



Tailored Supplemental Screening for Breast Cancer: What Now and What Next?

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OBJECTIVE. This article reviews breast cancer risk assessment and the rationale for current screening guidelines, including when to consider using supplemental screening with MRI or sonography in addition to mammography, and discusses other emerging technologies. Radiologists can help identify women who may benefit from supplemental screening and can help to recommend when and which techniques to perform for this additional screening.

CONCLUSION. Mammography remains the mainstay of breast cancer screening. Mammography should be performed as digital imaging when possible in women with dense breasts. In women at high risk, particularly if they also have dense breasts, annual MRI is recommended, although further validation of outcomes is needed. In intermediate-risk women with dense breasts, especially those with other risk factors, and in high-risk women with dense breasts who are unable to tolerate MRI, supplemental sonography screening is an option at facilities with availability of qualified personnel. Developing technologies are not appropriate for screening at this time, although further study is encouraged.

For many years, mammography has been the only imaging test recommended for screening for breast cancer. Although mammography remains the only screening test proven to reduce breast cancer mortality, there is increasing awareness of certain subpopulations of women for whom mammography alone has reduced performance characteristics, particularly those with dense parenchyma. Women who have been determined to be at high risk of developing breast cancer are of special interest because there is higher prevalence of disease; any additional screening would, therefore, have higher yield. Furthermore, screening may begin at an earlier age in women at high risk, when the breast tissue is often denser and mammography is less effective. The addition of either contrast-enhanced breast MRI or sonography to mammography increases the detection yield of small node-negative cancers beyond that achieved with mammography alone. This article reviews breast cancer risk assessment and the rationale for current screening guidelines, including when to consider using supplemental screening with MRI or sonography in addition to mammography, and discusses other emerging technologies.

In 2007, the American Cancer Society (ACS) [1] updated its breast cancer screening

guidelines and, for the first time, advocated supplemental screening beyond annual mammography in certain high-risk women. Specifically, annual contrast-enhanced MRI was recommended in addition to mammography for women known to carry a *BRCA* mutation and for their untested first-degree relatives [1] as well as women known or suspected to carry mutations for other syndromes conferring high risk of breast cancer. More challenging for radiology practices was the recommendation for supplemental annual MRI in those with a “lifetime risk 20–25% or greater, as defined by...models that are largely dependent on family history” [1]. Many practitioners, including radiologists, are not intimately familiar with the various risk assessment models. (Discussions of the models and links can be found at: <http://caonline.amcancersoc.org/cgi/content/full/57/2/75/DC1> [accessed December 9, 2008].) Such models are neither readily available nor widely used in most breast imaging centers, but we, as radiologists, typically collect family history information, age at first menstruation, age at first childbirth, prior breast biopsy information, and other details that are used in such models (reviewed in [2]). Further complicating the use of formalized risk assessment tools, the individualized predicted risk of breast cancer

Keywords: breast cancer screening, breast imaging, breast MRI, breast sonography, gamma imaging, mammography, PET

DOI:10.2214/AJR.08.1706

Received August 20, 2008; accepted after revision October 28, 2008.

W. A. Berg is a consultant for Naviscan, Inc.

W. A. Berg's research for this article was supported by funding from The Avon Foundation and the National Cancer Institute, CA80098.

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AJR 2009; 192:390–399

0361–803X/09/1922–390

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Screening for Breast Cancer

varies depending on which model is used [1]. The highest calculated risk should be used to determine screening recommendations (R.A. Smith, personal communication, November 30, 2008).

Breast cancer risk assessment models are developed based on populations with known risk factor information and, ultimately, known prevalence of breast cancer. Models are used to predict which patients will benefit from chemoprevention [3] and to help genetic counselors determine which women should receive genetic testing for *BRCA* mutations [4]. Models have also been used to determine eligibility for supplemental imaging screening in research trials [5]. Integrating risk assessment into the daily practice of breast imaging, including answering questions from patients and making appropriate imaging recommendations for screening, remains challenging. This article presents information to guide the radiologist and referring physician in broad terms as these issues and models are further refined. Formal assessment of genetic risk is clearly the domain of genetic counselors. That said, radiologists can help identify women who may benefit from supplemental screening and can help to recommend when and which techniques to use for this additional screening.

When to Start Mammographic Screening

In the United States, the following organizations recommend annual mammographic screening beginning at age 40: the American Cancer Society, American College of Radiology, American College of Surgeons, American Academy of Family Practice, and American College of Obstetrics and Gynecology. In most European countries, screening begins at age 50. The age at which to begin screening women at increased risk of breast cancer would reasonably be when the risk for a younger woman is equal to that of an average woman of age 40 or 50 years depending on national policy.

