Compelling Evidence Leads to Change in USPSTF Recommendations on Breast Cancer Screening

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Study Overview

Objective. To review new evidence on the effect of screening for breast cancer with mammography, clinical breast examination, and breast self-examination on breast cancer mortality.

Design. Systematic review and meta-analysis.

Methods. A search for randomized controlled trials and systematic reviews was conducted of the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews (both through the end of 2008), MEDLINE (through 1 Dec 2008), and reference lists of relevant articles. Two reviewers independently assessed the articles to determine if inclusion criteria were met. The target population was women without a high risk for breast cancer or a preexisting breast cancer, and reviewers focused on groups for which recommendations on breast cancer screening have been uncertain, including women aged 40 to 49 years and women older than 70 years. Meta-analyses were conducted using the available trials. To assess harms of screening, meta-analyses, systematic reviews, and recently published articles not captured by these prior systematic reviews were gathered, in addition to primary data from the Breast Cancer Surveillance Consortium (BCSC), a nationally representative sample from 5 mammography registries and 2 affiliated sites. Harms considered were those related to radiation exposure, negative psychological impacts, pain, overdiagnosis, and other consequences from false-positive or false-negative test results.

Main outcome measures. Mortality from breast cancer and harms associated with screening for breast cancer.

Main results. For women aged 39 to 49 years, reviewers found only 1 new randomized controlled trial on mammography and breast cancer mortality to add to 7 prior trials included in a 2002 systematic review. One of the 7 trials previously reviewed had been updated. A meta-analysis of the 8 trials found a significant 15% reduction in breast cancer mortality among women invited for screening mammography (relative risk [RR], 0.85; 95% credible interval [CrI], 0.75 to 0.96). This mortality reduction translates to a number needed to invite [NNI] for screening mammography of 1904 women (95% CrI, 929 to 6378) to prevent 1 breast cancer death. This NNI compares with an NNI of 1339 and a RR of 0.86 for women aged 50 to 59 years (based on 6 trials), an NNI of 377 and RR of 0.68 for women aged 60 to 69 years (based on 2 trials), and a RR of 1.12 with an unknown NNI for women age 70 to 74 years (based on 1 trial). One trial provided information on the effect of the clinical breast exam on mortality; however, these results were inconclusive because the study was discontinued early. Two trials and 3 systematic reviews of the effect of the breast self-exam found no benefit for the prevention of mortality and an increase in biopsy rates. For the review of harms related to screening, multiple studies and primary data from 600,830

women aged 40 years and older included in the BCSC were evaluated for mammography while 2 studies were included for the clinical breast exam and 3 for the breast self-exam. The primary harms from mammography, especially among women between 40 and 49 years of age, were a high false-positive rate, high rates of additional testing and biopsies, overdiagnosis, and an increase in breast cancer–specific distress and an increase in the self-perception of breast cancer risk after false-positive results on mammography. The false-positive rate for mammography annually over 10 examinations was found to be as high as 56% for women aged 40 to 49 years. Data from the BCSC showed that for every case of invasive breast cancer detected by mammography, 556 women between 40 and 49 years undergo mammography, 47 have additional imaging, and 5 have biopsies compared with 200 women aged 60 to 69 years undergoing mammography, 14 having additional imaging, and 2 having biopsies to diagnose 1 case. Overdiagnosis, defined as diagnosis of breast cancer that was unlikely to cause clinically relevant issues during a woman's lifetime, was estimated as 1% to 10%. International studies of the clinical breast exam found high rates of benign biopsies for breast masses, though complete data are not yet available. Other international studies have shown statistically increased rates of benign biopsies in studies of the effectiveness of teaching the breast self-exam.

Conclusion. The mortality benefit from mammography for women aged 40 to 49 years is mild at best, and harms have been identified, including high false-positive rates, increased rate of follow-up imaging studies, increased biopsies for benign lesions, and some increased psychological impact from false-positive results. The mortality benefit in women aged 50 to 69 years is modest, although false-positive rates are lower; the benefit among women over 70 is unclear. No conclusive data are available for the evaluation of the clinical breast exam. Teaching the breast self-exam is not associated with a mortality benefit and is associated with increased biopsies for benign breast disease.

