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Imaging Surveillance After Primary Breast Cancer Treatment

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Abstract

OBJECTIVE—Current clinical guidelines are consistent in supporting annual mammography for women after treatment of primary breast cancer. Surveillance imaging beyond standard digital mammography, including digital breast tomosynthesis (DBT), breast ultrasound, and MRI, may improve outcomes. This article reviews the evidence on the performance and effectiveness of breast imaging modalities available for surveillance after treatment of sporadic unilateral primary breast cancer and identifies additional factors to be considered when selecting an imaging surveillance regimen.

CONCLUSION—Evidence review supports the use of mammography for surveillance after primary breast cancer treatment. Variability exists in guideline recommendations for surveillance initiation, interval, and cessation. DBT offers the most promise as a potential modality to replace standard digital mammography as a front-line surveillance test; a single published study to date has shown a significant decrease in recall rates compared with standard digital mammography alone. Most guidelines do not support the use of whole-breast ultrasound in breast cancer surveillance, and further studies are needed to define the characteristics of women who may benefit from MRI surveillance. The emerging evidence about surveillance imaging outcomes suggests that additional factors, including patient and imaging characteristics, tumor biology and gene expression profile, and choice of treatment, warrant consideration in selecting personalized posttreatment imaging surveillance regimens.

Keywords

breast MRI; breast ultrasound; digital breast tomosynthesis; imaging surveillance after primary breast cancer treatment; mammography

Clinical Vignette

A 59-year-old, postmenopausal woman presents to your imaging clinic after having completed lumpectomy and radiation therapy for her T1N0 right breast cancer. She is currently undergoing adjuvant hormonal therapy with an aromatase inhibitor. Her breast cancer was diagnosed on a screening mammogram, which showed scattered fibroglandular

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densities and a mass in the upper outer quadrant of her right breast. Her primary cancer was a 12-mm grade 1 invasive ductal carcinoma. The tumor was positive for estrogen receptor (ER) and progesterone receptor (PR) and negative for human epidermal growth factor receptor 2 (HER2; also known as HER2/neu and ERB-B2) by immunohistochemistry, with a Ki-67 proliferation rate of 3%. She has no significant family history of cancer.

Imaging Questions

For patients with a personal history of sporadic breast cancer treated with breast conservation therapy or unilateral mastectomy, what is the best imaging modality and regimen to monitor for recurrence and second primary breast cancers (second breast cancers)? What factors should be considered to determine this management?

Background and Importance

Early breast cancer detection and advances in treatment have improved patient survival [1–8]. Consequently, the breast cancer mortality rate has declined by 36% from peak rates in the 1990s [9] with an estimated 1.9% annual decrease between 2003 and 2012 [10]. The corresponding number of breast cancer survivors has increased over time, with over 3.1 million women survivors living in the United States as of January 2014 [11]. According to data from the Breast Cancer Surveillance Consortium, approximately 8% of women undergoing a screening mammogram had a personal history of breast cancer [12]. Primary surgical breast cancer treatment includes breast conservation therapy or mastectomy. These women continue to be at risk of second breast cancers—that is, local breast cancer recurrence or contralateral breast cancer—which are associated with increased rates of distant metastasis and breast cancer mortality [13, 14]. The aim of surveillance in patients after primary breast cancer treatment is to detect second breast cancers before symptoms develop, which allows interventions that permit improved survival and quality of life [15].

Current guidelines support the use of mammography for breast cancer surveillance after treatment of women breast cancer [16–22] and do not apply to women who have undergone bilateral mastectomy, who have minimal residual breast tissue at risk. These guidelines factor in evidence from randomized controlled trials showing the effectiveness of screening mammography for reducing breast cancer mortality in the general population [4, 5], as well as observational mammography studies conducted in the surveillance setting [15, 23, 24]. In addition to standard digital mammography, additional imaging modalities such as digital breast tomosynthesis (DBT), whole-breast ultrasound, and breast MRI are available for breast cancer screening and surveillance. In this article, we review the available evidence for each breast imaging modality and additional factors to consider when making surveillance management decisions.

Synopsis and Synthesis of Evidence

To date, to our knowledge, there have been no randomized controlled trials comparing different imaging modalities and frequency of imaging for breast cancer surveillance of patients after primary breast cancer treatment. The evidence regarding the effectiveness of

available imaging modalities for posttreatment breast cancer surveillance varies across modalities.

Mammography

Mammography continues to be the imaging mainstay for breast cancer screening, on the basis of randomized controlled trials showing significant reductions in breast cancer mortality for women ages 40–74 years [4, 5]. The benefit of surveillance mammography is generalized from these trials and from observational studies evaluating mammography in the surveillance setting [15, 23–25]. For patients with a personal history of breast cancer undergoing mammographic surveillance, decreased mortality is associated with earlier detection of second breast cancers. This is true across different observational study designs: mammographic versus clinical detection, asymptomatic versus symptomatic presentation, or routine versus nonroutine follow-up [26]. A meta-analysis of the survival effect of early second breast cancer detection estimated an absolute breast cancer mortality reduction of 17–28% if the recurrence was found by surveillance mammography versus clinical detection [15]. The largest observational study of asymptomatic versus symptomatic detection of second breast cancers showed a hazard ratio for mortality of 0.53–0.73 for asymptomatic detection, after adjusting for length time bias [23].

