Clinic Perspective

Early Detection and Prevention of Breast Cancer - A reflection of the USPSTF 2009 recommendation

Shiao-Yu Lee, MD, FACOG

[N A J Med Sci. 2010;3(1): 009-013.]

As a practitioner focusing on women's health, I have seen many changes in the way that breast cancer detection has been addressed. One of the most notable events at the turn of the century was the new breast cancer screening recommendation. In 2009, after much analysis, the U.S. Preventive Services Task Force (USPSTF) changed its 2002 guideline.[1] Response from the public, other medical organizations and legislators was swift and at times, became harsh. This review outlines the rationale of the new recommendation, states the opposite opinions and describes possible ways to prevent breast cancer.

Breast Cancer Detection, Circa 2009

The USPSTF, a 16-doctor, federally funded panel, examined the evidence on the efficacy of 5 screening modalities in reducing mortality from breast cancer: film mammography, clinical breast examination, breast self-examination, digital mammography, and magnetic resonance imaging. To accomplish this update, the USPSTF commissioned 2 studies: 1) a targeted systematic evidence review of six selected questions relating to benefits and harms of screening[2] and 2) a decision analysis that used population modeling techniques to compare the expected health outcomes and resource requirements of starting and ending mammography screening at different ages and using annual versus biennial screening intervals.[3]

The USPSTF recommends against routine screening mammography in women aged 40 to 49 years. The decision to start screening mammography before the age of 50 years should be an individual one and take into account patient risk level and the patient's values regarding specific benefits and harms. (Grade C recommendation)

The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years. (Grade B recommendation)

Shiao-Yu Lee, MD, FACOG
Assistant Clinical Professor
Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
Beth Israel Deaconess Medical Center, Boston
Brigham and Women's Hospital, Boston
1180 Beacon Street, suite 7A, Brookline, MA 02446
Tel: 617-731-6670 Fax: 617-731-6690
Email: slee1@bidmc.harvard.edu

The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older. (I statement, insufficient evidence)

The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination. (I statement)

The USPSTF recommends against clinicians teaching women how to perform breast self-examination. (Grade D recommendation)

The USPSTF concludes that the current evidence is insufficient to assess additional benefits and harms of either digital mammography or magnetic resonance imaging instead of film mammography as screening modalities for breast cancer. (I statement)

The categories of USPSTF statements are as following:
A: High certainty that the net benefit is substantial.
B: High certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
C: Moderate or high certainty that the net benefit is small.
D: Moderate or high certainty that the net benefit is none or harm greater than benefits.
I: Insufficient evidence.

Start at 50:

The recommendation against routine mammography in the 40s created the strongest backlash. The panel emphasizes that the recommendation does not apply to women at high risk of breast cancer. The risk factors include a personal history of carcinoma in situ or invasive breast cancer, chest radiation before age of 30 years, family history of early breast cancer before age 50 years, two primary cancers or one breast and one ovarian cancer in same person, and male breast cancer. Nor does it apply to patients who value such screening. The benefit of mortality reduction for th age 40s and 50s groups is nearly identical (15% and 14%) for the age 40s and 50s groups. But larger numbers of mammograms are required when screening starts at age 40 years versus age 50 years. The number needed to invite for screening to extend one woman's life was 1904 for women aged 40 to 49 years and 1339 for women aged 50 to 59 years. About 19,000 mammograms over a decade in the 40s will save one life.

However, mammograms have its own complications such as false negatives and positives, over diagnosis and personal sufferings.

Mammograms rely on traditional X-ray to spot tiny calcium deposits, nodules, architectural distortion, or asymmetry that frequently signal the presence of cancer. The positive predictive values of specific findings are: Calcifications 12.7 percent, Architectural distortion 10.2 percent, Mass 9.7 percent, Developing asymmetry 7.4 percent, Focal asymmetry 3.7 percent, and Mass on one view only 3.6 percent.[4]

