COUNTERPOINTS

Current Controversies in Hematology and Oncology

Screening Mammography: Do the Benefits Always Outweigh the Harms?

"Mammography saved my life" is a common refrain from women who have been screened and treated for breast cancer. But even though screening mammography has a small effect on breast cancer mortality, it comes with risks. This month, Drs John Brodersen of the University of Copenhagen and Karsten Juhl Jørgensen of the Nordic Cochrane Centre weigh the harms against the benefits of screening mammography and conclude that it is reasonable not to screen. Dr Otis Brawley of the American Cancer Society weighs the same evidence and comes down in favor of screening, albeit with caveats.

The Balance Is Shifting Away From Screening

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The balance between benefit and harm is of great concern in breast cancer screening. As with all cancer screening, the target population is healthy people—which means that all participants will be at risk for physical and psychological harm, and the vast majority will not benefit. This being the case, cancer screening recommendations should be based on rigorously conducted randomized trials that quantify the benefits and the harms.

Even if we have firmly quantified the major benefits and harms, determining whether their balance favors screening is not straightforward. Natural science cannot tell us how many overdiagnoses in healthy women justify avoiding 1 death from breast cancer. This remains a value judgment, and the cutoff point will vary, even among well-informed, sensible individuals.

The fact that the decision to undergo breast cancer screening employs a value judgment is an important reason

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The Argument for Breast Cancer Screening

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The subject of breast cancer screening is complicated. True pros and cons exist, yet there is no way to explain this to the general population that is both quick and truly accurate. The sum of the scientific literature suggests that women who undergo regular, high-quality mammography and clinical breast examination have a reduced risk of dying from breast cancer. This is especially true of average-risk women aged 50 to 75 years, and likely extends to women aged 40 to 49 years, as well as to some healthy women older than 75 years. Although the clinical studies on which this statement is based are admittedly imperfect, I believe the weight of the evidence suggests that screening combined with high-quality treatment prevents deaths.

When discussing the benefits of breast cancer screening, it is appropriate to acknowledge that there are harms associated with screening. It is ironic, but the harms of screening are better proven than the benefits—even though many do not accept or acknowledge the existence of the harms. These harms include the inconvenience of work-ups for false-positive results, false-negative results, overdiagnosis, and radiation-induced cancer. One harm that is rarely mentioned is the fact that a proportion of US women with breast cancer, perhaps 20%, gets less than optimal care.

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The Balance Is Shifting Away From Screening (cont)

the debate about screening continues. Quantification of benefits and harms is complex, however. As stated by the European Network for Health Technology Assessment, "a balanced and meaningful presentation is difficult to reach."[1]

What the Evidence Says

Independent institutions have published 3 reviews on breast cancer screening over the past 5 years.[2-4] All of these reviews included the same randomized controlled trials (RCTs). Assuming that all the trials were equally reliable, the meta-analyses showed that the relative reduction in mortality from breast cancer among women aged 50 to 69 years was about 20% (relative risk [RR] for all included trials, 0.81; 95% CI, 0.74-0.87).[3] This means that about 2000 women had to be invited to screening for 10 years to prevent 1 death from breast cancer. The trials were not equally reliable, however. The trials with a high risk of bias due to suboptimal design showed a statistically significant mortality advantage with screening (RR, 0.75; 95% CI, 0.67-0.83), whereas trials with a low risk of bias did not (RR, 0.90; 95% CI, 0.79-1.02).[3] The quality issues were considerable. Some of the optimistic trials randomized clusters of participants rather than individual women and did not use blinded cause-of-death assessment, both of which could have substantially biased results in favor of screening.[3] Only the Canadian trial and the Age Trial from the United Kingdom were conducted in a setting where adjuvant therapy was available, which is important. The Canadian trial is arguably the most rigorously conducted of all the screening trials,[3] and it did not show any mortality benefit from screening.[3] The Age Trial is also modern and well-conducted, but showed a statistically nonsignificant mortality benefit from screening in younger women (RR, 0.83; 95% CI, 0.66-1.04).[3]

