade 3 invasive ductal cancer, lacking estrogen receptors (ER), progesterone receptors (PR), or human epidermal growth factor 2 (HER2) receptors, ie, an aggressive subtype of breast cancer called "triple negative" breast cancer. Such cancers can sometimes be difficult to distinguish from a cyst.

Image courtesy Wendie Berg, MD, PhD

Some ultrasound equipment also allows assessment of tissue stiffness through use of elastography, which can help determine the need for biopsy of low suspicion lesions. Soft lesions are more likely to be benign, and stiff lesions are more likely to be malignant.[123, 124]

Benefits of Breast Ultrasound

Physician-performed ultrasound finds an additional 3 to 4 cancers per thousand women already screened by mammography,[125, 126] and it appears that this benefit is still seen even after tomosynthesis,[127, 128, 129] though further study is warranted. Automated[130] or technologist-performed[131] ultrasound finds 2 to 3 cancers per thousand women previously screened with mammography.

Greater than 85% of cancers seen only on ultrasound are invasive, early stage, and lymph-node negative.[132] In a prospective randomized study from Japan, women who had screening ultrasound in addition to mammography were half as likely to have cancer detected because of a lump or other symptoms (interval cancer) before the next screen.[133]

Ultrasound is readily available and relatively low cost, though not all centers offer screening ultrasound due to a shortage of trained personnel.

Considerations

Performing ultrasound requires experience and expertise of both the individual performing the scanning and the radiologist who interprets the images. On average, ultrasound will show more areas that need follow-up than mammography. Some of those "finds" will be cancer, but the vast majority, determined after further imaging or biopsy, will not be cancerous, that is, a false positive. In two multicenter prospective trials, 20-30% of cancers were seen only on mammography and 29-33% of cancers were seen only on ultrasound.[134, 135] It is important to continue mammography in addition to ultrasound screening as the two tests are complementary.

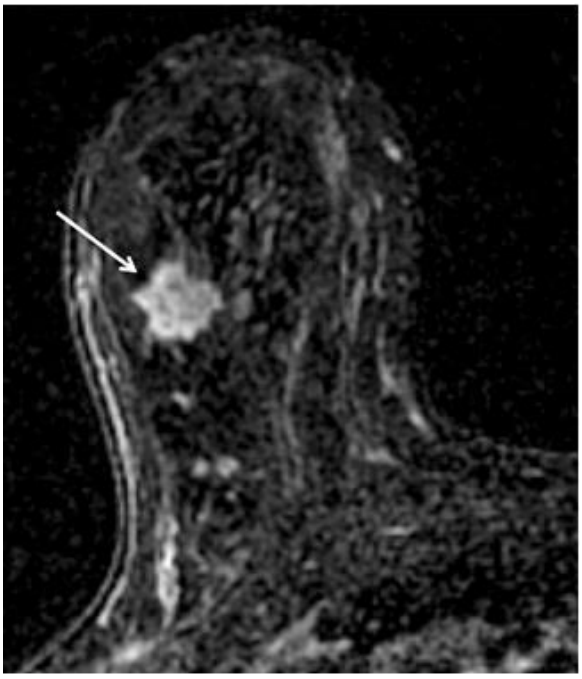


Figure 21. Contrast-enhanced breast MRI showing cancer. Axial MRI image of the right breast obtained after contrast injection (and after computer subtraction of non-enhanced images) in this 48-year-old woman shows irregular spiculated enhancing (white) mass (arrow) due to grade 2 invasive ductal carcinoma with DCIS.

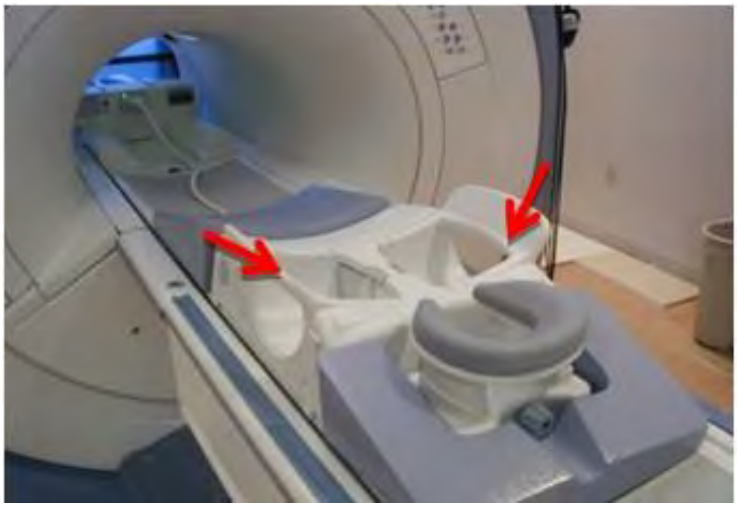
Image courtesy Wendie Berg, MD, PhD

Breast MRI

Contrast-enhanced magnetic resonance imaging (CE-MRI) is a noninvasive medical test that uses very strong magnets, pulses of radio waves to manipulate natural magnetic properties in the body, and a computer to produce detailed cross-sectional 3D images. When used in conjunction with a gadolinium-based intravenous contrast agent (GBCA), CE-breast MRI visualizes both structure and blood flow, critical for identifying cancerous tumors that typically show increased and abnormal blood flow (**Figure 21**).

How MRI Works

During an MRI exam, the patient lies in the prone position, and the breasts are positioned into two openings of a dedicated breast MRI coil. The breast-specific coil acts as an antenna or receiver that works in conjunction with the MRI scanner to transmit data to a computer for image generation (**Figure 22**). The usual breast MRI examination takes about 30 to 40 minutes.



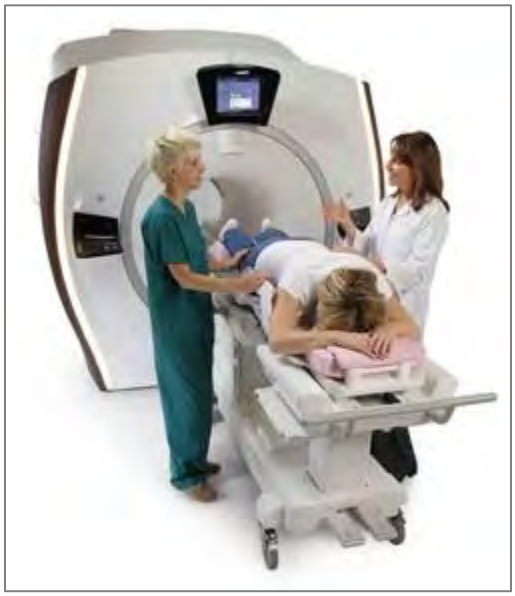


Figure 22. Dedicated breast coil and supports used to image the breasts for MRI. The patient lies prone with the head in the cushioned support and arms raised. The breasts are placed in the rectangular openings of the coil (arrows). The patient is then moved into the tunnel of the scanner for imaging, with the head facing out.

Benefits

Contrast-enhanced breast MRI reveals at least 10 additional cancers per thousand women screened even after both mammography and ultrasound have been performed.[136] MRI has high sensitivity and is recommended annually for women who are at high risk for breast cancer.

Considerations

A contrast-enhanced MRI offers greater sensitivity than either mammography or ultrasound and will find more areas of concern. Some of the findings will be cancer, but the majority will be false positives.

It is important to have the examination performed at a facility that performs correlation with previous mammograms and that also has the ability to perform MRI-guided breast biopsy or has a formal arrangement with a facility that will do this. Any facility accredited in breast MRI by the American College of Radiology will meet these requirements.