It is not perfect. In two out of ten women with cancer, the cancer will be missed or is invisible. The sensitivity of mammography screening is 77% to 95%. For a 1-year screening interval, the sensitivity of first mammography ranged from 71% to 96%. Sensitivity was significantly lower for women in their 40s than for older women. In the randomized trials, the specificity of a single mammographic examination was 94% to 97%.[5] This indicates that 3% to 6% of women who did not have cancer underwent further diagnostic evaluation.[6] With the recall rate at 8-12%, by the 9th mammogram, 43% will have been recalled. The number of women recalled per breast cancer detected ranged from 33 for radiologists in their 1st year of practice to 24 for radiologists with 3 years of experience to 19 for radiologists with 20 years of experience.[7] The additional visits, imaging and perhaps more biopsies cause physical harms and mental distress, pain and anxiety. Over diagnosis and unnecessary earlier treatment are important potential harms from screening breast cancer. For example, ductal carcinoma in situ (DCIS) does not always represent a precursor to invasive ductal cancer. Studies of women with untreated DCIS showed progression to invasive disease in half or fewer of the cases. Because DCIS is often found only by mammography, its incidence has increased steadily since the advent of widespread screening mammography. Because the likelihood that DCIS will progress to invasive cancer is unknown, surgical removal - with or without adjuvant treatment - may represent overdiagnosis and overtreatment. Lobular carcinoma in situ is not considered a true precursor lesion but connotes a higher risk for subsequent invasive lobular or ductal cancer in either breast. Lobular carcinoma in situ is often multifocal. Knowledge of what determines the rapidity with which invasive cancer can spread is limited, varied by tumor characteristics, host factors and hormonal triggers, etc. Mammography can not distinguish between slow and fast growing cancer. Because of these uncertainties, it is clear that lesion sensitivity alone is not a sufficient metric for assessing effectiveness of screening methods. Nevertheless, with our limited knowledge regarding the progression of DCIS, surgery and adjuvant therapy is the best we can do. Cochrane review reported a 30% rate of over diagnosis,[8] and probably over treatment.

Radiation itself may be a risk of cancer, including breast cancer. For all women, it is important to keep the radiation dose as low as possible without compromising image quality. The American College of Radiology recommends that the mean glandular dose exposure for a breast that is 4.2 cm thick should not exceed 0.3 rads (3 mGy) per image. The effective dose received from a routine screening mammogram is 0.7 mSv, equivalent to the dose received from natural background radiation over three months. There is yet no evidence that routine screening mammography in women, initiated at age 40, is associated with increased risk from radiation.[9]

Table 1. Average mammogram results for 1,000 women over their lifetimes, stratified by the beginning age of screening.

Age	Screening mammograms Over Life	Deaths Reduce	Mammograms per life saved	Unnecessary Biopsies per 1,000 women
40-69	27,583	8.3	3,323	158
45-69	22,623	8.0	2,828	126
50-69	17,759	7.3	2,433	95
55-69	13,003	6.1	2,131	67
60-69	8,406	4.6	1,827	42

Stanford University, modified from Annals of Internal Medicine, reported in Wall Street Journal, Dec 9, 2009

In 2009, the World Health Organization recommended mammography every 1 to 2 years for women aged 50 to 69 years. In 2012, the new UK screening guidelines will invite women for routine mammogram between 47 and 74 years. Most European program offer screening every 2-3 years from the ages of 50-70 years.

Examination Interval:

A decision analysis performed for the USPSTF from a National Cancer Institute sponsored study showed that most (at least 70% and as much as 99%) of the benefit of mammography is attained with every-other-year screening. Equally important, every-other-year screening reduces by

half the number of women who have a false-positive mammography test. For every thousand women between 50 to 69 years old, annual mammogram saves 132 life years. Biennial mammogram saves 99 life years, but avoids 8,815 mammograms, 430 false positives and 30 unnecessary biopsies (Stanford University). A longer interval may reduce

the benefit. Harms are a greater concern for younger women. Unnecessary treatments of cancer that would not become clinically apparent or life shortening is an increasing problem as women age.

Stop Mammography at Age 75 Years:

Breast cancer is a leading cause of death in older women. However, 3 facts suggest that benefits from screening would probably be smaller for this age group: 1. women may not survive long enough to benefit; 2. a higher percentage of breast cancer detected in this age group is the easier to treat estrogen receptor-positive type; 3, greater risk for dying of other conditions.

Screening between the ages of 50 and 69 years produced a projected 17% (range, 15% to 23%) reduction in mortality, whereas extending the age range produced only minor improvements (additional 3% reduction from starting at age 40 years and 7% from extending to age 79 years).

