Mammography for Breast Cancer Screening: Harm/Benefit Analysis

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Position

The scientific evidence from randomized trials on the impact of screening mammography in saving lives is conflicted, and the quality of the individual trials limited. The National Breast Cancer Coalition (NBCC) believes that the benefits of screening mammography in reducing mortality are modest and there are harms associated with screening. No individual woman can be assured that screening mammography will be effective for her, and from a public health perspective, the harms and public health costs of screening mammography may outweigh the modest benefits of the intervention. Mammography does not prevent or cure breast cancer, and has many limitations. Therefore, a woman's decision to undergo a screening mammogram must be made on an individual level, based on quality information about her specific risk factors, and her personal preferences. Women who have symptoms of breast cancer such as a lump, pain or nipple discharge should seek a diagnostic mammogram. Ultimately, resources must be devoted to finding effective preventions and treatments for breast cancer and tools that detect breast cancer truly early.

What is a Mammogram?

A mammogram is an x-ray of the breast that can reveal abnormalities (benign or malignant). The procedure involves compressing the breast between two plates and then applying a small dose of radiation to produce an x-ray image. Mammograms can be used for screening and for diagnosis.

- Screening Mammogram - is performed to attempt to detect breast cancer before symptoms occur. The goal of screening mammography programs is to decrease mortality from breast cancer.
- Diagnostic Mammogram - is performed to help detect breast cancer if a woman has symptoms, such as a lump that can be felt in her breast.

Screening Guidelines

In 2009, the U.S. Preventive Services Task Force (USPSTF) issued new mammography screening guidelines with a recommendation that women under age 50 do not need routine screening mammography[1], whereas its earlier stance was in accordance with American Cancer Society guidelines which recommended mammography every one to two years for all women age 40 and older.

[1]Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* Nov 17 2009;151(10):716-726, W-236.

The new guidelines state the following:

> "The USPSTF recommends against routine screening mammography in women aged 40 to 49 years. The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms. The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years."[1]

In making this new recommendation, the USPSTF was informed by a systematic review of published randomized clinical trials[2] (see descriptions below) and the Cancer Intervention and Surveillance Modeling Network (CISNET) modeling studies which showed only small gains but larger numbers of mammograms required when screening is started at age 40 years versus age 50 years.[3]

Research on Mammography Screening
Well-designed and conducted randomized trials are the most reliable way to assess the effectiveness of any medical intervention. In the case of screening for breast cancer, the goal is to decrease the death rate from the disease and, therefore, mortality is the most reliable outcome.

Mammography Screening Studies
The evidence of a mortality reduction from screening is conflicting and continues to be questioned by some scientists, policy makers and members of the public. While many still insist that mammography saves lives and criticize the 2009 USPSTF guidelines, the analyses to date of all randomized controlled trials for mammography have concluded only marginal benefit[2,4] and significant harms for breast cancer screening of healthy women.

There are eight published large, randomized, clinical trials that looked at the impact of mammography on breast cancer mortality. Four of the trials were conducted in Sweden, one was conducted in Canada, two were conducted in the United Kingdom, and one was conducted in the United States. The seven trials are known as:

- The New York trial or HIP trial (1963) - enrolled 60,495 women ages 40-64
- The Malmö trial (1976) - enrolled 42,283 women ages 45-69
- The Two-County trial (1977) - enrolled 133,065 women over age 40
- The Edinburgh trial (1978) - enrolled 44,268 women ages 45-64
- The Canadian trial (parts 1 and 2; 1980) - enrolled 89,835 women ages 40-59
- The Stockholm trial (1981) - enrolled 60,117 women ages 40-64
- The Göteborg trial (1982) - enrolled 49,924 women ages 39-59
- The Age trial (2006) – enrolled 160,921 women ages 39 - 41

[2] Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009;151:727-37.
[3]Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. Ann Intern Med. 2009;151: 738-47.
[4]Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev.* 2011;1:CD001877

These eight trials included few women over the age of 70 and very few women of color. None of the trials examined women younger than 39 years old, and only one trial -- the Age trial -- was specifically designed to look at the impact of mammography screening in women during their 40s.

