Advances in Breast Cancer Screening

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Learning Objectives:

Upon completion of this activity, participants will:

- Have increased knowledge regarding
  - the factors that affect breast density
  - the benefits of screening MRI in high-risk patients and those with dense breasts
- Have greater competence related to
  - identifying patients that may be indicated for breast cancer screening with MRI

CASE 1: PATIENT HISTORY AND PRESENTATION

Kate is a 35-year-old art teacher who is married and has a daughter in elementary school. She has well-controlled hypertension and no other major health issues. She comes in for her annual pelvic exam and Pap smear. Details of her work-up are included in Table 1.

Table 1. Kate's Clinical Work-Up

Demographics	• 35-year-old, female • Height: 5'3''; Weight: 153 lbs; BMI: 27.1
Personal Medical History	• No major surgeries • Well-controlled hypertension, no other health issues • Non-smoker, drinks alcohol approximately 2 times/week • No allergies; current medications include losartan (50 mg daily) and low-dose norethindrone/estradiol • First menses at age 12 • Breastfed her daughter for 1 year
Family History	• Mother diagnosed with breast cancer at age 50 • Father diagnosed with prostate cancer at age 61 • Maternal grandmother diagnosed with breast cancer at age 54, now deceased
Physical Exam	• Normal clinical breast exam; no lumps or palpable nodes • Normal pelvic exam • PS 0

BMI = body mass index; PS = performance status

Kate has a friend who was recently diagnosed with breast cancer and she is concerned about her risk.

What would you recommend?

- Screening mammography now
- Screening mammography starting at age 40
- Referral to a genetic counselor

Explanation: Kate should be referred to a genetic counselor or a high-risk clinic to discuss her risk for development of breast cancer and other malignancies and her need for genetic testing. Genetic counseling should be done prior to screening mammography to assess her risk.

Genetic Counseling in Patients at Risk for Breast Cancer

Greater understanding of the genes associated with a predisposition to cancer, coupled with increased availability of tests to identify these genetic variants, has improved the uptake of cancer genetic testing.[1] The decision to undergo genetic testing is influenced by many factors, including risk assessment and consideration for individual patient goals and preferences.[2] Genetic testing should only be considered when there is an established test with sufficient sensitivity and specificity to give a meaningful result and when that result is likely to influence subsequent risk management through increased screening and/or prophylactic approaches.

An important aspect of optimal breast cancer screening is identifying patients at higher risk who could benefit from further evaluation. Obstetricians and gynecologists (OB/GYNs), as well as primary care physicians (PCPs), should evaluate patients for breast cancer risk no later than age 30, to allow early identification and implementation of supplemental screening.[3] Clinicians need to carefully assess a patient's family and personal history to determine those at increased risk for development of breast cancer or other malignancies.[4] Patients with a personal or family history of cancer on either side of the family with features suggestive of hereditary cancer should be strongly considered for referral to genetic counseling.[1]

These features include:[1]

- Early age of onset (premenopausal)
- Bilateral breast cancers
- Multiple primary tumors (e.g. breast and ovarian)
- Breast cancers in multiple first-degree relatives
- Male breast cancers
- Ashkenazi Jewish heritage

Several guidelines are available to assist in patient selection for genetic testing, including recommendations from the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American College of Obstetricians and Gynecologists (ACOG), and the Society of Gynecologic Oncology (SGO).[2,5-7] Current NCCN recommendations regarding who should be tested for breast and ovarian cancer susceptibility genes are detailed in Table 2.[2]

Kate fits into this criteria based on the early breast cancer diagnosis for her mother (age 50) and diagnosis of breast cancer in her maternal grandmother at a relatively early age (age 54).

Table 2. NCCN Criteria for Hereditary Breast and Ovarian Cancer Testing[2]

Testing is Clinically Indicated For Individuals With a:
Blood relative with known pathogenic variant in a susceptibility gene

