AJR FOCUS ON:

Screening Guidelines Update for Average-Risk and High-Risk Women

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OBJECTIVE. The purpose of this study is to describe screening updates for women with average and high risk for breast cancer, compare different screening strategies, and describe new approaches in risk prediction, including radiomics.

CONCLUSION. All women are at substantial risk for breast cancer. For women with average risk, annual mammography beginning at 40 years old maximizes the life-extending benefits and provides improved treatment options. Women at higher risk need earlier and more intense screening. Delaying initiation or decreasing frequency of mammographic screening adversely affects breast cancer detection.

For women in the United States, breast cancer is the most common nonskin cancer, the second most common cause of cancer death, and a leading cause of premature death (mean and total years of life lost). In 2019, the American Cancer Society (ACS) estimates 268,600 new cases of invasive breast cancer and expects 41,760 women to die of breast cancer in the United States [1]. Fortunately, breast cancer is treatable, with better treatment options when detected early. The presentation of breast cancer has shifted from late to early stage disease because of national screening mammography programs. Across multiple study designs from randomized controlled trials to observational studies, regular mammographic screening results in a substantial reduction in breast cancer mortality [2–6].

Screening Guidelines for Average-Risk Women: Three Main Strategies

The ACS, U.S. Preventive Services Task Force (USPSTF), and American College of Radiology (ACR) all agree that annual mammographic screening starting at 40 years old saves the most lives [7–9]. This agreement is not transparent, however, and therefore debate persists regarding screening recommendations. Disagreement originates from how evidence is interpreted, what risks and benefits are included, and how each is weighed. The three main screening strategies for average-risk women are summarized in Table 1.

American College of Radiology, American Society of Breast Surgeons, Society of Breast Imaging, National Comprehensive Cancer Network, and National Consortium of Breast Centers

Updated in 2017, the ACR recommends annual mammographic screening for average-risk women starting at 40 years old [9] because it offers the most lives saved, the most life-years gained, and the largest mortality reduction. The ACR recommends that women continue screening for as long as they are healthy and desire to remain so; there is no specific age limit to stop screening. A recent study using U.S. data shows that annual mammographic screening starting at 40 years old would save an additional 12,216 lives in the United States each year compared with biennial screening at 50 years old as recommended by the USPSTF [10]. The ACR-recommended screening strategy is also recommended by the American Society of Breast Surgeons (ASBrS) [11], Society of Breast Imaging (SBI) [12], the National Consortium of Breast Centers (NCBC) [13], and the National Comprehensive Cancer Network (NCCN) [14].

American Cancer Society

Updated in 2015, the ACS guideline recommends that average-risk women have the opportunity to begin annual screening at 40 to 44 years old (qualified recommendation) and to undergo regular screening mammography by 45 years old (strong recommendation) [7]. Annual screening is recommended

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TABLE 1: Recommendations for Mammographic Screening for Women at Average Risk for Breast Cancer

Screening Mammography	American College of Radiology, SBI, NCCN, NCBC, ASBrS	American Cancer Society	U.S. Preventive Services Task Force, AAFP, ACP
Initiation age	Recommend at 40 y	Offer at 40 y to 44 y; recommend at 45 y	Begin at 50 y; individual decision from 40 y to 49 y
Interval	Annual	Annual from 40 y to 54 y; biennial or annual for 55 y or older	Biennial
Cessation age	Continue as long as healthy and desired to be screened	Continue as long as life expectancy is 10 y or more	Stop at 74 y; insufficient evidence to continue after 75 y

Note—SBI = Society of Breast Imaging, NCCN = National Comprehensive Cancer Center Network, NCBC = National Consortium of Breast Centers, ASBrS = American Society of Breast Surgeons, AAFP = American Academy of Family Physicians, ACP = American College of Physicians.

for women 45 to 54 years old and biennial screening can be considered for women 55 years and older (both qualified recommendations) [7]. Women should stop screening if life expectancy is less than 10 years (qualified recommendation). Both strong and qualified recommendations indicate endorsement. A strong recommendation means that the benefits of screening outweigh any undesirable effects and that most women would "want the recommended course of action" [7]. A qualified recommendation means that there is clear evidence of benefit but less certainty about the balance of benefits and harms; however, "the majority of individuals in this situation would want the suggested course of action" [7].