While gadolinium-based contrast agents are generally found to be safe, not all patients can tolerate the intravenous contrast. There are data showing that small amounts of gadolinium can accumulate in parts of the brain, especially after multiple MRI examinations.[137] The importance of this finding is unknown and has not been linked to any known negative health effects in patients with normal kidney function. The Food and Drug Administration has concluded that the benefit of all approved gadolinium-based contrast agents far outweighs any hypothetical risks. GBCAs also may pose a risk for women with kidney disease, and these patients should not undergo a contrast-enhanced MRI. Some women find claustrophobia an issue, and the loud clanking sounds produced by the scanner can be unsettling. Lying still for 30-40 minutes can be difficult for patients with neck problems, obesity, or pulmonary issues.

From a safety perspective, MRI cannot be performed in women who have certain metal implants such as pacemakers if they have not been rated MRI-safe, and all patients are carefully screened before ever entering the scanner room.

To reduce normal hormonal changes in the breast, screening MRI is best performed from day 7-10 after the start of the menstrual cycle. Breast MRI is not recommended for pregnant patients.

Data are emerging showing there can be accumulation of gadolinium in parts of the brain in patients who have multiple contrast-enhanced MRI studies.[138, 139] The importance of these findings is unknown, and this appears to be an issue only with certain types of gadolinium-based contrast agents.*

***** Early studies suggest that molecularly linear contrast agents accumulate in the brain whereas macrocyclic agents do not.[140] Linear agents include gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), and gadoversetamide (OptiMARK). Macrocyclic agents include gadoterate meglumine (Dotarem), gadobutrol (Gadavist), and gadoteridol (ProHance).

A last consideration for MRI currently is its high cost, which is not always covered by insurance. A lower cost, abbreviated-MRI has been developed which may take less than 10 minutes, but its availability is limited.[141]

If MRI screening has been performed, there is no added benefit to ultrasound screening, though ultrasound is sometimes performed to guide biopsy of suspicious masses seen on MRI.

Figure 23. (Top) MBI uses 2 detectors; (bottom) BSGI has 1 detector.

Molecular Breast Imaging and Breast Specific Gamma Imaging

Molecular breast imaging (MBI) and breast specific gamma imaging (BSGI) are both specialized nuclear medicine breast imaging techniques that require intravenous injection of a radioactive agent. MBI and BSGI can be useful diagnostic tools in dense breasts.

How it Works

The short-lived (6-hour half-life) radioactive agent 99mTc-sestamibi accumulates to a greater extent in cancer cells than in normal cells, allowing cancer to be visualized on the basis of differences in metabolism. Starting about 5 minutes after intravenous injection of the radiotracer, each breast is gently stabilized between two detectors on an MBI scanner or between one detector and a compression paddle on a BSGI scanner for about 10 minutes per view for a total of 40 minutes for a routine examination and with positioning otherwise similar to mammography (**Figure 23**). As for mammography, sometimes additional images are needed to fully include all the breast tissue.

Breast imaging using these two nuclear medicine technologies does not look at the anatomy of the breast as a mammogram or ultrasound does; rather, it examines the *functional* behavior of the breast tissue by showing differences in cellular uptake of the radioactive agent, which emits gamma rays that are detected by a gamma camera (**Figure 24**).

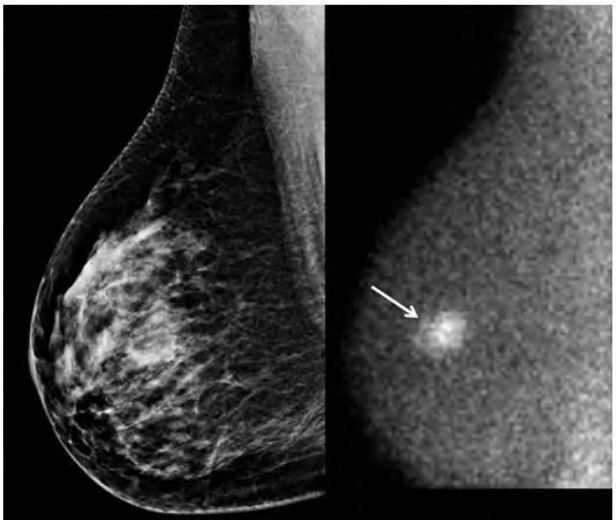


Figure 24. Use of MBI for screening. This 65-year-old woman has heterogeneously dense breasts, with no abnormality seen on mammography (left image, MLO view). MBI MLO image (right) obtained after IV injection of 8 mCi (300 MBq) 99mTc-sestamibi shows intense uptake of radiotracer (arrow) in a 1.9-cm grade 2 invasive ductal cancer with negative axillary node biopsy.

Courtesy Mayo Clinic

Radiation dose

New MBI systems make use of a pair of cadmium zinc telluride (CZT) digital detectors with specialized collimators, both of which improve detection of gamma rays and allow imaging to be performed using a lower amount of 99mTc-sestamibi, typically 6 to 8 mCi (an "off-label" dose), which delivers an effective radiation dose of 1.8 to 2.4 mSv.[142] This should be compared to an effective dose from mammography of 0.5 mSv and to the background radiation dose due to simply living on the Earth for a year of about 2 to 10 mSv (greater at higher elevations, such as Denver).[143]

BSGI employs sodium iodide scintillation crystals and requires a greater dose of 99mTc-sestamibi to be administered, in the range of 15 to 30 millicuries (mCi), which delivers an effective radiation dose of 4.5 to 9 mSv.

Benefits

MBI, performed with a low-radiation-dose protocol, detects an additional 7 to 8 cancers per thousand women screened compared to mammography alone and is being used at the Mayo Clinic in screening research trials in women with dense breasts and is now being used in usual clinical practice.[144, 145] A recent study from a community practice showed similar added cancer detection rate with MBI.[146]

MBI and BSGI can be helpful for some women who need but cannot tolerate contrast-enhanced MRI for reasons such as kidney failure, claustrophobia, or who have pacemakers or other metallic implants. MBI or BSGI can be used in women with dense breast tissue who have a suspicious area on mammography that cannot be identified on ultrasound. Uncommonly, lumps or areas of scarring can be concerning after mammography and ultrasound but are not able to be biopsied by mammography or ultrasound, and molecular breast imaging can be used for further evaluation of these types of findings.

Considerations

The Mayo Clinic and a few other centers have been using molecular breast imaging at effective radiation doses three-to-four-times higher than a mammogram for screening women with dense breasts with excellent results. The radiation from this test is to the whole body, unlike mammography which is a low dose to just the breasts. The effective radiation dose from common medical exams is shown in **Figure 25**.

Uptake of radiotracer in normal breast tissue increases in the luteal phase of the menstrual cycle and may complicate interpretation; screening studies are typically scheduled in days 7 to 14 of the cycle in premenopausal women. Due to the relatively small number of research studies performed as of the last review in 2012, the technology currently does not meet the American College of Radiology's Appropriateness Criteria for screening.[147]