All organizations issuing surveillance guidelines recommend mammography [16–19, 21, 22] (Table 1). Although there is consistency in the support of mammography as a surveillance modality, there is heterogeneity in the recommendations for the time of initiation, frequency, or cessation of mammography surveillance. A survey of breast surgeons and radiologists within the United Kingdom showed a wide variation in the time of initiation (i.e., 6–24 months after surgery) and frequency (annually, every 18 months, every 2–3 years, or annually for 5 years and then biennially) of surveillance mammography. The most common practice was annual mammography starting 12 months after surgery [27]. Support for a shorter surveillance interval, in particular semiannual surveillance, is based on the majority of in-breast recurrence events being observed within the first 5 years of treatment [8, 28, 29], and also observational evidence that semiannual follow-up may detect a higher proportion of cancer recurrences at an earlier stage than annual surveillance [30]. However, a more frequent surveillance regimen for the entire population of women treated for early-stage breast cancer may not be of benefit. Kokko et al. [31] compared diagnostic testing at 3- versus 6-month intervals in women treated for early-stage breast cancer. Additional arms of the trial compared routine testing versus testing only when clinically indicated. The study indicated that more intensive surveillance (either at increased frequency or with an increased number of tests) increased costs but did not improve patient overall survival.

Houssami et al. [32] evaluated the test performance characteristics of 58,870 mammograms in a cohort of 19,078 women and found that the sensitivity of mammography was lower in women with a history of breast cancer compared with those without this history, with a sensitivity of 65.4% (95% CI, 61.5–69.0%) versus 76.5% (95% CI, 71.7–80.7%), respectively, even as the underlying cancer detection rate in women with prior breast cancer was significantly higher: 6.8 versus 4.4 per 1000 mammograms, respectively ($p < 0.001$). The time from primary breast cancer treatment also influenced cancer detection, with

mammographic sensitivity lower within the initial 5 years (60.2%) compared with more than 5 years (70.8%) after primary breast cancer treatment.

Risk factors for the development of interval invasive second breast cancers within 1 year after negative surveillance mammography and within 5 years after primary breast cancer treatment have also been studied. Lumpectomy without radiation therapy and mammographically dense breasts were significant predictors of interval invasive second breast cancers within 1 and 5 years after surveillance mammography [33, 34]. Age at primary breast cancer diagnosis younger than 40 years was significant at 1 year but not within 5 years after treatment, which is attributable to fewer younger (< 40 years) and older (> 80 years) women in the dataset with longer follow-up. Primary breast cancer grade and mode of detection were also identified as significant predictors within 5 years of surveillance mammography [34].

These studies have identified factors known at the time of primary breast cancer diagnosis and treatment that predict an adverse surveillance outcome. In particular, evidence that interval presentation of a primary breast cancer after a negative screening mammogram predicts subsequent interval invasive second breast cancer suggests that the mode of detection may be important in imaging modality selection for posttreatment surveillance [34]. Additional research is warranted to tailor imaging (single or multiple modalities) to individual women's characteristics, risks, and preferences.

Digital Breast Tomosynthesis

Digital breast tomosynthesis (DBT) acquires mammographic projections at different angles in an arc over the breast, which are reconstructed to create multiple thin images through the breast. This technology was designed to eliminate overlapping breast tissue, which may either mimic or obscure breast cancer on standard mammography, and to increase conspicuity of true lesions [35] and is poised to replace mammography as the front-line imaging modality for breast cancer screening and surveillance.

Early reports of DBT for routine breast cancer screening in Europe and the United States have shown its potential to decrease recall rates by 13–48%, increase cancer detection rates (0.5–2.7 cancers per 1000 screening examinations), or both, compared with digital mammography alone [36–40]. The Oslo Tomosynthesis Screening Trial [37] was a prospective study comparing full-field digital mammography (FFDM) alone versus FFDM and DBT. The addition of DBT increased the cancer detection rate from 6.1 to 8.0 cancers per 1000 examinations, with an associated decrease in false-positive examinations from 61.1 to 53.1 false-positives per 1000 examinations [37]. The Screening with Tomosynthesis OR standard Mammography trial in Italy [36] also compared FFDM alone with FFDM and DBT. The addition of DBT increased the cancer detection rate from 5.3 to 8.1 cancers per 1000 examinations and reduced false-positive recalls from 19.5 to 10.1 recalls per 1000 examinations [36]. The largest multisite retrospective observational trial in the United States showed that the addition of DBT to FFDM increased the cancer detection rate from 4.2 to 5.4 cancers per 1000 examinations and decreased the recall rate from 107 to 91 recalls per 1000 examinations [38]. The sensitivity of DBT has yet to be reported because of the longer

follow-up time required, and whether the cancer detection rates seen at prevalence DBT screening will continue as incidence screening commences has not yet been established [41].

