Does screening mammography save lives?

A Canadian study has left some clinicians uncertain about when to recommend mammography—and to whom. Here, four experts in breast cancer screening offer insights.

Janelle Yates, Senior Editor

When 25-year follow-up data from the Canadian National Breast Screening Study—published earlier this year—showed no benefit for annual mammography in women aged 40 to 59 years, the findings generated renewed debate about whether screening mammography actually saves lives.[1]

In that study, Miller and colleagues continued their follow-up of almost 90,000 women who had been randomly assigned to mammography (five annual screens) or no mammography from 1980 to 1985. Women aged 40 to 49 in the mammography arm and all women aged 50 to 69 underwent annual clinical breast examination (CBE). Women aged 40 to 49 in the control arm had a single CBE and continued usual care in the community. The main outcome measure was death from breast cancer.[1]

During the entire 25-year study, 3,250 women in the mammography arm were given a diagnosis of breast cancer, and 3,133 in the control arm received the same

ILLUSTRATION: CHRISTY KRAMES FOR OBG MANAGEMENT

diagnosis. Of these, 500 and 505 women, respectively, died of the malignancy.

The overall hazard ratio for death from breast cancer in the mammography and control arms was 0.99 (95% confidence interval, 0.88–1.12). After 15 years of follow-up, 106 residual excess cancers (106/484; or 22%) were identified in the mammography arm and were attributed to "overdiagnosis."[1]

During the screening period the mean size of breast cancers identified was 1.91 cm and 2.10 cm in the mammography and control arms, respectively (P = .01), and 30.6% and 32.4% of tumors, respectively, were associated with positive lymph nodes (P = .53).

Professional societies stick by their guidelines

Following publication of the Canadian findings, the **American College of Obstetricians and Gynecologists** (ACOG) reaffirmed its recommendation for women at average risk for breast cancer to initiate annual screening at age 40. In an announcement issued February 14, 2014, ACOG noted that it had "a number of concerns" with the Canadian study.[2]

Similarly, the **American Cancer Society** reiterated its own recommendation that women aged 40 and older undergo annual mammography and CBE for as long as they remain healthy.[3]

The **American College of Radiology** went a few steps further, calling the Canadian study "incredibly flawed and misleading."[4] Its guidelines call for annual mammography beginning at age 40.

The **US Preventive Services Task Force** (USPSTF) 2009 guidelines on breast cancer screening also stand, with biennial mammography beginning at age 50 for women at average risk for breast cancer.[5]

The **Canadian Cancer Society** also reaffirmed its recommendations for breast cancer screening following publication of the Canadian trial 25-year follow-up data—although its recommendations call for screening to begin at age 50 and to be repeated thereafter at 2- to 3-year intervals.[6,7]

Experts featured in this article

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Dr. Monsees reports that she received grant or research support from The National Institutes of Health, and is a speaker for the American College of Radiology National Conference on Breast Cancer.

In short, nothing has changed…yet. But the Canadian trial raises a number of questions about breast cancer screening—and the answers aren't as clear-cut as you might imagine.

Is the Canadian trial credible?

Results from earlier randomized, controlled trials have indicated that screening mammography reduces death from breast cancer.

"The Canadian study is an outlier," says Barbara Monsees, MD, Ronald and Hanna Evens Professor of Women's Health in the department of radiology at Washington University in St. Louis, Missouri.

"There is an overwhelming amount of

evidence that tells us that screening mammography saves lives," says Dr. Monsees. "This evidence includes other randomized trials, case-control studies, results of organized screening programs, and downward trends in breast cancer deaths where screening is used."

Mark D. Pearlman, MD, also believes the body of evidence shows that screening mammography is effective. Dr. Pearlman is vice chair and service chief in the division of obstetrics and gynecology and professor of surgery and director of the breast fellowship in obstetrics and gynecology at the University of Michigan Health System in Ann Arbor, Michigan. He has been on the surgical staff of the Breast Care Center there since 1990, with expertise in the management of women with breast disease and increased genetic risks for breast and ovarian cancer.

The Canadian trial is "a reasonably done study," he says, "but there are some concerns. First, it's not a new study—it was initially published 22 years ago. This latest publication is just a continuation of following these women."

"This study, along with seven other randomized, controlled trials, was considered by the USPSTF in formulating its 2009 recommendations. In that meta-analysis, which included women in their 40s, screening mammography had benefit in every decade of life of interest.[8] That is the basis on which ACOG made its recommendation for women at average risk to start annual screening at age 40 and continue at least until age 70," Dr. Pearlman says. "When the USPSTF considered this negative study, it realized that there is benefit for mammography despite this single trial."