Policy decisions about when to start mammographic screening are based in part on the incidence of breast cancer, which is fewer than 40 cases per 100,000 women under age 35 years across all ethnic groups and increases moderately beginning at age 40 (Fig. 1 and Table 1). One in 2,500 American women without any known risk factors will be diagnosed with breast cancer by the age of 30 years, one in 200 by age 40, and one in 50 by age 50 years. Rates peak between age 75 and 79 years and decrease after age 80. One

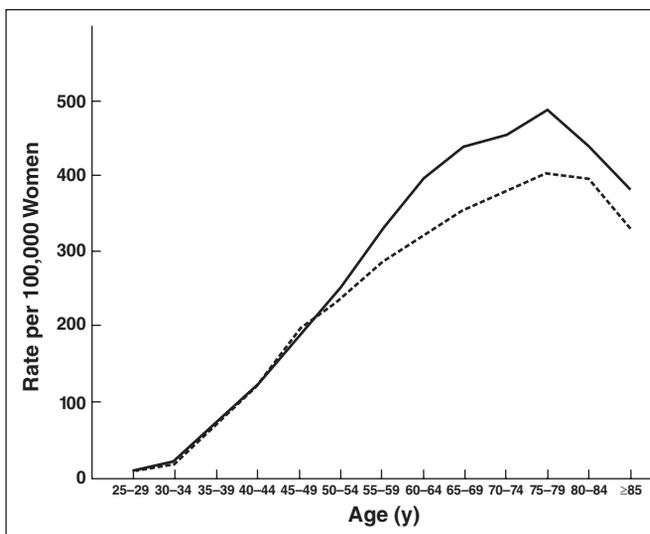


Fig. 1—Plot shows increasing incidence of newly diagnosed breast cancer among white (solid line) and African American (dashed line) women as function of increasing age. Note very low incidence in women younger than 30 years old. There is a steady increase in number of women diagnosed with breast cancer from age 30 to 69 years. Decline in breast cancer incidence after age 79 likely reflects both ascertainment bias and increased deaths due to other causes. Adapted with permission from [79].

in eight (12.5%) of all women who live to age 85 will be diagnosed with breast cancer [6].

One of the strongest and most well-studied risk factors for developing breast cancer is family history. The closer the relative is and the younger the age of the relative at diagnosis, the more the risk of developing breast cancer is increased. First-degree relatives are mother, sisters, daughters, father, brothers, and sons. The lifetime incidence of breast cancer (to age 80) among women with no first-degree relatives with breast cancer is 7.8% (just over 1 in 13) [7]. With one affected first-degree relative, this risk is 13.3% (1 in 7.5) and with two, 21.1% (more than 1 in 5) [7]. Researchers have proposed that screening start before age 40 if there is a family history of early breast cancer—specifically, 10 years before the age of diagnosis of the first-degree relative [8]. With one affected first-degree relative with breast cancer, the risk at age 35 is the same as the risk for a woman

with no affected relatives at age 40 [7]. With two affected first-degree relatives, the equivalent risk is seen at about age 32 [7].

In the absence of a *BRCA* mutation with known penetrance, the incidence of breast cancer in women—even those with a strong family history—is negligible before age 30; therefore, age 30 appears to be the lower age limit to begin screening other high-risk women. Further, in most series, there is an excess radiation risk to exposure at younger ages that decreases exponentially as a function of increasing age, with an estimated relative risk of 1.5 by age 30; below age 30, there may be a higher rate of causing cancer with screening mammography than of detecting early-stage cancer [9]. As such, mammography is not generally indicated for screening before implant placement or reduction surgery for a woman in her 20s.

Women who are known or suspected to carry *BRCA1* or *BRCA2* mutations are at

TABLE 1: Probability of Diagnosis with Breast Cancer Within the Next 10 Years as a Function of Age

Age of Woman at Risk (y)	Probability (%) of Breast Cancer Diagnosis Within Next 10 Years				
	Relatives with Breast Cancer			<i>BRCA1</i> Carrier [78]	<i>BRCA2</i> Carrier [78]
	None [7]	One First-Degree [7]	Two First-Degree [7]		
20	0.04	0.1	0.2	1.8	1.0
30	0.4	1.0	2.0	10	6.6
40	1.4	2.5	5.2	20	15
50	1.9	3.2	5.3	22	18
60	2.3	3.5	5.6	19	17
70	2.5	4.2	5.7	NS	NS

Note—NS = not stated.

particularly high risk of breast cancer, and *BRCA1* mutations especially confer high risk of early diagnosis of breast cancer. Although guidelines vary slightly [1, 10–12], the following women may benefit from genetic counseling and possible testing for *BRCA1* or *BRCA2* mutations:

- Currently untested first-degree relatives of a known *BRCA* mutation carrier;
- Women with a family history of both breast and epithelial ovarian cancer on the same (maternal or paternal) side especially if in the same woman;
- Breast cancer in a male family member;
- Very young age at diagnosis of breast cancer (i.e., before age 35 or 40) in the patient or a family member;
- Diagnosis \leq age 50 or two or more breast primaries (defined in [11]) and a family history of breast cancer diagnosed \leq age 50 or epithelial ovarian cancer at any age; and
- At least two family members on the same side of the family with breast cancer diagnosed before age 50.

About 2% of women of Ashkenazi Jewish heritage are estimated to be *BRCA*-mutation carriers [13]: a more aggressive testing approach is appropriate in such women.