Many women 75 years or older are currently being screened. Overdiagnosis and unnecessary earlier treatment are important potential harms from screening women in this age group.

Clinical Breast Examination (CBE) and Self Breast Examination (SBE):

Clinical breast examination has a sensitivity of 40% to 69% and a specificity in the range of 88% to 96%.

Self breast examination has a sensitivity ranges from 12% to 41%, lower than that of clinical breast examination and mammography, and is age-dependent. Self exams have shown little benefit in reducing death rates from breast cancer. A large randomized control study of Shanghai textile factory women failed to reduce the breast cancer mortality, or to reduce the size of tumors at detection.

Digital Mammography and Magnetic Resonance Imaging (MRI):

Digital mammography allows the image to be stored in a different format. The difference is somewhat like a film photography to a digital photography. A study reported in 2005 New England Journal of Medicine showed that this benefit may apply only to women under 50 and those with dense breast tissue. It is not clear whether this additional detection would lead to reduced mortality from breast cancer.[1]

Most radiologists use the four categories described in the BI-RADS atlas, based on the proportion of glandular (radiodense) tissue with respect to fatty (radiolucent) tissue. The four main categories are: predominantly fatty (0 to 25 percent dense), scattered fibroglandular densities (25 to 50 percent dense), heterogeneously dense (51 to 75 percent dense), and dense (greater than 75 percent). MRI checks blood flow, requiring the injection of a dye into the blood stream. MRI has a sensitivity of 71% to 100% and a specificity of 81% to 97%.[10] MRI is therefore recommended for women with a genetic mutation, a strong family history of breast or ovarian cancer, or a history of radiation to the chest. American Cancer Society suggests that, for women at more than 20% lifetime risk for breast cancer, magnetic resonance imaging (MRI) and mammography should be performed every year. Women at 15% to 20% lifetime risk should consult with their physicians about the benefits and limitations of adding MRI screening to their annual mammogram. For women whose lifetime risk for breast cancer is less than 15%, annual MRI screening is not recommended. However, no study has been done on using MRI to screen women at average risk.

Following the USPSTF publication, Medscape conducted an informal survey on Nov 25, 2009, asking if physicians are going to *stop* performing routine mammography on women between 40 and 49 years of age. Out of 2,737 responders, 2072 (76%) said no, 470 (17%) said yes, and the rest had other answers.

Opposite Views:

Studies have shown that breast cancer mortality decreased by nearly 2% per year during the 1990s, which was largely attributed to the benefits of screening. For women younger than 50 years, the decline was more than 3% per year. Since mortality rates peaked in 1989, a woman's risk of dying of breast cancer has decreased by 29%.

Mammography screening is also associated with detection of smaller tumors. In the early 1980s, when only 13% of US women had regular mammography, average tumor size at detection was about 3 cm. This decreased to 2 cm by the late 1990s, when 60% of women had regular mammography.

In addition, 17% of breast cancer deaths in 2006 were among women who were diagnosed between the ages 40 and 49 years, according to data from the American Cancer Society. A meta-analysis of randomized controlled trials published in a monogram of the National Cancer Institute also showed benefits of screening mammography specifically in women aged 40 to 49 years.[11]

Researchers said there was a 95% chance that to avert one cancer death, somewhere between 900 and 6,000 women in their 40s would have to be screened, though somewhere around 1,900 was their best estimate. That range is so broad that it is possible far more lives are saved with annual screening among 40-year-old than the studies indicated.

Robert A. Smith, director of cancer screening for the American Cancer Society, says failing to include results from observational studies was a missed opportunity. He noted a 2003 study in Lancet with a longer follow-up period of twenty years. This showed that only 726 women in their 40s must be screened to save one life. In the 40-49 year age-group, deaths from breast cancer fell significantly in those who were screened (0.52 [0.4-0.67]; p<0.0001).[12] The 1,900 figure is based on a relatively brief follow-up period.

And saving women in their 40s saves more life-years than saving someone older.

Currently, American Cancer Society recommends annual mammography and clinical breast examination beginning at age 40 years. American College of Obstetricians and Gynecologists recommends mammograms every 1-2 years for women in their 40s; annual mammograms age 50 and older; breast exam by a doctor annually from age 19; breast self-exam can be recommended.

USPSTF Response:

The benefit of screening starting in the 40s is small, that the harms are small, and that the benefits are larger with an age to start screening of 50 compared with earlier, and the harms are smaller.