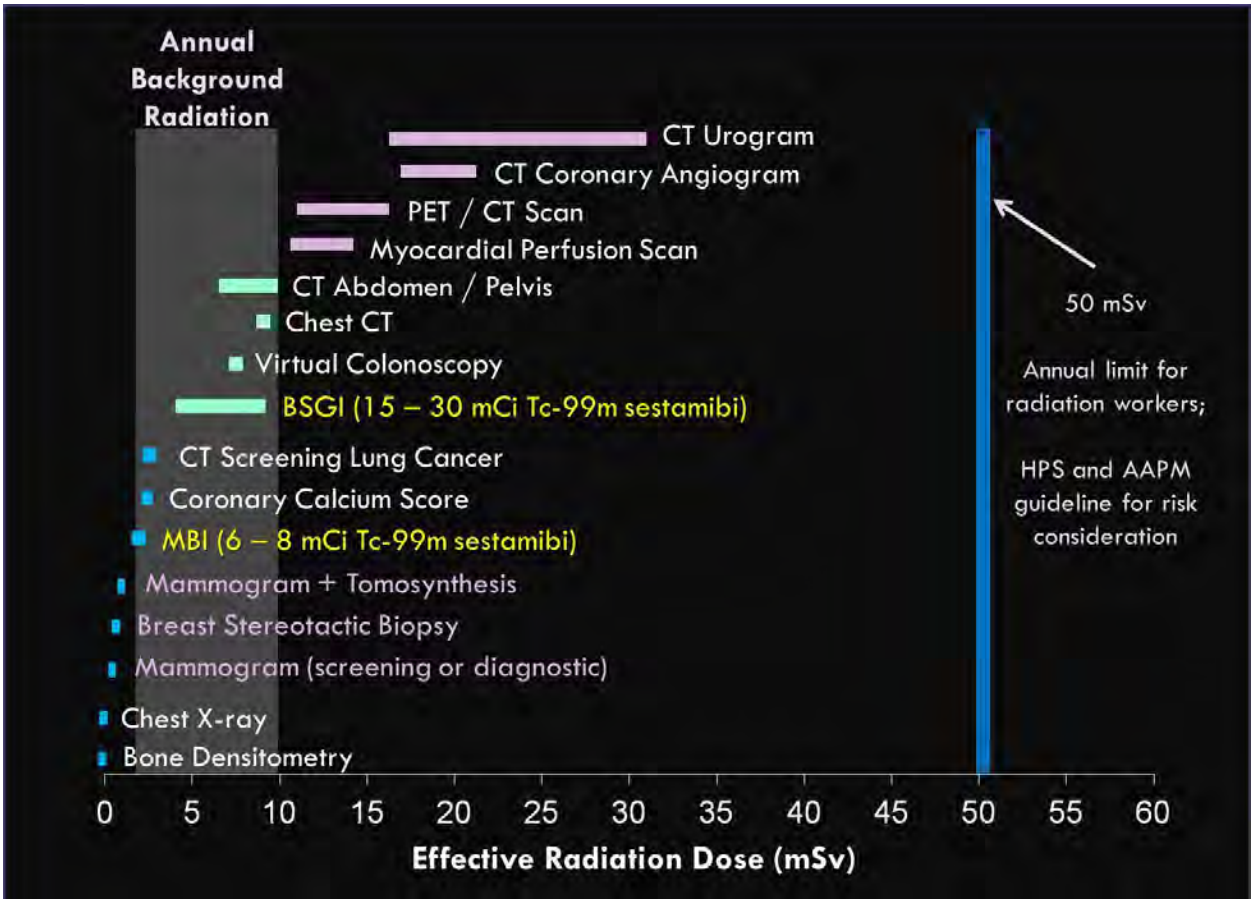


Figure 25. The effective radiation dose to the whole body from common medical exams.

Courtesy Michael K. O'Conner, MD, Mayo Clinic.

Figure 26. Example of a PEM scanner.

MBI and BSGI are never used in women who are pregnant. Importantly, BSGI does have direct biopsy capability, whereas dual-head MBI devices at this time do not (though one manufacturer has submitted an application to the FDA for approval). If a biopsy is needed because of a finding seen on MBI that cannot be seen on mammography or ultrasound, magnetic resonance imaging (breast MRI) may be needed.

Positron Emission Mammography

Positron emission mammography (PEM), also known as dedicated breast positron emission tomography (PET), uses an injection of a short-lived radioactive sugar (18FDG) into the body to detect metabolically active lesions like cancer.

How it Works

The radioactive sugar accumulates in the cancerous breast tissue and emits high-energy positron radiation that is detected and analyzed. For one such system, the breast is gently stabilized with positioning otherwise like mammography (**Figure 26**).

In the most widely validated approach to breast PET, imaging requires about 10 minutes per view (total of 40 minutes for a standard 4-view examination) and usually starts at least one hour after injection of the radiotracer. Twelve "slice" images are reconstructed from each view (**Figure 27**). The patient must fast for 4-6 hours before the test.

Benefits

Breast PET is generally considered a diagnostic tool used to determine the local *extent* of cancer once it is found or to assess possible recurrence of cancer vs scar.

In women with newly diagnosed breast cancer who are being treated with chemotherapy prior to surgery, PEM can help monitor *response* to treatment. It can be utilized for patients who are unable to have breast MRI. It is a relatively new modality and not widely available.

Considerations

Breast PET (PEM) exposes the patient to a moderately high whole body radiation dose and is not used for screening.

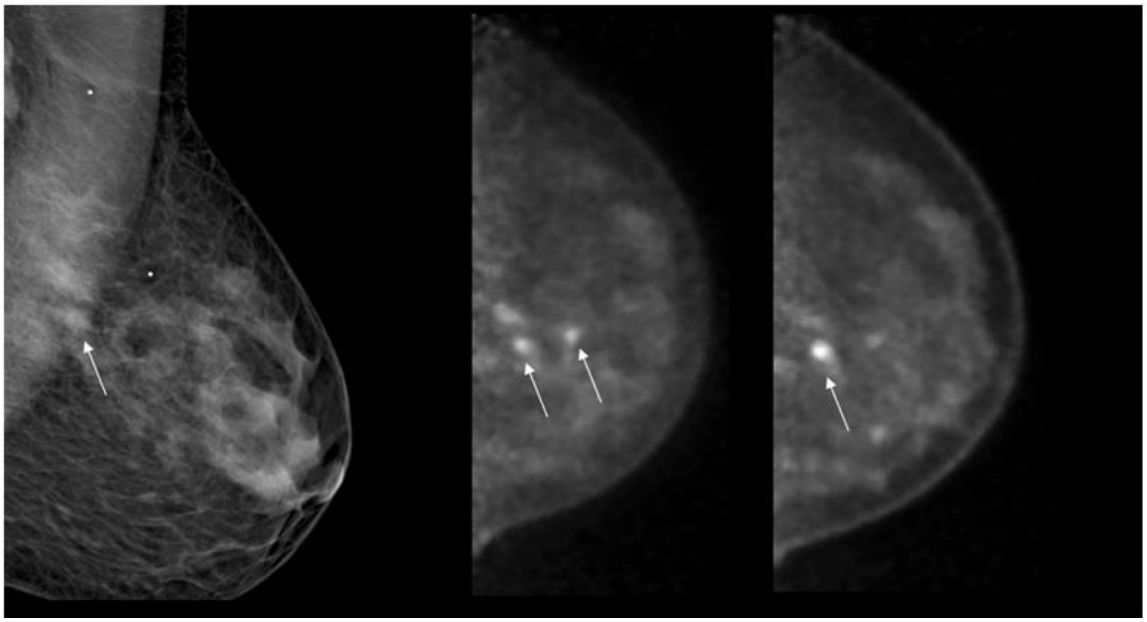


Figure 27. Digital mammogram and PEM Images of DCIS. Vague asymmetry (arrow, left image) is seen on the MLO mammogram of this 48-year-old woman with heterogeneously dense breasts. Stereotactic biopsy showed ductal carcinoma in situ (DCIS). PEM was performed 1 hour after IV injection of 10 mCi 18F-fluorodeoxyglucose (FDG), showing more extensive disease than was suspected on the mammogram, with segmental uptake of the radiotracer on CC (middle) and MLO (right) PEM 6-mm thick slice images (arrows).

Courtesy Lorraine Tafra, MD

Breast Imaging In Development: Contrast-Enhanced Digital Mammography

Contrast-enhanced digital mammography (CEDM) uses a standard iodinated IV contrast agent, like that used for a typical CT scan, in combination with mammography. The result is that cancers that are not visible on standard mammograms will show up as enhancing areas.

