THE JOURNAL OF FAMILY PRACTICE

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The authors reported no potential conflict of interest relevant to this article.

Mammography at age 40? A risk-based strategy

Breast cancer screening starting at age 40 continues to be controversial. Breast density—established with a baseline mammogram—is a key factor in the authors' algorithmic approach.

PRACTICE RECOMMENDATIONS

› *Recommend that women consider having a single mammogram at age 40 as a baseline so that breast density can be included in the assessment of risk.* (C)

› *Advise women with low breast density and no other significant risk factors that they are at lower than average risk for breast cancer and should consider this when discussing when to begin routine screening with their physician.* (C)

› *Recommend that women with a 2-fold increased risk for breast cancer begin regular screening in their 40s.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

"Doctor, when should I start having mammograms?" That's a question you're apt to hear again and again from women in their early 40s. It's also a question with no easy answer.

While deaths from breast cancer are declining, it remains the most commonly diagnosed cancer among US women. In 2012, approximately 229,060 new cases of breast cancer were detected and an estimated 39,920 women died from breast cancer[1]—about 10% of them in their 40s.[2]

Based on these numbers alone, it would seem that every woman should begin regular screening at age 40. Yet there are many other issues to consider, namely the high rate of false positives, as well as the overdiagnosis and overtreatment associated with such screening. Further complicating matters is the fact that there is no consensus as to whether screening mammography should be recommended—and if so, how often—for women ages 40 to 49 years who are at average risk.

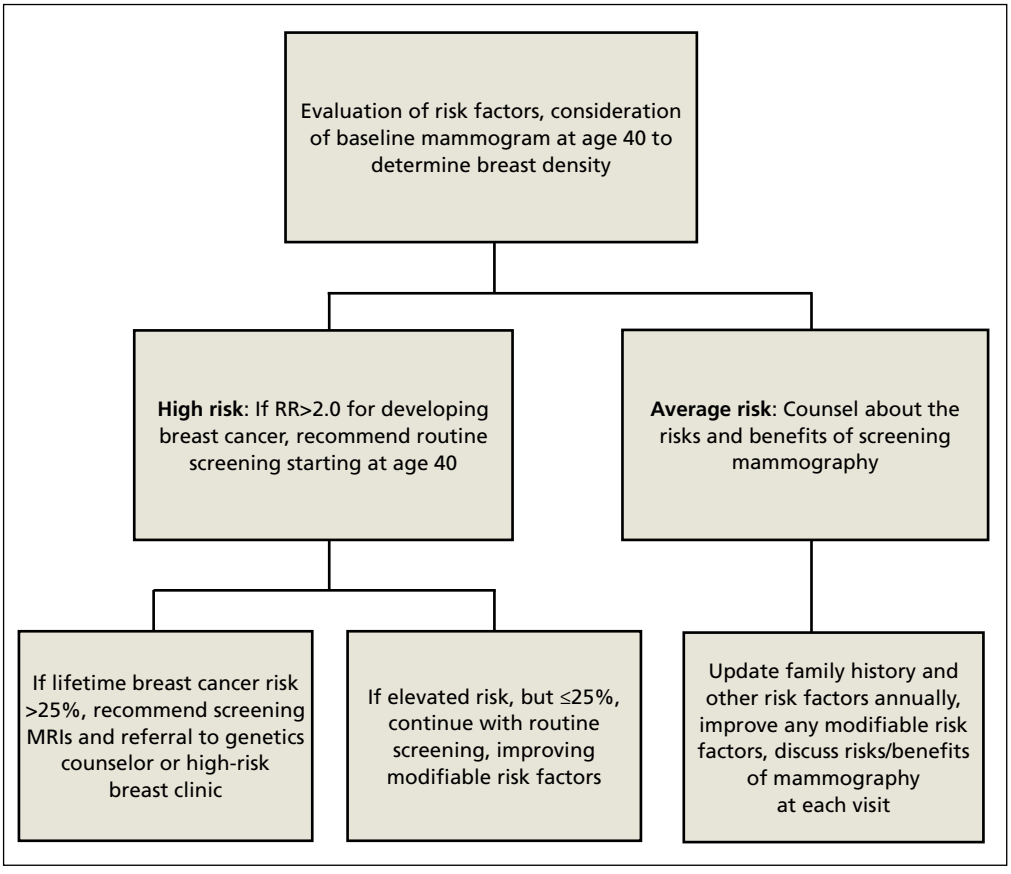
In light of this, we offer a risk-based strategy to mammography for younger women, which we've distilled into an **ALGORITHM**. But first, let's look at the evidence and what the US Preventive Services Task Force (USPSTF) and major medical groups have to say.