The harms of mammography become lower with increasing age because of biological changes in breast density that make it 'easier' for a mammogram to distinguish cancer from other normal breast structures.

There is no disagreement on the question of whether mammography has a benefit when done at ages 40 to 74. The question is about the absolute benefit as against the harms (false positives and too much unnecessary follow-up testing) to justify asking every woman under 50 to get a mammogram every year.

Cost was not a consideration.

Amid the criticism of less mammography in the 40s, eleven organizations affiliated with USPSTF, mainly in preventive medicine and primary care medicine, have written to Congress in support of the USPSTF position. Meanwhile, the legislators have attached amendments to the health care reform bill to guarantee women's right to mammogram according to the present standard.

In 2009, the World Health Organization recommended mammography every 1 to 2 years for women aged 50 to 69 years.

In 2012, the new UK screening guidelines will invite women for routine mammogram between 47 and 74 years. Most European program offer screening every 2-3 years from the ages of 50-70 years.

My Perspective:

Many women have inquired about this new guideline they learned in the media. Few know beyond the headline and the reasons for the change. It is upon the clinicians to explain the benefit and risk balance to their patients. For those who value annual mammogram, USPSTF agrees that they should continue to do so. For those who wish to start mammogram at 50, either on an annual or biennial interval, the new recommendation endorses that approach.

But age alone does not determine a woman's breast cancer risk. Using the Breast Cancer Assessment Tool (Gail model), that also incorporates race, age of menarche, age of first child birth, family and personal history, we may find that some younger women's breast cancer risk are higher than older women. They should start mammogram at an earlier age. Gail model is available at http://www.cancer.gov/bcrisktool/. Since quality of mammograms is paramount, women should only visit Mammography Quality Standards Act-certified facilities. A list is available at: http://www.fda.gov/cdrh/mammography/certified.html. (USPSTF)

The availability of prior studies facilitates the evaluation of subtle changes and may decrease the number of false positive results.

Physical examination of the breasts (CBE and SBE) can detect presymptomatic breast cancer. 40% of new cases are picked up by women or their physicians. I will continue the clinical examination as part of the well-visit evaluation. Suspicious nodules may require imaging studies but seldom unnecessary biopsies. Distinct nodule, unless its nature can be ascertained by imaging studies, needs biopsy. A negative mammogram should not deter further intervention if there is clinical suspicion for malignancy. The false negative rate of screening mammography has been reported between 10 to 30 percent.[13] We will be remiss if we do not do clinical breast examination and learn of a breast pathology not long after an office visit.

Ultrasound is the first line of imaging in a woman who is pregnant or less than 30 years old with focal breast symptoms or findings.

Many women like to do SBE. Other women are petrified at the thought of SBE. For the latter, there was never any reason to coerce them to perform the SBE. Because women find many breast cancers themselves, women should still be 'aware' of their breasts.

Risk Factors:

Age: Surveillance Epidemiology and End Result data estimates the lifetime risk for a woman to develop breast cancer at 12%.[14] The risk for breast cancer increases with age. The 10-year risk for breast cancer is 1 in 1,837 at age 20 years, 1 in 234 at age 30, 1 in 70 at age 40, 1 in 40 at age 50, 1 in 28 at age 60, and 1 in 26 at age 70.[15]

Race: The breast cancer incidence is 132.5 for every 100,000 Caucasian women, 118.3 for African women, and 89 for Asian or Hispanic/Latina women.[16]

There are other non-modifiable risk factors such as family history, personal history, first menstruation before age 12 years, first childbirth after 30 years, menopause after age 55 years, increased breast density and previous abnormal breast biopsy, etc. The Nurses' Health Study revealed that the incidence of breast cancer compared to nulliparous women was 20 percent lower if the first birth was at age 20, 10 percent lower for first birth at age 25, and 5 percent higher if the first birth was at age 35.[18]

There are also modifiable risk factors that form the basis of breast cancer prevention strategies.

Prevention:

Breastfeeding: for at least six months may decrease breast cancer risk. A large pooled analysis estimated that the relative risk of breast cancer was reduced by 4.3 percent for every 12 months of breastfeeding, in addition to a decrease of 7 percent for each birth.[19]

Regular physical exercise appears to provide modest protection against breast cancer. Obesity is associated with lower breast cancer rate before menopause, possibly due to less ovulation, and higher breast cancer rate after menopause, possibly due to adipose tissue production of estrogen.