Analyses of the Mammography Screening Studies

The studies listed above have been subject to meta-analyses and systematic reviews by the research community. NBCC believes that the most thorough evaluations to date have been conducted by researchers affiliated with the Cochrane Collaboration[4-5], by researchers for the U.S. Preventive Services Task Force (USPSTF) in 2009[2] and 2002[6], and by Dr. Armstrong, et al. in 2007 for the American College of Physicians.[7] These scientists reviewed and evaluated the evidence on benefits and harms of mammography screening and assessed the quality of the trials.

- *2011 Cochrane Review*[4]

  In an update of the 2006 review, Gøtzsche and Nielsen reassessed screening mammography's effect on mortality and morbidity. Eight eligible trials were identified, with one trial excluded due to bias, providing an analysis with 600,000 women.

  Consistent with the findings of the 2006 review, the three trials with adequate randomization did not show a significant reduction in breast cancer mortality at 13 years (RR= 0.90, 95% CI: 0.79-1.02). These trials did not find an effect of screening on cancer mortality, including breast cancer, after 10 years (RR=1.02, 95% CI: 0.95-1.10) or on all-cause mortality after 13 years (RR=0.99, 95% CI: 0.95 -1.03).

  According to the authors, "Screening is likely to reduce breast cancer mortality. As the effect was lowest in the adequately randomized trials, a reasonable estimate is a 15% reduction corresponding to an absolute risk reduction of 0.05%. Screening led to 30% overdiagnosis and overtreatment, or an absolute risk increase of 0.5%. It is thus not clear whether screening does more good than harm."[4]

- *2009 Review by Nelson et al.*[2]

  The 2009 review by Dr. Nelson and colleagues incorporated new data since the 2002 USPSTF recommendation on breast cancer screening and the Humphrey review. This review focuses on new studies and evidence gaps that were unresolved at the time of the 2002 USPSTF recommendation, which include the effectiveness of mammography screening in decreasing breast cancer mortality among average-risk women age 40 to 49 and 70 and older, and the harms associated with mammography.

[5]Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD001877. DOI: 10.1002/14651858.CD001877.pub2.

[6] Humphrey LL, Helfand M, Chan BK, et al. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med. 2002 Sep 3; 137(5 Part 1):347-60.

[7]Armstrong K, Moye E, Williams S, Berlin JA, Reynolds EE. Screening mammography in women 40 to 49 years of age: a systematic review for the American College of Physicians. Ann Intern Med 2007 Apr 3; 146(7): 516-26.

In addition to the 7 trials used in the 2002 meta-analysis, this review included the Age trial which evaluated the effect of mammography screening specifically in women age 40 to 49 years, as well as updated data from the previously reported Göteborg trial. In their review, Nelson et al. conclude that screening mammography reduced the relative risk of breast cancer mortality in screened women compared with unscreened women by 15% (RR= 0.85; 95% CI: 0.75-0.96) for women ages 39 to 49; data are lacking for ages ≥ 70. (Note that this conclusion is similar to the 15% reached by Gøtzsche and Nielsen in 2006.) The investigators conclude that "False positive results are common in all age groups and lead to additional imaging and biopsies. Women age 40 to 49 experience the highest rate of additional imaging while their biopsy rate is lower than older women."[2]

- *2006 Cochrane Review*[5]

  The 2006 Cochrane review by Gøtzsche and Nielsen incorporated new data since the 2002 Cochrane review and reassessed screening mammography's effect on mortality and morbidity. Using standard criteria, the researchers rated the quality of each trial's randomization methods as either adequate or suboptimal. The review included the Malmö, Canadian, New York, Two-County, Stockholm, and Göteborg trials. The Edinburgh trial was deemed biased and not included in the 2006 review.

  The Gøtzsche and Nielsen review concluded that only two of the trials were adequately randomized - the Malmö and Canadian trials - and these trials *did not* show that mammography screening decreased mortality from breast cancer. In these trials, the women who were offered mammography screening had the same breast cancer mortality (death rate) as the women who were not offered mammography screening. In contrast, the Göteborg, New York, Stockholm, and Two-County trials, which had suboptimal randomization according to the researchers, found that mammography *did* benefit women and reduced breast cancer mortality by about 25%, on average, after 13 years.