How it Works

Just as for a contrast-enhanced breast MRI, the cancer will take up more of the contrast agent than the surrounding normal tissue. The contrast agent is iodinated, and x-rays are absorbed by enhancing areas (and therefore do not reach the detector). Two short exposures are performed, one below and one above the "k-edge" of iodine, and the lower-energy exposure is subtracted from the higher-energy "iodine only" exposure. Cancers will show up as white areas on CEDM (**Figure 28**).

Benefits

In multiple studies, CEDM equaled or nearly equaled MRI in its ability to detect breast cancer and is superior in cancer depiction to standard mammography.[148, 149, 150, 151, 152] Compared to MRI, CEDM uses much less expensive equipment and so can be performed at less cost. It is also a shorter examination, lasting about ten minutes versus 30-40 minutes for an MRI.

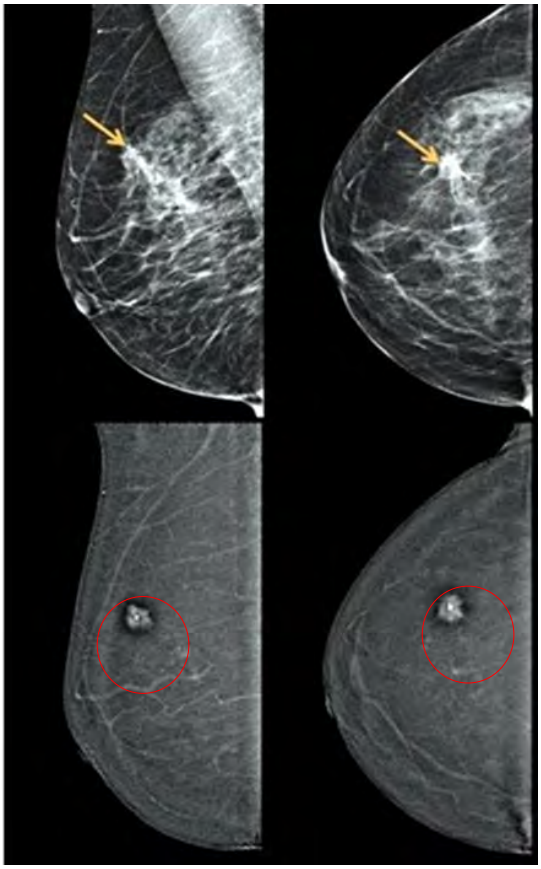


Figure 28. Contrast-enhanced digital mammography. (Top) Digital mammogram shows cancer (yellow arrows). (Bottom) CEDM in same patient; cancer (red circles) is more conspicuous.

Courtesy John Lewin, MD

Considerations

Contrast-enhanced digital mammography uses a small amount of radiation, about 50% more than for a standard mammogram. Until recently, there has been no direct method to biopsy abnormalities seen only on CEDM and many centers do not yet have CEDM-guided biopsy capability, so that MRI may be needed for further evaluation of areas of concern. Further, there is no insurance coverage of CEDM. In addition, iodinated contrast agents do carry some risks. Women with poor kidney function or prior contrast reaction should avoid CEDM. Mild allergic reactions like hives occur in about 1-4% of patients. Severe allergic reactions resulting in anaphylaxis and even death are rare but can occur. The risk of death from a reaction is estimated to be 1 in 100,000 to 1 in 200,000.[153]

Breast Density Assessment Software

Radiologists have traditionally determined breast density by visually comparing the amount of fibroglandular tissue (white) to fatty tissue (dark gray) areas on mammography. Since visual determination of density is a subjective assessment, it can vary from year to year even if there is no true change in the breast.

Computer software can also be used to automatically characterize breast density on a digital mammography exam. Any density assessment — radiologist/visual or radiologist + automated tool — should be tracked over time as some breasts will become fatty-replaced and therefore no longer as dense as a woman ages. Either visual or automated assessment of breast density can be used to determine that the breasts are dense and therefore as the basis for considering supplemental screening.

Software is available that presents interpreting radiologists with an automatic assessment of the percentage of dense tissue contained within the breast. The density assessment software distinguishes dense and nondense areas of the breast on the routine mammogram or digital breast tomosynthesis exam. Some current software requires the raw digital mammogram images or tomosynthesis projection datasets, and these are not routinely saved at most facilities. When software requires raw images, this analysis must be performed at the time of the initial mammogram or tomosynthesis using current approaches.

How it Works

Automated assessments calculate density as either area (length x width) or volume (length x width x height) percent density. The assessed area or volume of dense tissue is divided by the area or volume of the entire breast and then multiplied by 100 to yield a percentage. This percentage is generally then correlated to one of the four BI-RADS breast density categories: fatty, scattered fibroglandular tissue, heterogeneously dense, or extremely dense. We do not fully understand whether the *absolute amount/volume* of dense tissue or the *percent* of dense tissue is more important, though an analysis of multiple methods found percent density more predictive of risk.[154, 155] Complexity of the pattern of breast density may be more important in predicting risk than the amount of dense tissue, though further study is needed.

Benefits

Automated assessments automatically provide consistent breast density calculations across all patient populations, removing inter- and intra-radiologist subjectivity and greatly reducing variability in assessment of breast density.

Considerations

There are differences in software technology, with some algorithms calculating the amount of fibroglandular tissue, some calculating percent area or percent volume that is dense, and some also considering the texture and variability (complexity) of density within the breast. Automated software typically provides one “average” measurement across the whole breast, or the maximum density value of the left or right breast. If one quadrant of the breast is particularly dense, this may prompt a recommendation by the radiologist for supplemental screening, even though the software average density score across the entire breast would not be classified as dense. Finally, one software system might classify breasts as dense when another might not. It is important to note that any computerized measurement of density should be reviewed in the context of a particular woman’s mammograms.

Thermography

Thermography devices were cleared long ago by the FDA for use as an adjunct tool for detecting breast cancer. Thermography is a non-invasive technique that uses infrared technology to detect both heat and blood flow patterns very near the skin's surface, and some large cancers can be seen this way.

However, thermography has a high "false negative" rate (when a test result indicates "no cancer," though cancer is actually present), especially for small breast cancers, and a high rate of indeterminate findings, when follow-ups are recommended for observation but ultimately no cancer is found. The FDA's Center for Devices and Radiological Health states that this means thermography *should not be used by itself to screen for or to diagnose breast cancer*.[156]

Legislation: State and National

State Level Notification

Currently, more than half of the states in the United States have active breast density inform laws. Patients in these states must be provided some level of information about their breast density status after undergoing their mammogram. There is no state-to-state standard on what patients are told or how they should be informed.

Insurance Coverage

- Screening mammography (using 2D mammography) is fully covered by all insurance under the Affordable Care Act with no copay or deductible. Coverage for 3D mammography (tomosynthesis) varies, as does coverage for supplemental screening such as ultrasound or MRI.
- If there ***is*** a state insurance law, are all women covered? No. A state insurance law does not necessarily apply to all policies within the state. Further, national insurance providers may be exempt from state laws.
- If there is *no* state insurance law, or if a plan is exempt from state law, might additional screening be covered? Yes. While indicated states have some level of insurance coverage, generally in other states, an ultrasound or possibly other screening will be covered (subject to deductible/copay) if ordered by a physician.

Please note: Employer plans set up as "self-funded" or "self-insured" (check with the plan's benefit administrator) generally do not have to comply with state insurance laws.

Figure 29 shows the states that require density notification as well as those that mandate insurance coverage. Always check with the insurer regarding coverage details.

