Screening Mammography for Women in Their 40s: A Retrospective Study of the Potential Impact of the U.S. Preventive Service Task Force's 2009 Breast Cancer Screening Recommendations

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OBJECTIVE. The objective of our study was to review screening mammography examinations performed at our institution from 2007 through 2010 with the primary endpoint of determining the incidence of breast cancer and associated histologic and prognostic features in women in their 40s.

MATERIALS AND METHODS. Patients who presented for screening mammography who ultimately (i.e., after additional imaging, including diagnostic mammographic views and ultrasound) received a BI-RADS assessment of a category 4 or 5 for a suspicious abnormality were followed retrospectively through completion of care and were analyzed with respect to pathology results after biopsy, treatment, and family history.

RESULTS. During the study period, 43,351 screening mammography examinations were performed; 1227 biopsies were recommended on the basis of those studies and yielded 205 breast cancers (cancer detection rate of 4.7 per 1000 screening examinations). These screening examinations included 14,528 (33.5%) screening examinations of patients in their 40s; 413 biopsies were recommended and yielded 39 breast cancers (39/205 = 19%) (cancer detection rate of 2.7 per 1000 screening examinations). More than 50% (21/39) of the cancers in women in their 40s were invasive. Only 8% (3/39) of the women in their 40s with screening-detected breast cancer had a first-degree relative with breast cancer.

CONCLUSION. From 2007 through 2010, patients in their 40s accounted for one third of the population undergoing screening mammography and for nearly 20% of the screening-detected breast cancers—more than half of which were invasive. This information should be a useful contribution to counseling women in this age group when discussing whether or not to pursue regular screening mammography.

Keywords: breast cancer, screening mammography, U.S. Preventive Services Task Force (USPSTF), women in their 40s

DOI:10.2214/AJR.12.10390

Received November 29, 2012; accepted after revision March 21, 2013.

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AJR 2013; 201:1401–1406

0361–803X/13/2016–1401

Breast cancer is the second most common cancer among American women [1], and multiple studies have shown that screening mammography reduces breast cancer mortality for women over 40 years old [2, 3]. For example, in one of the longest running studies to date, the Swedish Two-County Trial [4], has shown a 30% risk reduction in breast cancer mortality over a follow-up period of nearly 3 decades. Other studies have shown that women in their 40s with breast carcinoma who undergo regular screening mammography have a more favorable cancer stage at diagnosis than those who do not undergo regular screening; however, critics argue that downstaging represents overdiagnosis of ductal carcinoma in situ (DCIS) and nonaggressive cancers that might not impact survival [5]. Between 1990 and 2007, breast cancer deaths decreased 3.2% per year among women younger than 50 years and 2.0% per year among women 50 years old and older; whereas some attribute these decreases to earlier detection with screening mammography, others favor advances in adjuvant therapy as the dominant reason [6]. The bottom line is that screening mammography is one of the most thoroughly scrutinized tests in the history of medicine.

The most recent chapter in this long-standing debate started in November 2009 when the U.S. Preventive Services Task Force (USPSTF) updated its previous 2002 statement and continues today with the recent controversial *New England Journal of Medicine* article by Bleyer and Welch [7]. In contrast to the USPSTF's 2002 recommendations [8], which advised screening mammography every 1–2 years for all women older than 40 years, the 2009 USPSTF guidelines [9] recommend "biennial screening mammography for women aged 50 to 74 years" and state the following:

> The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms.

This recommendation is incongruous with the guidelines of the American Cancer Society [10] and the American College of Radiology (ACR) [11], both of which recommend annual screening mammography for women starting at age 40.

The goal of this study was to review the screening mammography examinations performed at our institution from 2007 through 2010 with the primary endpoint of determining the incidence of breast cancer and associated histologic and prognostic features of breast cancer in women in their 40s, a cohort for whom the USPSTF 2009 guidelines does not recommend routine surveillance. Although the U.S. Department of Health & Human Services in implementing the Affordable Care Act used the 2002 recommendations [9] and although American women may understand that there is no absolute certainty in medicine and that there are differing interpretations of data surrounding breast cancer diagnosis and treatment, this objective is still important because the persistence of the 2009 guidelines causes confusion in patients and physicians alike as a result of the mixed messages and may potentially impact compliance with screening for women in their 40s. This topic is worthy of attention because the USPSTF guidelines represent important public policy referred to by physicians, legislators, and patients, many of whom are increasingly consulting the medical literature. The specific purpose of this article is to present our experience to contribute to the ongoing medical and policy discussion about this important women's health issue.