Adjuvant therapy is, by far, the major driver behind the decrease in breast cancer mortality rates that we see across the Western world. Across Europe, these declines have been almost twice as large in young women (<50 years) never invited to breast cancer screening compared with women in age groups that have been most commonly invited to screening (50-69 years).[5] Further, simple comparisons of breast cancer mortality rates between countries that introduced breast cancer screening early and those that introduced screening late demonstrate that they have enjoyed similarly large, persistent declines in breast cancer mortality, both in younger age groups and in those that could benefit from screening.[5] Declines in breast cancer mortality in North America are comparable to those in European countries, despite the more aggressive screening approach. Some observational studies have claimed to show large effects of breast cancer screening, but observational studies have an even greater risk of bias than estimates from RCTs. We must ask why we can see the impact of adjuvant therapy so clearly in simple population statistics, yet the impact of breast cancer screening—estimated in RCTs to have a similar effect—is practically invisible.

The incidence of advanced tumors is a surrogate endpoint that may be easier to detect than a mortality reduction. If screening mammography is to be effective, it must reduce the incidence of late-stage disease. As seen in the figure, the incidence rate of breast cancer with metastases to distant organs has been nearly constant in the United States. One could speculate that screening has precisely balanced out an underlying increase in incidence, but this seems unlikely considering the flatness of the graph. Several studies have found similar results, bolstering the case that screening mammography does not result in an absolute stage shift.[5,6] The most likely explanation is that fast-growing tumors with aggressive biology tend to "slip through the screen." This finding places into question any mortality benefit or potential for less-invasive treatment with the use of breast cancer screening.

> Although the benefits of breast cancer screening are increasingly being questioned, the harms are certain.

Many observational studies have shown a relative shift in tumor stage at diagnosis with screening—ie, a decrease in the percentage of late-stage tumors—but this is misleading. An increase in the number of small, inconsequential tumors will cause the percentage of late-stage tumors to decrease in comparison, even if screening has no benefit.[7]

The Certainty of Harm

Having a negative screening mammogram makes some women feel reassured. This has been confirmed in qualitative and quantitative studies.[8] However, if reassurance is an argument for cancer screening in its own right, one might ask why we do not screen for every known type of cancer, regardless of other benefits and despite the fact that the reassurance is false because of the substantial number of tumors detected between screening rounds.[8]

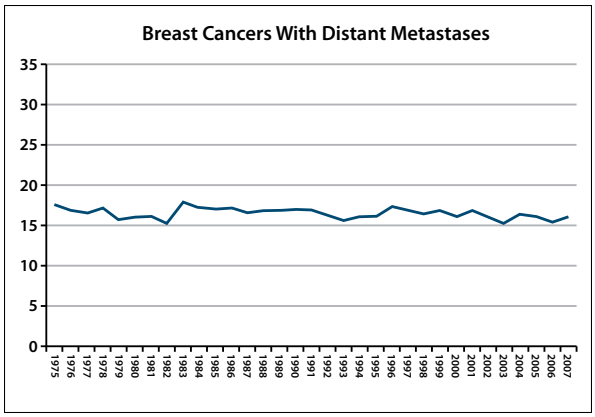

Figure. This graph depicts the rate of breast tumors with distant metastases, based on data from the Surveillance, Epidemiology, and End Results program of the National Cancer Institute (seer.cancer.gov). The effect of breast cancer screening appears to be flatlining. Although screening may have caused a small decline in cancers with regional metastases, this decline is insignificant compared with the massive increases in localized and in situ cases.[12,13]