Personal history of cancer
• Breast cancer with ≥ 1 of the following:
  ○ Diagnosed at age ≤ 45 y
  ○ Diagnosed at age 46-50 y with:
  ▪ Unknown or limited family history
  ▪ A second breast cancer diagnosed at any age
  ▪ ≥ 1 close relative with breast, ovarian, pancreatic, or high-grade or intraductal prostate cancer
  ○ Diagnosed at age ≤ 60 y with TNBC
  ○ Diagnosed at any age with:
  ▪ Ashkenazi Jewish ancestry
  ▪ ≥ 1 close relative with breast cancer at age ≤ 50 y
  ▪ ≥ 1 close relative with ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age
  ▪ ≥ 3 breast cancers in patient and/or close relatives
  ○ Male breast cancer
• Epithelial ovarian cancer at any age
• Exocrine pancreatic cancer at any age
• Metastatic or intraductal prostate cancer at any age
• High-grade prostate cancer with:
  ○ Ashkenazi Jewish ancestry
  ○ ≥ 1 close relative with breast cancer at age ≤ 50 y
  ○ ≥ 1 close relative with ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age
  ○ ≥ 2 close relatives with breast or prostate cancer at any age
• A mutation identified on tumor genomic testing that has implications if present in the germline

Family history of cancer • First or second-degree relative meeting any of the criteria above • Individual with a probability >5% of a *BRCA1/2* pathogenic variant based on available probability models
Testing May Be Considered For Individuals With:
Bilateral breast cancer diagnosed at age 50 to 65 y
Ashkenazi Jewish ancestry
A 2.5% to 5% probability of a BRCA1/2 pathogenic variant based on available probability models

TNBC = triple-negative breast cancer

It is critical that patients undergo genetic counseling prior to testing in order to improve their understanding of the potential medical and psychological implications associated with finding a pathogenic variant.[2] A positive genetic test can have far-reaching effects on an individual and their family. Pre-test counseling focuses on addressing patient goals and concerns regarding risk assessment

and educating patients on the benefits and limitations. A detailed family history is constructed, as well as evaluation of the patient's medical and surgical history (e.g. reproductive history, hormone or oral contraceptive use, carcinogen exposure, prior breast biopsies). The type of genetic testing should also be discussed, weighing the pros and cons of each approach. While genetic testing historically focused on individual gene assessment, multi-gene testing through next-generation sequencing is increasing and allows simultaneous analysis of many potential genetic variants. While multi-gene testing can improve the probability of identifying existing hereditary cancer syndromes, it also increases the likelihood of finding variants of unknown clinical significance or those without clearly defined risk management approaches. Patient education regarding potential test results is important, including discussion of cancer surveillance options, available risk-reducing therapy, and prophylactic surgical approaches.

Kate has a consultation with a genetic counselor and decides to proceed with genetic testing using a multigene panel test. Her results show a BRCA2 mutation; no other pathogenic variants are found.

What is Kate's lifetime risk of developing breast cancer?

- Substantially higher than her risk for ovarian cancer
- Substantially lower than her risk for ovarian cancer
- Substantially higher than someone with a BRCA1 mutation
- Substantially lower than someone with a BRCA1 mutation

Explanation: The presence of a BRCA2 mutation increases Kate's risk of developing breast cancer by the age of 80 to approximately 70%, compared with a 17% risk for ovarian cancer. The risk for breast cancer is similar for patients with BRCA1 and BRCA2 mutations.

Interpreting a Positive *BRCA* Genetic Test

The results of genetic testing should be discussed with a genetic counselor to ensure patients understand any pathogenic variants found and the associated risk for specific cancers.[2] Recommendations should also be made regarding the need for increased surveillance and the potential implementation of risk-reducing therapy or prophylactic surgery. Given Kate's family history of breast cancer and the confirmed presence of a *BRCA2* mutation, she is at an increased risk for both breast and ovarian cancer, as well as other malignancies.

Both *BRCA1* and *BRCA2* are involved in DNA repair and regulation of cell-cycle checkpoints after DNA damage.[2] Mutations in these two genes has been associated with a significant increase in the risk for development of several types of cancer. The prevalence of mutations in *BRCA1* is estimated at 1 in 300, while mutated BRCA2 is found in approximately 1 in 800 individuals.[2,6] The probability of developing breast or ovarian cancer varies considerably within the patient population with *BRCA1/2* mutations, with a penetrance ranging from 41% to 90% for breast cancer and 8% to 62% for ovarian cancer.[2]

A prospective cohort study of over 9,800 unaffected *BRCA1/2* carriers showed a cumulative risk of breast cancer by the age of 80 of 72% for *BRCA1* and 69% for *BRCA2* mutation carriers (Table 3).[8] Risk of ovarian cancer by age 80 was 44% and 17% for *BRCA1* and *BRCA2* mutation carriers,

respectively. In *BRCA1* mutation carriers, the risk for breast cancer increased rapidly during early adulthood until the age of 40, then leveled off and was consistent until age 80. For *BRCA2* mutation carriers like Kate, the risk for breast cancer increased rapidly until age 50, then remained constant.

