BREAST CANCER SCREENING
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Week 4

Educational Objectives:

1. Describe the major benefits and harms of screening mammography in women of different age groups
2. Compare and contrast available breast cancer screening modalities
3. Apply breast cancer screening guidelines in women of different age groups
4. Identify screening controversies in women with dense breasts

Background:

Mammography has been the mainstay of screening for breast cancer in women for more than 30 years and is credited with decreasing mortality from this disease. Current studies, however, point to the limitations of this technology and its potential harms. A particular concern is the harm of over-diagnosing cancers that may never become clinically significant, resulting in unnecessary treatment and surgery. In 2009, the U.S. Preventive Services Task Force (USPSTF) changed existing screening guidelines to acknowledge the limitations of mammography in decreasing mortality, especially in younger age women, and highlighted its benefits and harms in all age groups. Updated guidelines from the USPSTF (Siu, 2016), the American Cancer Society (ACS) (Oeffinger, 2015), and other policy-making groups are reviewed here and provide additional information to guide screening decisions in the following areas:

- The age to start and stop screening
- The optimal screening interval
- The efficacy of newer screening technologies, such as digital mammography and digital breast tomosynthesis (DBT)
- Screening in women with dense breasts

CASE ONE:

A 47-year-old woman with no family or personal history of breast cancer or current breast symptoms presents for routine care. She takes no medications. She has never had a mammogram and asks you when screening should start.
Questions:

1. **What are the potential benefits of screening mammography in this patient?**  
   The main benefit from screening mammography is a decrease in breast cancer mortality. Updated meta-analysis of eight randomized trials of screening mammography show a reduction in breast cancer deaths from mammography that is greatest in women age 60 to 69 years (33% reduction). The reduction in breast cancer deaths is much smaller for women ages 39 to 49 (8% reduction). (Corresponding numbers for women age 50 to 59 are 14%, and for women 74 years and older, 20%.) (Nelson, 2016).

2. **What are the potential harms?**  
   The most common harm from mammography is a false positive result that can lead to additional testing, including biopsy, and associated anxiety and psychological distress. These harms are greatest in younger age women who engage in annual mammography. For example, the accumulated 10-year probability of a false positive test in a woman who undergoes annual digital mammography starting at age 40 is estimated to be 61%; this decreases to 42% with biennial screening (Nelson, 2016). Biopsy rates decrease accordingly from 7% with annual screening to 5% with biennial screening (Nelson, 2016). Women at highest risk of a false positive result, and an unnecessary biopsy, include those who engage in annual screening and are either on menopausal estrogen/progesterone replacement therapy, and/or are younger with dense breasts. False negative results leading to false reassurance and a missed cancer diagnosis also occur, but rates are low.

   The most important harm from mammography, however, is the over-diagnosis of early-stage cancers that may never have become clinically significant, resulting in unnecessary treatment and surgery. Estimated rates of over-diagnosis increase with age and vary widely from 0 to 80% in non-randomized studies to 11% to 22% in three RCTs (Lannin, 2017; Nelson, 2016). The 22% rate implies that one in five women diagnosed with breast cancer over a 10-year period will be treated for a cancer that would never have become clinically important. The increasing evidence supporting this harm, along with the recognition that better breast cancer treatments may account for up to 50% of the decrease in breast cancer mortality previously attributed to mammography, have led some to question the value of screening mammography.

   Another potential harm from mammography is radiation–induced breast cancer due to accumulated exposure from long-term regular screening. The only data that assess this risk come from simulation models. Estimates of radiation-induced breast cancer in these models are estimated to be roughly 125 cases per 100,000 women age 40 to 74 years screened annually. These numbers become more concerning with the introduction of newer imaging technologies, such as breast tomosynthesis, that increase radiation exposure (Miglioretti, 2016). Women with
large breasts are at highest risk, because they often require extra views to adequately image the breast with higher attendant radiation doses.