Although the benefits of breast cancer screening in a modern setting are increasingly being questioned, the harms are certain. The risk of having a false-positive screening mammogram varies substantially among countries. In the United States, at least half of women attending 10 rounds of screening will experience a false-positive result.[9] In Europe and Australia, the frequency is between 1 in 5 and 1 in 3 after 10 screening rounds, reflecting the uncertainty surrounding mammogram interpretation.[9] Studies consistently show that false-positive results have negative psychological consequences, and a survey that used a condition-specific questionnaire with high content validity and adequate psychometric properties revealed that even 3 years after a false-positive finding, women reported substantial negative psychosocial consequences.[9] Furthermore, the many false-positive results might lead to increased use of health care resources that would better be applied to those who are ill.[10]

Absolute numbers were used to summarize the consequences of breast cancer screening in the Independent UK Panel on Breast Screening report by Marmot and colleagues, which is an informative approach when balancing benefits against harms.[4] Based on the summary results taken from the Cochrane review of all randomized trials, irrespective of quality, the panel estimated that 1400 women avoid a breast cancer death each year in the United Kingdom because of screening, and that 4000 healthy women receive an unnecessary breast cancer diagnosis and treatment.[4] This is likely optimistic in today's setting, which features both adjuvant therapy and more-sensitive mammograms that could increase overdiagnosis. The report clearly emphasized that both estimates relate a sense of precision that is unjustified. The remaining harms are more easily measurable and are much more frequent in a North American setting. Over a 1-year period in the United Kingdom, 65,094 women received a false-positive result. Of these, 19,467 healthy women received a benign core biopsy and 1539 received a benign open surgical biopsy.[4] The Marmot report was important in terms of increasing the recognition of overdiagnosis as a harm of breast cancer screening. The United Kingdom has had organized screening for 25 years, and the panel found that the balance was favorable and that breast cancer screening should continue. In contrast, Switzerland—which does not have a national organized screening program—found that the "desirable effect is offset by the undesirable effects" and that the cost effectiveness ratio is "very unfavourable" based on the same evidence.[11] Our value judgments are clearly influenced by more than the evidence.

Most countries have embraced new evidence about overdiagnosis that has fundamentally changed the balance between benefit and harm, making breast cancer screening much less appealing than it once seemed. Authorities and bodies that have favored routine screening mammography in the past need to find the courage to reassess their previous positions on breast cancer screening with an open mind.

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The Argument for Breast Cancer Screening (cont)

Despite this, I argue that the totality of the data suggests that the benefits of breast cancer screening in most age groups outweigh the harms on a population basis. Some individuals will be harmed by screening, but more will benefit in that their lives will be saved from a breast cancer death.

I do worry that many medical professionals and many members of the general public believe screening is more effective than it truly is. This is not to say, however, that screening is ineffective and should not be used.

The Recommendations of Professional Organizations

A number of professional organizations have commissioned groups of experts to review the literature, and they have come to conclusions similar to mine.

The American Cancer Society and most other medical groups recommend that average risk women undergo clinical breast examination and screening mammograms annually beginning at age 40 years.[1] Most organizations also say that women should be informed of the benefits, limitations, and harms associated with breast cancer screening. Mammography will not detect all breast cancers, and some breast cancers detected with mammography will still have a poor prognosis.

The United States Preventive Services Task Force (USPSTF), the American College of Physicians, and the Canadian Task Force on the Periodic Health Examination recommend routine screening beginning at age 50 years.[2] An advisory committee on cancer prevention in the European Union recommends that women between the ages of 50 and 69 years enroll in an organized program of screening mammography. These latter groups recommend limited screening of women aged 40 to 49 years, taking into account individual risks and concerns.

The Scientific Data

These recommendations are based on the findings of a group of long-term, prospective, randomized, screening trials reported over the past 50 years (see the eTable at www.hematologyandoncology.net). These trials are imperfect. Some trials used suboptimal randomization methods, others reported varying numbers of participants over the years, and still others had substantial contamination (drop-ins). Perhaps more importantly, most trials were started and concluded before the widespread use of more advanced mammographic technology, the modern era of adjuvant therapy, and the advent of targeted therapy. Although each trial has flaws, each one has added to our knowledge. One must carefully assess each study in an attempt to ameliorate its biases.