In addition, breast cancer risk increased significantly in *BRCA* carriers who had ≥ 2 first and second-degree relatives with breast cancer (*BRCA1*: HR 1.99; $P < .001$, *BRCA2*: HR 1.91; $P = .02$).

Table 3. Cumulative Risk for Cancer in *BRCA* Mutation Carriers

	Risk in General Population	Risk in *BRCA1*-Mutated[8]	Risk in *BRCA2*-Mutated[8]
Breast cancer	12.8% lifetime risk[9]	72% by age 80	69% by age 80
Contralateral breast cancer	6.5% to 7% within 15 y of diagnosis[10]	40% within 20 y of diagnosis	26% within 20 y of diagnosis
Ovarian cancer	1.3% lifetime risk[9]	44% by age 80	17% by age 80

Studies have also demonstrated increased risk for prostate cancer and pancreatic cancer in patients with *BRCA1/2* mutations.[11,12] These risks should be discussed to encourage increased awareness and early screening when appropriate.[2] The importance of informing other at-risk family members should be emphasized, including any siblings. Kate's daughter will also need to be informed once she is older that she has a 50% chance of also carrying the *BRCA2* genetic variant and should consider genetic counseling and testing.

Other Factors that Contribute to Breast Cancer Risk

Beyond the presence of *BRCA1/2* mutations and other cancer susceptibility genes, other factors can increase a woman's risk for development of breast cancer.[4] Numerous risk models are available and are largely based on age, race/ethnicity, reproductive history, family history of breast cancer, and breast density.[4,13] Even without genetic testing to identify hereditary breast cancer, patients with a substantial risk of breast cancer according to current models (≥ 20% lifetime risk or ≥ 1.7% 5-year risk for invasive cancer in women age ≥ 35 years) should be considered for early initiation of screening and supplemental screening modalities. This is also the case for patients with a prior history of lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS), or thoracic radiation therapy between the ages of 10 and 30 years.

Kate is now aware of her risk for breast and ovarian cancer, as well as other malignancies. You discuss screening recommendations with Kate, including a pelvic ultrasound to monitor her ovaries.

What method of breast cancer screening would you recommend?

- Baseline mammography
- Baseline mammography and ultrasound
- Baseline mammography and breast magnetic resonance imaging (MRI)
- Baseline mammography, followed by breast MRI 6 months later if mammogram is negative

Explanation: It is important to establish a baseline with both mammography and MRI in a patient at high risk for breast cancer. It would not be optimal to wait 6 months for the MRI, as complete imaging is needed up front to identify suspicious breast lesions.

Breast Cancer Screening Guidelines

The NCCN guidelines provide detailed recommendations for breast cancer screening in patients with a *BRCA* pathogenic variant.[2] Women should be encouraged to be familiar with the look, shape, and feel of their breasts and promptly report any changes. A clinical breast exam should be performed every 6 to 12 months, starting at the age of 25 or at the time the *BRCA* mutation is identified. Breast imaging is crucial to identify suspicious lesions and encourage early diagnosis. There are a number of breast imaging modalities currently available, including digital 2-D mammography, digital breast tomosynthesis (DBT or 3-D mammography), breast ultrasound, and breast MRI.[14] Each of these approaches has unique advantages and disadvantages and should be carefully considered for breast cancer screening.

Current NCCN guidelines recommend mammography and breast MRI with contrast for patients like Kate aged 30 to 75 years with a *BRCA* mutation.[2] Guidelines from the American Cancer Society (ACS) and the American College of Radiology (ACR) also recommend mammography and breast MRI for patients with *BRCA* mutations starting at age 30.[3,15] DBT can also be considered when screening patients with *BRCA* mutations based on availability and patient preferences.[2,3] Breast MRI should not be delayed 6 months, as there is an urgency to fully image both breasts in a 35-year-old patient with a *BRCA2* mutation and no prior breast cancer screening.

Neither mammography alone nor mammography with breast ultrasound are optimal, as these approaches may not provide sufficient data to identify any potential breast lesions. Ultrasound can, however, be useful for patients at high risk for breast cancer who cannot undergo breast MRI.[3] Younger patients (aged 25 to 29 years) should receive breast MRI with contrast, with consideration for mammography only in situations where MRI is unavailable or cannot be performed.[2,3]

Kate's mammogram and breast MRI are negative and she is not interested in risk-reducing mastectomy or salpingo-oophorectomy at this time. She begins prophylactic tamoxifen to lower her risk of breast cancer. You discuss current recommendations for her continued screening.