The BRCAPRO [14], Tyrer-Cuzick (IBIS) [15] (<http://ems-trials.org/riskevaluator/>; accessed December 9, 2008), and BOADICEA [16] models can each be used to calculate risk of carrying a *BRCA* gene mutation and to help determine the risk of developing breast or ovarian cancer for individuals in families with known or suspected carriers. The Gail model [17] is not acceptable for estimating risk based on family history as it includes only first-degree affected maternal relatives. The Gail model does not predict mutation risk, although it is the only model that has been validated for predicting breast cancer risk in African American populations [18]. The Claus model [19] presumes a single autosomal-dominant gene and incorporates both first- and second-degree relatives and age of diagnosis but does not predict mutation risk per se.

Randomized trials of mammography were not stratified by risk. That said, the reduction in breast cancer mortality seen across women undergoing mammographic screening [20] is assumed to be valid for high-risk women as well, although this assumption may not be true. Because the incidence of breast cancer among *BRCA1* carriers even in their 20s exceeds that of women with no

family history in their 40s (Table 1), screening *BRCA1* carriers as early as age 20 may be reasonable, although National Comprehensive Cancer Network (NCCN) guidelines state that screening of this population should begin at age 25 [21] and the ACS [1] recommends that screening begin at age 30 for most women at high risk. Across two series evaluating 361 women with *BRCA1* mutations, mammographic screening revealed only 11 of 21 (52%) of cancers and nearly half of the cases (10/21, 48%) presented as interval cancers between annual screens [22, 23], suggesting that mammography alone is inadequate for screening *BRCA1*-mutation carriers. Of note, *BRCA1* carriers are particularly likely to be diagnosed with grade III invasive cancers and those with basal phenotype (estrogen and progesterone receptor-negative, *HER2/neu* oncogene-negative) [24]. It is not yet clear that even aggressive screening will alter the natural history of breast cancer in such women.

For *BRCA2* carriers, beginning screening at age 25–30 appears reasonable ([1]; Table 1), and NCCN guidelines recommend beginning at age 25 for all women with a strong family history [21]. Although there is the possibility of increased radiation sensitivity in some high-risk women, the very high rates of breast cancer are thought to justify any slight increased radiation risk from mammography [21]. The alternative to screening women at very high risk is prophylactic mastectomy, which has been shown to reduce the incidence of breast cancer by at least 90% [25].

In women younger than age 40 diagnosed with breast cancer or prior lobular intraepithelial neoplasia (atypical lobular hyperplasia [ALH] or lobular carcinoma in situ [LCIS]) or atypical ductal hyperplasia, it is reasonable to begin annual mammographic surveillance thereafter.

Early studies of women with prior mantle radiation therapy to the mediastinum or axilla (e.g., for Hodgkin's disease) after the age of 18 years and before the age of 30 years showed a high incidence of breast cancer beginning 8 years after treatment and peaking 15 years after treatment [26]. Newer (since the mid 1990s) treatments use lower radiation doses and more limited fields, and reduced rates of secondary breast cancer are expected, although this requires further study. The Children's Oncology Group [27] evaluates risk of secondary malignancies after treatment; in 2009, their recommendations will include annual mammography and MRI beginning 8

years after radiation treatment of ≥ 20 Gy to the chest and/or mediastinum, or by age 25, whichever is latest (Oeffinger K, personal communication, December 24, 2008).

Recommendations should serve as background information: Women and their doctors should engage in shared decision making as to when to begin screening. Based on the evidence available at this time, annual mammographic screening is recommended to begin by age 40 years or earlier as follows:

- Ten years before the age of diagnosis of a first-degree relative with breast cancer, but not before the age of 30 years unless suspected or known *BRCA* carrier;
- After the diagnosis of breast cancer;
- 6–12 months after radiation therapy if breast tissue is conserved, then every 6–12 months for 1–2 years, then annually per NCCN guidelines [28];
- After a breast biopsy shows lobular intraepithelial neoplasia or atypical ductal hyperplasia;
- As early as age 25–30 years if known or suspected *BRCA2* carrier;
- As early as age 20–25 years if known or suspected *BRCA1* carrier; and
- 8 years after radiation therapy to the chest and/or mediastinum, or by age 25, whichever occurs last.

When to Stop Mammographic Screening

Randomized controlled trials of mammography have included women only up to age 70 or 74 [20]. The mortality benefit from mammographic screening begins to be seen 5–7 years after the onset of screening; therefore, annual mammographic screening can be continued as long as there is reasonable expectation of a life expectancy of at least 5–7 years, provided that treatment would be pursued if a diagnosis is made. Retrospective studies have shown a downward shift in the stage distribution among women diagnosed with breast cancer who have continued mammographic screening [29, 30], suggesting that older women may benefit from continued screening. Badgwell et al. [29] recently showed that in women 80 years and older, each mammogram obtained produced a 37% reduction in risk of being diagnosed with late-stage breast cancer. Reduced all-cause mortality was associated with mammography use, which indicates that mammography users were healthier than nonusers and suggests that the benefit attributable to mammography may be smaller than that observed

TABLE 2: Summary of Studies of Mammography, Sonography, Combined Mammography and Sonography, MRI, and Combined Mammography and MRI in High-Risk Women