U.S. Preventive Services Task Force, American College of Physicians, and American Academy of Family Physicians

The USPSTF guidelines for screening average-risk women were last updated in 2016 [8]. The USPSTF recommends biennial screening mammography for women 50 to 74 years old (Grade B: moderate certainty that the net benefit is moderate to substantial). The task force states that beginning biennial screening before 50 years old should be individualized (Grade C: balance of benefits and harms is close with small net benefit). For women older than 75 years old, the USPSTF concluded that evidence is insufficient to determine the balance of risks and benefits. This screening strategy is supported by the American Academy of Family Physicians [15] and the American College of Physicians [16].

Differences and Similarities Between the Guidelines

Differences between the three screening strategies stem from which data are included, how the data are valued, and which benefits and risks are considered. Regarding data inclusion, the USPSTF considers only a few of the randomized controlled trials, resulting in a much smaller net benefit (15% mortality reduction) than produced by the inclusion of all trials (22% mortality reduction) [17]. The ACR and ACS consider all types of evidence and emphasize more recent observational data because they better reflect current practices, although none fully show the added benefits of digital mammography and digital breast tomosynthesis.

Both the ACS and USPSTF only include one benefit—mortality reduction—and ignore the other benefits of screening, which affects their benefit-to-risk consideration. The ACR includes other established benefits: less frequent and less toxic chemotherapy, less aggressive surgery, and early detection and treatment of high-risk lesions [9]. The ACR also finds the life-years lost in delaying screening onset to 45 or 50 years old unnecessary and unacceptable [9].

Moreover, the risks of screening are valued differently by the different organizations. Overdiagnosis, for example, is the detection of breast cancer by screening that would have never been clinically identified in the woman's lifetime [18]. The ACS and ACR agree that there is low-quality evidence available to estimate overdiagnosis, which cannot be measured directly [7, 9]. Most estimates of overdiagnosis are inaccurate and inflated because they do not properly account for incidence trends, lead time, and population characteristics. The USPSTF states that reducing overdiagnosis is a reason to delay initiation of screening until 50 years old and to increase the screening interval to biennial. However, because overdiagnosed cancers on screening do not disappear spontaneously without treatment, they will be detected at the next screening [19]. Delaying the onset or increasing the interval of screening would only delay, not reduce, the small amount of overdiagnosis that exists. Overdiagnosis should not be a factor in deciding when to start screening or choosing a screening interval.

Despite the differences in recommendations, several similarities between the different screening recommendations are notable. All organizations agree that the most lives are saved with initiation of annual mammographic screening at 40 years old, which was confirmed in a recent study [10]. All recommend that patients discuss the benefits and risks with their physicians before making an informed decision. All support that women should have the choice to begin screening at 40 years old and to decide when to stop screening. Women should be helped to understand the risks and benefits of screening, so that they can make an appropriately informed decision.

Special Considerations

Screening Mammography in Younger Women 40 to 49 Years Old

The incidence of breast cancer in women in the United States increases sharply around 40 years of age [20]. In 2015, approximately one in six breast cancers diagnosed in the United States occurred in women 40 to 49 years old [1]. Approximately 30% of the years lost to breast cancer occur in women diagnosed at 40 to 49 years old [7]. Eight screening mammography randomized controlled trials included women 40 to 49 years old; a meta-analysis of these showed a statistically significant mortality reduction of 15–18% for women 40 to 49 years old after 10 to 18 years of follow-up [21]. The Swedish Gothenburg trial found 45% mortality reduction for women 39 to 49 years old at the time of randomization, and the Swedish Malmo trial found 35% mortality reduction for women 45 to 49 years old at the time of trial entry [22–24]. Randomized controlled trials, however, underestimate the magnitude of screening benefits. Observational studies more closely reflect actual clinical practice using more current technology

in larger populations; they have found much greater mortality reduction (26–48%) for women 40 to 49 years old than randomized controlled trials [2, 6, 25].

