Breast Cancer Screening: Successes and Challenges

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One of the greatest successes in cancer control has been the dramatic decline in the death rate from breast cancer over the past 20 years in the United States. In 1989, the death rate for female breast cancer, corrected to the 2000 US standardized population, was 33.2 per 100,000. In 2007, the last year for which data are available, the death rate was 22.8 per 100,000. This is a 31.3% decrease, and American Cancer Society (ACS) epidemiologists estimate that this translates into more than 75,000 American women saved from a death from breast cancer. If the decrease continues at this same rate, the mortality reduction will approach 50% by 2015.

The decline in breast cancer mortality is due to a combination of factors, but most experts conclude that improvements in screening and treatment are the primary causes. Technologies have improved, cancers are being detected earlier, and oncologic specialists have become more proficient at providing care. The specific contribution of screening and treatment to the decline has been debated and is difficult and perhaps impossible to fully discern. Estimates from computer models suggest that mammography alone, as used over the past 2 decades, is responsible for 28% to 65% of the mortality reduction, depending on the assumptions used. However, several studies from Sweden and the Netherlands suggest that most of the breast cancer mortality reduction is due to screening, in keeping with the upper range of the modeling estimates.

Benefits of Mammography Screening

The first prospective randomized trial to show that mammography screening and clinical breast examination (CBE) could reduce the breast cancer mortality rate was the Health Insurance Plan (HIP) Study. It began in New York State in 1963 and randomized about 60,000 women ages 40 to 64 years to usual care or to annual mammography and CBE. After 10 years of follow-up, breast cancer-specific mortality was 29% lower in the mammography and CBE group. This trial, like all large, prospective, randomized screening studies, had some logistical challenges that weaken confidence in its result. The prestudy breast cancer status of the control group was not well defined. Mammogram quality, although state of the art at the time, was considerably inferior to today’s techniques.

The HIP study set the stage for the ACS’s nationwide Breast Cancer Detection Demonstration Project in the late 1970s, which reported, in comparison with cases from the National Cancer Institute’s Surveillance, Epidemiology, and End Results program, a substantial shift toward earlier disease stages and higher 8-year relative survival rates. With open discussion about breast cancer led by Happy Rockefeller and Betty Ford, who were both diagnosed with the disease, and the newly recognized capability for detecting breast cancer with imaging before it could be palpated, mammography was widely accepted.

Other large randomized controlled trials (RCTs) were launched in Europe and Canada. These studies validated a benefit attributable to mammography, showing mortality reductions of 15% to 32%. Some of the largest European studies with the highest benefits were criticized due to unique randomization...
schemes and the lack of an independent audit. The Canadian National Breast Screening Study-1 (NBSS-1) trial, which began in 1980, was the only trial of its time designed to focus specifically on women in their 40s, and it failed to show a screening benefit in this age group. However, the study was found to have a bias in randomization that most consider to be a fatal flaw. Rather than a true randomization, it seems many women at high risk for a breast cancer diagnosis were steered toward the screening arm. Even with these limitations, the overwhelming consensus based on the results of the RCTs was that screening with mammography saves lives.

It is known that RCTs underestimate the benefit of screening because of noncompliance in the study group and contamination of the control group. There will be women in the invited-to-screen group who die of breast cancer but were not screened and those in the control group who do not die of breast cancer because they were screened outside of the study. At best, only 70% of those invited will actually undergo screening.

After RCTs have confirmed a positive effect for screening, observational studies may represent a better method for determining the benefit to those women who were actually screened, rather than those who were invited and may or may not have been screened. Some of the best of these studies were performed in British Columbia and Sweden. In British Columbia during the period from 1988 through 2003, deaths among women between the ages of 40 and 79 years who were screened annually decreased by 40%. Among women ages 40 to 49 years, there was a 39% mortality reduction at first screening. In Sweden, after 20 years of follow-up, women screened had a 44% lower risk of death from breast cancer across all age groups than those not screened. A 48% decrease in breast cancer deaths was found in women ages 40 to 49 years. These studies were not considered in the 2009 US Preventive Services Task Force (USPSTF) report on breast cancer screening guidelines.

However, in a review commissioned in 2002 by the USPSTF, it was estimated that the RCTs collectively suggest that mammography screening decreases the risk of death by at least 20% in women ages 50 to 69 years and by 15% in women ages 40 to 49 years. Much has been made of the confusing 2009 recommendation of the USPSTF, but one should focus on this most important finding. Screening mammography saves lives among women ages 40 to 49 years, even though the benefit was underestimated by at least 2 times (20% vs 39%-48%).

### Harms of Screening

Although imaging technology and mammographic interpretation have improved over time, mammography is not perfect and will not benefit all women equally. Mammography is less sensitive in women with dense breast tissue than those with nondense tissue. There are false-positive (possible abnormalities that turn out not to be cancer or not even an abnormality) and false-negative (cancers that are present but go undetected on mammography) findings. In the United States, of 1000 women screened, 10% or 100 will be recalled for additional evaluation of a possible abnormality. About two-thirds of or 67 women in the recalled group will be found to have nothing of concern (false-positive finding), and approximately 18 will be asked to return in 6 months for follow-up of a probably benign lesion. The remaining 15 women will have a suspicious lesion and undergo biopsy, and 3 to 5 of the original 1000 women will be diagnosed with breast cancer. Those with a benign biopsy (10–12 women of 1000) will also be considered to have a false-positive result.

