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Annual mammography starting at age 40: More talk, less action?

In view
of potential
harm,
we question
starting
annual
screening
at age 40

NATIONAL SOCIETIES agree on the value of mammographic screening at age 50 through 69 (though the frequency is still debated), but there is no consensus about whether to screen at age 40 through 49, or age 70 and older. The US Preventive Services Task Force (USPSTF) recommends against routinely screening women age 40 through 49, while the American Academy of Family Physicians and the American College of Physicians recommend screening every 1 to 2 years for women in this age group. The American Cancer Society, the American Medical Association, the National Cancer Institute, the American College of Radiology, and the American Congress of Obstetricians and Gynecologists recommend yearly mammography starting at age 40.¹

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Besides female sex, the major risk factor for breast cancer is increasing age. Thus, women in their 40s are at significantly lower risk of breast cancer than those in their 50s. As emerging evidence focuses on the potential harms and benefits from screening, we must question the practice of annual screening starting at age 40.

■ DOES MAMMOGRAPHIC SCREENING SAVE LIVES?

The main goal of screening for any type of cancer is to reduce the death rate. A 2014 meta-analysis of randomized controlled trials found a 15% to 20% relative decrease in the

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breast cancer mortality rate with screening mammography, approximately 15% for women in their 40s and 32% for women in their 60s.² Since the prevalence of breast cancer is lower in younger women, many more women in their 40s must be screened to prevent one breast cancer death. For women age 60 to 69, 377 must be screened to prevent one breast cancer death, whereas for women age 39 to 49 the number is 1,904.³

Whether screening for breast cancer reduces the death rate has been questioned following the 2014 publication of 25-year follow-up data from the Canadian National Breast Screening Study.⁴ This randomized controlled trial of screening mammography and clinical breast examination, launched in 1980, involved 89,835 women and 5 years of screening. Women age 40 to 49 were randomly assigned to undergo either five annual mammographic screenings and annual clinical breast examinations or no mammography and a single clinical breast examination, followed by usual care in the community. Those age 50 to 59 received annual clinical breast examinations and were randomized to either mammography or no mammography.

During 25 years of follow-up, 3,250 women in the mammography group and 3,133 in the control group were diagnosed with breast cancer, and 500 and 505, respectively, died of breast cancer. No difference in mortality rate was found between the mammography and control groups (hazard ratio 0.99, 95% confidence interval 0.88–1.12), and the findings in both age cohorts were similar.⁴

Criticisms of this study include that it was performed using outdated imaging technology, and that a significant proportion of the control group also received mammography, although it is also possible that the mortality benefit from mammographic screening alone may not be as high as once predicted.

Reduction in breast cancer mortality is likely from a combination of screening mammography and better treatment. The number of women presenting with late-stage cancers has decreased in the past 3 decades, but only slightly; and most of the decrease has been in regional, node-positive disease, a stage that can now often be treated successfully (the expected 5-year survival rate is 85% in women age 40 or older).⁵ For women with estrogen receptor-positive tumors, the combination of hormonal therapy and adjuvant chemotherapy has reduced the death rate by half.⁶

It has been 50 years since a large randomized controlled trial of mammographic screening has been done in the United States. Thus, further study is needed to understand whether screening is less valuable now that better treatments are available.

■ DOES MAMMOGRAPHIC SCREENING REDUCE LATE-STAGE CANCERS?

To be effective, screening must detect disease at an earlier, more curable stage. Although screening mammography has substantially increased the number of early-stage breast cancers detected, it has only marginally decreased the rate of diagnosis of late-stage cancers.⁵

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data⁵ show that between 1976 and 2008 screening mammography was associated with a doubling in early-stage breast cancer cases detected (from 112 to 234 cases per 100,000 women per year, an absolute increase of 122 cases per 100,000 per year). In contrast, late-stage cancer diagnoses decreased by 8% (from 102 to 94 cases per 100,000 women per year, or an absolute decrease of 8 per 100,000 women per year). Assuming a constant underlying disease burden, only 8 of the 122 early-stage cancers diagnosed would be expected to progress to advanced disease, suggesting that the rest would have never harmed these wom-

en—ie, they were *overdiagnosed*. The authors estimated that in 2008, breast cancer was overdiagnosed in more than 70,000 women, accounting for 31% of all diagnosed breast cancers.⁵

■ HARMS OF OVERDIAGNOSIS

Based on SEER data, Bleyer and Welch⁵ estimated that more than 1 million US women may have been overdiagnosed with breast cancer in the past 3 decades. Many women in this situation subsequently undergo surgery, radiation therapy, hormonal therapy, chemotherapy, or a combination of these for a cancer that may never become clinically significant. Until we can differentiate deadly from indolent cancers, highly sensitive screening tests will increase the risk of overtreatment.

Breast cancer has increased in incidence since the 1990s, mostly from the detection of more early-stage cancer or ductal carcinoma in situ (DCIS). Rare before widespread screening, DCIS now accounts for 20% to 30% of all breast cancer diagnoses.^{6,7} However, DCIS is not always a precursor to invasive cancer: untreated, it progresses to invasive disease in half of cases or fewer. Because DCIS is usually diagnosed only with mammography, its incidence has been steadily on the rise since screening became widespread.¹

Welch and Passow⁶ reviewed the available evidence and attempted to provide a range of estimates for three outcomes important to the mammography decision: breast cancer deaths avoided, false alarms, and overdiagnosis. For every 1,000 US women screened yearly for a decade starting at age 50, an estimated 0.3 to 3.2 avoided breast cancer death, 490 to 670 had at least one false alarm, and 3 to 14 were overdiagnosed and treated needlessly.