First Author of Study [Reference No.]	No. of Women with Cancer	No. of Women/ Total No. of Screening Examinations	No. (%) of Cancers ^a		No. (%) of Cancers Detected Using				No. of Cancers/ No. of Biopsies Prompted by MRI (%)	No. of Interval Cancers	
			Invasive	Node-Positive Invasive	Mammography	Sonography	Mammography and Sonography	MRI			Mammography and MRI
Hartman [40]	1	41/41	0	0	0	NP	NA	1 (100)	1 (100)	1/11 (9.1)	NA
Warner [46]	22	236/457	16	2	8 (36)	7 (32)	12 (55)	17 (77)	20 (91)	17/37 (46)	1
Kuhl [13]	43	529/1,542	34	5	14 (33)	17 (40)	21 (49)	39 (91)	40 (93)	39/78 (50)	1
Leach [42]	35	649/1,881	29	5	14 (40)	NP	NA	27 (77)	33 (94)	27/107 (25)	2
Lehman [43]	4	367/367	3	0	1 (25)	NP	NA	4 (100)	4 (100)	4/23 (17)	NA
Kriege [41]	45 ^b	1,723/4,039 ^b	39	5	14 (31)	NP	NA	34 (76)	41 (91)	32/56 (57) ^b	4
Sardanelli [45]	15 ^c	278/377	12	1	9 (60)	9 (60)	10 (67)	13 (87)	15 (100)	15/24 (63)	0
Lehman [44]	6	171/171	6	1	2 (33)	1 (17)	2 (33)	4 (67)	6 (100)	6/14 (43)	NA
Hagen [39]	21 ^d	491/867	19	5	8 (38)	NP	NA	16 (76)	18 (86)	NS	2 ^d
Total	192	4,485/9,742	158 (82.3)	24 (15)	70 (36)	34/86 (40)	45/86 (52)	155 (80.7)	178 (92.7)	141/350 (40.3)	10/184 (5.4)

Note—If there was no follow-up, NA is entered for interval cancers. NP = not performed, NA = not applicable.
^aOnly the most severe cancer is counted in each woman in these series, i.e., no more than one cancer per woman is considered.
^bAnother five cancers were diagnosed in five women who did not undergo all screening. There were 1,723 assessable women who underwent a total of 4,039 MRI screening examinations. In the first year, eight of 22 cancers were seen on mammography and 18 of 22 on MRI; there were two interval cancers. In subsequent rounds, there were six of 21 cancers seen on mammography and 16 of 21 on MRI; two cancers in subsequent rounds were interval cancers. Results for MRI-prompted biopsies are from an earlier report of Kriege et al. [48], not specifically stated in the later report [41].
^cOf 18 women diagnosed with cancer, only 15 underwent all three imaging techniques; the results of these 15 women are summarized.
^dTwenty-five women were diagnosed with cancer, but only 21 women with cancer had both mammography and MRI; results from these 21 women are summarized. Another three interval cancers were diagnosed in women who did not undergo MRI.

[29]. The average life expectancy of a woman reaching age 80 is 8.6 years, and that of an average woman reaching age 85 is 5.9 years [31]; the upper quartile of women reaching age 90 years have a life expectancy of 6.8 years, although women reaching the age of 95 years—even those in the upper quartile—have a life expectancy of only 4.8 years [31]. Given these life expectancy data, mammographic screening can reasonably be continued up to age 90 in the healthiest women and, rarely, longer at the patient's and care provider's discretion. Certainly screening is appropriate only when intervention would be performed if a suspicious finding is identified.

How to Screen
Mammography

The randomized trials that have shown reduced mortality from mammographic screening used film-screen mammography. In several large multicenter imaging trials, digital mammography had equivalent [32] or higher [33] cancer detection rates than film-screen mammography. Mammographic sensitivity is inversely proportional to breast density. Among women with heterogeneously dense or extremely dense parenchyma and the overlapping groups of premenopausal women and those under age 50, digital mammography has been shown to be more sensitive than film-screen mammography [32] and its use is encouraged in such populations. Interestingly, based on modeling from the Digital Mammographic Imaging Screening Trial (DMIST) [34], the use of digital instead of film-screen mammography in all women, including those with fatty breasts, has been estimated to cost approximately \$331,000 per quality-adjusted year of life saved (QALY), far exceeding the commonly accepted cost-effectiveness threshold of \$50,000 per QALY [35].

The targeted use of digital mammography only in women with dense breasts was estimated to cost a more acceptable rate of \$97,000 (95% CI, \$77,000–\$131,000) per QALY using DMIST data [34], but triaging each woman to undergo film or digital mammography on the basis of breast density is not practical for most facilities. Importantly, nearly all of the studies of supplemental screening methods to date have been in women who underwent film-screen mammography: Supplemental screening may have a smaller incremental yield when combined with digital mammography.

In women with a history of mastectomy for breast cancer and autologous tissue flap reconstruction, data on outcomes from mammography of the reconstructed breast are sparse. Helvie et al. [36] reported detection of two nonpalpable recurrences among 106 women (with 214 screen examinations) with transverse rectus abdominis myocutaneous (TRAM) flap reconstructions, with a positive predictive value of biopsy of 33%. In a series of 267 women (554 mammograms) with TRAM flaps, Lee et al. [37] found no malignancies and three benign biopsies were prompted. There are no data on long-term patient outcomes attributable to mammography use in this setting.