James Dickinson, MBBS, PhD, a family physician and member of the Canadian Task Force on Preventive Health Care (a forerunner of the USPSTF), which has published its own set of guidelines on breast cancer screening, has a different perspective. Dr. Dickinson teaches at the University of Calgary in Alberta.

"One of the tendencies—particularly in medicine driven by commercial interests—is that as soon as there is even the slightest hint that something is worthwhile, there's a rush to have everybody do it and make lots of profit from it. People don't wait for the evidence. They jump to assume guilt or innocence without even looking for the evidence."

"I give all credit to the Canadian trial investigators," Dr. Dickinson says. "The world had jumped ahead of them and just assumed that breast screening worked. But they kept looking. They set up a good trial to start with and then followed it through and helped us understand that things aren't as good as we would like them to be."

Andrew M. Kaunitz, MD, professor and vice chair of obstetrics and gynecology at the University of Florida–Jacksonville also believes that the Canadian study's findings are reliable. Dr. Kaunitz serves on the OBG Management Board of Editors.

"As pointed out in an editorial accompanying the Canadian trial, this study's findings of a lack of efficacy of screening mammograms are 'strikingly similar' to other recent studies assessing breast cancer screening."[9–11]

"Further, mammograms are costly and associated with a high rate of false-positive findings," Dr. Kaunitz says.

"Too many weak links"

Among the main criticisms of the Canadian trial is a claim of flawed methodology.

"The Canadian trial is an update of a flawed study that was previously discredited for good reasons," says Dr. Monsees. "In short, the quality of the mammograms was poor, and the overall study design did not reflect a true randomization process."

"For example, true randomization requires eligible patients to be randomly divided into two or more groups, without any knowledge of their specific conditions that might bias trial results," Dr. Monsees explains. "In the most valid randomized trials, this was accomplished by invitation. Without knowing anything about the women, investigators randomly assigned them to a group invited to be screened and a group not invited. In this manner, two equal groups were produced, with no way to corrupt the randomization process."

"In the Canadian National Breast Screening Study, in contrast, once the women volunteered, they were given a clinical breast examination, and women with

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A meta-analysis of eight trials, which included women in their 40s, found that screening mammography was beneficial in every decade of life of interest

ON THE WEB
FROM THE ARCHIVES

Dr. JoAnn V. Pinkerton discusses how she screens patients at increased risk for breast cancer, at obgmanagement.com

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breast lumps and large lymph nodes in their underarms were identified. This information was provided to study coordinators, who assigned women on open lists to the mammography group or the control group," Dr. Monsees says.

"Those of us in the imaging field know that the quality of mammography is only as good as the weakest link in the imaging chain. This study had far too many weak links. These criticisms are not new; they were raised during and after the trial and remain valid today."

Dr. Pearlman does not believe that the Canadian trial reflects modern breast cancer screening.

"There are things in the Canadian trial that differ from what we see in modern mammography," he says. "In the Canadian trial, in women diagnosed with breast cancer, they noted whether there was a palpable mass in the area of cancer. In the Canadian trial the percentage of palpable masses was approximately 66%, and that's very very different from what we see with modern mammography. In current practice, about 15% of breast cancers diagnosed by mammography are palpable. And so it appears that, for some reason, they were seeing more advanced breast cancers when they were screening by mammography."

Another concern focuses on the technology used in the trial.

"It appears that the Canadian investigators pulled old machines into service for the trial," Dr. Pearlman says.

In addition, more recent advances, such as digital mammography and tomosynthesis, were not available at the time of the Canadian trial.

"Overall, the Canadian trial appears to be looking at a different group of women than what we typically see in the United States in women diagnosed with breast cancer," says Dr. Pearlman. "And if they were, then it makes sense that there would be no benefit in mortality, since they were detecting more advanced breast cancers in that population."

Dr. Pearlman also points to other studies of screening mammography that have produced findings contrasting those of the Canadian trial.

How much does screening mammography cost?

After the US Preventive Services Task Force (USPSTF) recommended biennial mammography screening beginning at age 50 for women at average risk for breast cancer, one of the many variables debated in the medical community and media was cost. A recent study focused on cost more explicitly, estimating the expense (based on Medicare reimbursement) associated with four screening approaches:

- **actual US screening in 2010** (~70% of eligible women screened), when many women initiated annual screening in their 40s – **$7.8 billion**
- **annual screening from age 40 to 84 years – $10.1 billion** (simulated annual cost; 85% of eligible women screened)
- **biennial screening from age 50 to 69 years – $2.6 billion** (simulated annual cost; 85% of eligible women screened)
- **screening according to USPSTF guidance,** which calls for biennial mammography for women aged 50 to 74 years and personalized care based on risk for those younger than 50 years (and based on comorbid conditions for those aged 75 and older) – **$3.5 billion** (simulated annual cost; 85% of eligible women screened).[12]

The parameters that most directly influenced cost were screening frequency, proportion of women screened, cost of mammography, use of digital technology, and percentage of women recalled for further testing.