Regarding the sustainability of DBT outcomes, two studies published to date have reported results for prevalence versus incidence screening of DBT. In one study [42], over a 3-year period DBT recall rates at the population level remained statistically significantly lower than those for digital mammography alone, with recall rates of 88, 90, and 92 cancers per 1000 women screened for the first 3 years of DBT, respectively, versus a recall rate of 104 recalls per 1000 women screened with FFDM alone. A nonsignificant trend of increasing cancer detection rate over time was noted, from 5.5 at the prevalence screening examination to 6.1 cancers per 1000 women in year 3 of DBT [42]. A prospective trial conducted within a European screening program [43] reported a significantly increased cancer detection rate for women screened with both FFDM and DBT compared with FFDM alone (6.3 vs 8.5 cancers per 1000 women, respectively). However, for the subset of women undergoing incidence screening with combination FFDM and DBT (1771/9672; 18%), the incremental increase in cancer detection rate compared with FFDM alone was not significant [43].

A single study of DBT for surveillance published to date included 618 women with a personal history of breast cancer treated with lumpectomy with or without radiation or mastectomy [44]. Patient characteristics, including age, initial tumor characteristics, and time from cancer diagnosis, were not reported. The addition of DBT to FFDM reduced recall rates from 131 to 105 recalls per 1000 screening examinations ($p = 0.018$), suggesting that the decrease in recall rates seen in general screening may be extended to the surveillance setting. Further research is needed to evaluate whether DBT use will improve longer-term outcomes for women with treated breast cancer.

Breast MRI

Breast MRI takes advantage of tumor neovascularity to identify cancers with intravenous contrast agents. As invasive breast cancers develop, their demand for oxygen and nutrients exceeds that available from the normal blood supply of breast parenchyma. These cancers stimulate the release of growth factors that promote the formation of new blood vessels in the peritumoral stroma, a process referred to as neoangiogenesis [45]. Breast cancer detection with contrast-enhanced breast MRI is based on uptake of contrast agents by these new and abnormal blood vessels. Consequently, breast MRI is not limited by mammographic breast density. MRI has no role in surveillance of women treated with bilateral mastectomies.

Studies of breast MRI in women with increased genetic or familial risk of breast cancer have shown a high sensitivity for detecting breast cancer, ranging from 71% to 100% [46]. In a meta-analysis of 11 studies evaluating the use of MRI in screening high-risk women, for a positivity threshold of a BI-RADS category 3, 4, or 5 lesion, sensitivity and specificity were 77% (95% CI, 70–84%) and 86% (95% CI, 81–92%), respectively. With a positivity threshold of BI-RADS category 4 or 5 lesions, the sensitivity and specificity were 75% (95% CI, 62–88%) and 96% (95% CI, 95–97%), respectively [47]. These studies included women with high familial and genetic breast cancer risk factors; nine of the 11 studies included women with a personal history of breast cancer in the setting of genetic predisposition.

Women with nonhereditary sporadic breast cancers were excluded. The current evidence for breast MRI surveillance of patients with a personal history of sporadic breast cancer is based on relatively small single-institution retrospective studies [48–54] and is summarized in Table 2. The largest of these studies, by Lehman et al. [52], showed that breast MRI in patients with a personal history of cancer had sensitivity and cancer detection rate similar to those for patients with a genetic or family history of breast cancer, with a lower false-positive rate. The range of cancer detection rates across these studies of MRI surveillance may be attributed in part to the differential selection and small number of women in these surveillance cohorts. Additional research studies of MRI performance and outcomes in women with a personal history of sporadic breast cancer are needed.

Whole-Breast Ultrasound

Breast ultrasound has traditionally been used to aid in the evaluation of palpable breast abnormalities in the diagnostic setting, as well as the evaluation of masses seen on mammography. More recently, whole-breast ultrasound, performed either using handheld ultrasound or an automated whole-breast ultrasound device, is considered an appropriate supplemental screening examination for women who are at high risk for developing breast cancer and cannot undergo breast MRI [55]. To our knowledge, there have been no studies of automated whole-breast ultrasound for surveillance of women after breast conservation therapy.

A recent systematic review identified 12 screening ultrasound studies since 2000 in women with dense breast tissue [56]. Although the proportion of patients with a personal history of breast cancer varied in these studies from 6% to 53%, only one study specifically reported the results of these women as a separate subgroup [57]. This was the American College of Radiology Imaging Network 6666 study, which evaluated the combination of mammography and handheld ultrasound compared with mammography alone in women with dense breasts and additional risk factors, including personal history of breast cancer, lifetime risk of 25% or higher by the Gail or Claus models, 5-year Gail model risk of 2.5% or higher, known *BRCA* gene mutation, atypia on prior biopsy, or prior chest, mediastinal, or axillary irradiation [57, 58]. In that study, 53% of the women studied had a personal history of breast cancer. The cancer detection rate for mammography alone was 7.6 cancers per 1000 examinations for the first screening round, whereas the combination of mammography and handheld ultrasound detected an additional 5.3 cancers per 1000 examinations. Of note, women with a personal history of breast cancer had a similar incremental cancer detection rate for combination of mammography and handheld ultrasound compared with those without this history. Nonetheless, there was a 2.3-fold increase in recalls and 4.2-fold increase in the number of breast biopsies for the patients in the combination mammography and handheld ultrasound arm. The cancer yield overall was 8.6% for handheld ultrasound, signifying that over 90% of the biopsies were performed for benign lesions. For women with a personal history of breast cancer who had lesions biopsied because of an ultrasound-only finding, the cancer yield was higher (15.3%) and was still lower than the mammography benchmark of 31.0% [59].