Supplemental Screening with MRI

There are no data to show reduction in mortality from breast cancer from any screening technique other than mammography. In the randomized controlled trials of mammographic screening, the rates of observed reduction in mortality from

mammographic screening parallel the rates of reduction in node-positive cancers [38]. Other techniques that depict node-negative breast cancers not shown on mammography should further reduce mortality, but this has not been shown.

Once women are of mammographic age as defined earlier, some at very high risk for developing breast cancer may also benefit from annual supplemental screening with contrast-enhanced MRI. Across nine nonoverlapping series in which 4,485 very high-risk women were screened with mammography and MRI [12, 39–46], only 70 of 192 (36%) cancers were identified on mammography, with an additional 108 (56%) cancers detected when MRI was used in addition, for an overall sensitivity of 92.7%. These studies are summarized in Table 2, with eligibility criteria summarized in [47] and paralleling recent guidelines [1]. Most cancers were node-negative (Table 2), and the median size of invasive cancers depicted on MRI was 7–18 mm [12, 39–46]. In an initial report of Kriege et al. [48], two control groups underwent only mammography: 43% of invasive cancers were < 10 mm in the group also undergoing MRI versus 13–14% in the control groups, and 21% of invasive cancers were node-positive in the MRI group versus 52–56% in the control groups.

As discussed earlier, the American Cancer Society guidelines [1] recommend annual supplemental screening with MRI in the following groups of women: known *BRCA*-mutation carriers; first-degree relatives of a *BRCA*-mutation carrier but untested; and those with a lifetime risk of breast cancer of ≈ 20% or greater, as defined by BRCAPRO [14] or other models that are largely dependent on family history (such as Tyrer-Cuzick [15] or BOADICEA [16] as discussed). Women with a first-degree relative with a *BRCA1* or *BRCA2* mutation who themselves test negative for known mutations would no longer be considered at high risk of inherited cancer: Screening recommendations default to those based on any other risk factors the woman may have. Based on self-administered questionnaires of risk, 0.43% of women undergoing mammographic screening met the > 20% lifetime risk criterion in one series [49]. Those same authors [49] noted that genetic testing is usually performed for women with ≥ 10% risk of *BRCA* mutation and that another 2% of women undergoing screening mammography meet that level of risk but have < 20% lifetime risk of breast cancer by

TABLE 3: Probability (%) of Diagnosis with Breast Cancer in the Next 10 Years as a Function of Age at Diagnosis of One Affected First-Degree Relative

Age of Woman at Risk (y)	Age of First-Degree Relative at Diagnosis (y)					
	20–29	30–39	40–49	50–59	60–69	70–79
30	1.8	1.2	0.9	0.6	0.4	0.4
40	3.7	2.7	2.0	1.5	1.2	1.0
50	5.4	4.2	3.2	2.6	2.2	2.0
60	5.5	4.4	3.7	3.3	3.0	2.7
70	4.0	3.5	3.1	2.8	2.6	2.6

Note—Adapted with permission from Claus et al. [19].

current models, which underscores the need for more consistent methods to identify high-risk women.

Based on consensus, women with other genetic syndromes conferring high risk of breast cancer were also recommended for annual MRI screening including those with Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndrome and their first-degree relatives [1]. Women with Peutz-Jeghers and hereditary diffuse gastric cancer syndrome are also at high risk for breast cancer but were not addressed in the American Cancer Society guidelines [1]. Women with a history of radiation therapy to the chest between the ages of 10 and 30 years were also among the groups recommended for annual MRI [1].

The lifetime risk of breast cancer decreases with the patient’s age despite an increasing incidence of breast cancer. For example, a

35-year-old woman with two first-degree relatives with breast cancer—using onset of menstruation at age 12–13, first child at age 25–29, and one prior benign biopsy—will have a lifetime risk of 24.7% by the Gail model, but only a 1% 5-year risk of breast cancer. By contrast, a 60-year-old woman with the same history will have a lifetime risk of 17.3% and a 5-year risk of 3.6%. As such, lifetime risk may not be ideal to guide supplemental screening practices. The Gail model [17, 50] does not consider the age at diagnosis of first-degree relatives and is not recommended to be used to determine risk to guide the use of screening MRI.

The 10-year risk may be the most appropriate for deciding screening guidelines (Robson M, presented at the 2008 National Conference on Breast Cancer) because it is a reasonable time frame in which to see a benefit

TABLE 4: Combinations of Age at Diagnosis of Two First-Degree Relatives Affected by Breast Cancer Yielding a 10-Year Probability (%) of Diagnosis with Breast Cancer Within the Next 10 Years of Greater than 5%

Age of Woman at Risk (y)	Age at Diagnosis of the Younger of the First-Degree Relatives (y)					
	20–29	30–39	40–49	50–59	60–69	70–79
30	None	None	None	None	None	None
	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>
40	20–79	30–69	40–59	None	None	None
	<i>20–49</i>	<i>30–39</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>
50	20–79	30–79	40–69	50–59	None	None
	<i>20–79</i>	<i>30–59</i>	<i>40–49</i>	<i>None</i>	<i>None</i>	<i>None</i>
60	20–79	30–79	40–69	50–69	None	None
	<i>20–69</i>	<i>30–59</i>	<i>40–49</i>	<i>None</i>	<i>None</i>	<i>None</i>
70	20–79	30–69	40–59	None	None	None
	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>

Note—“None” means that all age combinations have a 10-year estimated risk of less than 5% or less than 8%: MRI would not be recommended based solely on family history risk. Numbers in cells refer to the age (in years) of the older of the affected first-degree relatives needed to meet a 5% or, in italics, 8% 10-year risk threshold. *Italics* show > 8% 10-year risk. Adapted with permission from Claus et al. [19].