To screen or not to screen? A look at the evidence

A decision to perform screening mammography in premenopausal women should be made by weighing benefits vs harms. Benefits include diagnosis of breast cancer when it's in an early stage and a reduction in death. Meta-analyses have consistently shown that routine screening mammograms for women in their 40s can reduce mortality from breast cancer by 15% to 20%.[3-5] As noted by Cochrane reviewers in a meta-analysis

ALGORITHM

An algorithmic approach to breast cancer screening for women in their 40s



MRI, magnetic resonance imaging; RR, relative risk.
Sources: van Ravesteyn NT, et al. *Ann Int Med*. 2012[21]; Saslow D, et al. *CA Cancer J Clin*. 2007[26]; Berg WA, et al. *JAMA*. 2012.[27]

of 7 randomized controlled studies of breast cancer screening in younger women, a 15% relative risk (RR) reduction represents an absolute risk reduction of 0.05%.[5]

Potential harms include the financial cost; the screening regimen itself, which includes radiation exposure, pain, inconvenience, and anxiety; the ensuing diagnostic workup in the case of false positive results; and overdiagnosis—ie, detection of low-grade cancer that would not have otherwise become clinically evident—and subsequent overtreatment.[6] Diagnosis of ductal carcinoma in situ (DCIS) was rare before the advent of screening mammography. Now, DCIS accounts for 25% of all breast cancer diagnoses, and more than 90% of cases are detected only by imaging.[6] A large epidemiologic review published in 2012 suggested that the increase in breast cancer survival over the last 30 years is due to improved treatment regimens, not early detection.[7]

Recommendations are equivocal

Groups like the USPSTF, the American College of Obstetricians and Gynecologists, and the American Cancer Society, among others (See **TABLE W1**,[8-17] available at jfponline), recognize that women in their 40s may benefit from screening mammography. They generally acknowledge, however, that, the evidence is not strong enough to definitely recommend routine screening mammograms due to the higher risk of false positives and the lower

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TABLE 1

False positive mammogram risk decreases with age[8]

Age (y)	Receiving false positive results (%)	Receiving additional imaging (%)
40-49	9.78	8.43
50-59	8.66	7.59
60-69	7.9	7.02

overall incidence of breast cancer in this age group.

The USPSTF set off a firestorm in 2009 with its initial recommendation *against* routine screening for women in their 40s.[8] Shortly after, the group issued an update to "clarify their ... intent," stating that the decision to start regular screening mammography before age 50 should be an individual one based on patient values as well as an assessment of benefits and risks.[8]

More than 1900 women in their 40s need to undergo screening mammography in order to prevent just one death from breast cancer in 11 years of follow-up.

False positives decline with age

The risk of having a false positive result on a screening mammography decreases with increasing age, as the incidence of breast cancer rises (**TABLE 1**).[8] More than 1900 women in their 40s need to undergo screening mammography in order to prevent just one death from breast cancer in 11 years of follow-up,[8] with a direct cost of more than 20,000 visits for breast imaging and approximately 2000 false positive mammograms. In contrast, fewer than 400 women in their 60s would need to be screened in order to prevent one breast cancer death in 13 years of follow-up.[18] A large prospective cohort study (N=169,456) found that women who started annual screening at age 40 had a 61% chance of receiving at least one false positive mammogram result over the course of 10 years; the chance of a false positive dropped to 41.6% with biennial screening.[19]

The impact of a false positive lingers. A cohort study that followed 454 women for 3 years after they received a false positive mammogram result found that it continued to have a negative psychological impact on them.[20]

A risk-based screening approach

With no clear consensus on when to begin screening, primary care physicians and their patients would be wise to adopt a risk-based approach. Risk-based screening would focus efforts on women ages 40 to 49 who are more likely to benefit from screening mammography, which would represent a more effective use of resources.[2] To implement such an approach, it is critical to know the magnitude of risk reduction that would tip the balance of benefits and harms in favor of early screening, and which risk factors are associated with such an elevated risk (**TABLE 2**).[21]

A recent comparative modeling study found that for women with a 2-fold increased risk for breast cancer, the benefits and risks of starting biennial screening at age 40 are about the same as that of women at average risk who start biennial screening at age 50. As biennial screening at age 50 is widely recommended, the results of this study suggest that ≥2-fold risk is a useful threshold in determining when to start mammography screening for women in their 40s.[21]

The traditional counseling of women about breast cancer risks focuses on parity and age of first delivery, breastfeeding, obesity, and alcohol use, in addition to family history. However, none of these has an RR >1.5.[22]

Two risk factors are associated with ≥2-fold RR for breast cancer:

- having one or more first-degree relatives with breast cancer
- having extremely dense breasts.