Commentary

This systematic review and meta-analysis commissioned by the U.S. Preventive Services Task Force (USPSTF) informed their decision to change their prior recommendations on breast cancer screening for women at average risk for breast cancer [1]. In 2002, the USPSTF guidelines recommended mammography every 1 to 2 years for women aged 40 years and older [2]. Their new guidelines recommend against regular mammography for women aged 40 to 49 years. While the USPSTF continues to recommend routine mammography for women aged 50 to 74 years, similar to the 2002 recommendation, they now call for mammography every 2 years rather than 1 to 2 years. Further expanding the prior 2002 guideline, they now recommend against teaching the breast self-exam. Evidence was inconclusive to recommend for or against the use of the clinical breast exam or mammography in women aged 75 years and older.

The recommendation against screening younger women with mammography was a C recommendation, which states that while the task force recommends against the service, "there may be considerations that support providing the service in an individual patient" despite the fact that "there is moderate or high certainty that the net benefit is small" [1]. The meta-analysis used to inform these new recommendations found a significant 15% reduction in breast cancer mortality in the mammographic screening group among women aged 40 to 49 years. However, none of the individual studies used for this meta-analysis found a significant reduction in mortality. Further, the absolute risk reduction in the screened group was only 3 fewer breast cancer deaths per 10,000 women, and the false-positive rate in this age-group was high, leading to unnecessary testing and biopsies. The largest of the studies included in the meta-analysis was the only new study added to the prior meta-analysis from 2002. The Age trial was a randomized controlled trial of annual mammography versus usual care, including over 160,000 women aged 39 to 41 years at baseline [3]. Women in the intervention were invited for annual mammography until age 48, and outcomes were followed for a mean of 10.7 years. 81% of women in the intervention group had a least 1 mammogram, with a mean of 4.5 screens per women. The study, conducted in 23 breast-screening units of the National Health Service (NHS) in the United Kingdom, found a nonsignificant 17% reduction in breast cancer mortality (absolute reduction of 0.4 deaths per 1000 women invited to screen) for women invited for annual screening compared with those in the usual care group. Since the study was conducted in the UK, the usual care group began screening at age 50 in concordance with prevalent NHS guidelines. Adjustment for not attending the first mammography screen found a 24% reduction in mortality for the intervention group, which was still not a significant reduction.

In addition to the systematic review and meta-analysis, the task force considered additional new data, especially on screening frequency, from a modeling study that accompanied the publication of the recommendations and the systematic review [4]. This study created 6 simulation models of the effects of mammography screening on mortality and potential harms related to screening. Mandelblatt et al found that 81% of the benefit of annual mammography screening is retained with biennial screening (range across models, 67%–99%), with a nearly 50% reduction in false-positive rates. Biennial screening starting at age 40 achieved an additional 3% absolute reduction in mortality (range, 1%–6%) above the 16.5% reduction in mortality from biennial

screening between 50 and 69 years of age (range, 15%–23%). The ultimate recommendation for screening women between ages 50 and 74 was a B recommendation such that "there is a high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial" [1].

The USPSTF recommendation against teaching the breast self-exam was graded as a D recommendation, the strongest possible recommendation against a test, which means that there was a "moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits" [1]. The evidence utilized for this recommendation came from countries that do not have routine access to mammography, thereby making these studies only marginally applicable to the U.S. population [5,6]. Yet, the evidence was clear. The studies were both large cluster-randomized controlled trials, including over 260,000 Chinese women for the first study and over 120,000 Russian women for the second. Both studies found no change in mortality between women taught the breast self-exam and the control group. The rate of benign breast biopsies was significantly higher in the intervention groups.