3. **What are the similarities and differences between the USPSTF and ACS guidelines regarding screening mammography in women in your patient’s age group?**

   It is important to note that USPSTF and ACS guidelines apply only to women at average risk of developing breast cancer, generally defined as less than a 15% lifetime risk. For guideline purposes, the USPSTF and ACS defined average risk specifically as women who have none of the following risk factors: a personal history of breast cancer or high-risk breast lesion, a family cancer syndrome, chest radiation at a young age, or, by the USPSTF only, a first-degree relative with breast cancer. Weaker risk factors for breast cancer, such as race (white women have the highest overall incidence of breast cancer followed closely by African-American women; Asian-American, Hispanic and American-Indian/Alaskan Native women have the lowest rates), reproductive history (being nulliparous or first birth ≥ age 30), or biopsy with a benign breast lesion are not included in the USPSTF and ACS definitions but are included in the most widely used breast cancer risk assessment tool, the Gail Model, available at the National Cancer Institute website: http://www.cancer.gov/bcrisktool/.

Most major U.S. guideline-making groups (the USPSTF, American College of Physicians, American College of Obstetricians and Gynecologists, American Academy of Family Physicians) recommend that decisions about when to start screening in women age 40 to 49 should be individualized based on a discussion of a woman’s personal preference and values (see the section below on shared decision-making). If a woman age 40 to 49 decides to initiate screening, recommended screening intervals range from one-to-two years.

Recommendations on when to initiate screening in women age 40 to 49 are based on data that show that the benefits of screening in this age group are low compared to its potential harms. Breast cancer incidence is also lower in women age 40 to 49 than in older age groups, and more women would need to be screened over a decade to prevent one cancer death.

The ACS also endorses individual decision-making in women in their early 40s, but their guidelines differ from those of the USPSTF and the other groups in two important ways. The ACS recommends that women start screening at age 45 and have annual screening until the age of 55, at which time they can transition to biennial screening. They point out that the benefit of screening mammography increases gradually with age and that women in their later 40s may derive more benefit than younger women. Indeed, models suggest that most of the benefit of mammography in women in their 40s may be in those 45 years and older, whose balance of benefit and harms is more favorable and closer to that of women age 50 to 55 than to women age 40 to 45.
ACS interval screening guidelines are based on indirect evidence from mathematical models that suggest that cancers detected in younger-age women who undergo annual screening have more favorable prognostic characteristics than those detected by biennial screening. The difference may be related to menopausal status and estrogen levels, implying that women who have higher estrogen levels because they are pre-menopausal, or are post-menopausal and use hormone replacement therapy, may benefit more from annual screening (Miglioretti, 2015).

4. **How do you engage your patient, as well as other women in your patient panel, in shared clinical decision making?**
   Several tools are available to guide this process, but none currently are broadly applicable (Keating, 2018). All suggest a step-wise approach: initiate a discussion about screening and assess a woman’s risk of developing breast cancer (using the Gail or other risk assessment tools); if she is at low to average risk (less than a 15% lifetime risk), review with her a simple chart or figure that shows visually the benefits and harms of screening in women in her age group (as an example, see the Table in the Keating article, 2018); elicit her personal views on how she weighs the potential benefits and harms of screening and arrive with her at a screening decision. For example, some women may value a small, but important, reduction in breast cancer mortality over the risk of experiencing significant harm from screening.

5. **Your patient is not particularly concerned about developing breast cancer and wishes to minimize medical testing that is not “essential.” You obtain more history and determine that she is at low risk for breast cancer. What is a reasonable screening decision in this patient?**
   After discussing the benefits and risks of mammography at her age, your patient decides to engage in the least intensive screening strategy, biennial mammography starting at age 50. You support her decision knowing that it is within USPSTF guidelines.

   Of note, the Affordable Care Act mandates coverage for USPSTF category “A” or “B” recommendations (higher levels of evidence that show significant benefit) but not for category “C” recommendations (moderate certainty of a small net benefit). Since screening guidelines in women age 40 to 49 are a category C recommendation, there has been public concern about their insurance implications. Congress responded to these concerns by passing the 2016 Consolidated Appropriations Act requiring insurers to provide coverage for screening mammography in women age 40 to 49.

6. **Would you perform a clinical breast exam (CBE)?**
   The USPSTF and the ACS do not recommend CBE in women at any age without breast symptoms or abnormalities, based on no proven benefit. Neither recommends self-breast exam for the same reason.
CASE TWO:

A 63-year-old woman with no personal or family history of breast cancer presents to your office for routine health care. Since age 40, she has participated in routine annual screening mammography. An abnormal mammogram at age 50 led to a breast biopsy that showed normal fibro-glandular tissue. A follow-up targeted mammogram six months later was normal, and she returned to annual screening. She asks how often she should have breast cancer screening and with what test.