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TABLE 5: Combinations of Age at Diagnosis of Mother and Maternal Aunt Affected by Breast Cancer Yielding a Probability (%) of Diagnosis with Breast Cancer within the Next 10 Years of Greater Than 5%

Age of Woman at Risk (y)	Age of Mother at Diagnosis (y)					
	20–29	30–39	40–49	50–59	60–69	70–79
30	None	None	None	None	None	None
	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>
40	20–79	20–69	20–59	20–49	20–39	None
	<i>20–49</i>	<i>20–39</i>	<i>20–29</i>	<i>None</i>	<i>None</i>	<i>None</i>
50	20–79	20–79	20–79	20–59	20–49	20–39
	<i>20–79</i>	<i>20–59</i>	<i>20–49</i>	<i>20–39</i>	<i>20–29</i>	<i>None</i>
60	20–79	20–79	20–79	20–69	20–49	20–39
	<i>20–69</i>	<i>20–59</i>	<i>40–49</i>	<i>20–39</i>	<i>20–29</i>	<i>None</i>
70	20–79	20–69	20–49	20–39	20–29	None
	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>	<i>None</i>

Note—“None” means that all age combinations have a 10-year estimated risk of less than 5% or less than 8%: MRI would not be recommended based solely on family history risk. Numbers in cells refer to the age (in years) of the maternal aunt needed to meet a 5% or, in italics, 8% 10-year risk threshold. *Italics* show > 8% 10-year risk. Adapted with permission from Claus et al. [19].

from screening. Given that models underestimate actual observed risk by approximately 50% [51], a 5% 10-year risk of developing breast cancer may be an appropriate threshold. This translates to an actual risk of 20% over 20 years (i.e., a surrogate time frame for “lifetime” risk). Indeed, using data derived from the Claus model [19] (Tables 3–5), use of a 5% 10-year threshold closely parallels groups of women for whom the lifetime risk is more than 20%. In general, with only a single first-degree relative with breast cancer, the relative must be diagnosed in her 20s for the woman at risk to meet the 5% 10-year “high-risk” criterion, and even then, only women currently in their 50s or 60s will meet this threshold (Table 3). Most women over age 40 with two first-degree relatives with breast cancer (Table 4) or with both mother and a maternal aunt with breast cancer (Table 5) will also meet this definition of high risk. As discussed later, an 8% 10-year risk threshold has been proposed for MRI in the United Kingdom: Combinations of relatives yielding at least an 8% 10-year risk are also presented (in italics in Tables 4 and 5).

The cost-effectiveness of MRI depends on the incidence of breast cancer. In the United Kingdom, MRI was deemed to be cost-effective for *BRCA1* carriers between ages 30 and 49, at < \$100,000 per QALY, when the 10-year risk was 5% or higher [52]. In the United Kingdom, MRI is offered only to women at familial risk between ages 30 and 39 with an 8% 10-year risk or women 40–49

years old with at least a 20% 10-year risk. The number of years of life to be saved by any screening technique will decrease with increasing patient age and thereby diminish its cost-effectiveness.

The presence of dense breast tissue reduces mammographic sensitivity and thereby increases the cost-effectiveness of MRI. Based on modeling from the Canadian experience with screening MRI [53], the cost per QALY for women 35–54 years old with a *BRCA1* mutation was \$55,420 for all such women and \$41,183 in those younger than age 50 with dense breasts; for *BRCA2* carriers, the respective cost per QALY was \$130,695 overall and \$98,454 among those younger than age 50 with dense breasts. Importantly, in an analysis of cancers in a Canadian study [54], the sensitivity of mammography in *BRCA* carriers with fatty breasts or only minimal scattered fibroglandular density was only 33% compared with 94% for MRI, indicating that mammography alone is not sufficient for *BRCA* carriers even when the parenchyma is not dense.

Estimates of cost-effectiveness must also consider the tolerability of the screening test—that is, the quality of the estimated years of life saved. Not all women can tolerate MRI. Women with claustrophobia, aneurysm clips, pacemakers, and other metallic implants may not be candidates for MRI. Women with renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m²) may be at increased risk of nephrogenic

systemic fibrosis [55] and thus not eligible for injection of gadolinium-based contrast agents. For some women, the substantial (3–19%) [12, 41, 42, 46] risk of needing a biopsy on the basis of MRI, with approximately 60% of such biopsies proving not to be cancer (i.e., false-positives, Table 2), is not tolerable (Schleinitz MD, personal communication June 1, 2008). Given the high likelihood of a suspicious lesion needing biopsy being seen only on MRI, it is incumbent on imaging centers that perform contrast-enhanced breast MRI to have the ability to offer MRI-guided biopsy when necessary, although in a recent survey of members of the Society of Breast Imaging performing breast MRI, 31% did not perform MRI-guided interventional procedures [56].