Materials and Methods

This study was HIPAA compliant and was approved by the institutional review board at our institution. All patients presenting for screening mammography without clinical findings between January 1, 2007, and December 31, 2010, were included. Patients who indicated the presence of a palpable abnormality at screening that necessitated diagnostic workup were excluded from this study.

Patients who presented for screening mammography who ultimately (i.e., after additional imaging including diagnostic mammographic views and ultrasound) received a BI-RADS assessment of a category 4 or 5 for a suspicious abnormality were followed retrospectively through completion of care with attention to pathology results, staging, and treatment, as well as family history of breast cancer and genetic testing results when available.

The positive predictive value (PPV) of screening mammography was calculated by dividing the number of true-positive examinations by the sum of the true-positive and false-positive examinations. Two additional separate PPV calculations were performed using BI-RADS methods [12] (Tables 1 and 2): PPV2, defined as the probability of cancer after a BI-RADS category 4 or 5 assessment, and PPV3, defined as the probability of cancer among patients who underwent biopsy after a BI-RADS assessment of category 4 or 5. All types of biopsy (ultrasound-guided, stereotactic, and surgical) were included. The breast cancer detection rate was calculated as the number of breast cancers divided by the number of screening examinations.

True-positives were defined as patients with a BI-RADS assessment of category 4 or 5 who underwent biopsy and pathology yielded invasive breast cancer or DCIS; patients found to have other forms of cancer were not included in this "true-positive" category because the goal of our study was to examine the efficacy of screening mammography in detecting breast cancer. False-positives were defined as patients with a BI-RADS category 4 or 5 assessment who underwent biopsy and pathology yielded nonmalignant results, including atypical ductal hyperplasia and atypical lobular hyperplasia. Patients with atypia were followed through excisional biopsy for definitive pathology to exclude the possibility of upgrades to DCIS or invasive carcinoma; in such occurrences, patients were reclassified as true-positives and included in the total cancer detection rate. Patients with a BI-RADS assessment of category 4 or 5 who were lost to follow-up or who underwent biopsy and pathology yielded nonbreast malignancy were included in the PPV2 calculation (i.e., the All Other column in Table 1).

Results

During the 4 years included in this study, 43,351 screening mammography examinations were performed at our institution, averaging more than 10,000 annually (Table 1). The women ranged in age from 31 to 88 years old at the time of screening, with patients 40–49 years old comprising 33.5% (14,528/43,351) of those screened.

Overall, on the basis of the 43,351 screening mammography examinations performed from 2007 through 2010, 1227 biopsies were ultimately recommended (BI-RADS assessment of category 4 or 5 for a suspicious abnormality) (1227/43,351 = 2.8%). Of those biopsies, 205 yielded DCIS or invasive breast carcinoma, which corresponds to a breast cancer detection rate of 4.7 per 1000 screening examinations, a PPV2 of 17%, and a PPV3 of 18% (Table 1). Of the 43,351 screening mammography examinations performed during this time frame, 14,528 were of women in their 40s (33.5%). On the basis of these 14,528 studies, 413 biopsies were ultimately recommended (BI-RADS assessment of category 4 or 5 for a suspicious abnormality) (413/14,528 = 2.8%) (Table 1). Of those biopsies, 39 yielded DCIS or invasive breast cancer, which corresponds to a breast cancer detection rate of 2.7 per 1000 screening examinations, a PPV2 of 9.4%, and a PPV3 of 10%. Thus, 19% (39/205) of all screening-detected breast cancers were in women in their 40s. The percentage of biopsies recommended (2007–2010), out of the total number of screening examinations, was the same for women in their 40s (413/14,528 = 2.8%) as it was for women of all ages (1227/43,351 = 2.8%).