The only randomized controlled trial of screening ultrasound conducted to date was performed in Japanese women 40–49 years old and excluded those with a personal history of breast cancer. Their results indicated that screening adjunct whole-breast ultrasound had a higher sensitivity of 91.1% versus 77.0% for mammography alone. Increased sensitivity was also associated with significantly lower specificity of 87.7% versus 91.4% [60]. Although handheld ultrasound may increase the number of cancers detected, the substantially higher number of false-positive findings offset its benefits and may outweigh them.

The Adjunct Screening With DBT or Handheld Ultrasound in Mammography Negative Dense Breast trial in Italy [61] showed that handheld ultrasound had a higher incremental cancer detection rate of 7.1 cancers per 1000 screening examinations versus 4.0 cancers per 1000 screening examinations with DBT, with no significant difference between false-positive recalls from screening or biopsy between the two modalities. Of note, patients with a personal history of breast cancer were excluded from this study. In addition, the screening ultrasound cases were a mix of prevalence and incidence screening with radiologists who had expertise in whole-breast ultrasound screening, compared with prevalence DBT screening [61].

Operator dependency for handheld ultrasound and length of acquisition time are additional considerations for this imaging modality as a screening examination [56, 62, 63]. An evaluation of lesion detection by 64 potential investigators of the American College of Radiology Imaging Network 6666 trial showed that detection was more consistent for lesions at least 5 mm in size, with decreased detection with increasing lesion depth [64]. A separate study of handheld ultrasound in 10 women with numerous known breast lesions also supports that larger lesions (> 11 mm) are more consistently detected; overall sensitivity was 55% (536 detections of 968 potential lesions). Once the lesions were identified, there was substantial agreement for shape and margins of solid lesions (κ = 0.62 and 0.67, respectively) with moderate agreement (κ = 0.52) for the final BI-RADS assessment, comparable to those for mammography and MRI. The average time to complete the examination for the 11 breast radiologists trained in handheld ultrasound was 31 minutes [65].

Other Imaging Modalities

Other imaging modalities available for breast cancer screening include contrast-enhanced spectral mammography, positron emission mammography, and gamma imaging, including molecular breast imaging or breast-specific gamma imaging. To our knowledge, no studies to date have evaluated these imaging modalities for posttreatment imaging surveillance of women with a personal history of breast cancer, and there is insufficient evidence to support their use.

Guidelines for metastatic disease evaluation are consistent in their recommendations. In the United States, guidelines from the Choosing Wisely initiative of the American Board of Internal Medicine Foundation, American Cancer Society and American Society of Clinical Oncology, and National Comprehensive Cancer Network recommend against advanced imaging (e.g., PET, PET/CT, or radionuclide bone scan) or circulating biomarker testing to monitor for recurrence in patients without symptoms who have been treated for breast

cancer with curative intent [66]. Internationally, multiple organizations [20–22] also recommend against additional imaging to evaluate for metastatic disease. These recommendations are based on randomized trials that showed no survival benefits in screening for metastasis in the population without symptoms. Specifically, routine use of imaging such as a chest radiograph, a bone scan, or abdominal ultrasound in patients without symptoms had no survival benefit for patients [32, 67–69].

Breast Cancer Subtype and Imaging Characteristics

Conventional pathologic features of breast cancer, such as tumor size, histologic grade, and lymph node status, have helped direct treatment and predict patient outcomes. The ability to classify breast cancer according to the expression of hormone receptors (ER, PR, and HER2) has also led the way toward targeted therapies against these receptors. Furthermore, with gene expression profile analysis (also known as molecular subtyping), breast cancer development and progression are now recognized to have multiple pathways regulated by expression of different genes with varying clinical manifestations.

There were originally four major breast cancer subtypes identified, each with its own clinical behavior, imaging appearance, and response to therapy [70–74] (Table 3). Subsequently as more-robust DNA microarrays have been developed and larger clinical datasets are available, at least eight molecular subtypes have now been described: luminal A, luminal B, luminal C, basal, HER2-enriched (or *ERB-B2* positive), normal breast–like, claudin-low, and molecular apocrine [73, 75–77]. The clinical significance of some of these newer subgroups, such as claudin-low, has yet to be determined. Furthermore, a new hormone receptor, androgen receptor, may play a role in differentiating these newer subtypes [73]. However, in current clinical practice, the critical issue is not the separation of genetically distinct subtypes but rather the discrimination between patients who will or will not benefit from specific therapies. Consequently, some studies define luminal B as ER- and PR-positive with either HER2-positive or high proliferation. Other studies separate luminal B into two subtypes: luminal B (HER2 negative with high proliferation) versus luminal *HER2* (HER2 positive with any level of proliferation) because patients in these two groups will receive different targeted treatment regimens.