These estimated costs likely are conservative, as Medicare reimburses at a lower rate than commercial payers. These costs also remind us that substantial expense also is associated with newer diagnostic breast imaging technologies, including magnetic resonance imaging and tomosynthesis.

Women's time away from work, as well as treatment of "overdiagnosed" cancers, represent additional costs.

Breast cancer mortality rates are similar in the European Union and the United States, even though European women are screened every 2 to 3 years.

—ANDREW M. KAUNITZ, MD

"At least eight large observational trials, case-control studies, and randomized, controlled trials of screening mammography have been published and were later evaluated by meta-analysis.[8] That analysis showed a 50% reduction in mortality in women who had screening mammography. In both randomized, controlled trials, it showed a decrease of about 15% in mortality. In practice, looking at large populations of women who died of breast cancer and comparing them to women who had breast cancer but didn't die, there is a 50% *increased* likelihood of dying if you don't have screening mammography. So looking in both directions—both

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Overdiagnosis versus overtreatment

Many articles have described the "overdiagnosis" of cancer—the detection of cancers that might never become lethal. It is said to occur when a lesion found in the breast by mammography alone or palpation is biopsied and interpreted by the pathologist as cancer, but if left alone would not harm the patient during the course of her life (ie, she would die of some other cause). These overdiagnosed lesions have all the characteristics of cancer—even when assessed using the most modern pathologic techniques—and cannot be differentiated by the pathologist from cancers that would go on to kill the woman. When treatment is applied to women who have cancers that would never progress, that is "overtreatment." (Note that we cannot currently tell who these overtreated women are prospectively.)

Opponents to screening argue that by curtailing use of mammography, we will diminish overdiagnosis. But the view in the radiology specialty is that women should not be denied access to screening that has been proven to save lives. Rather, newer and better methods need to be developed to determine which cancers will progress, so that overtreatment is reduced.

Ductal carcinoma in situ (DCIS) is a more complicated story. There is no consensus as to how long DCIS can go untreated before it breaks through the duct wall and becomes invasive cancer. The optimal approach to DCIS may be identified in the future with advances in biological knowledge. We do know, however, that when a DCIS lesion has been incompletely treated, many recur, and half of the recurrences are invasive cancers.

—BARBARA MONSEES, MD

prospectively and retrospectively—there appears to be a substantial benefit to undergoing routine screening mammography in reducing breast cancer mortality," Dr. Pearlman says.

Dr. Dickinson asserts that criticisms of the Canadian National Breast Screening Study were disproved long ago.

"Many of those accusations were brought out very early in the course of the Canadian trial and investigated in great detail and rejected. After all, this trial was funded by a major research funding body in Canada. And when it was informed that it had funded a 'fraudulent' trial, it investigated and found that the findings actually were legitimate," says Dr. Dickinson.

"I think that the people who are still bringing up those accusations are doing it primarily because the results don't fit what they wanted. It's attacking the messenger because they don't like the results."

Weighing benefits and harms

When the Canadian Task Force on Preventive Health Care formulated its guidelines on screening mammography, it considered the same body of evidence assessed by the USPSTF for its 2009 guidelines. Dr. Dickinson, a member of the Canadian Task Force, notes that the Canadian approach differed from the American approach in several distinct areas.

"We used the USPSTF literature search up to 2008 and then we did an updated search, looking for papers published up to that time. But there were no new trials published from 2008 to 2011," he says.

"So we looked at the same data but used the GRADE scheme, which carefully separates the strength of the evidence from the strength of the recommendations. It's a 'newish' way of evaluating evidence," Dr. Dickinson says. "It's different from the USPSTF approach, which involves a different scale."

"We used to assess preventive measures purely on the basis of efficacy—if they worked, we'd recommend them. Now we look at the balance of benefits and the potential for causing harm. So it's not just about whether an intervention works, but about whether it works more than it causes harm," he says.

"That means that you can have statistically significant benefits that are fairly small and are outweighed by harms. So, while screening mammography can significantly reduce the risk of death from breast cancer by a small amount, our recommendation for it is very weak because, to achieve that benefit, you also incur a lot of harm," Dr. Dickinson says.