The tumor characteristics for women in their 40s diagnosed with breast cancer are summarized in Table 2. Eighty-two percent (32/39) had stage 0 DCIS (18/39 = 46%) or stage I disease (14/39 = 36%); 15% (6/39), stage II disease; 3% (1/39), stage III disease; and no patients (0%), stage IV disease. Histologic analysis of these breast cancers showed a ductal subtype in 92% (18 DCIS + 3 DCIS with microinvasion + 15 invasive ductal carcinoma [IDC] = 36/39), two cases of invasive mammary carcinoma not otherwise specified (NOS), and one case of invasive mucinous carcinoma. Overall, there was an invasive component in 54% (3 DCIS with microinvasion + 15 IDC + 2 invasive mammary carcinoma NOS + 1 invasive mucinous carcinoma = 21/39). The majority (32/39 = 82%) of the tumors were intermediate to high nuclear grade. In terms of hormone receptor status, 82% (32/39) of the tumors were estrogen receptor (ER)–positive, 67% (26/39) were progesterone receptor (PR)–positive, and 18% (7/39) were human epidermal growth receptor 2 (HER2/neu)–positive. Surgical treatment was known for 33 of the 39 patients: 70% (23/33) had lumpectomy and 30% (10/33) had mastectomy. The remaining six patients pursued treatment outside our institution; thus, the surgical details of those cases are not known.

Table 3 summarizes potential breast cancer risk factors for the women in their 40s diagnosed with breast cancer in our study. Only 8% (3/39) had a first-degree family member with a history of breast cancer. Genetic status was known for 24 patients; four had the *BRCA1* or *BRCA2* mutation (4/24 = 17%). Ninety per-

TABLE 1: Screening Mammography Examinations Performed at Our Institution From 2007 Through 2010

Year	No. of Screening Examinations	No. (%) of Biopsies Recommended (BI-RADS Categories 4 and 5)	Breast Cancers[a] (No. of Patients)	Benign Pathology[b] (No. of Patients)	All Other[c] (No. of Patients)	PPV2[d]	PPV3[e]	Breast Cancer Detection Rate
2007	8267	290	46	211	33	0.16	0.18	0.0056
2008	11,108	283	42	226	15	0.15	0.16	0.0038
2009	12,193	331	59	254	18[f]	0.18	0.19	0.0048
2010	11,783	323	58	248	17	0.18	0.19	0.0049
2007–2010								
All women	43,351	1227 (2.8)	205	939	83	0.17	0.18	0.0047
Women in their 40s	14,528	413 (2.8)	39	346	28[g]	0.094	0.10	0.0027

Note—PPV = positive predictive value.
[a]True-positive = invasive breast cancer or ductal carcinoma in situ.
[b]False-positive = all nonmalignant pathologic diagnoses including atypical ductal hyperplasia and atypical lobular hyperplasia.
[c]Patients lost to follow-up and patients with nonbreast malignancies.
[d]PPV2 = TP / (TP + FP + All Other) = TP / biopsies recommended.
[e]PPV3 = TP / (TP + FP + nonbreast malignancies) = TP / biopsies performed.
[f]Includes a 64-year-old patient who had a biopsy performed with pathology yielding chronic lymphocytic leukemia and a 40-year-old patient who had a biopsy performed with pathology yielding plasma cell myeloma versus B-cell lymphoma.
[g]Includes the 40-year-old patient who had a biopsy performed with pathology yielding plasma cell myeloma versus B-cell lymphoma.

cent (35/39) had heterogeneously dense (n = 26) or extremely dense (n = 10) breasts, 8% (3/39) had scattered fibroglandular densities, and no patients (0%) had fatty breasts.