How often should Kate have a mammogram and breast MRI?

- Every 6 months for both
- Yearly for both
- Mammogram every 6 months and MRI yearly
- Mammogram yearly and MRI every 2 years

Explanation: Current guidelines recommend yearly mammography and breast MRI for patients with *BRCA* mutations. Once a baseline has been established, mammography and MRI could be alternated every 6 months to reduce the likelihood of an interval cancer between yearly screening visits.

How Often Should High-Risk Patients Be Screened?

Guidelines from the NCCN, ACS, and ACR recommend yearly screening with both mammography and breast MRI for patients with *BRCA1* or *BRCA2* mutations (Table 4).[2,3,15] Imaging every 6 months or biennially is not recommended. Once baseline imaging with mammography and MRI have been established, these tests can be alternated every 6 months to improve the likelihood of identifying interval cancers that could occur between annual screening visits.

Table 4. Screening Recommendations for Women With a *BRCA1* or *BRCA2* Gene Mutation

Source	Clinical Breast Exam	Mammogram	Breast MRI
NCCN[2]	**≥25 y**: every 6 to 12 months	**25 to 29 y**: only if breast MRI not available, every year **30 to 75 y**: every year	**25 to 29 y**: every year; if breast MRI not available, then mammogram **30 to 75 y**: every year
ACS[15]	Not recommended, breast awareness emphasized	Every year **starting at age 30** or age recommended by HCP	Every year **starting at age 30** or age recommended by HCP
ACR[3]	Not discussed in guidelines	Every year **starting at age 30**	Every year **starting at age 25 to 30**

HCP = healthcare provider

CASE 1 CONCLUSION

Kate is continuing to receive annual mammograms, breast MRIs, and clinical breast exams. At her last visit, she was doing well with no evidence of breast cancer.

CASE 2: PATIENT HISTORY AND PRESENTATION

Amanda is a 42-year-old yoga instructor with a husband and two children. She is active and healthy with no major medical issues. Following her first breast cancer screening exam with conventional mammography, she received a letter stating that her mammogram was normal and informing her that she had extremely dense breast tissue. The letter indicated that she should speak with her gynecologist regarding the effect of her breast density on breast cancer risk and optimal screening. She makes an appointment with her gynecologist for her annual exam and brings the letter to discuss her breast cancer risk. Details of her work-up are included in Table 5.

Table 5. Amanda's Clinical Work-Up

Demographics	• 42 years old, female • Height: 5'5''; Weight: 130 lbs; BMI: 21.6
Personal Medical History	• Major surgeries: C-section for second birth • No other health issues • Non-smoker; no alcohol • No allergies; current medications include medroxyprogesterone acetate contraceptive injection and a daily vitamin • First menses at age 11 • Did not breastfeed
Family History	• Paternal grandfather had colon cancer, now deceased • No family history of breast or ovarian cancer
Physical Exam	• Normal clinical breast exam; no lumps or palpable nodes • Normal pelvic exam • PS 0
Mammography	• BI-RADS category 1 • Breast composition category D (extremely dense)

BI-RADS® = Breast Imaging Reporting and Data System

Amanda asks why her breast density is important. What should you tell her regarding extremely dense breast tissue?

- It makes it difficult to find breast tumors with standard mammography, but does not increase her cancer risk
- It increases her breast cancer risk, but does not affect the ability of mammography to find breast tumors
- It increases her breast cancer risk and makes it difficult to find breast tumors with standard mammography