Some centers offer MRI and mammography at the same time, and others advocate staggering these examinations by 6 months (e.g., mammography in January and MRI in July). Most cancers are seen on only one of the two examinations, so it is not clear that the staggered approach will provide earlier breast cancer detection. Furthermore, correlation with a current mammogram is often helpful to establish benignity of findings on MRI. Either approach is acceptable at this time, although further study of this issue is encouraged.

Intermediate-Risk Women

The greatest area of debate at present centers on what to recommend for screening for the many millions of women at moderate increased risk who do not meet the current criteria for supplemental screening with MRI, but for whom mammography may be of limited sensitivity. This group includes women with a personal history of breast cancer; those with LCIS or atypical ductal or lobular hyperplasia; those with dense breasts; and those with intermediate family history (lifetime risk of 15–20%) [1]. The American Cancer Society [1] indicates the evidence for or against the use of MRI in such women is insufficient, although the NCCN guidelines [21] recommend annual MRI in women with prior LCIS. Clearly, the lower the prevalence of disease, the lower the cost-effectiveness and the higher the false-positive rates will be: Using MRI in all intermediate-risk women would be problematic.

It seems intuitive that a woman with a personal history of breast cancer who otherwise meets the established high-risk criteria could be considered “high risk” and thereby be rec-

ommended for annual supplemental screening with MRI; this assumption may be correct, although few series [12] have included such women. Determination of risk in women with prior breast cancer is often complicated by concurrent risk-reduction treatments, such as aromatase inhibitors or tamoxifen, that significantly decrease the risk of breast cancer [3]. Additional data are needed to guide the use of supplemental screening MRI in women with a personal history of breast cancer.

Approximately half of women under age 50 have dense breast tissue, and roughly one third of women over age 50 still have dense breasts [57]. Cancers diagnosed during the interval between screening examinations have a worse prognosis and are increasingly common with increasing breast density, with an odds ratio of 17.8 for interval cancer among women with > 75% dense breasts compared with those with ≤ 10% breast density [58]. Breast density is not included in models used to predict breast cancer risk, although extremely dense parenchyma appears to confer at least 4–5 times increased risk in and of itself [58, 59]. Although there are some situations in which estimated breast density from two-view mammography may be inaccurate [60], the visual assessment of “dense” can be made quite consistently at the extremes [61] where the risk is highest. It appears likely that extremely dense parenchyma alone or heterogeneously dense parenchyma in combination with any other risk factor would confer “high risk,” but current guidelines do not fully address this issue.

Screening Sonography

Sonography has advantages over MRI as a screening test: It is well tolerated by patients, is widely available, and is relatively inexpensive. Across four series in which screening mammography, sonography, and MRI were performed in high-risk women, however, the combined sensitivity of mammography and sonography was only 52%, compared with 92.7% after combined mammography and MRI [12, 44–46] (Table 2). Thus, in high-risk women, when supplemental screening is planned, MRI should be performed in lieu of sonography when possible. If MRI is performed, screening sonography offers essentially no additional cancer detection yield [12, 44–46]: In women screened with both mammography and MRI, sonography should be reserved for further evaluation or biopsy of mammographic or MRI abnormalities as needed.

Seven single-center studies (reviewed in [62]) and two multicenter trials, the Italian study [63, 64] and the American College of Radiology Imaging Network (ACRIN) protocol 6666 [5], have shown remarkably consistent supplemental detection yields of 2.7–4.6 per 1,000 women screened with sonography. Although Kolb et al. [65] performed multiple rounds of screening, they did not distinguish results from each round. The other series to date report on a single prevalence screen; data from subsequent rounds in ACRIN 6666 will be forthcoming. Almost all of the cancers found on screening sonography are invasive and most are node-negative, with a median size of 9–11 mm in the series to date [5, 64–70]. False-positives are more common with sonography than with MRI, in part because of the lower prevalence of disease in women screened with sonography; in the ACRIN 6666 protocol, 8.8% of biopsies prompted only by sonography showed cancer [5] even with examinations performed by specialist radiologists using a standardized protocol.

At this time, screening sonography should be considered in the following women in decreasing order of priority:

- Very high-risk women who cannot tolerate MRI;
- Women at intermediate risk (personal history of breast cancer, prior LCIS, prior atypical hyperplasia, or intermediate family history) with dense parenchyma; and
- All women with dense breasts.

There are several barriers to implementing widespread screening sonography, at least in the United States. First, there is a shortage of trained radiologists able to perform screening sonography. It is not possible to offer this examination to all women with dense breasts. At this time, there is insufficient evidence to address the efficacy of technologist-performed screening sonography; only one single-center study evaluated technologist-performed screening sonography [69], with 1,862 women evaluated and six cancers detected. Automated breast sonography devices may facilitate capture of standardized images for later radiologist review, but at present, there are concerns that the resolution of the images obtained by most automated scanners is limiting and that unacceptably high recall rates will result.