Discussion

The USPSTF's November 2009 change in recommendations regarding the age and frequency at which to start routine screening mammography reignited widespread debate and gave impetus to new research on the issue [13, 14]. In our study, from 2007 through 2010, nearly 20% of all screening-detected breast cancers at our institution were in women in their 40s. The majority of these cancers had an invasive component and were intermediate to high grade and thus are associated with an intrinsically worse survival rate [15]; however, most were early stage with a favorable hormonal receptor status, factors associated with both a reduction in breast cancer mortality [14] and positive treatment response to hormonal therapies [16]. Our main finding that nearly 20% of all screening-detected breast cancers were in women in their 40s is important because other studies have shown that more than 40% of the years of life lost to breast cancer are among women diagnosed in their 40s [17]. Our other main finding is that more than half of these cancers were already invasive. However, the flip side of the argument—that almost half of the breast cancers detected in women in their 40s were "only" DCIS, potentially representing a substantial degree of overdiagnosis—could certainly be made by Bleyer and Welch [7], authors of the well-publicized 2012 *New England Journal of Medicine* article, and others. For more information on the important topic of overdiagnosis, please see *The Big Squeeze: A Social and Political History of the Controversial Mammogram* by Handel Reynolds [18].

If the goal of a screening test is to detect a treatable entity earlier in its natural history to enable early intervention and reduce morbidity and mortality, then we believe that our data support that screening mammography is accomplishing its goal for women in their 40s. By study definition, women included in this review were asymptomatic, thus qualifying for screening (as opposed to diagnostic) mammography. The screening-detected breast cancers in women in their 40s were predominantly early stage (82% stage 0 or stage I disease, consistent with or slightly better than ACR guidelines [11], which recommend that screening examinations yield 76% stage 0 or I cancers). Detection of early-stage breast cancer has been associated with a reduction in breast cancer mortality [16]. This result is also consistent with multiple mammography screening trials that have shown downstaging of tumors in women who have undergone screening versus those who have not [19]. Although the literature on DCIS is mixed in the sense that no one knows which cases of DCIS—if left untreated—would develop into invasive cancer and which would remain indolent for the remainder of a woman's life, it appears that the cancers we detected were not necessarily of the indolent variety because an invasive component was already evident in 54% and 82% were of an intermediate to high nuclear grade; these findings are consistent with studies showing higher nuclear grades in the breast cancers of younger women [20]. However, at the same time, the cancers detected were potentially treatable ones. The expression of ER and PR is well recognized as a predictive factor for response to tamoxifen [21] and 82% of the screening-detected cancers in women in their 40s were ER-positive and 67% were PR-positive; these findings are similar to the distributions noted in previous studies [21–23]. Although almost half our patients with screening-detected breast cancers in their 40s had unknown (n = 18) or indeterminate (n = 1) HER2/neu status (likely because of its relatively recent discovery), 18% had HER2/neu-positive cancers; this finding is consistent with several studies that have reported HER2/neu positivity in 15–20% of breast cancers [24, 25]. Of the patients with screening-detected breast cancer in their 40s with complete ER, PR, and HER2/neu information (n = 21) (Table 3), 48% had ER-positive, PR-positive, and HER2/neu-negative cancer, which is associated with a 5-year relative survival of 96.4%; 33% had ER-positive, PR-positive, and HER2/neu-positive cancer, which is associated with a 5-year relative survival of 91.3%; and 14% had ER-positive, PR-negative, and HER2/neu-negative cancer, which is associated with a 5-year relative survival of 91.9% [22]. In short, these cancers are potentially survivable cancers if identified. The analysis also revealed a lack of triple receptor–negative cancers in our study group, which could reflect a relatively homogeneous patient population, a limitation of our study.

TABLE 2: Tumor Characteristics and Treatments of Women in Their 40s Diagnosed With Breast Cancer at Our Institution From 2007 Through 2010

Characteristic	No. (%) of Patients (*n* = 39)
Stage	
0	18 (46)
I	14 (36)
II	6 (15)
III	1 (3)
IV	0 (0)
Histology of breast cancers	
DCIS	18
Invasive ductal carcinoma	15
DCIS with microinvasion	3
Invasive mammary carcinoma NOS	2
Invasive mucinous carcinoma	1
Grade of breast cancers	
High	11 (28)
Intermediate to high	6 (15)
Intermediate	15 (39)
Low to intermediate	4 (10)
Low	3 (8)
ER status	
Positive	32 (82)
Negative	7 (18)
Unknown	0 (0)
PR status	
Positive	26 (67)
Negative	5 (13)
Unknown	8 (20)
HER2/neu status	
Positive	7 (18)
Negative	13 (33)
Unknown	18 (46)
Indeterminate	1 (3)
Status of at least one hormone receptor known	18 (46)
Status of all hormone receptors known	21 (54)
ER+, PR+, HER2/neu–	10 (48)
ER+, PR+, HER2/neu+	7 (33)
ER+, PR–, HER2/neu–	3 (14)
ER+, PR+, HER2/neu indeterminate	1 (5)
ER–, PR–, HER2/neu–	0 (0)
Surgical treatment	
Unknown	6 (15)
Known	33 (85)
Lumpectomy	23 (70)
Mastectomy	10 (30)