To facilitate comparison of different screening regimens, modeling studies can be helpful. Updated Cancer Intervention Surveillance Modeling Network (CISNET) models indicate that only 20 women 40 to 49 years old need to undergo annual screening to save 1 life-year [26, 27]. Years of life gained are an important benefit of screening. By focusing on only mortality reduction and not considering life-years gained, the USPSTF undervalued screening in those 40 to 49 years old. CISNET models also show that annual rather than biennial digital mammography screening results in 42% more lives saved and life-years gained in women 40 to 49 years old [27]. Adding annual digital mammographic screening of women 40 to 49 years old to biennial film screening of women 50 to 74 years old yields 47% more life-years gained and 27% more lives saved [9].

A criticism of screening younger women is the relatively higher number of recalls and false-positives. The USPSTF reported that the numbers of women recalled from screening to find one cancer are 47 at 40 to 49 years old, 22 at 50 to 59 years old, and 14 at 60 to 69 years old [28]. However, initial or prevalent screening is well-documented to result in a higher recall rate than subsequent incident screening because of the lack of prior examinations for comparison [29]. Therefore, delaying screening until 50 years old would simply delay the higher recall rates of baseline screening to a later age rather than eliminate it. This is also evident in Table 5 of the 2016 USPSTF guidelines that shows identical rates of false-positives and recalls for starting screening at 40 and 50 years old [8].

All current data show that annual mammographic screening beginning at 40 years old results in the greatest mortality reduction and the most life-years gained. As screening technology continues to improve, bringing increasing cancer detection and reducing false-positives, the benefit-to-risk ratio will increasingly favor annual screening of women 40 to 49 years old.

Screening Mammography in Women Older Than 75 Years Old

In the United States, the number of women older than 75 years old is projected to reach 25 million by 2040 [30]. Almost one in five breast cancers occur in women older than 75 years old, and women older than 75 years old accounted for 37% of U.S. breast cancer deaths in 2014 [31, 32]. Older women are a vulnerable and rising population at risk from breast cancer, but screening remains underutilized in these women [33–35]. Because women older than 75 years old were excluded from the randomized controlled trials, observational and modeling studies are the best available data to assess screening for them. The benefits of screening remain the same for older women—earlier detection and lower stage tumors resulting in less aggressive treatment, decreased morbidity, and lower breast cancer mortality [36–42]. The risk of overdiagnosis is estimated to be low, between 1–10% [18]. In fact, screening benefits significantly outweigh the risk of overdiagnosis until 90 years old [43] and even better results will occur as life expectancy continues to increase. Because breast density decreases and breast cancer incidence increases with age, cancer detection rate (CDR) and sensitivity and specificity are higher and false-positives fewer in older women [28, 44, 45].

Compelling new evidence for women older than 75 years old comes from a 2017 National Mammography Database study including 5.6 million screening mammograms performed across the United States (2008–2014); the study showed higher CDR and positive predictive values and a lower recall rate with advancing age, persisting until 90 years old [46]. A 2016 systematic review concludes that screening would likely extend the life expectancy in women 65 years old and older without severe comorbidity [47], and a recent modeling study showed an inverse relationship between the benefits of screening and the extent of comorbidity [48]. Early detection is particularly crucial for older women who have higher incidence of comorbidities and may be less tolerant of aggressive treatments. A recent 10-year cohort study of 393 women older than 75 years old confirmed that women with screen-detected breast cancers had a significantly higher rate of small node-negative tumors and were more likely to receive conservative surgery and less chemotherapy, resulting in significantly lower overall and cancer-specific mortality rates at 2 and 5 years [41]. The group with screen-detected cancer also had a significantly longer overall and disease-free 10-year survival by 14.2 months and 18.4 months ($p < 0.05$) [41]. These studies indicate that the benefits of screening mammography extend to women older than 75 years old and support the argument for eliminating the age-based upper limit. The decision regarding when to stop screening should not be on the basis of age alone.

Harms of Restrictive Risk-Based Screening

In an attempt to reduce the alleged harms of screening mammography, some have proposed a risk-based approach with less screening for average-risk women [49–53] on the basis of family history or dense breasts. However, most women with breast cancer have no family history of the disease. A British study showed 89% of 160,195 women with breast cancer did not have a first-degree family relative with breast cancer [54]. Neal and colleagues found that up to 80% of patients could have received a delayed diagnosis of breast cancer if a restrictive risk-based screening approach for patients with family history had been used [55]. Using breast density to guide a risk-based screening strategy is also problematic. It is estimated that 36% of all breast cancers occur in nondense breasts [56]. Up to 60% of patients could have a delayed diagnosis of breast cancer if a restrictive screening strategy for women with dense breasts were used [55]. Although breast density may decrease with older age, overall breast cancer risk increases [57]. Another recent study including 71,148 screening mammograms in 24,928 women found that age-based mammographic screening detected significantly more cancers than risk-based screening in women 40 to 49 years old, many of whom would be excluded in a risk-based strategy [58].