Because molecular subtyping is not routinely performed in the clinical setting and definitions of subtype have varied across studies [78–83], the imaging appearance of each distinct subtype is not well characterized at the present time [74]. Immunohistochemical classification of tumor phenotype has also been used as a surrogate for molecular subtype, with imaging studies focusing on the original four breast cancer subtypes (luminal A, luminal B, HER2-enriched, and basal). In particular, the luminal A and luminal B molecular subtypes are approximated by ER- and PR-positive HER2-negative cancers with varying levels of proliferative markers; HER2-enriched with HER2-positive cancers, stratified by hormone receptor status; and basal subtype with triple-negative cancers [83]. Although most triple-negative breast cancers are the basal subtype, approximately 25% are not [84].

Trop et al. [74] reviewed the imaging characteristics of the different molecular subtypes in invasive breast cancers. In their review, the luminal A and luminal B subtypes (described as ER-positive HER2-negative cancers) often appear as masses with or without calcifications

on mammography [74, 85]. It is important to note that microcalcifications are present in the majority of breast cancers (both luminal and nonluminal) with the exception of the basal or triple-negative type and should not be used to distinguish different molecular subtypes. On ultrasound, HER2-negative tumors present more often as masses compared with HER2-enriched or HER2-positive tumors, which were more frequently nonmass lesions [85]. ER-positive HER2-negative breast cancers more often have associated segmental nonmass enhancement on MRI, likely reflecting associated ductal carcinoma in situ compared with basal, or triple-negative, cancers [79, 85, 86].

Basal subtype, or triple-negative, tumors are associated with interval breast cancer diagnosis (with a clinical abnormality) after a negative screening mammogram [87–91]. On imaging, these tumors usually appear as irregularly shaped masses with noncircumscribed margins. Sonographically, triple-negative tumors can have benign features, including an oval shape, circumscribed margins, with marked hypoechogenicity [74, 85, 91–93], which are also features associated with high-grade cancers in general [94]. Although irregular margins also are commonly seen in these types of tumors, circumscribed margins are thought to be more specific for triple-negative tumors [79, 75]. In high-risk patients, particularly those with *BRCA1* mutations, triple-negative tumors may look similar to fibroadenomas on ultrasound [96]. Similarly, on MRI, triple-negative tumors typically present as unifocal lesions with a round or oval shape and high T2 internal signal intensity, reflecting high grade and proliferation and associated necrosis.

In the context of surveillance for breast cancer recurrence, subtype is associated with local and regional relapse [80, 81, 97]. In a study of 2985 women, 42% of whom underwent breast conservation treatment with radiation, those with luminal A breast cancers had the lowest local recurrence rate (8% at 10 years), whereas women with HER2-enriched subtype had significantly higher 10-year local recurrence rates (21%). Of note, none of the patients in that study received HER2-targeted chemotherapy agents [80]. In a separate study of women with invasive breast cancer treated with lumpectomy and radiation therapy, the local recurrence rates at 5 years varied significantly depending on subtype, with luminal A having the best prognosis and HER2-enriched and triple-negative subtypes having the worst prognosis [81]. Mammographically occult primary breast cancer diagnosis is associated with both basal subtype and with subsequent interval presentation of relapse after negative mammography, with a lower disease-free survival rate at 10 years [98].

In addition to local recurrence, breast cancer subtype is also associated with the development and pattern of distant metastasis, with luminal B and basal subtypes associated with increased rate of distant metastasis at 5 years compared with luminal A, luminal-HER2, HER2-enriched, and triple-negative subtypes [99]. Bone is the most common site of metastasis in all subtypes except for basal tumors, where there are higher rates of brain, lung, and distant nodal metastasis [100]. The timing of recurrence also differed, with nonluminal subtypes experiencing relapse within the first 5 years after primary breast cancer treatment, and luminal subtypes relapsing beyond this period, up to 15 years after treatment.

Evidence-Based Guidelines

Current clinical guidelines for imaging surveillance after primary breast cancer treatment are summarized in Table 1. These guidelines are from the leading medical oncologic organizations in the United States (American Society of Clinical Oncology and National Comprehensive Cancer Network) and in Europe (European Society for Medical Oncology), as well as the national agency providing guidance on quality standards, technology appraisals, and clinical pathways in the United Kingdom (National Institute for Health and Care Excellence). Recommendations from the American Cancer Society and the American College of Radiology are also included.

These guidelines are consistent in recommendations for at least annual surveillance mammography to evaluate for local recurrence or contralateral breast cancers. The timing of initiation for mammographic surveillance after breast conservation treatment is less clearly defined. Both American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines recommend the first posttreatment mammogram no earlier than 6 months after definitive radiation therapy [17, 18]; it is not otherwise mentioned in other guidelines. Guidelines supporting consideration of a more frequent semiannual surveillance interval also support a return to routine annual surveillance either after 2 years [20] or when “mammographic findings are stable” [17]. The American College of Radiology notes that “frequency of imaging may vary by institution, based on local protocol” [19]. The decision on when to end surveillance mammography is also not presented in most guidelines. The National Institute for Health and Care Excellence in the United Kingdom [22] recommends risk stratification for surveillance mammography beyond the first 5 years of primary breast cancer treatment. The American Cancer Society supports the cessation of screening mammography in the general population if the patient has less than a 10-year life expectancy [101].