Note—DCIS = ductal carcinoma in situ, NOS = not otherwise specified, ER = estrogen receptor, PR = progesterone receptor, HER2/neu = human epidermal growth receptor 2, plus sign (+) = positive, minus sign (–) = negative.

Although performing more than 10,000 screening studies annually may represent only a small to moderate-sized breast cancer screening program when compared with others nationally, it nevertheless represents a large sample size statistically. Women in their 40s comprised one third (33.5%) of our screening population, consonant with National Cancer Institute data [26], and nearly one fifth (19%) of breast cancers diagnosed at our institution, consistent with the literature as well [26, 27]. Both our overall cancer detection rate (4.7 per 1000 screening examinations) and cancer detection rate for women in their 40s (2.7 per 1000 screening examinations) meet the ACR desired goals for medical audit data (2–10 per 1000 screening examinations) [28].

A major study limitation is its retrospective design. Furthermore, the low PPVs might be an area of critique. However, both PPVs and cancer detection rates tend to be lower for younger populations, and although the PPVs were low, the cancer detection rates for women in their 40s and for women of all ages were satisfactory as discussed. Given the equation for PPV ([$PPV = TP / (TP + FP)$], where TP = true-positive and FP = false-positive) and that the true-positive cancer detection rate was satisfactory, the low PPV is the result of a high false-positive rate, which may be caused by several factors. First, because the incidence of breast cancer increases with increasing age, there is, accordingly, a lower incidence of breast cancer in younger women. Second, younger patients such as those in their 40s may lack prior mammography examinations with which to establish stability. Third, 90% of women diagnosed with breast cancer in their 40s had heterogeneously dense or extremely dense breasts, which led many referring clinicians to order breast ultrasound as well. Although all of the breast cancers diagnosed in women in their 40s were initially detected mammographically (i.e., no cancers were picked up on screening breast ultrasound alone after a negative mammography examination), many biopsies are driven by ultrasound findings; the PPV of screening breast ultrasound as reported in the literature extends from 5.6% to 19% [29–32], placing our PPVs within this range. Thus, our calculated PPVs would have been higher if ultrasound information had not been included. However, we chose to include this information not only because we wanted to follow each woman through completion of care, but also because the number of screening breast ultrasound examinations is only expected to increase statewide (with the Breast Density Inform legislation taking effect in New York in January 2013) and possibly na-

TABLE 3: Potential Risk Factors for Breast Cancer in Women in Their 40s Diagnosed With Breast Cancer at Our Institution From 2007 Through 2010

Risk Factor	No. (%) of Women
First-degree family member with history of breast cancer	
Absent	36 (92)
Present	3 (8)
BRCA status	
Negative for mutation	20 (51)
Positive for mutation	4 (10)
Unknown	15 (39)
Breast tissue density	
Extremely dense	10 (25.6)
Heterogeneously dense	26 (66.7)
Scattered fibroglandular elements	3 (7.7)
Fatty	0 (0)

tionwide as well (with the Breast Density and Mammography Reporting Act of 2011 [House of Representatives bill 1302] introduced at the 112th U.S. Congress) [33].

Although our study does not specifically address the issue of annual versus biennial screening, it is relevant to briefly consider the literature on this topic, which is mixed. In *AJR* in 1999, Hunt, et al. [34] reported that annual screening mammography results in lower recall rates than does biennial screening and that annual screening results in the detection of smaller tumors that have a more favorable prognosis. On the other hand, the USPSTF [9] argued 10 years later in 2009 that:

> a large proportion of the benefit of screening mammography is maintained by biennial screening, and changing from annual to biennial screening is likely to reduce the harms of mammography screening by nearly half.