  The researchers then calculated an overall effect on mortality by taking into account the quality of all but the Edinburgh trial. They concluded that mammography decreases the risk of death from breast cancer by about 15% in relative terms, or 0.05% in absolute terms. This means that throughout a ten-year period, 2000 women need to get screened to prevent one death from breast cancer. Of note is the fact that the methodology to estimate the overall reduction of 15% was not disclosed.

  Finally, Gøtzsche and Nielsen found that mammography screening leads to more false-positives, more unnecessary surgeries, and more use of aggressive breast cancer treatments. They concluded that mammography screening increased the relative risk of overdiagnosis and overtreatment by 30%. This translates to an absolute risk increase of 0.5%; which means that throughout a ten-year period, for every 2000 women screened, ten healthy women will undergo unnecessary diagnostic procedures and treatment.

- *2002 Review by Humphrey, et al.*[6]

  Similar to the Cochrane reviews, Dr. Humphrey and colleagues produced a summary review of the most up to date results from the seven trials for the USPSTF. Their analysis deemed the Canadian trial as fair or better quality, the New York, Göteborg, Stockholm,

Malmö and Two-County trials as fair quality, and the Edinburgh trial as poor quality (the Edinburgh trial was not included in their analysis). In their review, they conclude that screening mammography significantly reduced the risk of breast cancer mortality in screened women compared with unscreened women by 16%. (Note that this conclusion is very similar to the 15% reached by Gøtzsche and Nielsen in 2006.)

For women between the ages of 40-49 years, they found a 15% relative reduction in risk associated with screening mammography. This means that throughout a fourteen-year period, 1792 women in their 40s need to get screened to prevent one death from breast cancer. However, this finding had only borderline statistical significance (RR=0.85 (CI: 0.73-0.99)).

The Humphrey review concluded that "the absolute benefit of mammography screening on mortality is very small, and that biases in the trials could either erase or create it." Furthermore, they state: "even in the best screening settings, most deaths from breast cancer are not currently prevented."

- *2006 Systematic Review by Armstrong, et al.*[7]
  This review for the American College of Physicians focused on screening mammography in women 40-49 years of age. It included publications from the original mammography trials as well as 117 other studies. The reviewers indicate that studies have estimated a 7% to 23% reduction in breast cancer mortality rates with screening mammography in women in this age group. They also point to rates of false-positive results as high as 20% to 56% after 10 mammograms with consequent increases in unnecessary procedures and breast cancer-related anxiety; as well as discomfort at the time of screening and exposure to low-dose radiation. They conclude that the evidence suggests that more women in the 40-49 years age range have risks that outweigh the benefits of screening mammography. Subsequently, the American College of Physicians issued detailed guidelines for screening mammography among younger women that encourage doctors to carefully assess an individual woman's risks for breast cancer, and to discuss with them the potential benefits and harms of screening mammography in order to make informed individual decisions about screening.[8]

Is the Benefit from Screening or Treatment?

A more recent analysis of the Norwegian screening program showed much less impact from mammography than expected.[9] Researchers compared the incidence-based rates of death from breast cancer in four groups: two groups of women who from 1996 through 2005 were living in counties with screening programs (screening group) or without screening programs (nonscreening group); and two historical-comparison groups that from 1986 through 1995 mirrored the current groups.

[8]Qaseem A, Snow V, Sherif K, et al. Screening mammography for women 40 to 49 years of age: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2007; 146: 511-15.
[9]Kalager M, Zelen M, Langmark F, Adami HO. Effect of Screening Mammography on Breast-Cancer Mortality in Norway. N Engl J Med 2010; 363:1203-1210

Participation in the Norwegian breast cancer screening program was associated with a 10% reduction in the rate of death from breast cancer among women 50 to 69 years of age. However, by looking at changes in mortality in groups outside of screening age ranges and looking at historical comparison groups, researchers estimated that at least two-thirds of the improvement in mortality rates was due to differences other than screening mammography, such as advances in breast cancer awareness and treatment.

A shift to personalized mammography screening guidelines?