A prior breast biopsy is also associated with a high RR (1.87).[21]

Does your patient have dense breasts? A baseline mammogram is necessary to determine a woman's breast density. The American College of Radiology developed BI-RADS (Breast Imaging Reporting and Data System) to standardize the reporting of density on mammograms.[23] BI-RADS has 4 categories of breast density:

1. Breast tissue is almost entirely fatty. (Adipose tissue is radiolucent and makes the mammogram easier to read.)
2. There are scattered fibroglandular

densities in the breast.
3. The breasts are heterogeneously dense.
4. The breasts are extremely dense.

When there is a discrepancy between the density of the left and right breasts, radiologists are instructed to use the higher density.[23] Another method of documenting density assesses the percentage of the breast tissue that is dense as compared to fatty tissue.

Increased density (BI-RADS category 3 or 4) likely accounts for a sizeable proportion of nonfamilial breast cancers.[24] In a large case control study (N=1112), density in ≥75% of the breast was associated with 26% of all breast cancers diagnosed in women under 56 years.[25] While a number of other risk factors for breast cancer are related to breast density (nulliparity, positive family history of breast cancer, and hormone therapy), higher density is associated with large increased risks of breast cancer independent of the other factors.[24]

TABLE 2

Which risk factors have the highest impact in women ages 40 to 49?[21]

Risk factor	RR
Three or more first-degree relatives with breast cancer	12.05
Two first-degree relatives with breast cancer	3.84
Age at diagnosis of first-degree relatives: <40 y	3.0
Age at diagnosis of first-degree relatives: 50-59 y	2.3
One first-degree relative with breast cancer	2.14
Breast density: BI-RADS Density Category 4	2.04
Age at diagnosis of first-degree relatives: 40-49 y	2.0
Any prior breast procedure	1.87
Other relative (not first-degree) with breast cancer	1.86
Age at diagnosis of first-degree relatives: >60 y	1.7
Breast density: BI-RADS Density Category 3	1.62
Breast density: BI-RADS Density Category 1	0.46

BI-RADS, Breast Imaging Reporting and Data System; RR, relative risk.

Initiate regular screening for women at high risk

Most high-risk women should have regular screening beginning at age 40. The American Cancer Society recommends screening with magnetic resonance imaging (MRI) as opposed to mammography for women with ≥20% lifetime risk of developing breast cancer.[26]

Adding an annual ultrasound to mammography may be another method of screening for high-risk women. A study of 2809 women with elevated breast cancer risk and dense breasts demonstrated that the addition of annual screening with either ultrasound or MRI detected an additional 3.7 cancers per 1000 women per year beyond mammography alone.[27] In that study, however, there was a significant number of false positive results, as well.

MRI is not indicated for women with a 15% to 20% lifetime risk. These women will benefit from routine screening starting at age 40, as well as genetic counseling if they have a family history of breast cancer. Increased breast density can also make mammograms harder to read, and there is concern that density can mask an early cancer. In fact, multiple studies have refuted that claim.[28] Breast density does tend to decrease with age, but the relationship between increased density and elevated risk of breast cancer persists through all age groups.

Get a baseline mammogram for those at lower risk

One approach to risk-based screening is to recommend that all women at average risk have an initial screening mammogram at age 40 to determine breast density and discuss other pertinent risk factors. If they are found to have BI-RADS density category 3 or 4, regular screening mammography throughout their 40s is a reasonable approach.

For those at low or average risk, things are less clear, and a discussion to determine the appropriate course of screening is needed. Some women with no family history of breast cancer will elect to wait until age 50 to

start screening mammography; others may not be comfortable doing so. It is important to point out to patients with very low density (BI-RADS density category 1) breasts that their risk for breast cancer is very low (RR=0.46) and that waiting until age 50 to start regular screening mammography would be a reasonable decision. JFP

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TABLE W1

Summary of screening mammography recommendations

Source (Year issued)	Should women in their 40s get mammograms?	If yes, how frequently?
American Academy of Family Physicians (2009)[10]	Maybe	Individualized decision (every 1-2 years, if performed)
American Cancer Society (2010)[14]	Yes	Annually
American College of Obstetricians and Gynecologists (2011)[15]	Yes*	Recommends offering screening annually, but acknowledges that biennial screening may be more appropriate for some
American College of Physicians (2007)[9]	Maybe	Individualized decision (every 1-2 years, if performed)
Canadian Task Force on Preventive Health Care (2011)[12]	No	Weak recommendation
Institute for Clinical Systems Improvement (ICSI)[11]	Maybe	Yearly (depending on medical history and preference)
National Cancer Institute (2010)[16]	Yes	Every 1-2 y
National Comprehensive Cancer Network (2011)[17]	Yes	Annually
National Health Service, United Kingdom (2011)[13]	Yes†	Every 3 years starting at age 47
USPSTF (2009)[8]	Maybe	Decision to start regular, biennial screening mammography should be an individual one, taking patient context and values into account

USPSTF, US Preventive Services Task Force.

*Annual screening should be offered.

†Start screening at age 47.