Second, the reimbursement for screening breast sonography (at a global fee of \$85 national Medicare average in 2008 for any breast sonography, screening or diagnostic) does not fully cover the costs of offering this service. If screening sonography is performed, high-res-

olution linear-array transducers (maximum frequency ≥ 12 MHz) should be used. A minimum of standard four-quadrant images and one behind the nipple should be documented as in the ACRIN 6666 protocol (www.acrin.org). Training materials used in the ACRIN protocol are archived at ACRIN headquarters (Philadelphia, PA).

Average-Risk Women

There are no data to support supplemental screening with either MRI or sonography among women with nondense breasts who do not fall into the high- or intermediate-risk groups defined earlier. This group includes women whose lifetime risk is < 15% [1].

What Next?

Tomosynthesis provides mammographic images as slices through the breast. The potential advantage to this is that normal overlapping tissues may no longer obscure or simulate underlying masses. At present, lower recall rates have been shown using tomosynthesis (Moore RH, presented at the 2007 annual meeting of the Radiological Society of North America [RSNA]). Concerns persist that the morphology of calcifications may be difficult to discern due to blurring from the tomographic technique. Because observing the distribution of calcifications is necessary for appropriate management, it is necessary to “slab” together multiple individual tomosynthesis images to assess calcifications and thus review each set of images twice (i.e., once image by image and then “slabbed”). Storage and image transmission requirements are very large, with over 1 GB required per case. Further, it appears that tomosynthesis images will still need to be acquired in both craniocaudal and mediolateral oblique projections (Rafferty EA, presented at the 2006 annual meeting of the RSNA), thereby increasing the radiation dose, time to acquire and review the images, and storage requirements.

Multicenter data characterizing the sensitivity and overall performance characteristics of tomosynthesis for screening are eagerly awaited, and approval by the U.S. Food and Drug Administration (FDA) is pending at this time. If substantial success is shown, tomosynthesis could reduce the efficacy of supplemental MRI or sonography screening.

Experience with dedicated breast gamma camera imaging to date is limited: Results for fewer than 1,000 patients have been published at this time [71–73], with 79%–94% sensitivity to known cancers reported. This

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approach requires injection of 20–30 mCi (740–1,110 MBq) of ^{99m}Tc -methoxyisobutyl isonitrile (Sestamibi, DuPont Pharmaceuticals), a wait time of about 10 minutes, and then imaging with gentle compression for about 10 minutes per view (i.e., ≈ 40 minutes for a standard four-view bilateral examination). There is loss of about 1 cm of tissue at the chest wall and, in addition to cancers, fibroadenomata, fat necrosis, and fibrocystic change can show abnormal tracer accumulation. Broader validation of this technology is needed, as is standardized methodology to biopsy lesions seen only on gamma camera imaging, before gamma camera imaging can be considered appropriate for general use.

Dedicated PET of the breasts (“positron emission mammography” [PEM]) is possible using high-resolution dedicated devices. At present, this technology is approved for Medicare payment for evaluating local extent of disease; for assessing treatment response to neoadjuvant chemotherapy; and for evaluating for possible recurrence, but not for screening. This technology requires extensive shielding because of the high energy (511 keV) of positrons. The use of ^{18}F -FDG as the tracer mandates that the patient fast for at least 4, if not 6, hours before injection. At least 60 minutes of “soak time” is required for tracer to accumulate in areas of interest and the patient must not be active during that time. Gentle compression, with positioning similar to mammography, and a 10-minute acquisition time per image are required. As with gamma camera imaging, approximately 1 cm of tissue is inadequately imaged at the chest wall.

Although the specificity of PEM may be more than 80% among benign lesions with suspicious findings on mammography and/or sonography [74], the sensitivity of this approach to cancers not recently biopsied requires further study. Multicenter evaluation comparing PEM with MRI in women with newly diagnosed cancer is in progress. PEM technology is unlikely to have a role in screening as it is presently performed given its high cost and high, nearly 1 rad (0.01 Gy), whole-body radiation dose.

Thermography assesses differences in temperature, and cancers can be identified because of differential blood flow. In the multicenter Breast Cancer Detection and Demonstration Project in the 1970s [75], thermography was found to have very low sensitivity and specificity in women with stage I breast cancer. More recent devices have not overcome low specificity [discussed

in reference 76]. Because of the lack of any proven efficacy, thermography has no validated role in screening.

Dedicated breast CT scanners are being developed, and early results from 79 women appear promising [77], although further study is needed. Compression is not needed, and radiation exposure, averaging 6 mGy (600 mrad) for average-sized breasts, is comparable to that from four mammographic images. Dense breast parenchyma can obscure detection of malignant masses on breast CT unless contrast material is used. In preliminary work, calcifications were better depicted on mammography than on CT [77].

Summary

Mammography remains the mainstay of breast cancer screening. Mammography should be performed as digital imaging when possible in women with dense breasts. In women at high risk, particularly if they also have dense breasts, annual MRI is recommended, although further validation of outcomes is needed. In intermediate-risk women with dense breasts, especially those with other risk factors, and in high-risk women with dense breasts who are unable to tolerate MRI, supplemental sonography screening is an option at facilities with availability of qualified personnel. Developing technologies are not appropriate for screening at this time, although further study is encouraged.

Acknowledgments

Special thanks to Edward A. Sickles, Robert A. Smith, Daniel Lehrer, and Laura Amodei for thoughtful review and helpful comments.

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