We looked at family history not only because it is a risk factor for the development of breast cancer, but also because the USPSTF suggests that women in their 40s should be screened only if they are considered at high risk of breast cancer. However, there are no data from randomized controlled trials to support screening only high-risk women [35], and in our study, only 8% of the women in their 40s who were diagnosed with breast cancer had a family history of breast cancer in first-degree family member. Thus, 92% of the women in their 40s with breast cancer in our study did not have an elevated risk and routine screening mammography would not have been recommended for them on the basis of the USPSTF 2009 guidelines. Furthermore, Hendrick and Helvie [36] reexamined the scientific evidence considered by the USPSTF in recommending against screening mammography in women in their 40s using six Cancer Intervention and Surveillance Modeling Network models of benefit and found that screening mammography shows greatest benefit—nearly a 40% mortality reduction—from annual screening mammography of women starting at age 40.

In our cohort of women in their 40s diagnosed with breast cancer, at minimum approximately two thirds (24/39 = 62%) underwent genetic testing as a result of their new diagnosis and four women had positive findings for a *BRCA1* or *BRCA2* mutation (4/24 = 17%); genetic testing was not mentioned in the charts of 15 patients, but they may have undergone genetic testing elsewhere. If recalculated using 39 as the denominator (i.e., including the 15 patients for whom genetic status is unknown), then this corresponds to a 10% (4/39) genetic mutation rate. In either case, both percentages are much higher than reported national averages. Among the general population, the likelihood of having any *BRCA* mutation is 1 in 50 (2%) for women with breast cancer (any age) [37]. Although the prevalence of *BRCA1* mutations in breast cancer patients of Ashkenazic Jewish descent is higher (range, 8.3–10.2% for women < 65 years old) [38], only one of the four *BRCA* mutation–positive women was indicated to be Ashkenazic Jewish on rereview of these charts. Thus, it is unclear what accounts for the high rate of *BRCA* mutation positivity in our patient population. However, the bottom line is that getting screened for and subsequently diagnosed with breast cancer led them to learn this important genetic information, which is critical both for the immediate treatment planning (lumpectomy vs mastectomy) and long-term health care (possible prophylactic oophorectomy) of the patient and for the health care of first-degree family members.

In their 2009 statement of rationale for increasing the age to start routine screening mammography from 40 to 50 years, the USPSTF [9] explains that:

> although false-positive test results, overdiagnosis, and unnecessary earlier treatment are problems for all age groups, false-positive results are more common for women aged 40 to 49 years.

False-positive results are more common in younger women because, as discussed, the incidence of breast cancer increases with age and younger women may lack prior mammography examinations to establish stability. However, the statement that "false-positive results are more common for women aged 40 to 49 years" suggests that something changes at the age of 50, which is inaccurate. The "false-positive" rate for women in their 50s is also higher than for women in their 60s because the prior probability of breast cancer goes up with increasing age, so singling out women in their 40s is arbitrary without basis in science or biology. Furthermore, although the USPSTF never stated that women 40–50 years old should not be screened, and although it would be incorrect to assume that no 40- to 50-year-old women now undergo screening mammography (our numbers prove otherwise), recent literature nevertheless suggests that the USPSTF recommendations may be having an impact on the number of women presenting for screening. For example, Sharpe et al. [39] found an abrupt decrease in the utilization of screening mammography in 2010 and concluded that:

> Because there are no other factors to explain a decrease of this magnitude, it would seem that the USPSTF recommendations…resulted in a decrease in the utilization of screening mammography in the Medicare population in the first year after issuance of the new recommendations.

The Medicare population is older than the cohort this study focuses on. It is impossible to know how many of the 39 women diagnosed with breast cancer in our study would have decided not to undergo mammographic screening, with or without consultation with a physician, and it is also impossible to know how many women who did not undergo screening

initially would have undergone screening later or would have had their cancers detected by either noticing a breast lump or having a lump detected by a physician. In conclusion, however, at the very least, our finding of a 19% cancer incidence in women in their 40s should be a useful contribution to the counseling of women in this age group when discussing whether or not to pursue regular screening mammography.

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