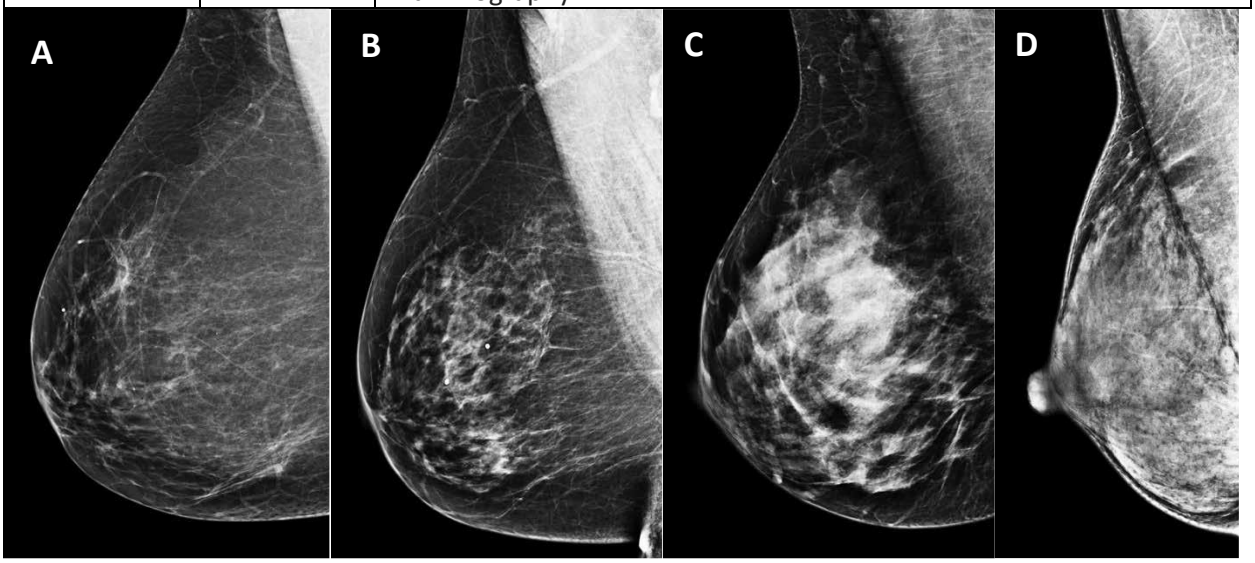
Explanation: Extreme breast density is associated with a 4-fold to 5-fold increase in the risk of developing breast cancer and can mask existing breast lesions and other abnormalities during standard mammography.

Implications of Breast Density

Breast density is based on evaluation of the composition of the breast, which varies widely among women. Fatty tissue is radiographically lucent and appears dark on a mammogram.[16] In contrast, epithelium and stroma are radiographically dense and appear light on a mammogram, which can mask breast cancers and prevent their detection. The ACR published BI-RADS® definitions specifically for breast density, outlined in Figure 1. For breasts that are almost entirely fatty or only have scattered areas of fibroglandular density (BI-RADS categories A and B, respectively), mammography remains highly sensitive for identification of suspicious areas. Heterogeneous areas of density or extreme density throughout the breast (categories C and D, respectively) lowers the sensitivity of standard 2-D mammography. A retrospective analysis of over 1.5 million mammograms showed 43% of women aged 40 to 74 years had mammographically dense breasts, defined as either heterogeneously dense or extremely dense.[17] This indicates over 27 million women in the US have dense breasts, reinforcing the importance of density considerations when screening for breast cancer.

Figure 1. BI-RADS® Breast Composition Categories[16]

BI-RADS® Category	Distribution in General Population	Description of Composition
A	10%	Breasts are almost entirely fatty
B	40%	There are scattered areas of fibroglandular density
C	40%	Breasts are heterogeneously dense, which may obscure small masses
D	10%	Breasts are extremely dense, which lowers the sensitivity of mammography



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

Breast density not only masks breast lesions during standard mammography, it also increases an individual's risk for development of breast cancer. Retrospective studies suggest greater density is associated with a greater risk, ranging from a 3-fold to 6-fold increase.[18] In a series of nested case-control studies, women with density in ≥ 75% of their mammographic image had an increased risk of breast cancer compared to those with density in < 10% (odds ratio [OR] 4.7; 95% CI: 3.0, 7.4).[19] In a comparison of women with ≥ 50% vs < 10% mammographic breast density, the OR was 3.39 (95% CI: 2.46, 4.68).[20] However, this increase in risk for breast cancer may not translate to an increased risk for breast cancer-related death. Analysis of over 9000 women from the US Breast Cancer Surveillance Consortium showed that high breast density was not related to the risk of death from breast cancer (HR 0.92; 95% CI: 0.71, 1.19) or death from all causes (HR 0.83; 95% CI: 0.68, 1.02).[21]

The association of breast density with both increased breast cancer risk and the masking effect during mammography lead to breast density inform laws in 38 states to date, requiring women with dense breasts to be notified of their breast density status following screening mammography.[22] Recently, the FDA proposed a new rule requiring letters be sent to every woman after breast cancer screening, informing her of her breast density and the associated risks. Of note, a large survey-based study showed that while notification of breast density increased the likelihood of women discussing breast density with their physician for those with education beyond high school, this was not the case for women with less education.[23] In addition, only 68% of women overall understood that breast density decreased the sensitivity of mammography and only 23% knew their dense breasts increased their risk of developing breast cancer. This reinforces the need for timely, effective patient education regarding the risks of breast density.