Limited evidence was available to evaluate the clinical breast exam, and the USPSTF responded with an inconclusive recommendation about its use. One study that could have provided useful information, conducted in the Philippines, was discontinued prior to the availability of outcome data. Two studies, in Egypt and India, will provide additional information about the clinical breast exam but are not yet available. Similar to studies on teaching the breast self-exam, these studies on the clinical breast exam are being conducted in countries without ready access to mammographic screening, limiting their applicability to the United States.

Publication of the recommendations has generated considerable controversy. Politicians, activist organizations, and even celebrities have weighed in, commonly to criticize the recommendation against the breast self-exam and mammography in younger women. Other organizations producing breast cancer screening guidelines have also responded. The American Cancer Society (ACS) released a critical public statement noting that the "USPSTF also says screening 1904 women ages 40 to 49 in order to save 1 life is not worthwhile. The American Cancer Society feels that in both cases, the lifesaving benefits of screening outweigh any potential harms" [7]. The ACS continues to recommend annual mammography and clinical breast exams annually after age 40. The American College of Physicians (ACP) had a more conservative recommendation to begin with, recommending in their 2007 guidelines that "clinicians should base screening mammography decisions on benefits and harms of screening, as well as on a woman's preferences and breast cancer risk profile" for women aged 40 to 49 years [8]. The leadership of the ACP released a statement criticizing the politicization of the reaction to the new USPSTF guidelines [9]. The American Academy of Family Physicians endorsed the 2002 USPSTF guideline but has not provided an official reaction to the new guideline [10]. The American College of Obstetricians and Gynecologists released a statement stating that they continue to recommend mammography every 1 to 2 years for women aged 40 to 49 years and annually after 50 years and that they continue to recommend that breast self-exam can be performed to detect palpable breast cancer [11].

Overall, the recommendations are based on the most rigorous scientific evidence available on the harms and benefits of breast cancer screening. The recommendations feel somewhat arbitrary regarding how low the number needed to invite to prevent 1 death from breast cancer must be to justify a recommendation for screening. In the case of mammography, they state that a NNI of 1904 (the NNI for women 40–49 years) is too high, yet a NNI of 1339 (the NNI for women 50–59 years) is adequate, especially when viewed in the context of the significantly higher rate of false-positives and unnecessary breast biopsies for younger women. Yet, cutoffs are necessary for guidelines to be informative and useful. Making inconclusive recommendations in the face of copious data would be inadequate in helping clinicians to make decisions with their patients. The USPSTF makes an important effort to provide neutral recommendations, balancing a complex array of risks and benefits for breast cancer screening. In making a C recommendation against mammographic screening for young women, they clearly state that mammographic screening may be appropriate for women in this age-group based on other considerations, including individual preference. The most arbitrary component of the recommendations is the decision to support screening for women between ages 70 and 74. They base this decision not on data available for this specific population but rather on the 2002 meta-analysis, which found studies showing a mortality benefit of screening for women aged 65 to 74 years [12]. Because of the very limited actual data from studies that restrict the population to women aged 70 to 74 years, it seems unclear why the task force chose to avoid an inconclusive recommendation for this age group.

Additional recommendations from the USPSTF dealt with digital mammography and breast MRI for screening, compared to traditional film mammography. The USPSTF concluded that insufficient evidence was available to take a stance on these new screening modalities.

Applications for Clinical Practice

New USPSTF recommendations on breast cancer screening are clear and neutral. Based on their findings, clinicians should initiate conversations with their younger patients aged 40 to 49 about the risks and benefits to mammographic screening

and should discuss with them these new USPSTF recommendations against screening for average-risk women. Recommendations remain intact for mammography between ages 50 and 74; however, the interval of screening has been altered to every 2 years from the prior recommendation of every 1 to 2 years. The USPSTF recommendations against teaching the breast self-exam and on increasing the interval of screening are compelling, and clinicians should consider changing their practice accordingly. Data for the benefit of mammography in patients older than 75 and for the usefulness of the clinical breast exam at any age are still inconclusive.

—Review by Jason P. Block, MD, MPH

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