Efforts toward a National Standard

As a result of the 1992 U.S. Food and Drug Administration's (FDA) Mammography Quality Standards Act (MQSA), amended/effective April 28, 1999, a summary of a mammography center's written report must be sent to the patient and written in terms easily understood by a layperson within 30 days of the mammographic examination. Unfortunately there is no federal law or regulation requiring a patient's breast density status to either be included in the report or communicated directly to the patient, though most centers at least include this information in the report sent to the referring physician (if any).

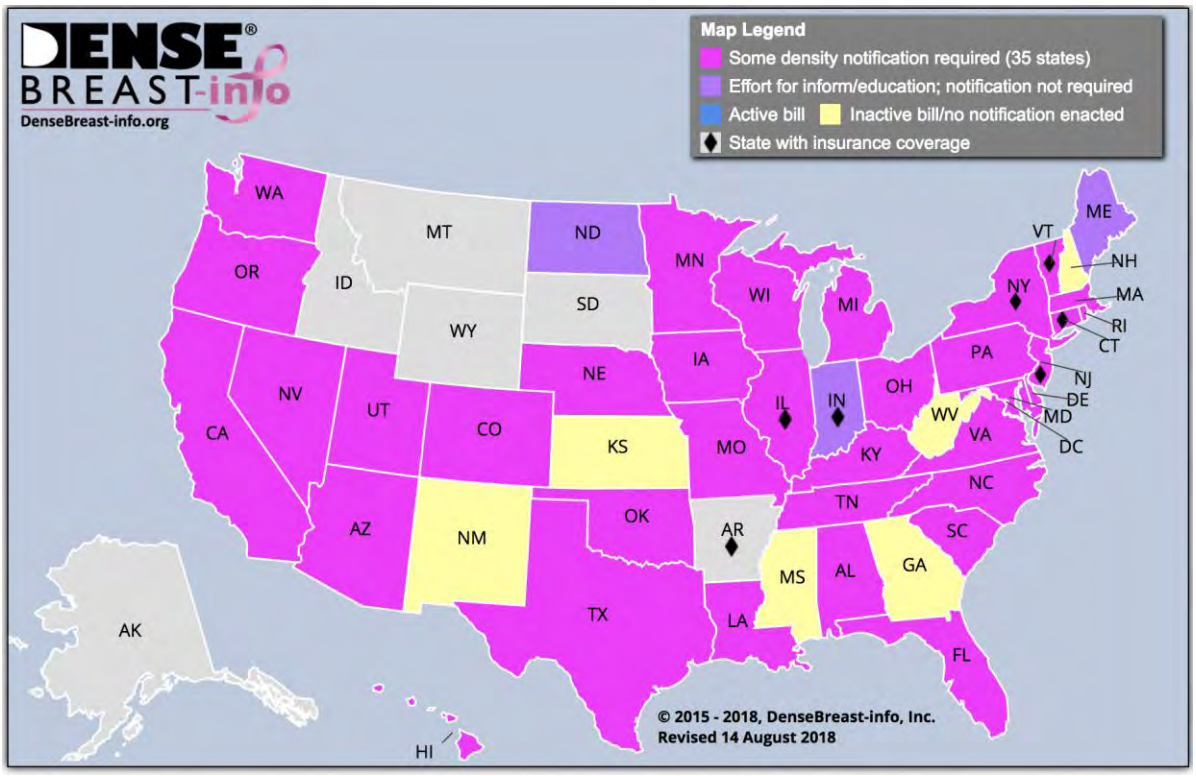


Figure 29. Status of density notification laws by state.

To create a national standard so that *all* women receive notification of their breast density, an MQSA amendment to the "lay" letter reporting requirement is needed.

Creating and enacting federal laws through the U.S. Congress is referred to as the *legislative* process, while creating and enacting regulations, which are equally enforceable, is generally referred to as the *rulemaking* process. After Congress passes a law designed to address a social or economic need, the appropriate regulatory agency creates regulations necessary for implementing that law.

An MQSA amendment could be accomplished either through federal legislation or through the FDA as a change in federal regulation, and advocacy efforts have been initiated on both fronts. In 2017, federal legislation was introduced into both the U.S. House of Representatives (H.R. 4122) and U.S. Senate (S.2006 and identical to the House bill) requiring that mammography reports include information about breast density and “convey the effect of breast density in masking the presence of breast cancer on mammography...” Many existing state breast density inform laws already meet or surpass the scope of information in this proposed legislation. Unless federal requirements are more stringent than state laws, the state laws will continue to be in effect.

A national density inform standard could become law even if a bill does not progress through Congress through a regulatory amendment to the FDA's MQSA. The FDA, which oversees the MQSA program, anticipates publishing proposed amendments to the MQSA regulations for notice and comment. Among other things, the proposed amendments are expected to address breast density reporting. The proposed language has not been made public as of September 13, 2018.

Summary

Forty to fifty percent of women in the United States have heterogeneously or extremely dense breasts. Dense breast tissue not only makes it more difficult to detect cancer on mammography but is an independent factor for the development of breast cancer. Annual screening with mammography starting at age 40 for women who are not at high risk is a great start, but knowing one's own breast density status provides women information with which to discuss supplemental screening. Referring physicians and midlevel providers should carefully review radiologists' assessments of their patients' breast density status to launch a discussion about additional imaging, if any, and to advise their patients to immediately report any suspicious lumps or breast changes in the interval between annual mammograms. It is hoped that as patients and referrers become more knowledgeable about breast density and related implications in terms of screening and risk, more breast cancers will be discovered early when they are most treatable and survivable.

References

[1] American Cancer Society website. http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics Accessed August 15, 2018.

[2] Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K, Breast Cancer Surveillance Consortium.. Population-Attributable Risk Proportion of Clinical Risk Factors for Breast Cancer. JAMA Oncol. 2017 Sep 1;3(9):1228-1236.

[3] Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology. 2002;225(1):165-175.

[4] Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology. 2002;225(1):165-175.

[5] Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst. 2014;106(10).

[6] Sickles EA, D'Orsi CJ, Bassett LW, et al. ACR BI-RADS Mammography. ACR BI-RADS Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology, 2013.

[7] Mendelson EB, Böhm-Vélez M, Berg WA, et al. ACR BI-RADS Ultrasound. ACR BI-RADS Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology, 2013.

[8] Morris EA, Comstock CE, Lee C, et al. ACR BI-RADS Magnetic Resonance Imaging. ACR BI-RADS Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology, 2013.

[9] Lehman CD, Arao RF, Sprague BL, et al. National Performance Benchmarks for Modern Screening Digital Mammography: Update from the Breast Cancer Surveillance Consortium. Radiology 2017; 283:49-58.

[10] Mammography and Breast Imaging Resources. American College of Radiology website. http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Breast%20Imaging/Breast%20Density%20bro_ACR_SBI_F.pdf Accessed September 16, 2018.

[11] Cummings SR, Tice JA, Bauer S, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. J Natl Cancer Inst. 2009;101(6):384-398.

[12] Couch FJ, DeShano ML, Blackwood MA, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med. 1997;336(20):1409-1415.

[13] Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57(2):75-89.

[14] Berg WA. Tailored supplemental screening for breast cancer: what now and what next? AJR Am J Roentgenol. 2009;192(2):390-399.

[15] Genetics of Breast and Gynecologic Cancers (PDQ®)–Health Professional Version. National Cancer Institute website. http://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#link/_2503_toc Accessed September 17, 2018.

[16] Monticciolo DL et al. Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR. J Am Coll Radiol. 2018 Mar;15(3 Pt A):408-414.

[17] Stapleton SM, Oseni TO, Bababekov YJ, Hung Y, Chang DC. Race/Ethnicity and Age Distribution of Breast Cancer Diagnosis in the United States. JAMA Surg. 2018 Jun 1;153(6):594-595.