7. What are your screening recommendations? Upon what do you base your opinion?

This patient is in an age group that benefits the most from screening mammography (33% reduction in breast cancer mortality). All policy-making groups agree that she should participate in screening using digital mammography. Most would recommend decreasing her screening interval to every two years.

Screening interval:
The eight randomized trials that showed mortality benefit from mammography used screening intervals that ranged from 12 to 24 months; no trial, however, directly compared different intervals. The USPSTF recommends biennial rather than annual screening in average-risk women ages 50 to 74 years. This recommendation is based on mathematical models that show that screening every two years is almost as good as yearly screening in reducing breast cancer deaths and is associated with less harm (Mandelblatt, 2016). (Biennial screening retains 81% of the benefits of annual screening [range 67%-99%] and reduces false-positive results by almost half.) ACS guidelines differ from those of the USPSTF. The ACS recommends annual screening to age 55 years; women can then transition to biennial screening.

Screening technology:
Most randomized trial data that guide screening guidelines used plain film mammography as the screening tool. Digital mammography (DM) that converts X-rays into an electronic digital image has largely replaced plain film mammography. DM has approximately the same diagnostic test characteristics as plain film mammography in women of all ages (sensitivity for both modalities ranges from 77% to 95%; specificity ranges from 94% to 97%). Its advantages over plain film mammography are restricted to younger women and those with dense breasts and include lower recall rates (related to equivocal findings that require additional imaging), and higher sensitivity in detecting breast cancer (Pisano, 2005). The fair-price cost for screening DM is $281.00 (https://healthcarebluebook.com/).
Digital Breast Tomosynthesis (DBT), also called 3D mammography, has been introduced as a primary screening tool in average-risk women and in those with dense breasts and is expected to rapidly replace DM. (On MDsave, the cost of 3D mammography in CT ranges from $143 to $350. [https://www.mdsave.com/procedures/3d-mammogram-screening/d784fbc5](https://www.mdsave.com/procedures/3d-mammogram-screening/d784fbc5).) Recent data from a large cohort study that compared DBT with DM reported that DBT was associated with higher detection rates (OR 1.41; 95% CI 1.05-1.89) and lower recall rates (OR 0.64; 95% CI 0.57-0.72) (Conant, 2019). These favorable screening parameters were seen in all age groups and in women with dense breasts. Moreover, 25% of cancers detected by DBT in women age 40 to 49 were advanced. There are no data, however, with either screening modality on other important outcomes, such as rates of over-diagnosis and breast cancer mortality. An ongoing randomized clinical trial, the Tomosynthesis Mammographic Imaging Screening Trial (TMIST) ([https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/tmist](https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/tmist)), is comparing the efficacy of DBT with DM and will provide additional information on the biology and clinical outcomes of cancers detected by these modalities. The USPSTF concluded in 2016 that there is insufficient evidence to assess DBT as a primary screening tool. Some experts anticipate that results from TMIST could favorably change the balance of benefits and risks of screening in women age 40 to 49 and may lead to a reconsideration of guidelines in this age group (Bahl, 2019).

**CASE THREE:**

A 75-year-old woman with well-controlled hypertension and type 2 diabetes has a 35-year history of normal annual mammograms. She asks you if she still needs mammograms.

8. **How do you answer her question?**

The answer to her question is a qualified yes. The sensitivity and specificity of mammography increase with age as breast tissue is replaced with fat; however, few studies of the benefits of mammography on cancer mortality have included women over the age of 70. Therefore, there are insufficient data to guide screening decisions in older women. Based on data extrapolated from women ages 60 to 69, the USPSTF recommends biennial screening in healthy women ages 70 to 74. They do not make recommendations in women 75 years or older due to insufficient evidence. In contrast, the ACS recommends continued screening every two years if a woman is in general good health and has a life expectancy of at least 10 years. Although no randomized trials have been done in women over age 74, the ACS recommendations are based on a few models that suggest that women 75 years or older without significant comorbid conditions may still benefit from screening. Because of the uncertainty, this is an area where
you should encourage discussion and individual decision-making based on a woman’s preferences.