A well-designed, well-run, prospective, randomized clinical trial is the gold standard to determine screening effectiveness, but observational and modeling studies can provide important, complementary information. A systematic review of the data sponsored by the very conservative and orthodox USPSTF concluded that regular mammography reduces breast cancer mortality in women aged 40 to 69 years. The relative risk reduction was estimated to be about 15% for women in their 40s, and as high as 35% for women in their 60s.[2,3]

Epidemiologic data also suggest some benefit to screening. Although screening correlates with a dramatic rise in breast cancer incidence, it also correlates with a dramatic decrease in breast cancer death rates of approximately 30% to 40%. On the other hand, incidence-by-stage data show a dramatic increase in the proportion of early-stage cancers without a concomitant decrease in the incidence of regional and metastatic cancers. These findings raise questions regarding the extent to which early diagnosis is responsible for declining breast cancer mortality rates. The data suggest that improvements in treatment during the same period play a substantial role in the mortality decline. Indeed, the National Cancer Institute (NCI)-sponsored Cancer Intervention and Surveillance Modeling Network has estimated that two-thirds of the observed breast cancer mortality reduction is attributable to modern therapy, rather than to screening.

> The benefits of breast cancer screening in most age groups outweigh the harms on a population basis.

The Harms of Screening

The proven harms and disadvantages of screening mammography include false-negative findings, false-positive findings, overdiagnosis, and radiation-induced cancer.

False-negative results, which are more common in

younger women, delay diagnosis and provide false reassurance. Their existence provides evidence that mammography is an imperfect test, and that we need a better test.

False-positive results lead to substantial inconvenience and anxiety, as well as unnecessary invasive biopsies and their related complications. The risk of a false-positive result on screening mammography is greater among women in their 40s than among older women. In the United States, about 10% of all women screened for breast cancer are called back for additional testing and less than half of them will be diagnosed with breast cancer. Some women grow so frustrated by the false positives of mammography when they are in their 40s that they drop out of screening in their 50s and 60s, when it is more effective.

Demographic data also provide evidence of overdiagnosis; that is, the finding of cancers that have no clinical significance to the patient. These patients get unnecessary cancer treatment. In the United States, there has been a discrepancy between the magnitude of the increase of early disease and the decrease of late-stage cancer and cancer mortality. This suggests that a proportion of invasive breast cancers diagnosed by screening represents overdiagnosis. NCI Surveillance, Epidemiology, and End Results data show that from 1976 to 2008, the incidence of early-stage breast cancer for American women aged 40 years and older increased from 112 per 100,000 to 234 per 100,000—a rise of 122 cases per 100,000. By contrast, late-stage cancers decreased from 102 per 100,000 to 94 per 100,000, an absolute decrease of just 8 cases per 100,000.

Most experts estimate that 11% to 19% of breast cancers diagnosed by screening represent overdiagnosis, and some believe that up to one-third of all localized breast cancers fall into this category. It is unfortunate that we do not have a test to show with certainty that a tumor represents overdiagnosis.

A typical screening mammogram provides approximately 4 mSv of radiation to the breast and 0.4 mSv to the body.[4] There is a real concern that radiation causes a small number of breast cancers, especially among women with certain mutations related to DNA repair such as mutations of *BRCA1* or *BRCA2*.

The True Benefit of Screening

It is my contention that a combination of high-quality screening and treatment leads to a decline in breast cancer death rates. Some women will be harmed, but far more women will benefit. I estimate that the decrease in relative risk of breast cancer mortality is 15% among women aged 40 to 49 years, and as high as 35% among women aged 60 to 69 years.

I worry that many do not understand that a decrease of 35% in relative risk among women in their 60s means that 65% of women destined to die of breast cancer will still die of breast cancer, even with good screening and treatment. A 15% decrease in death rate among women aged 40 to 49 years translates into a small number of lives saved, given the fact that breast cancer is not common among women aged 40 to 49 years.