The results of an analysis estimating the cost-effectiveness of mammography by age, breast density (the strongest risk factor for breast cancer), history of breast biopsy, family history of breast cancer, and screening interval were published recently in the *Annals of Internal Medicine*.[10] Based on the results, the authors recommend that all women have an initial screening at age 40 to assess breast density, and then develop a schedule for mammography based on individual risk factors and a woman's personal beliefs about the potential benefit and harms of screening. According to Dr. Steven R. Cummings, senior author of the study and senior researcher at the California Pacific Medical Center Research Institute, "Previous guidelines are trying to make one-size-fit-all, while we think of this as a personalized approach."

The study was based on a computer simulation model comparing the lifetime costs and health benefits for women who got mammograms every year, every two years, every three to four years or never. The outcome measures of the study were the costs per quality-adjusted life-year (QALY) gained and number of women screened over 10 years to prevent 1 death from breast cancer. Considering false-positive mammography results and the costs of detecting cancers that are ultimately nonprogressive and nonlethal, results showed that annual mammography was not cost-effective for any woman, regardless of age or breast density.

On the other hand, mammography every two years was beneficial for many groups of women with a wide range of individual risk factors. In women aged 40 to 49 years with high breast density and either a previous breast biopsy or a first-degree relative with breast cancer, biennial mammography was beneficial. But for women ages 50 to 79 with low breast density and no other risk factors, mammography every three to four years was cost-effective. The authors did not include genetics in their analysis, and therefore the results are not applicable to carriers of *BRCA1* or *BRCA2* mutations.

Limitations and Potential Harms of Mammography Screening

Screening mammography can produce inaccurate results, and as a result, many women receive false-positive or false-negative results. A false-positive result occurs when a mammogram shows a suspicious image, but there is actually no breast cancer. A false-negative result occurs when a woman's mammography results are normal, but she actually has breast cancer. In the United States, it has been estimated that a woman's cumulative risk for a false-positive result after ten

[10]Schouseboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing Mammography by Breast Density and Other Risk Factors for Breast Cancer: Analysis of Health Benefits and Cost-Effectiveness. Ann Intern Med 2011; 155(1): 10-20.

mammograms is almost 50% and the risk for undergoing an unnecessary biopsy is almost 20%.[11] Although biopsies are relatively simple surgeries, they can cause distress, scarring and disfigurement, and add to health care costs.

Another related potential harm of screening is overtreatment. There is a growing body of evidence that breast cancer is not one, but several diseases. Clinicians and researchers believe that some breast cancers will never spread to other parts of the body. Detecting and removing breast cancers that would never have spread to other parts of the body does not save any lives. This is an active area of research, but unfortunately, scientists have not figured out which breast cancers will eventually spread and which will not.

Conclusion

Evidence from studies of varied quality indicate that, overall, mammography screening has a modest effect on breast cancer mortality. When analyzed in absolute terms, the death rate is reduced by just 0.05%. Like with all medical interventions, there are harms associated with screening mammography such as misdiagnosis and overtreatment. Two comprehensive reviews of the evidence conclude that the overall impact in mortality is small and biases in the trials could either "erase or create it." Women should discuss with their doctors their own risk profile, the potential benefits, harms, and complexities of screening mammography, and make informed decisions about screening. Mammography may provide benefits for some women, but it may also harm others.

NBCC embraces a philosophy of evidence-based health care, and has long raised questions about the value of mammography screening and other interventions. Women need honest information regarding the value of all medical interventions. Public health resources need to be used with certainty to improve the public's health. The reality is that screening has not been effective. While the incidence of ductal carcinoma in situ and localized invasive breast cancer increased substantially as a result of screening programs, the incidence of regional or distant stage disease has not.

NBCC believes that in order to make true progress in breast cancer we need to better understand what causes this disease and how to prevent it, what puts individual women at risk beyond the known risk factors, how different types of breast cancer behave, which treatments are appropriate and effective for each type of breast cancer, and how to prevent metastasis. With that knowledge, and with improved screening methodologies, we could target screening to those who would truly benefit from it.

Women need to know the truth about mammography screening, including its potential benefits, harms, and limitations. As breast cancer activists, NBCC welcomes discussion of the effectiveness of all breast cancer interventions. We must recognize that we do not know how to detect breast cancer truly early, how to prevent or cure this disease, and focus our attention on getting these answers.

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[11]Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 1998 Apr 16; 338(16): 1089-96.