The principal goal of breast cancer screening is to detect small, nonpalpable, node-negative breast cancers to allow earlier treatment and greatest reduction in mortality and morbidity. Risk-based screening should focus on providing supplemental screening to higher-risk women rather than restricting access to screening for the average-risk woman.

Women at Above-Average Risk for Breast Cancer

Breast Cancer Risk Assessment

The ACR recommends that all women be evaluated for breast cancer risk by 30 years old so that those at higher risk can be identified and can benefit from supplemental screening [59]. The ASBrS recommends all women undergo formal risk assessment at 25 years old [11]. Risk for breast cancer is usually calculated on the basis of family history, genetic testing, and clinical history (personal history of breast cancer, chest radiation,

high-risk lesions, and mammographic density). Many models estimate the risk for breast cancer and the risk of carrying high-risk genetic mutations [60]. However, these models are complex [61, 62]. Each model uses different sets of risk factors and weighs them differently, resulting in different predictions for the same patient [60]. Hence, the models perform variably with modest accuracy among individuals and across populations. With model validation aside, clinical context will take precedence over the risk model results for any individual woman. Not all models incorporate mammographic breast density, which is an important risk factor [60, 61].

New Approaches in Risk Prediction: Machine Learning, Radiomics, and Genetic Polymorphism

In the era of machine learning (ML) and artificial intelligence, there are new advances in breast cancer risk prediction and automated breast density measurement. Multiple automated programs of measuring mammographic density exist. A 2016 study found that a mammographic textural quantification combining mammographic density and structural features improved risk stratification and identified women at higher-than-average risk [63]. Another ML approach segmented the fibroglandular tissue on mammography and identified 44 parenchymal features that increased the accuracy of risk prediction by 9.7% [64]. A 2019 retrospective study developed a hybrid deep learning model that used both traditional risk factors and mammograms in risk prediction. The model yielded substantially improved risk discrimination compared with the Tirer-Cuzick model (version 8) [65]. Although ML models can potentially improve risk prediction, they are not yet ready for clinical use.

Radiomics is an emerging field that converts medical images into mineable data via extraction of quantitative imaging features followed by data analysis and integration with clinical, histopathologic, and genomic data [66]. Studies suggest that radiomics may discriminate benign breast lesions from cancers on MRI [67, 68], ultrasound [69], and digital breast tomosynthesis [70] or predict cancer prognosis by lymph node metastasis [71], protein Ki-67 proliferation marker [72], and hormone receptor status [73, 74]. Despite encouraging preliminary results, larger prospective studies are needed for validation.

Recently, risk-associated genetic variants called single nucleotide polymorphisms (SNPs) were identified in 46,450 breast cancer patients in the Collaborative Oncologic Gene-Environment Study [75]. SNPs are common, low-risk genetic variants of different enzymes. Although risks from individual SNPs are too low to be useful, the combined risk of multiple SNPs could be useful in risk prediction [75, 76]. A polygenic risk score, constructed on the basis of multiplicative interactions of multiple SNPs, can further stratify risk in women with and without family history of breast cancer [77].

Screening Guidelines for High-Risk Women

Women with risk factors for breast cancer need earlier and more intensive screening. The ACR, ACS, and ASBrS issued screening guidelines for these women [11, 59, 78] (Tables 2 and 3). The ACS recommends supplemental annual screening breast MRI for all high-risk women with lifetime risk of 20% or greater [78]. Other international organizations, including the European Society of Breast Imaging, National Institute for Health and Care Excellence, and Cancer Australia, recommend annual MRI screening in addition to mammography for high-risk women [79–82]. Although the definition of "high-risk" and recommendations vary, there is consensus regarding women with high-risk genetic mutations. The risk of breast cancer for *BRCA1* and *BRCA2* mutation carriers is 75–82% and 76–82%, respectively. Other high-risk mutations include *TP53* (95% by 90 years old), *PTEN* (85% by 80 years old), *CDH1* (53% by 80 years old), and *STK11* (32% by 60 years old) [83, 84]. However, known genetic mutations are identified in only 5–10% of women with breast cancers [85]. For *BRCA* mutation carriers, the ACS recommends risk reduction strategies including chemoprevention and prophylactic surgery; both the ACS and ACR recommend more intensive screening [59, 78] (Tables 2 and 3). Even without a known genetic