The harms of recall for additional imaging after screening and false-negative and false-positive results are more likely in younger women (Table 1).
The number of lives saved among younger women is smaller compared with older women, in part due to the lower incidence of breast cancer in those women ages 40 to 49 years (Table 2). However, tumors in younger women tend to be biologically more aggressive, and women in their 40s may receive the most benefit from annual screening due to the number of years of life saved. It has been estimated that mammography detects 75% of breast cancers in women ages 40 to 49 years and 90% of tumors among women in their 60s. More recently, it has been shown that digital mammography is more sensitive than film mammography for younger women and those with dense breast tissue.

**Overdiagnosis**

A concern generated by screening is “cancer over-diagnosis.” These are tumors that fulfill the histologic criteria for cancer but do not spread or cause harm within the patient’s lifetime. Overdiagnosis can lead to unnecessary testing and treatment and the related psychological and/or physical consequences. Some studies suggest that up to 35% of screen-detected breast cancers are overdiagnosis tumors, while others state that such tumors are only a small fraction of all breast cancers. Some cases of low-grade ductal carcinoma in situ (DCIS) may be examples of overdiagnosis. However, high-grade DCIS, especially that with casting calcifications, is a significant disease requiring treatment. Currently, it is not possible to determine prospectively which breast cancers will remain indolent if left untreated. Therefore, suspicious lesions that develop mammographically or clinically are assumed to be progressive and are treated appropriately. It is hoped that genomic research will eventually redefine malignancy such that histologically confirmed cancers without lethal potential may be distinguished from those genomically programmed to grow and spread.

Women should be informed of and understand the potential benefits and harms of breast cancer screening before they are screened. This may reduce anxiety, increase understanding, and improve long-term adherence to guidelines.

**Other Screening Modalities**

A number of additional screening technologies have been proposed, including magnetic resonance imaging (MRI), ultrasound, nuclear medicine techniques, and mammographic tomosynthesis. At present, none have gained widespread acceptance for general population screening, as there have been no studies that demonstrate a mortality reduction with the use of these tests alone. MRI and ultrasound have been used in conjunction with mammography for screening women at high risk of developing breast cancer. In this group, the addition of screening ultrasound has been shown to increase the detection of lymph node-negative breast cancer by 28%, but screening MRI improves the detection of early breast cancer by 56% in patients initially screened with mammography and ultrasound. While additional screening may be warranted in high-risk individuals, the improved detection comes with a greater cost and an increased rate of false-positive examinations.

The value of CBE has been questioned by some. A literature review led the USPSTF to conclude that the effectiveness of CBE in saving lives has not been proven in well-designed trials. The Centers for Disease Control’s National Breast and Cervical Cancer Early Detection Program showed that CBE found about 5% of cancers that were missed with mammography alone. The ACS continues to recommend CBE, particularly for women younger than age 40 years. The ACS also stresses breast awareness. Breast awareness is the concept that women should know how their breasts normally look and feel and seek...
assessments of any breast change promptly from their health care provider. The movement away from monthly breast self-examination recognizes that most breast masses are discovered while dressing or in the shower, even among those women who perform the intense monthly examination. The newer recommendation is more of a daily, quick, and less extensive assessment than the intense monthly evaluation.

Breast Cancer Screening and Its Challenges

Screening with mammography has the ability to reduce the number of women dying of breast cancer. Unfortunately, in the United States, the percentage of women aged 40 years and older who reported having a mammogram within the previous 2 years declined from 70% in 2000 to 66% in 2005. Women with only a high school education have much lower screening rates than those with a college education. Women without insurance coverage also are screened much less frequently than those with insurance. Despite considerable efforts by the ACS and other organizations to increase awareness, a substantial proportion of American women are not getting screened.

The dramatic declines in the breast cancer death rate have been noted principally among white women. The African American death rate in 1990 was 38 per 100,000, decreasing to 31.4 per 100,000 in 2007, a 17.4% decline in 17 years. A study of mammography screening in more than one million American women found that African American women were more likely to have inadequate mammographic screening compared with white women. A survey of women diagnosed with breast cancer in metropolitan Atlanta showed that African American women were more likely to have delays in treatment or even receive no therapy at all. Indeed, in the year 2000, more than 7% of African American women in metropolitan Atlanta who were diagnosed with clinically localized disease received no therapy in the year after diagnosis.

It is estimated that more than 75,000 breast cancer deaths have been averted over the last 20 years. With compliance to ACS guidelines and current mammography rates, an additional 65,000 lives could be saved over the next 10 years, and with greater access to mammography screening, even more lives could be saved. The ACS would like to see the mammography rate increase to 90% of all eligible women.

To further decrease the number of deaths from breast cancer, we need to reemphasize the ACS screening guidelines for average-risk women: begin screening at age 40 years and continue annually. We need to develop systems to increase the proportion of the population receiving high-quality screening, support programs to improve and standardize the quality of screening and treatment, and continue efforts to ensure all women receive high-quality treatment. We must continue to support basic science as well as clinical research and promote getting proven technologies, interventions, and therapies to all who need them.

Although there has been tremendous progress, and we should be proud of this accomplishment, we must not be satisfied. Women still die of this disease, and more must be done. We can save far more lives if we use the knowledge we have, provide access to those who need it, and develop new technologies that further reduce mortality with less harm.

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