Alcohol: limit to less than two drinks (24g of alcohol) a day.
Hormone therapy (HT): Women's Health Initiative reported that long-term use of HT is associated with higher risk. Short-term HT seems not to increase the risk of breast cancer significantly.[20] Unopposed estrogen exhibits slightly lower breast cancer risk.[21]

Chemo-prevention: Tamoxifen and Raloxifene are both breast estrogen antagonists. They reduce the estrogen receptor positive invasive breast cancer similarly, by about half. The former increases early stage endometrial cancer of the uterus. The latter does not reduce DCIS and is not indicated in pre-menopausal women. These agents both are linked to a slight increase in thrombosis, pulmonary embolism and stroke.[22]

The suggested candidates with evidence for a net benefit of tamoxifen chemoprevention, based on five-year risk of invasive breast cancer of Caucasian women, are: all women under the age of 50 who have a risk of between 1.5 and 7 percent, women ages 50 to 59 years who have a uterus and a risk of $\geq$ 6 percent, women ages 50 to 59 years without a uterus who have a risk of $\geq$ 3 percent, and women ages 60 to 69 years without a uterus who have a risk of $\geq$ 5.5 percent.[23]

Prophylactic surgery for high risk candidates such as inherited BRCA gene carriers.

References

1. US Preventive Services Task Force. Screening for Breast Cancer. Ann Intern Med. 2009;151(10):716-726.
2. Nelson HD, Tyne K, Naik A, et al; U.S. Preventive Services Task Force. Screening for Breast Cancer. Ann Intern Med. 2009;151(10):727-737.
3. Mandelblatt JS, Cronin KA, Bailey S, et al; Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network. Effects of Mammography Screening Under Different Screening Schedules. Ann Intern Med. 2009;151(10):738-747.
4. Venkatesan A, Chu P, Kerlikowske K, Sickles EA, Smith-Bindman R. Positive predictive value of specific mammographic findings according to reader and patient variables. Radiology. 2009;250(3):648-657.
5. Mushlin AI, Kouides RW, Shapiro DE. Estimating the accuracy of screening mammography: a meta-analysis. Am J Prev Med. 1998;14(2):143-153.
6. Humphrey LL, Helfand M, Chan BK, Woolf SH. Breast cancer screening: A summary of evidence for the U.S. preventive services task force. Ann Intern Med. 2002;137(5 Part 1):347-360.
7. Miglioretti DL, Gard CC, Carney PA, et al. When radiologists perform best: the learning curve in screening mammogram interpretation. Radiology. 2009;253(3):632-640.
8. Cochrane Database Syst. Rev. 2009.
9. Mettler FA, Upton AC, Kelsey CA, Ashby RN, Rosenberg RD, Linver MN. Benefits versus risks from mammography: a critical reassessment. Cancer. 1996;77(5):903-909.
10. Kriege M, Brekelmans CT, Boetes C, et al; Magnetic Resonance Imaging Screening Study Group. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med. 2004;351(5):427-37.
11. Hendrick RE, Smith RA, Rutledge JH 3rd, Smart CR. Benefit of screening mammography in women aged 40-49: a new meta-analysis of randomized controlled trials. J Natl Cancer Inst Monogr. 1997;(22):87-92.
12. Tabar L, et al. Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening. Lancet. 2003;361:1405-1410.
13. Ciatto S, Ambrogetti D, Risso G, et al. The role of arbitration of discordant reports at double reading of screening mammograms. J Med Screen. 2005;12(3):125-127.
14. National Cancer Institute, Surveillance Epidemiology and End Result. Sept 25, 2009.
15. American Cancer Society, 2002-2004.
16. American Cancer Society Breast Cancer Facts and Figures 2008. www.cancer.org/docroot/STT/STT_0.asp. January 1, 2010.
17. 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.
18. Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. Am J Epidemiol. 1994;139(8):819-835.
19. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding. Lancet. 2002;360(9328):187-195.
20. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA. 2003;289(24):3243-3253.
21. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004;291(14):1701-1712.
22. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. Lancet. 2003;361(9354):296-300.
23. Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst. 1999;91(21):1829-1846.