[18] Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: relationship with breast cancer risk. Radiology. 2004;230(1):29-41.

[19] Kerlikowske K, Cook AJ, Buist DS, et al. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. J Clin Oncol. 2010;28(24):3830-3837.

[20] Chiu SY, Duffy S, Yen AM, Tabár L, Smith RA, Chen HH. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. Cancer Epidemiol Biomarkers Prev. 2010;19(5):1219-1228.

[21] Gierach GL, Ichikawa L, Kerlikowske K, et al. Relationship between mammographic density and breast cancer death in the Breast Cancer Surveillance Consortium. J Natl Cancer Inst. 2012;(16):1218-1227.

[22] Masarwah A, Auvinen P, Sudah M, et al. Very low mammographic breast density predicts poorer outcome in patients with invasive breast cancer. Eur Radiol. 2015;25(7):1875-1882.

[23] Smith RA, Duffy SW, Gabe R, Tabar L, Yen AM, Chen TH. The randomized trials of breast cancer screening: what have we learned? Radiol Clin North Am. 2004;42(5):793-806, v.

[24] Tabár L, Yen AM, Wu WY, et al. Insights from the breast cancer screening trials: how screening affects the natural history of breast cancer and implications for evaluating service screening programs. Breast J. 2015;21(1):13-20.

[25] Tabár L, Vitak B, Chen TH, et al. Radiology. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. 2011;260(3):658-663.

[26] Coldman A, Phillips N, Wilson C, et al. Pan-Canadian study of mammography screening and mortality from breast cancer. J Natl Cancer Inst. 2014;106(11).

[27] van der Waal D, Ripping TM, Verbeek AL, Broeders MJ. Breast cancer screening effect across breast density strata: A case-control study. Int J Cancer 2017; 140:41-49.

[28] Nelson HD, Tyne K, Naik A, et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151(10):727-737, W237-242.

[29] Stapleton SM, Oseni TO, Bababekov YJ, Hung Y, Chang DC. Race/Ethnicity and Age Distribution of Breast Cancer Diagnosis in the United States. JAMA Surg. 2018 Jun 1;153(6):594-595.

[30] Mammography and Breast Imaging Resources. American College of Radiology website. http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Breast%20Imaging/Breast%20Density%20bro_ACR_SBI_F.pdf Accessed September 16, 2018.

[31] Monticciolo DL, Newell MS, Hendrick RE, et al. Breast Cancer Screening for Average-Risk Women: Recommendations From the ACR Commission on Breast Imaging. J Am Coll Radiol 2017; 14:1137-1143.

[32] Tabar L, Yen MF, Vitak B, Chen HH, Smith RA, Duffy SW. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet. 2003;361(9367): 1405-1410.

[33] Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA. 2001;285(21):2750-2756.

[34] Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA. 2001;285(21):2750-2756.

[35] Oeffinger KC, Fontham ET, Etzioni R, et al. Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society. JAMA. 2015;314(15):1599-1614.

[36] 27. Smith RS, Herman C. Breast Cancer Screening 101: Screening Guidelines and Imaging Modalities. https://www.youtube.com/watch?v=6SKh6Tm2HZs&feature=youtu.be Accessed September 17, 2018.

[37] ACOG Statement on Breast Cancer Screening Guidelines. American Congress of Obstetricians and Gynecologists website. http://www.acog.org/About-ACOG/News-Room/Statements/2016/ACOG-Statement-on-Breast-Cancer-Screening-Guidelines Accessed September 17, 2018.

[38] Mammography and Other Screening Tests for Breast Problems. American Congress of Obstetricians and Gynecologists website. http://www.acog.org/Patients/FAQs/Mammography-and-Other-Screening-Tests-for-Breast-Problems Accessed September 16, 2018.

[39] ACR and SBI Continue to Recommend Regular Mammography Starting at Age 40 [news release]. Reston, VA: American College of Radiology Media Center; October 20, 2015. https://www.sbi-online.org/Portals/0/ACR-SBI%20press%20release%20ACS%20FINAL%20for%20web.pdf Accessed September 20, 2018.

[40] Lee CH, Dershaw DD, Kopans D, et al. Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. J Am Coll Radiol. 2010;7(1):18-27.

[41] Comparison of Breast Cancer Screening Guidelines. American Medical Association website. http://www.facingourrisk.org/our-role-and-impact/advocacy/documents/breast-screening-comparison-chart.pdf Accessed September 17, 2018.

[42] NCCN Guidelines for Treatment of Cancer by Site. National Comprehensive Cancer Network website. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp Accessed September 17, 2018.

[43] Siu AL; U.S. Preventive Services Task Force. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(4):279-296.

[44] Hendrick RE, Helvie MA, Hardesty LA. Implications of CISNET modeling on number needed to screen and mortality reduction with digital mammography in women 40-49 years old. AJR Am J Roentgenol. 2014;203(6): 1379-1381.

[45] Bailey SL, Sigal BM, Plevritis SK. A simulation model investigating the impact of tumor volume doubling time and mammographic tumor detectability on screening outcomes in women aged 40-49 years. J Natl Cancer Inst. 2010;102(16):1263-1271.

[46] Mandelblatt JS, Stout NK, Schechter CB, et al. Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies. Ann Intern Med. 2016;164(4):215-225.

[47] Leung JW, Kornguth PJ, Gotway MB. Utility of targeted sonography in the evaluation of focal breast pain. J Ultrasound Med. 2002;21(5):521-526.

[48] Tumyan L, Hoyt AC, Bassett LW. Negative predictive value of sonography and mammography in patients with focal breast pain. Breast J. 2005;11(5):333-337.

[49] Kushwaha AC, Shin K, Kalambo M, et al. Overutilization of Health Care Resources for Breast Pain. AJR Am J Roentgenol 2018; 211:217-223.

[50] Lehman CD, Arao RF, Sprague BL, et al. National Performance Benchmarks for Modern Screening Digital Mammography: Update from the Breast Cancer Surveillance Consortium. Radiology 2017; 283:49-58.

[51] Yen MF, Tabár L, Vitak B, Smith RA, Chen HH, Duffy SW. Quantifying the potential problem of overdiagnosis of ductal carcinoma in situ in breast cancer screening. Eur J Cancer. 2003;39(12): 1746-1754.

[52] McCarthy AM, Kontos D, Synnestvedt M, et al. Screening outcomes following implementation of digital breast tomosynthesis in a general-population screening program. J Natl Cancer Inst. 2014;106(11).

[53] Lehman CD, White E, Peacock S, Drucker MJ, Urban N. Effect of age and breast density on screening mammograms with false-positive findings. AJR Am J Roentgenol. 1999;173(6):1651-1655.

[54] Lehman CD, White E, Peacock S, Drucker MJ, Urban N. Effect of age and breast density on screening mammograms with false-positive findings. AJR Am J Roentgenol. 1999;173(6):1651-1655.

[55] Bent CK, Bassett LW, D'Orsi CJ, Sayre JW. The positive predictive value of BI-RADS microcalcification descriptors and final assessment categories. AJR Am J Roentgenol. 2010;194(5):1378-1383.

[56] Burnside ES, Ochsner JE, Fowler KJ, et al. Use of microcalcification descriptors in BI-RADS 4th edition to stratify risk of malignancy. Radiology. 2007;242(2):388-395.

[57] Partyka L, Lourenco AP, Mainiero MB. Detection of mammographically occult architectural distortion on digital breast tomosynthesis screening: initial clinical experience. AJR Am J Roentgenol. 2014;203(1):216-222.

[58] Gaur S, Dialani V, Slanetz PJ, Eisenberg RL. Architectural distortion of the breast. AJR Am J Roentgenol. 2013;201(5):W662-670.