Amanda has always been very proactive regarding her health and well-being and asks if there are lifestyle changes that could lower her breast density.

What lifestyle change would you recommend to reduce her breast density?

- Diet with lower carbohydrate intake
- Cardiovascular exercise and weight training
- Reduced caffeine consumption
- None of these lifestyle changes will significantly lower her breast density

Explanation: Breast tissue typically becomes less dense as patients age and is associated with hormone exposure and BMI changes that generally accompany menopause. There are no healthy lifestyle changes that have definitively shown effectiveness in reducing breast density.

Factors That Affect Breast Density

Influence of Age, Hormones, and Cellular Makeup

Multiple studies have evaluated the factors that influence breast density and the mechanisms that link this characteristic to increased risk for breast cancer. Density is thought to be primarily related to hormone exposure and genetics.[18] Twin studies have shown heritability for breast density in identical vs fraternal twins, suggesting specific genes may be directly responsible for this phenotype.[24,25] Racial/ethnic differences may also influence breast density. A study of almost 9500 women screened with digital mammography showed that black women were significantly more likely to have dense breasts than white women, even after adjusting for age, BMI, age at menarche, menopausal status, family history, parity, and hormone replacement therapy.[26]

Increased exposure to endogenous and exogenous hormones also appears to increase breast density. As women age and go through menopause, hormone levels decrease and the breasts typically become more fatty in composition.[18,27] Women also tend to gain weight as they age and this increase in BMI is associated with reduced breast density. In a large retrospective analysis of data from over 1.5 million mammograms, breast density decreased with increasing BMI and increasing age, in younger women age 40 to 49 years making up 44% of those with dense breasts.[17] Endogenous hormone exposure related to parity and breast feeding may also influence breast density, although data has been conflicting regarding the exact relationship between these factors and density.[18,27-29] Hormone replacement therapy in post-menopausal women substantially increases breast density, reinforcing the role for exogenous hormone exposure.[18,30] Moreover, the higher levels of hormones often present in women with dense breasts could be a factor in the increased risk for breast cancer.

The cellular makeup of breast tissue may also contribute to the risk for breast cancer, as a dense breast contains a higher proportion of stromal, epithelial, and extracellular matrix components compared to fatty breasts.[18] More glandular cells present in dense breasts translates to more cells subject to possible cancer development. In addition, the complex interactions between stroma, epithelium, and extracellular matrix components leads to activation of cellular signaling pathways, creating increased opportunities for dysregulation of survival and proliferation-related pathways.

Influence of Lifestyle

With regard to most lifestyle factors, studies to date have shown conflicting results related to their contribution to breast density. For instance, while some studies suggest increased alcohol consumption could increase breast density, other studies have demonstrated no relationship between alcohol intake and breast density.[31,32] There is also uncertainty regarding the precise effect of diet and exercise on breast density. Data from the randomized Italian DAMA study suggest increased physical activity and plant-based diets with low saturated fats and low glycemic index may reduce breast density in postmenopausal women.[33] Other studies suggest physical activity may have the opposite effect or not influence density at all.[32,34] A recent study of 751 cancer-free premenopausal women showed no association between caffeine intake and mammographic breast density.[35]

Based on currently available data, there are no specific lifestyle adjustments that should be recommended to Amanda to reduce her breast density. She should be reassured that her breast density is most likely related to genetics and her age/premenopausal status and will likely decrease as she gets older.

Amanda wants to make sure she is receiving optimal breast cancer screening and asks which test is best to evaluate her dense breasts.

Which breast imaging technique is most likely to detect an abnormality in dense breast tissue?

- DBT
- Breast ultrasound
- Breast MRI
- DBT combined with ultrasound

Explanation: Studies in the United States and Europe have shown that breast MRI identifies approximately twice as many significant breast cancers compared with DBT or standard mammography. This imaging method is also superior to ultrasound in detecting breast abnormalities.

MRI Imaging of Dense Breasts

A number of studies have demonstrated superior sensitivity for breast MRI compared to standard mammography, DBT, or breast ultrasound. The randomized, multicenter DENSE trial in the Netherlands enrolled over 40,000 women with extremely dense breast tissue and normal screening mammography and invited one-fourth of the patients to undergo supplemental MRI.[36] The other three-fourths received mammography screening only. A total of 59% of patients in the MRI invitation group accepted the invitation. Supplemental MRI identified more cancers than mammography alone, with twice as many interval cancers found in the mammography control group (5.0 vs 2.5 per 1000 screenings; $P < .001$). Eighty percent of the interval breast cancers found in the MRI invitation group occurred in women who did not accept the invitation and did not receive supplemental MRI.