Although DBT has recently been added as a modality to consider for screening mammography in the National Comprehensive Cancer Network guidelines [102], it is not discussed separately from mammography in any current guidelines for breast cancer surveillance. The guidelines do not support the use of breast ultrasound for supplemental surveillance in women, except for the European Society for Medical Oncology [21], which recommends annual mammography with ultrasound. Routine MRI surveillance is also not recommended; however, breast MRI is supported for supplemental screening for women with a lifetime risk of breast cancer greater than 20%, with use of familial risk assessment models, and selectively in women with a personal history of sporadic breast cancer, after risk assessment [16, 19–21].

The use of additional imaging studies, such as chest x-ray, bone scan, liver ultrasound, nonbreast MRI, PET/CT, or tumor markers, to evaluate for recurrent or metastatic disease is not recommended in any of the guidelines.

Considerations for Further Research

As health care shifts from volume-based care to value-based care, risk-based surveillance of breast cancer survivors offers the potential to optimize the balance of benefits and harms by tailoring surveillance regimens to a woman's individual second breast cancer risk. As discussed above, some of these individual risk factors have been identified and relate to a woman's clinical, tumor, imaging, and treatment characteristics. Improvements in our understanding of tumor biology with the use of DNA microarrays for molecular subtyping suggest additional important factors worth considering in creating tailored surveillance imaging plans.

Further evaluation of patient characteristics (age, clinical presentation, and mammographic breast density), primary tumor characteristics (histologic grade and molecular subtypes), and how these aspects relate to second breast cancer risk and imaging detection is needed. Improved understanding of these factors can potentially guide the development and selection of more patient-specific surveillance regimens, such as a more-frequent interval surveillance for those at increased risk for interval cancers [30] or with a supplemental modality like breast MRI [48, 50–53] or ultrasound [57, 58]. Evaluation of the comparative effectiveness of multimodality surveillance regimens will also be needed.

Given the evolving paradigms of breast cancer treatment, conducting prospective trials with large enough sample sizes to evaluate meaningful outcomes in breast cancer survivors is challenging. Large-scale observational databases such as the National Cancer Institute–funded Breast Cancer Surveillance Consortium offer resources to address this challenge [103]. The Breast Cancer Surveillance Consortium is composed of six regional registries that collect data on patient demographics, clinical risk factors, breast imaging examinations (mammography, DBT, ultrasound, and MRI) and results. The data are linked to regional Surveillance, Epidemiology, and End Results programs or state tumor registries to determine breast cancer outcomes. Data on breast cancer recurrence are supplemented with biopsy and pathology data from Breast Cancer Surveillance Consortium facilities. Prior Breast Cancer Surveillance Consortium studies have provided the evidence basis for the American College of Radiology's BI-RADS performance benchmarks for breast imaging [59], as well as the American Cancer Society's 2015 guidelines for screening mammography [104]. The National Mammography Database, originally designed as a quality improvement tool by the American College of Radiology as part of the National Radiology Data Registry, is also a potential source of facility-level data for future studies [105]. Current limitations of the National Mammography Database are incomplete data on patient demographic factors (race, breast density, and personal history of breast cancer) and incomplete biopsy follow-up compared with the Breast Cancer Surveillance Consortium, as well as lack of tumor registry linkage to determine breast cancer status.

For rapidly evolving imaging technologies, studies of long-term outcomes are not possible because of insufficient length of follow-up. One approach to addressing this challenge is the Cancer Intervention and Surveillance Modeling Network, which is also supported by the National Cancer Institute. The Cancer Intervention and Surveillance Modeling Network uses multiple computer simulation models to integrate common input parameters from multiple

sources and predict the long-term clinical outcomes and costs of different cancer screening strategies [106]. Results from Cancer Intervention and Surveillance Modeling Network breast models have informed U.S. Preventive Services Task Force recommendations for breast cancer screening in average-risk women [107].

The six-tiered model of clinical efficacy proposed by Fryback and Thornbury [108], ranging from technical efficacy to societal efficacy, provides a useful framework for considering the effect and outcomes of diagnostic imaging. As the imaging research community seeks to show the value of imaging beyond diagnostic accuracy and the ability to reduce disease-specific mortality, future studies will increasingly include patient-centered outcomes research, to understand effects on quality of life and costs of care, and to guide shared decision making on the basis of patients' tumor biology, risk tolerance, preferences, and values.

Summary and Recommendations for Best Practices

Current clinical guidelines are consistent in recommending a minimum of annual screening mammography for posttreatment surveillance. Variability exists in recommendations for surveillance initiation, interval, and cessation. Although DBT has been shown to decrease the number of false-positive findings with stable to increased cancer detection, studies evaluating the performance of DBT in the surveillance setting are sparse and incomplete. The state of evidence for the performance of DBT is evolving rapidly with the publication of ongoing studies and is an area where guidelines are likely to change as new evidence emerges.