TABLE 2: Recommendations for Mammographic Screening for Women at Higher-Than-Average Risk for Breast Cancer

Organization and Indication	Interval
American College of Radiology, 2018	
Lifetime risk of 20% or more	Annual starting at 30 y
Genetic mutation carriers and their untested first-degree relatives	Annual starting at 30 y
Chest radiation before 30 y	Annual starting at 25 y or 8 y after radiation, whichever is later
Personal history of breast cancer before 50 y	Annual
History of breast cancer and dense breasts	Annual
History of atypia or LCIS	Annual
American Society of Breast Surgeons, 2019	
Hereditary susceptibility from pathogenic mutation	Annual starting at 30 y
Prior chest wall radiation at 10 y to 30 y	Annual starting at 30 y
Lifetime risk greater than 20% by any model	Annual starting at 35 y
Strong family history	Annual starting at 35 y
History of breast cancer at 50 y or older with nondense breasts	Annual
History of breast cancer at younger than 50 y or with dense breasts	Annual
American Cancer Society, 2007	
High risk (lifetime risk greater than 20%)	
BRCA1 and *BRCA2* carriers and their untested first-degree relatives	Annual starting at 30 y
Chest radiation at 10 y to 30 y	Annual starting at 30 y
Specific genetic mutations	Annual starting at 30 y
Intermediate risk (lifetime risk of 15–20%)	
History of atypia or LCIS	Annual starting at 30 y
Dense breasts	Annual starting at 30 y
Personal history of breast cancer	Annual starting at 30 y

Note—LCIS = lobular carcinoma in situ.

TABLE 3: Recommendations for Supplemental MRI Screening in Women at Higher-Than-Average Risk for Breast Cancer

Organization and Indication	Interval
American College of Radiology, 2018	
Lifetime risk of 20% or greater	Annual MRI starting at 25 y to 30 y
Genetic mutation carriers and their untested first-degree relatives	Annual MRI starting at 25 y to 30 y
Chest radiation before 30 y	Annual MRI starting at 25 y to 30 y
Personal history of breast cancer before 50 y	Annual MRI
History of breast cancer and dense breasts	Annual MRI
Personal history of atypia or LCIS	Consider annual MRI, especially if other risk factors are present
American Society of Breast Surgeons, 2019	
Hereditary susceptibility from pathogenic mutation	Annual MRI starting at 25 y
Prior chest wall radiation at 10 y to 30 y	Annual MRI starting at 25 y
Lifetime risk 20% or greater by any model	Annual MRI starting at 35 y
Strong family history	Annual MRI starting at 35 y
History of breast cancer at younger than 50 y or with dense breasts	Annual MRI
History of breast cancer at 50 y or older with nondense breasts	No recommendation for or against MRI
American Cancer Society, 2007	
High risk (lifetime risk of less than 20%)	Annual MRI
BRCA1 and *BRCA2* carriers and their untested first-degree relatives	
Chest radiation at 10 y to 30 y	
Specific genetic mutations	
Intermediate risk (lifetime risk of 15–20%)	No recommendation for or against MRI
History of atypia or LCIS	
Dense breasts	
Personal history of breast cancer	

Note—LCIS = lobular carcinoma in situ.

mutation, women with a strong family history of breast cancer are at higher risk. As a result, the Cancer Australia guidelines state that women with "more than three first or second degree relatives with breast cancer" should undergo annual MRI [82]. For women with lifetime risk of 20% or greater and women with a genetics-based increased risk and their untested first-degree relatives, the ACR recommends annual screening mammography starting at 30 years old with annual screening breast MRI starting at 25 to 30 years old [59].

Any women treated with chest radiation (cumulative dose of 10 Gy or greater) before 30 years old are considered to be at high risk for breast cancer, starting approximately 8 years after treatment [86, 87]. Up to 20% of these women may develop breast cancer by 40 to 45 years old. Studies have shown the improved sensitivity (94–100%) of combining mammography and MRI [88, 89]. The ACR recommends annual mammographic screening beginning at 25 years old or 8 years after radiation, whichever is later, as well as annual screening MRI beginning at 25 years old [59].