BONUS CASE:

A 43-year-old woman just completed her first mammogram. She receives a letter, copied to you, that includes the following statement, "Your mammogram demonstrates that you have dense breast tissue, which could hide small abnormalities. You might benefit from supplementary screening tests, which can include a breast ultrasound screening or a breast MRI examination, or both, depending on your individual risk factors. A report of your mammography results, which contains information about your breast density, has been sent to your physician's office and you should contact your physician if you have any questions or concerns about this report."

9. How do you respond to this information?

Dense breast tissue, defined by the breast imaging-reporting and data system (BI-RADS) as more than 50% heterogeneous or extremely dense tissue on conventional mammography (BI-RAD categories C and D respectively), is very common; 43% of women age 40 to 70 have dense breasts by this definition. The incidence is highest in younger women and decreases with age as breast tissue is replaced by fat. The finding of dense breasts is important, because it decreases the sensitivity and specificity of mammography and is also an independent risk factor for breast cancer. Younger women in the highest density quartile have an almost two-fold increased risk of breast cancer. Although women with dense breasts are at increased risk of breast cancer, breast cancer mortality rates are not higher in these women. Recent studies suggest that not all women with dense breasts have the same risk and that other risk factors, specifically increasing age and family history, may be more important than dense breasts alone (Trentham-Dietz, 2016).

Currently, 35 states, including Connecticut, mandate that women and their providers receive formal notification of heterogeneous or extremely dense breast tissue on mammography that may obscure other abnormalities. Most require a statement that women should consider additional screening, specifically ultrasound (US) or MRI. Findings from three studies suggest that, when used as adjunctive screening in women with an otherwise normal mammogram, ultrasound and MRI detect more cancers compared with digital mammography, but also increase recall rates (Melnikow, 2016). (Ultrasound detected 4.4 additional cases per 1,000 examinations; MRI detected 3.5 to 28.6 additional cases, depending on the study. Recall rates were 14% with US and up to 24% with MRI, compared with 7% to 17% with digital mammography.) The fair-price
cost for unilateral US is $162.00, and for bilateral MRI, $1,490.00 (https://healthcarebluebook.com/).

DBT is the newest screening technology. Observational data suggest that, compared with DM, DBT detects more breast cancers in women with dense breasts and decreases recall rates. In one multicenter study, invasive cancer detection rates per 1,000 screens increased from 2.9 to 4.2 (difference, 1.4 [95% CI 0.9-1.9], p < .001). Recall rates decreased from 127 to 109 (difference -18 [95% CI -21 to – 15] p < .001) (Rafferty, 2016). These favorable effects were greatest in women with heterogeneously dense breasts. Clinical trial findings are scant and too early, but no data currently demonstrate that any of the modalities described above decrease breast cancer mortality in women with dense breasts. The USPSTF concluded that, “current evidence on the use of adjunctive screening in women with increased breast density is not sufficient to recommend a specific screening strategy.” Some states are required by law to reimburse for ultrasound examinations in women with dense breasts; MRI is not yet included under this mandate.

Connecticut and other state mandates present a conundrum for physicians trained to practice evidence-based medicine. The practice at our institution, where DBT is the predominant screening modality, and where there is extensive experience with breast ultrasound, is to offer annual diagnostic DBT and ultrasound to women with dense breasts. Some experts, however, would not recommend additional testing in women at otherwise low risk for breast cancer (Smetana, 2018). Until more data are available to guide screening decisions, I suggest a prudent approach: obtain additional risk factor information, particularly family history; discuss with radiology the performance of screening modalities at your institution; and make individual screening decisions with women based on this information, their understanding of the benefits and harms of additional testing, and their preferences.
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<th>Screening Question</th>
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<td>Age to initiate screening</td>
<td>50 years, all women</td>
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<td>40 to 49 years, individual</td>
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<td>Screening interval</td>
<td>Biennially at any age</td>
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<td>Age to stop screening*</td>
<td>No recommendations, insufficient evidence</td>
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<td>DBT for primary screening</td>
<td>No recommendations, insufficient evidence</td>
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<tr>
<td>Dense breasts</td>
<td>No recommendations, insufficient evidence</td>
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|                                  | ACS                                                 |
| Age to initiate screening        | 45 years, all women                                 |
|                                  | 40 to 44 years, individual                          |
|                                  | decision-making                                    |
| Screening interval                | Annually to age 55, then biennially                 |
| Age to stop screening*            | Continue screening as long as in good health with life expectancy of at least 10 years |
| DBT for primary screening         | Not addressed                                       |
| Dense breasts                     | No recommendations                                  |