[59] Gierach GL, Ichikawa L, Kerlikowske K, et al. Relationship between mammographic density and breast cancer death in the Breast Cancer Surveillance Consortium. J Natl Cancer Inst. 2012;(16):1218-1227.

[60] Arora N, King TA, Jacks LM, et al. Impact of breast density on the presenting features of malignancy. Ann Surg Oncol. 2010;17 Suppl 3:211-218.

[61] Raghavendra A, Sinha AK, Le-Petross HT, et al. Mammographic breast density is associated with the development of contralateral breast cancer. Cancer 2017; 123:1935-1940

[62] Sandberg ME, Li J, Hall P, et al. Change of mammographic density predicts the risk of contralateral breast cancer--a case-control study. Breast Cancer Res. 2013;15(4):R57.

[63] del Carmen MG, Halpern EF, Kopans DB, et al. Mammographic breast density and race. AJR Am J Roentgenol. 2007;188(4):1147-1150.

[64] Ursin G, Ma H, Wu AH, et al. Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev. 2003;12(4):332-338.

[65] del Carmen MG, Halpern EF, Kopans DB, et al. Mammographic breast density and race. AJR Am J Roentgenol. 2007;188(4):1147-1150.

[66] McCarthy AM, Keller B, Synnestvedt M, Conant E, Armstrong K, Kontos D. Racial differences in quantitative measures of area and volumetric breast density [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18-22; Philadelphia, PA. Philadelphia (PA): AACR; 2015. Abstract nr 2770.

[67]. Breast Cancer in Men. American Cancer Society website. http://www.cancer.org/cancer/breastcancerinmen/detailedguide/breast-cancer-in-men-key-statistics Accessed August 24, 2018.

[68] Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst. 2014;106(10).

[69] Kerlikowske K, Ichikawa L, Miglioretti DL, et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. J Natl Cancer Inst. 2007;99(5):386-395.

[70] Boyd NF, Dite GS, Stone J, et al. Heritability of mammographic density, a risk factor for breast cancer. N Engl J Med. 2002 Sep 19;347(12):886-94.

[71] Ursin G, Lillie EO, Lee E, et al. The relative importance of genetics and environment on mammographic density. Cancer Epidemiol Biomarkers Prev. 2009;18(1):102-112.

[72] van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. Am J Epidemiol. 2000;152(6):514-527.

[73] Huo CW, Chew GL, Britt KL, et al. Mammographic density-a review on the current understanding of its association with breast cancer. Breast Cancer Res Treat. 2014;144(3):479-502.

[74] Crandall CJ, Aragaki AK, Cauley JA, et al. Breast tenderness after initiation of conjugated equine estrogens and mammographic density change. Breast Cancer Res Treat. 2012;131(3):969-979.

[75] Grady D, Vittinghoff E, Lin F, et al. Effect of ultra-low-dose transdermal estradiol on breast density in postmenopausal women. Menopause. 2007;14(3 Pt 1):391-396.

[76] Nielsen M, Raundahl J, Pettersen PC, et al. Low-dose transdermal estradiol induces breast density and heterogeneity changes comparable to those of raloxifene. Menopause. 2009;16(4):785-791.

[77] Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010;304(15):1684-1692.

[78] Hormone Therapy for Breast Cancer. National Cancer Institute website. http://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet Accessed September 16, 2018.

[79] Hormone Therapy for Breast Cancer. National Cancer Institute website. http://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet Accessed September 16, 2018.

[80] Cuzick J. Breast density predicts endocrine treatment outcome in the adjuvant setting. Breast Cancer Res. 2012;14(4):109.

[81] Changes in breast density point to tamoxifen's effectiveness. Auntminnie website. http://www.auntminnie.com/index.aspx?sec=sup&sub=wom&pag=dis&ItemID=103197 Accessed September 17, 2018.

[82] Cuzick J, Warwick J, Pinney E, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. J Natl Cancer Inst. 2011;103(9):744-752.

[83] Li J, Humphreys K, Eriksson L, Edgren G, Czene K, Hall P. Mammographic density reduction is a prognostic marker of response to adjuvant tamoxifen therapy in postmenopausal patients with breast cancer. J Clin Oncol. 2013;31(18):2249-2256.

[84] Hormone Therapy for Breast Cancer. National Cancer Institute website. http://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet Accessed September 16, 2018.

[85] Kim J, Han W, Moon HG, et al. Breast density change as a predictive surrogate for response to adjuvant endocrine therapy in hormone receptor positive breast cancer. Breast Cancer Res. 2012;14(4):R102.

[86] Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer. 1994;73(3):643-651.

[87] 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.

[88] Vachon CM, Pankratz VS, Scott CG, et al. The contributions of breast density and common genetic variation to breast cancer risk. J Natl Cancer Inst. 2015;107(5).

[89] Tice JA, O'Meara ES, Weaver DL, Vachon C, Ballard-Barbash R, Kerlikowske K. Benign breast disease, mammographic breast density, and the risk of breast cancer. J Natl Cancer Inst. 2013;105(14):1043-1049.

[90] 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):3137-3143.

[91] Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371-1388.

[92] Hernandez RK, Sørensen HT, Pedersen L, Jacobsen J, Lash TL. Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: a Danish population-based cohort study. Cancer. 2009;115(19):4442-4449.

[93] Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97(22):1652-1662.

[94] Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. Proc Natl Acad Sci U S A. 2014;111(39):14205-14210.

[95] Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57(2):75-89.

[96] Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA. Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR. J Am Coll Radiol 2018; 15:408-414.

[97] Moskowitz CS, Chou JF, Wolden SL, et al. Breast cancer after chest radiation therapy for childhood cancer. J Clin Oncol. 2014;32(21):2217-2223.

[98] Monticciolo DL, Newell MS, Moy L, Niell B, Monsees B, Sickles EA. Breast Cancer Screening in Women at Higher-Than-Average Risk: Recommendations From the ACR. J Am Coll Radiol 2018; 15:408-414.

[99] NCCN Guidelines for Treatment of Cancer by Site. National Comprehensive Cancer Network website. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp Accessed October 13, 2016.

[100] NCCN Guidelines for Treatment of Cancer by Site. National Comprehensive Cancer Network website. https://www.nccn.org/professionals/physician_gls/f_guidelines.asp Accessed October 13, 2016.

[101] Lowry KP, Lee JM, Kong CY, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. Cancer. 2012;118(8):2021-2030.

[102] Cohen SL, Margolies LR, Schwager SJ, et al. Early discussion of breast density and supplemental breast cancer screening: is it possible? Breast J. 2014;20(3):229-234.

[103] Cohen SL, Margolies LR, Schwager SJ, et al. Early discussion of breast density and supplemental breast cancer screening: is it possible? Breast J. 2014;20(3):229-234.

[104] Hooley R. Tomosynthesis. In: Berg WA, Yang WT, eds. *Diagnostic Imaging: Breast*. 2nd ed. Salt Lake City, UT: Amirsys; 2014:2-14 - 2-19.

[105] Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. JAMA. 2014;311(24):2499-2507.

[106] Berg WA. Screening Ultrasound. In: Berg WA, Yang WT, eds. *Diagnostic Imaging: Breast*. 2nd ed. Salt Lake City, UT: Amirsys; 2014:9-38 - 9-43.

[107] Berg WA. Screening MRI. In: Berg WA, Yang WT, eds. *Diagnostic Imaging: Breast*. 2nd ed. Salt Lake City, UT: Amirsys; 2014:9-44 - 9-49.

[108] 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.

[109] Smith RA, Duffy SW, Gabe R, Tabar L, Yen AM, Chen TH. The randomized trials of breast cancer screening: what have we learned? Radiol Clin North Am. 2004;42(5):793-806, v.

[110] Siu AL; U.S. Preventive Services Task Force. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(4):279-296.