The cancer detection rate for those who underwent MRI was 16.5 per 1000 screenings, for a sensitivity of 95.2% and a positive predictive value of 17.4%.[36] MRI detected more invasive cancers than mammography alone and resulted in earlier diagnosis for patients with dense breasts. The false positive rate was 79.8 per 1000 screenings, for a specificity of 92%. A total of 300 women underwent breast biopsy after supplemental MRI, with 64 diagnosed with invasive breast cancer and 15 diagnosed with DCIS. Only 0.1% of patients who had a breast MRI experienced an adverse event during or immediately following screening, primarily consisting of vasovagal responses, contrast reactions, and intravenous line infiltration.

A breast cancer screening study in the US and Germany directly compared abbreviated breast MRI vs DBT in 1444 women aged 40 to 75 years with heterogeneously dense or extremely dense breasts.[37] The median age was 54 years and each woman received both screening modalities, with the results read independently to avoid any interpretation bias. Abbreviated MRI identified invasive breast cancers in all 17 women who had a confirmed cancer, for a detection rate of 11.8 per 1000 women.

In contrast, DBT found significantly fewer invasive cancers (7 of the 17 affected women), for a detection rate of 4.8 per 1000 women (difference of 7 cancers per 1000 screenings; *P* = .002). The sensitivity of abbreviated breast MRI for invasive cancers or DCIS was significantly higher than that of DBT (95.7% vs 39.1%; *P* = .001). However, the specificity for abbreviated MRI was significantly lower (86.7% vs 97.4%; *P* < .001). The rate of callback was 10.1% for DBT vs 0% for abbreviated breast MRI, although more patients undergoing MRI had short-term follow-up and the overall rate of additional imaging was similar between the two study groups (7.5% for MRI vs 10.1% for DBT). Both imaging modalities were well tolerated, with adverse events primarily grade 1 or lower and consisting of mild allergic reactions and anxiety.

A meta-analysis comparing supplemental screening techniques in women with dense breasts and negative screening mammograms showed a sensitivity ranging from 80% to 83% for breast ultrasound, compared to a sensitivity of 75% to 100% for breast MRI.[38] In addition, a study of over 2800 women with dense breasts showed that supplemental MRI identified breast cancers that were missed by both mammography and ultrasound.[39] While the sensitivity of combining mammography, ultrasound, and MRI was 100%, the specificity was 65% and the positive predictive value for biopsy was only 19%, suggesting a high false-negative rate.

While breast MRI is highly sensitive for detection of cancers in women with dense breasts, the rate of false positives raises questions regarding how to best utilize this approach as supplemental breast imaging. Unnecessary biopsies and patient anxiety regarding false positive screening results can negatively affect quality of life and should be carefully considered. Ongoing studies are investigating strategies to improve the specificity of breast MRI, including a recent study looking at the data from the DENSE trial.[40] This analysis showed that the use of computer-aided diagnosis for patients with extremely dense breasts and BI-RADS® 3 or 4 lesions by MRI could identify benign lesions, reducing the false-positive rate in this subset from 87.3% to 63.9% and reducing the benign biopsy rate without missing invasive cancers.

Breast cancer screening guidelines from the NCCN, ACS, and US Preventive Services Task Force (USPSTF) state that there is currently insufficient evidence to recommend for or against MRI screening for women with heterogeneously dense or extremely dense breasts on mammography.[2,15,41] The ACR recommends consideration of breast MRI for patients with dense breasts only if they have a personal history of breast cancer.[3] MRI should not be utilized alone, as this technique could miss microcalcifications and breast cancers that would otherwise be found with mammography. Additionally, breast MRI is not feasible in all patients, including women who are claustrophobic or cannot comfortably lie on their stomach. Some women have allergies to the contrast agent or are concerned about heavy metal exposure from the gadolinium-based contrast agents commonly used for breast MRI.[42,43] If this situation arises, alternative imaging modalities should be considered.[3]

Amanda wants to have additional breast imaging to screen for breast cancer, but she is concerned about heavy metal exposure associated with the contrast agent for MRI.

What type of breast imaging would you recommend?