Despite the lack of consensus, there is increasing interest in performing annual screening MRI in women with intermediate risk of breast cancer because of personal history of breast cancer, dense breasts, or history of high-risk lesions on biopsy (atypical ductal hyperplasia [ADH], atypical lobular hyperplasia [ALH], and lobular carcinoma in situ [LCIS]). Whereas the ACS guidelines cite insufficient evidence for using MRI in these groups, the more recent guidelines from ACR and the NCCN suggest that MRI should be considered, especially in combination with other risk factors.

Personal History of Breast Cancer

Women with a personal history of breast cancer have higher risk for recurrence as well as for a second primary breast cancer. Their risk for recurrence is 19.3% for the first 10 years after diagnosis with a 15-year mortality rate of 21.4% [90]. For women diagnosed with breast cancer before 50 years old, their lifetime risk for another breast cancer is 20% or more [91]. The sensitivity of mammography for early detection of second breast cancers is low due to postsurgical scarring and dystrophic calcifications. Multiple studies found remarkably concordant results [92] with MRI sensitivities ranging from 80–100%, whereas mammography sensitivities ranged from 0–53% [92]. Therefore, the ACR recommends annual screening MRI in conjunction with mammography for women with breast cancer diagnosis before 50 years old, as well as for women with breast cancer diagnosis and dense breasts [59]. The ACR is unique in considering the risk of multiple lower-risk factors, which can contribute to a sufficiently high lifetime risk of 20% or more (i.e., personal history of breast cancer and dense breasts).

Atypical Epithelial Hyperplasia

Women with history of ADH, ALH, and LCIS have a relative risk of 3–10 times greater for developing breast cancer compared with the general population [93, 94]. Sung et al. [95] found cancers in 14 patients with history of LCIS after 840 screening rounds of MRI and mammography; sensitivity was 71% and 36% for MRI and mammography, respectively. Friedlander et al. [96] found five cancers in 307 examinations with a relatively high biopsy rate (8.8%). Both studies reported a similar CDR (1.6%) and high rates of additional high-risk lesions at biopsy (35% and 25.9%). In a study of women with history of LCIS undergoing MRI and mammographic screening versus mammographic screening alone, there was a high incidence of detection (13% in 5 years), but no significant difference in overall CDR or tumor stage [97]. The benefit of MRI in women with history of LCIS is not entirely evident but likely present. For ADH and ALH, the overall evidence is scarce, with smaller studies showing lower CDR (0–1.5%) in supplemental MRI screening [98, 99]. For these reasons, the ACR recommends annual screening mammography with consideration for annual MRI in women with history of atypia, especially if other risk factors are present [59].

Two recent studies compared the benefits of MRI screening in these moderate risk groups. A 2019 retrospective study compared the performance of 5,170 screening MRI examinations in 2,637 women with different risk factors for breast cancer [100]. Whereas MRI performs well for women with a personal history of breast cancer or high-risk lesion, the lowest CDR was seen in women with family history of breast cancer, which suggests the need for better risk assessment strategies. Another recent study including 33,938 mammograms and 2,506 MRI examinations in 13,266 women with a personal history of breast cancer compared the performance of surveillance mammography with breast MRI [102]. Although MRI leads to higher biopsy rate ($p < 0.001$) and CDR ($p = 0.03$), there was no significant differences in sensitivity or interval cancers rather than mammography alone [101]. In summary, although supplemental MRI is not universally recommended in women with moderate risk, evidence for the use of MRI screening in the high-risk groups is clear.

Conclusion

All women are at substantial risk for breast cancer, even without dense breasts or family history of breast cancer. Hence, all women should undergo risk assessment for breast cancer by 30 years old so that higher-risk women can be identified and offered supplemental screening. For average-risk women, annual mammographic screening beginning at 40 years old maximizes the life-extending benefits and provides improved treatment options. For high-risk women, earlier and more intensive screening with mammography and MRI are needed. Delaying initiation or decreasing frequency of mammographic screening will not reduce overdiagnosis, but will likely result in delayed breast cancer detection.

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