Dr. Pearlman agrees that "mammography is not a perfect test, by any means."

"It's inconvenient, people get worried, it's uncomfortable, and it isn't perfectly sensitive," he says. "It's also somewhat nonspecific, which means that about 10% of women who don't have breast cancer will be called back for additional images, and about 10% of that group will get called back for a biopsy that is not due to cancer."

How we counsel our patients

Dr. Kaunitz says he is less likely to recommend

annual mammography screening in the wake of the Canadian trial and other findings.

"For decades, we have marched to the drumbeat of 'mammograms save lives,'" he says. "Annual screens have become an easy recommendation for us to make and, for our patients, the reassurance that accompanies a normal mammogram is comforting. Many patients will be perplexed by this new information; others may view it with suspicion. While we await updated guidance from professional societies, my approach is to encourage patients to follow the 2009 USPSTF guidelines, which recommend that screening start at age 50 in average-risk women and be repeated every 2 years."

Dr. Dickinson takes a similar approach. "I recommend that people be cautious about having screening, but I listen to their stories. Someone may say, 'My sister had breast cancer and I want a mammogram.' Overall, I don't encourage people to undergo mammography unless they have a strong reason for doing so. I try to follow the latest [Canadian] guidelines because I feel they're based on the best available evidence."

In contrast, Dr. Pearlman advises his patients according to ACOG guidelines (guidelines that he formulated on ACOG's behalf), which call for annual screening to begin at age 40.

Dr. Monsees counsels her patients similarly.

"The scientific evidence clearly shows that screening saves the most lives if average-risk women begin annual screening at the age of 40," she says. "For high-risk women, our recommendations are tailored to each woman's individual case and made in conjunction with the referring physician. For example, we often begin screening earlier or perform supplemental screening with breast magnetic resonance imaging for women who are at high risk due to prior chest wall radiation or a strong family history."

"Others have argued against screening average-risk women in their 40s," Dr. Monsees notes. "But if diagnosed with breast cancer, women in their 40s have more years of life to lose. More than 40% of the years of life lost to breast cancer are among women diagnosed in their 40s. Others also have argued that only high-risk women should be screened in their 40s or yearly after 50. However, that is problematic because more than 75% of women diagnosed with breast cancer each year are not at elevated risk. If you screen only high-risk women you will miss most breast cancers."[13–15]

"Mammography screening has been proven to save lives," Dr. Monsees says. "It can't find every cancer, and it can't find every cancer early enough to save all women. Nevertheless, screening should not be abandoned while we are awaiting better screening tests, better pathological markers to differentiate which tumors should be treated more aggressively, and the development of better therapies. The bottom line: Mammography

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The evolution of breast screening technology

The need for sensitive breast cancer screening modalities has become increasingly evident over the past 50 years, as clinicians have searched for effective ways to identify early breast cancer for prompt treatment. Although mammography has been around since about 1913, it did not gain widespread acceptance in the medical community until the latter half of the 20th century. Since then, a number of other developments have enhanced breast cancer screening:

- **Digital mammography** was first approved in 2000. Women with radiographically dense breasts are especially likely to benefit from use of this modality. However, the 2009 USPSTF guidelines for breast cancer screening cited insufficient evidence of digital mammography's benefits as an alternative to conventional film mammography.[16]
- **Ultrasound screening.** In women who are found to have mammographic abnormalities, ultrasound can help clarify their implication. For example, in an analysis of 2,500 women older than age 30 who underwent a physical examination and screening mammography followed by ultrasound assessment, ultrasound provided the most meaningful information for the diagnosis of these abnormalities.[16] Today, ultrasound is used to distinguish cystic and solid masses, as well as palpable and nonpalpable masses. It also is used to guide needle-aspiration procedures.
- **Magnetic resonance imaging.** This modality is effective in the detection of occult breast cancer and is often used in women given a diagnosis of breast cancer to more fully assess the affected and contralateral breasts prior to development of a treatment plan.
- **Breast tomosynthesis,** sometimes known as 3D imaging, takes multiple images of the breast from multiple angles to form a 3D replica of the entire breast. Its greater sensitivity, compared with mammography, means that fewer unnecessary tests and biopsies are performed in women with breast abnormalities.

saves lives now, and we should embrace it."

Dr. Dickinson is more cautious.

"There isn't a perfect answer," he says. "That's the sad thing."

ACOG's stance

Current ACOG guidelines recommend that annual screening mammography begin at age 40 for women at average risk for breast cancer. Women with an elevated risk of breast cancer require a more complex assessment and thorough counseling and may begin screening even before age 40 in some cases.

FAST TRACK

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