Esserman et al⁷ calculated that in women age 50 to 70, prevention of one breast cancer death would require that 838 women be screened for 6 years, leading to 5,866 screening visits, 535 recalls, 90 biopsies, and 24 cancers treated (18 invasive, 6 DCIS).

■ SCREENING EVERY YEAR VS EVERY 2 YEARS

Also controversial is whether screening mammography should be done annually or every 2

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years. For women in their 50s, the American Cancer Society recommends mammography every year, the American College of Physicians and American Academy of Family Physicians recommend it every 1 to 2 years, and the USPSTF recommends it every 2 years.

A prospective analysis of 11,474 women with breast cancer and 922,624 controls⁸ found that performing mammography every 2 years instead of annually for women age 50 to 74 did not increase the risk of advanced-stage or large-size tumors regardless of breast density or hormone therapy use. But women undergoing annual mammography had a higher risk of false-positive results and biopsy recommendations.⁸ Women age 40 to 49 with extremely dense breasts were the only subgroup who derived additional benefit from annual screening, as they had a higher risk of advanced-stage cancer if they were screened every 2 years instead of yearly (odds ratio [OR] 1.89; 95% CI 1.06–3.39) and a higher risk of larger tumors (OR 2.39; 95% CI 1.37–4.18). However, the probability of a false-positive result in these younger women undergoing annual mammography was also very high at 65.5%.⁸

For most women in their 40s (other than those with extremely dense breasts) and 50s, biennial and annual mammography were associated with a similar risk of advanced-stage disease. Women with fatty breasts are at low risk of breast cancer regardless of other risk factors and did not appear to benefit from annual screening.⁸ The 12% to 15% of women in their 40s with extremely dense breasts (whose risk of breast cancer is similar to that in average-risk women in their 50s) should decide if the added benefit of annual screening is outweighed by the additional harms, including doubling the number of mammograms, as well as more false-positive results and breast biopsy recommendations.⁸

Mandelblatt et al⁹ statistically evaluated 20 screening strategies, ie, screening every year or every 2 years, and starting and stopping at various ages. On average, screening every 2 years was 81% as beneficial as annual screening but caused only about half as many false-positive results. Women age 50 through 69 who were screened every 2 years achieved a median 16.5% (range 15%–23%) reduction in breast cancer deaths compared with no screen-

ing. Initiating screening every 2 years at age 40 reduced the death rate by an additional 3% (range 1%–6%) compared with starting at age 50. Not surprisingly, starting screening at age 40 consumed more resources and yielded more false-positive results. After age 69, screening every 2 years yielded some additional mortality reduction in all models, but overdiagnosis increased most substantially at older ages, as the ratio of slow- to fast-growing tumors increases with age. The authors concluded that screening every 2 years achieves most of the benefit of annual screening with less harm.

■ FALSE-POSITIVE RESULTS AND ANXIETY

False-positive results on mammography can increase distress and anxiety about breast cancer and perceived breast cancer risk in some women.³ After 10 years of annual screening, more than half of women receive at least one false-positive recall, and 7% to 9% receive a false-positive biopsy recommendation. It is helpful for women to understand this risk when deciding whether to start mammographic screening.¹⁰

■ OUR VIEWS

There are two major issues to address in clinical practice regarding mammographic screening: at what age to start, and how often to screen. For years, women have been instructed to start annual mammographic screening at age 40, and such established patterns can be difficult to change.

When deciding whether to have a mammogram at age 40, women should be aware of the full range of risks and benefits. Assessing a woman's individual risk of breast cancer (based on family history and number and age of pregnancies) can be an important starting point for assessing the potential benefits and risks of screening.

Although a shared decision-making approach is intuitively appealing, it takes much more time than simply ordering a mammogram. Time constraints during a medical appointment may make it challenging to have a prolonged discussion about the pros and cons of screening. Patient education materials about the risks vs benefits of screening initiation may be useful, and because the decision

does not usually need to be made urgently, women can be given the opportunity to consider the decision outside of the primary care appointment.

The issue of annual vs biennial screening presents an additional challenge, because women have come to expect annual screening. Studies show that the only subgroup of women who appear to benefit from annual screening are those in their 40s with dense breasts. Although breast cancer is rarer in younger women, when it does develop, it is often more aggressive, so offering annual screening to this subpopulation may make sense. For all other women, since there is no evidence that annual mammography offers clinical benefit over biennial screening, clinicians can be comfortable with offering screening every 2 years.

Future research must focus on developing

better tools for differentiating women who are at higher vs lower risk for breast cancer and on developing methods to determine which DCIS cancers are more likely to be indolent and therefore amenable to watchful waiting.

In the interim, we must continue to identify women at high risk who will benefit from magnetic resonance imaging, genetic testing, and prophylactic medications, in accordance with USPSTF recommendations. Women with new breast symptoms or concerns should continue to undergo evaluation with diagnostic imaging, including mammography. However, for most women who are at average risk and have no symptoms, we must ensure that they are fully aware of the possible benefits and risks of screening mammography so that they can make an informed decision about when to start screening and how often to be screened. ■

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Women need to be aware of the benefits and risks to make an informed decision