There is increasing interest in creating breast cancer risk profiles, especially among younger women. It might be possible to identify women who are at greatest risk of breast cancer, and refocus screening efforts on those most likely to benefit. This might be a way of reducing the inconveniences and harms of screening.[5]

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"Counterpoints" is a section in *Clinical Advances in Hematology & Oncology* in which we address clinical controversies and other questions of importance to oncologists and hematologists. We feature between 2 and 8 panelists for each question.

What topics would you like to see addressed in future issues? Please send your ideas to editor@clinicaladvances.com.

Supporting Online Material for "The Argument for Breast Cancer Screening"

This eTable accompanies an opinion piece by Otis W. Brawley, MD—part of "Screening Mammography: Do the Benefits Always Outweigh the Harms?"—in the June 2014 issue of *Clinical Advances in Hematology & Oncology*.

eTable. Randomized, Controlled, Breast Cancer Screening Trials

Study	Sample Size	Intervention	Follow-up	Finding
Health Insurance Plan,[1,2] 1963 (United States)	60,565-60,857	MMG and CBE for 3 y	18 y	RR, 0.77 (95% CI, 0.61-0.97) at 15 y
Malmo,[3,4] 1976 (Sweden)	42,283	Two-view MMG every 18-24 mo × 5	12 y	RR, 0.81 (95% CI, 0.62-1.07)
Ostergotland, County E of 2-County Trial,[5-7] 1977 (Sweden)	38,405-39,034: study 37,145-37,936: control	Three single-view MMG: Every 2 y, women <50 y Every 33 mo, women 50+ y	12 y	RR, 0.82 (95% CI, 0.64-1.05)
Kopparberg, County W of 2-County Trial,[5-7] 1977 (Sweden)	38,562-39,051: intervention 18,478-18,846: control	Three single-view MMG: Every 2 y, women <50 y Every 33 mo, women 50+ y	12 y	RR, 0.68 (95% CI, 0.52-0.89)
NBSS-1,[8] 1980 (Canada)	25,214: study (100% screened after entry CBE) 25,216: control	Annual 2-view MMG and CBE for 4 to 5 y	13 y	RR, 0.97 (95% CI, 0.74-1.27)
NBSS-2,[9] 1980 (Canada)	19,711: study (100% screened after entry CBE) 19,694: control	Annual 2-view MMG and CBE	11 to 16 y (mean, 13 y)	RR, 1.02 (95% CI, 0.78-1.33)
Stockholm,[10] 1981 (Sweden)	40,318-38,525: intervention 19,943-20,978: control	Single-view MMG every 28 mo × 2	8 y	RR, 0.80 (95% CI, 0.53-1.22)
Gothenberg,[4] 1982 (Sweden)	21,650: invited 29,961: control	Initial 2-view MMG Then, single-view MMG every 18 mo × 4 Single-read first 3 rounds, then double-read	12 to 14 y	RR, 0.79 (95% CI, 0.58-1.08) in evaluation phase RR, 0.77 (95% CI, 0.60-1.00) in follow-up phase
Edinburgh,[11] 1990 (United Kingdom)	23,266: study 21,904: control	Initially, 2-view MMG and CBE Then, annual CBE with single-view MMG at y 3, 5, and 7	10 y	RR, 0.84 (95% CI, 0.63-1.12)
Age Trial,[12] 2006 (United Kingdom)	160,921 (53,884 invited; 106,956 not invited)	Invited group aged 48 and younger offered annual screening by MMG (double-view first screen, then single mediolateral oblique view thereafter); 68% accepted screening on the first screen and 69% and 70% were reinvited (81% attended at least 1 screen)	10.7 y	RR, 0.83 (95% CI, 0.66-1.04)

CBE, clinical breast examination; MMG, mammography; mo, month(s); y, year(s).

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