- Digital 2D mammogram
- Breast ultrasound
- DBT
- DBT + ultrasound

Explanation: The combination of DBT and ultrasound is the best option to evaluate her extremely dense breasts. DBT and ultrasound have demonstrated superiority to mammography alone in detection of breast cancers in patients with dense breasts.

Other Imaging Modalities for Women with Dense Breasts

Several breast imaging techniques have demonstrated superiority to standard film mammography for the detection of breast cancer in women with dense breasts.

Digital Mammography vs Film Mammography

Analysis of over 42,000 women who underwent both digital and film mammography showed improved accuracy for digital mammography over film mammography in women under the age of 50 years, women with heterogeneously dense or extremely dense breast tissue, and pre- or perimenopausal women.[44] A US community practice cohort study also showed a higher sensitivity for digital mammography compared with film mammography in women aged 40 to 49 years (82.4% vs 75.6%; *P* = .071), those with extremely dense breasts (83.6% vs 68.1%; *P* = .051), and pre- or perimenopausal women (87.1% vs 81.7%; *P* = .057), although these comparisons were not statistically significant.[45]

DBT vs Digital Mammography

A retrospective analysis of over 180,000 breast cancer screenings compared the accuracy of digital mammography vs DBT in women aged 40 to 74 years.[46] Twenty-eight percent of patients were aged 40 to 49 years and 35.6% had dense breasts, similar to Amanda. DBT had a higher cancer detection rate compared with mammography (OR 1.41; *P* = .02) for all age groups and regardless of breast density. In patients aged 40 to 49 years with dense breasts, DBT identified 5.20 cancers per 1000 examinations, compared with 2.93 cancers per 1000 mammograms. Sensitivity was similar between the two modalities in the overall patient population (90.6% for DBT vs 91.5% for mammography), while DBT was associated with a significantly higher specificity (91.3% vs 88.9%, OR 1.46; *P* < .001). Overall, higher recall rates were associated with younger age and dense breasts, although the rate of recall was lower for those receiving DBT (OR 0.65; *P* < .001). The cancers found by DBT were generally smaller and node negative, while those found on mammography tended to be more aggressive. These data suggest a benefit for DBT, particularly in younger patients with dense breasts.

Addition of Ultrasound to Screening Mammography

A recent meta-analysis of 29 studies investigating the use of screening mammography supplemented with ultrasound in women with dense breasts demonstrated increased cancer detection with the addition of ultrasound.[47] A total of 29% of the total breast cancers detected were found by ultrasound only, translating into an additional 3.8 cases per 1000 women. Ultrasound approximately doubled the referral for further imaging in these studies. The ACRIN 6666 study directly compared mammography plus ultrasound vs mammography alone in over 2800 women with dense breasts.[48] Adding ultrasound resulted in diagnosis of 4.2 additional cancers per 1000 women compared to mammography alone, increasing the diagnostic accuracy from 78% to 91% (P = .003). However, the rate of benign breast biopsies increased substantially with the addition of ultrasound.

Breast Ultrasound vs DBT

The prospective ASTOUND-2 trial directly compared DBT to ultrasound in 5300 women with dense breasts and negative screening mammograms.[49] A total of 29 additional breast cancers were detected; 12 by both DBT and ultrasound, 3 by only DBT, and 13 by only ultrasound. While ultrasound detected more breast cancers (4.90 vs 2.83 per 1000 screenings), this imaging modality was associated with a significantly higher false-positive rate (1.0% vs 0.3% for DBT; P < .001). The contrasting strengths and weaknesses of these two breast imaging modalities supports the potential benefit of using them together to image patients with dense breasts.

Current Recommendations for Supplemental Screening of Dense Breasts

Current NCCN guidelines for breast cancer screening recommend counseling patients with dense breasts regarding the risk and benefits of supplemental screening.[4] Compared to standard mammography, full-field digital mammography or ultrasound is beneficial in women with dense breasts.[44,45,47,48] According to ACR guidelines, breast ultrasound can be considered for adjunctive screening in women with dense breasts.[3] However, ultrasound has been associated with increased call back rates and unnecessary breast biopsies.[47-49] DBT can improve cancer detection rates and decrease call back rates, but is associated with a higher dose of radiation compared to standard mammography.[4,46] Shared decision-making is crucial to ensure women are aware of their cancer risk and the options available for screening.

CASE 2 CONCLUSION

Amanda undergoes DBT and ultrasound, which does not find any areas of concern. She is doing well at last follow-up.

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