[111] 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.

[112] 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.

[113] McDonald ES, Oustimov A, Weinstein SP, Synnestvedt MB, Schnall M, Conant EF. Effectiveness of Digital Breast Tomosynthesis Compared With Digital Mammography: Outcomes Analysis From 3 Years of Breast Cancer Screening. JAMA Oncol. 2016;2(6):737-743.

[114] Rafferty EA, Durand MA, Conant EF, et al. Breast Cancer Screening Using Tomosynthesis and Digital Mammography in Dense and Nondense Breasts. JAMA. 2016;315(16):1784-1786.

[115] Kim WH, Chang JM, Lee J, et al. Diagnostic performance of tomosynthesis and breast ultrasonography in women with dense breasts: a prospective comparison study. Breast Cancer Res Treat. 2017 Feb;162(1):85-94.

[116] McDonald ES, Oustimov A, Weinstein SP, Synnestvedt MB, Schnall M, Conant EF. Effectiveness of Digital Breast Tomosynthesis Compared With Digital Mammography: Outcomes Analysis From 3 Years of Breast Cancer Screening. JAMA Oncol. 2016;2(6):737-743.

[117] Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology. 2002;225(1):165-175.

[118] 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.

[119] Berg WA, Mendelson EB. Technologist-performed handheld screening breast US imaging: how is it performed and what are the outcomes to date? Radiology. 2014;272(1):12-27.

[120] Brem RF, Tabár L, Duffy SW, et al. Radiology. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study.2015;274(3): 663-673.

[121] Mendelson EB, Berg WA. Training and standards for performance, interpretation, and structured reporting for supplemental breast cancer screening. AJR Am J Roentgenol. 2015204(2):265-268.

[122] Kelly KM, Dean J, Comulada WS, Lee SJ. Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. Eur Radiol. 2010;20(3):734-742.

[123] Berg WA, Cosgrove DO, Doré CJ, et al. Shear-wave elastography improves the specificity of breast US: the BE1 multinational study of 939 masses. Radiology. 2012;262(2):435-449.

[124] Lee SH, Chang JM, Kim WH, et al. Added value of shear-wave elastography for evaluation of breast masses detected with screening US imaging. Radiology. 2014;273(1):61-69.

[125] Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA. 2012;307(13): 1394-1404.

[126] 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.

[127] Corsetti V, Houssami N, Ferrari A, et al. Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost. Eur J Cancer. 2008;44(4):539-544.

[128] Destounis, S. Comparison of cancers detected by Screening Breast Ultrasound and Digital Breast Tomosynthesis [abstract]. American Roentgen Ray Society. May 3, 2017, New Orleans, LA.

[129] Kim WH, Chang JM, Lee J, et al. Diagnostic performance of tomosynthesis and breast ultrasonography in women with dense breasts: a prospective comparison study. Breast Cancer Res Treat. 2017 Feb;162(1):85-94.

[130] Brem RF, Tabár L, Duffy SW, et al. Radiology. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study.2015;274(3): 663-673.

[131] Berg WA, Mendelson EB. Technologist-performed handheld screening breast US imaging: how is it performed and what are the outcomes to date? Radiology. 2014;272(1):12-27.

[132] Berg WA. Screening Ultrasound. In: Berg WA, Yang WT, eds. *Diagnostic Imaging: Breast*. 2nd ed. Salt Lake City, UT: Amirsys; 2014:9-38 - 9-43.

[133] Ohuchi N, Suzuki A, Sobue T, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. Lancet. 2016;387(10016):341-348.

[134] Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA. 2012;307(13): 1394-1404.

[135] Ohuchi N, Suzuki A, Sobue T, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. Lancet. 2016;387(10016):341-348.

[136] Berg WA. Screening MRI. In: Berg WA, Yang WT, eds. *Diagnostic Imaging: Breast*. 2nd ed. Salt Lake City, UT: Amirsys; 2014:9-44 - 9-49.

[137] FDA Drug Safety Communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings. U.S. Food & Drug Administration website. https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm Accessed September 20, 2018.

[138] McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology. 2015;275(3):772-782.

[139] Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology. 2015;275(3):783-791.

[140] Radbruch A. Gadolinium Deposition in the Brain: We Need to Differentiate between Chelated and Dechelated Gadolinium. Radiology 2018; 288:434-435.

[141] Kuhl CK, Schrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection-a novel approach to breast cancer screening with MRI. J Clin Oncol. 2014 Aug 1;32(22):2304-2310.

[142] Hruska CB, O'Connor MK. Curies, and Grays, and Sieverts, Oh My: A Guide for Discussing Radiation Dose and Risk of Molecular Breast Imaging. J Am Coll Radiol. 2015;12(10):1103-1105.

[143] Hruska CB, O'Connor MK. Curies, and Grays, and Sieverts, Oh My: A Guide for Discussing Radiation Dose and Risk of Molecular Breast Imaging. J Am Coll Radiol. 2015;12(10):1103-1105.

[144] Rhodes DJ, Hruska CB, Phillips SW, Whaley DH, O'Connor MK. Dedicated dual-head gamma imaging for breast cancer screening in women with mammographically dense breasts. Radiology. 2011;258(1):106-118.

[145] Rhodes DJ, Hruska CB, Conners AL, et al. Journal club: molecular breast imaging at reduced radiation dose for supplemental screening in mammographically dense breasts. AJR Am J Roentgenol. 2015;204(2):241-251

[146] Shermis RB, Wilson KD, Doyle MT, et al. Supplemental Breast Cancer Screening With Molecular Breast Imaging for Women With Dense Breast Tissue. AJR Am J Roentgenol. 2016;207(2):450-457.

[147] Mainiero MB, Lourenco A, Mahoney MC, et al. ACR Appropriateness Criteria Breast Cancer Screening. J Am Coll Radiol. 2013;10(1):11-14.

[148] Lewis TC, Pizzitola VJ, Giurescu ME, et al. Contrast-enhanced Digital Mammography: A Single-Institution Experience of the First 208 Cases. Breast J. 2016 Oct 2.

[149] Jochelson MS, Dershaw DD, Sung JS, et al. Bilateral contrast-enhanced dual-energy digital mammography: feasibility and comparison with conventional digital mammography and MR imaging in women with known breast carcinoma. Radiology. 2013;266(3):743-751.

[150] Chou CP, Lewin JM, Chiang CL, et al. Clinical evaluation of contrast-enhanced digital mammography and contrast enhanced tomosynthesis--Comparison to contrast-enhanced breast MRI. Eur J Radiol. 2015;84(12): 2501-2508.

[151] Lewin JM, Isaacs PK, Vance V, Larke FJ. Dual-energy contrast-enhanced digital subtraction mammography: feasibility. Radiology. 2003;229(1):261-268.

[152] Jochelson MS, Pinker K, Dershaw DD, et al. Comparison of screening CEDM and MRI for women at increased risk for breast cancer: A pilot study. Eur J Radiol 2017; 97:37-43.

[153] Hunt CH, Hartman RP, Hesley GK. Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: retrospective review of 456,930 doses. AJR Am J Roentgenol. 2009;193(4):1124-1127.

[154] Pettersson A, Graff RE, Ursin G, et al. Mammographic density phenotypes and risk of breast cancer: a meta-analysis. J Natl Cancer Inst. 2014;106(5).

[155] Eng A, Gallant Z, Shepherd J, et al. Digital mammographic density and breast cancer risk: a case-control study of six alternative density assessment methods. Breast Cancer Res. 2014;16(5):439.

[156] Thermogram No Substitute for Mammogram. U.S Food & Drug Administration website. http://www.fda.gov/forconsumers/consumerupdates/ucm257499.htm Accessed September 17, 2018.