*Of note, updated 2019 guidelines from the American College of Physicians (ACP), which are based on a review of existing guidelines from other organizations and the evidence used to support those guidelines, follow closely the recommendations of the USPSTF, with the following exception. The ACP recommends stopping screening “in average-risk women aged 75 years or older or in women with a life expectancy of 10 years or less”. [https://www.acponline.org/acp-newsroom/acp-issues-guidance-statement-for-breast-cancer-screening-of-average-risk-women-with-no-symptoms](https://www.acponline.org/acp-newsroom/acp-issues-guidance-statement-for-breast-cancer-screening-of-average-risk-women-with-no-symptoms)
Primary References:


Additional References:

4. Lannin DR, Wang S. Are small breast cancers good because they are small or small because they are good? N Engl J Med. 2017;376:2286-91


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Knowledge Questions:

1. A 44-year-old woman presents for routine health care. She wishes to discuss breast cancer screening. In reviewing with her the benefits and risks of mammography, which of the following statements is true?

   a. Screening mammography has a major impact on saving lives from breast cancer in women age 40 to 49.
   b. The harms of screening are low in women age 40 to 49 and increase with age.
   c. False positive results leading to additional testing, including biopsies, are the most important harm of mammography.
   d. Overdiagnosis of breast cancers that would never become clinically significant is the most important harm of mammography.

2. Which of the following statements regarding dense breasts is true?

   a. The presence of dense breasts on mammography is the most important risk factor for developing breast cancer in women with this finding.
   b. DBT is more sensitive than digital mammography in detecting cancers in women with dense breasts and decreases recall rates.
   c. Used as an adjunctive test in women with dense breasts, ultrasound further increases cancer detection rates and decreases recall rates.
   d. Used as adjunctive tests in women with dense breasts, both ultrasound and MRI decrease mortality from breast cancer.

3. The USPSTF and the ACS screening guidelines agree or overlap for which of the following recommendations?

   a. Initiate screening in women at age 45
   b. Perform annual screening from ages 40 to 49 years
   c. Engage in shared decision-making in women less than 45 years
   d. Perform biennial screening in women ages 55 years and older
   e. Continue screening in women ages 75 years and older
   f. c and e
   g. c and d
Answers:

1. d Although false positive results are the most common harm of mammography, over diagnosis is the most important since it can result in unnecessary surgery and treatment. Choice “a” is an incorrect answer as is “b”. The reduction in breast cancer deaths with screening mammography is small in women age 40 to 49 (8% reduction) and lower than other age groups. Its benefits are also low compared to its potential harms, which are high in this age group.

2. b Compared with digital mammography, limited data suggest that DBT increases detection rates in women with dense breasts while also decreasing recall rates. Both US and MRI increase detection rates but at the expense of an increase in false positive findings, so choice “c” is false as is choice “d” as no data currently demonstrate that ultrasound or MRI decrease breast cancer mortality in women with dense breasts. Choice “a” is incorrect based on studies that suggest that not all women with dense breasts have the same risk and that other risk factors, specifically increasing age and family history, may be more important than dense breasts alone.

3. g Both the USPSTF and the ACS recommend shared decision-making in women ages 40 to 44; however, while the USPSTF recommends shared decision-making in women ages 40 to 49 years, the ACS restricts this recommendation to women ages 40 to 44 and recommends annual screening starting at age 45 years. Similarly, both the USPSTF and the ACS recommend biennial screening in women ages 55 years and older. While the USPSTF recommends biennial screening from age 50 to 74 years, the ACS recommends biennial screening starting at age 55 and continuing beyond age 74 if a woman is healthy and has a life-expectancy of at least 10 years. Choice “a” is an ACS recommendation only and choice “b” is not recommended by either group. Choice “c” is a qualified recommendation by the ACS. The USPSTF makes no recommendation in women ≥ age 75, due to insufficient evidence.