Most guidelines do not support the use of whole-breast ultrasound in breast cancer surveillance. Regarding breast MRI, current data suggest that, for selected women with a personal history of breast cancer, surveillance MRI may have cancer detection rates comparable to those of high-risk women with genetic predisposition to developing breast cancer [59, 109–111]. More specific characterization of breast cancer survivors who may benefit from supplemental surveillance is a critical current knowledge gap. Currently, most guidelines recommend surveillance MRI only for patients who are also at high (> 20%) lifetime risk.

Patient, tumor, imaging, and treatment factors may contribute to a higher risk of developing an interval second breast cancer. Current evidence supports consideration of these factors when developing patient-centered surveillance regimens. Additional studies are needed to more definitively identify strategies for specific subgroups of breast cancer survivors.

For the woman in the initial clinical vignette, a postmenopausal woman with a personal history of a T1aN0M0 breast cancer with favorable prognostic factors and molecular subtype (luminal A) and no additional breast cancer risk factors, the evidence supports annual surveillance mammography without supplemental imaging.

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References

1. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005; 353:1784–1792. [PubMed: 16251534]
2. Shapiro S, Venet W, Strax P, Venet L, Roeser R. Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. Natl Cancer Inst Monogr. 1985; 67:65–74. [PubMed: 4047153]
3. Strax P, Venet L, Shapiro S. Value of mammography in reduction of mortality from breast cancer in mass screening. Am J Roentgenol Radium Ther Nucl Med. 1973; 117:686–689.
4. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. Ann Intern Med. 2009; 151:727–737. [PubMed: 19920273]
5. Tabár L, Vitak B, Chen TH, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology. 2011; 260:658–663. [PubMed: 21712474]
6. McGale P, Taylor C, Correa C, et al. Early Breast Cancer Trialists' Collaborative Group. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet. 2014; 383:2127–2135. [PubMed: 24656685]
7. Mathew A, Davidson NE. Adjuvant endocrine therapy for premenopausal women with hormone-responsive breast cancer. Breast. 2015; 24(suppl 2):S120–S125. [PubMed: 26255743]
8. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 365:1687–1717. [PubMed: 15894097]
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66:7–30. [PubMed: 26742998]
10. National Cancer Institute (NCI). [Accessed December 13, 2015] SEER stat fact sheets: cancer of any site. NCI website. seer.cancer.gov/statfacts/html/all.html
11. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014; 64:252–271. [PubMed: 24890451]
12. National Cancer Institute, Breast Cancer Surveillance Consortium (BCSC). [Accessed May 1, 2016] Distribution of key variables: personal history of breast cancer. BCSC website. breastscreening.cancer.gov/data/variables/distribution_n.html#previouscancerUpdated February 7, 2014
13. Anderson SJ, Wapnir I, DignAm JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. J Clin Oncol. 2009; 27:2466–2473. [PubMed: 19349544]
14. Wapnir IL, Anderson SJ, Mamounas EP, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five National Surgical Adjuvant Breast and Bowel Project node-positive adjuvant breast cancer trials. J Clin Oncol. 2006; 24:2028–37. [PubMed: 16648502]
15. Lu WL, Jansen L, Post WJ, Bonnema J, Van de Velde JC, De Bock GH. Impact on survival of early detection of isolated breast recurrences after the primary treatment for breast cancer: a meta-analysis. Breast Cancer Res Treat. 2009; 114:403–412. [PubMed: 18421576]

16. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol. 2016; 34:611–635. [PubMed: 26644543]
17. Khatcheressian JL, Hurley P, Bantug E, et al. Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013; 31:961–965. [PubMed: 23129741]
18. National Comprehensive Cancer Network (NCCN). [Accessed June 26, 2016] Clinical practice guidelines in oncology: breast cancer, version 2.2016. NCCN website. www.nccn.org/professionals/physician_gls/pdf/breast.pdf
19. Moy L, Newell MS, Mahoney MC, et al. ACR Appropriateness Criteria stage I breast cancer: initial workup and surveillance for local recurrence and distant metastases in asymptomatic women. J Am Coll Radiol. 2014; 11:1160–1168. [PubMed: 25444069]
20. Lin NU, Thomssen C, Cardoso F, et al. International guidelines for management of metastatic breast cancer (MBC) from the European School of Oncology (ESO)-MBC Task Force: surveillance, staging, and evaluation of patients with early-stage and metastatic breast cancer. Breast. 2013; 22:203–210. [PubMed: 23601761]
21. Senkus E, Kyriakides S, Ohno S, et al. ESMO Guidelines Committee. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015; 26(suppl 5):v8–v30. [PubMed: 26314782]
22. National Institute for Health and Care Excellence. Review of clinical guideline (CG80): breast cancer (early & locally advanced)—diagnosis and treatment. Manchester, UK: National Institute for Health and Care Excellence; 2012.
23. Houssami N, Ciatto S, Martinelli F, Bonardi R, Duffy SW. Early detection of second breast cancers improves prognosis in breast cancer survivors. Ann Oncol. 2009; 20:1505–1510. [PubMed: 19297316]
24. Paszat L, Sutradhar R, Grunfeld E, et al. Outcomes of surveillance mammography after treatment of primary breast cancer: a population-based case series. Breast Cancer Res Treat. 2009; 114:169–178. [PubMed: 18368477]
25. Lu W, Schaapveld M, Jansen L, et al. The value of surveillance mammography of the contralateral breast in patients with a history of breast cancer. Eur J Cancer. 2009; 45:3000–3007. [PubMed: 19744851]
26. Houssami N, Ciatto S. Mammographic surveillance in women with a personal history of breast cancer: how accurate? How effective? Breast. 2010; 19:439–445. [PubMed: 20547457]
27. Robertson C, Arcot Ragupathy SK, Boachie C, et al. The clinical effectiveness and cost-effectiveness of different surveillance mammography regimens after the treatment for primary breast cancer: systematic reviews registry database analyses and economic evaluation. Health Technol Assess. 2011; 15:1–322.
28. Clarke M, Collins R, Darby S, et al. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 366:2087–2106. [PubMed: 16360786]
29. Davies C, Godwin J, Gray R, et al. Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011; 378:771–784. [PubMed: 21802721]
30. Arasu VA, Joe BN, Lvoff NM, et al. Benefit of semiannual ipsilateral mammographic surveillance following breast conservation therapy. Radiology. 2012; 264:371–377. [PubMed: 22692036]
31. Kokko R, Hakama M, Holli K. Follow-up cost of breast cancer patients with localized disease after primary treatment: a randomized trial. Breast Cancer Res Treat. 2005; 93:255–260. [PubMed: 16132530]
32. Houssami N, Abraham LA, Miglioretti DL, et al. Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. JAMA. 2011; 305:790–799. [PubMed: 21343578]
33. Houssami N, Abraham LA, Kerlikowske K, et al. Risk model for second screen-detected or interval breast cancers in women with a personal history of breast cancer participating in

mammography screening. Cancer Epidemiol Biomarkers Prev. 2013; 22:946–961. [PubMed: 23513042]

34. Lee JM, Buist DSM, Houssami N, et al. Five-year risk of interval invasive second breast cancer. J Natl Cancer Inst. 2015; 107:djv109. [PubMed: 25904721]
35. Vedantham S, Karellas A, Vijayaraghavan GR, Kopans DB. Digital breast tomosynthesis: state of the art. Radiology. 2015; 277:663–684. [PubMed: 26599926]
36. Ciatto S, Houssami N, Bernardi D, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol. 2013; 14:583–589. [PubMed: 23623721]
37. Skaane P, Bandos AI, Gullien R, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology. 2013; 267:47–56. [PubMed: 23297332]
38. Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. JAMA. 2014; 311:2499–2507. [PubMed: 25058084]
39. Haas BM, Kalra V, Geisel J, Raghu M, Durand M, Philpotts LE. Comparison of tomosynthesis plus digital mammography and digital mammography alone for breast cancer screening. Radiology. 2013; 269:694–700. [PubMed: 23901124]
40. Rose SL, Tidwell AL, Bujnoch LJ, Kushwaha AC, Nordmann AS, Sexton R. Implementation of breast tomosynthesis in a routine screening practice: an observational study. AJR. 2013; 200:1401–1408. [PubMed: 23701081]
41. Houssami N, Skaane P. Overview of the evidence on digital breast tomosynthesis in breast cancer detection. Breast. 2013; 22:101–108. [PubMed: 23422255]
42. McDonald ES, Oustimov A, Weinstein SP, Synnestvedt MB, Schnall M, Conant EF. Effectiveness of digital breast tomosynthesis compared with digital mammography: outcomes analysis from 3 years of breast cancer screening. JAMA Oncol. 2016; 2:737–743. [PubMed: 26893205]
43. Bernardi D, Macaskill P, Pellegrini M, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. Lancet Oncol. 2016; 17:1105–1113. [PubMed: 27345635]
44. Sia J, Moodie K, Bressel M, et al. A prospective study comparing digital breast tomosynthesis with digital mammography in surveillance after breast cancer treatment. Eur J Cancer. 2016; 61:122–127. [PubMed: 27163158]
45. Kuhl C. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. Radiology. 2007; 244:356–378. [PubMed: 17641361]
46. Sung JS, Dershaw DD. Breast magnetic resonance imaging for screening high-risk women. Magn Reson Imaging Clin N Am. 2013; 21:509–517. [PubMed: 23928241]
47. Warner E, Messersmith H, Causer P, Elsen A, Shumak R, Plewes D. Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer. Ann Intern Med. 2008; 148:671–679. [PubMed: 18458280]
48. Brennan S, Liberman L, Dershaw DD, Morris E. Breast MRI screening of women with a personal history of breast cancer. AJR. 2010; 195:510–516. [PubMed: 20651211]
49. Elmore L, Margenthaler JA. Breast MRI surveillance in women with prior curative-intent therapy for breast cancer. J Surg Res. 2010; 163:58–62. [PubMed: 20605594]
50. Giess CS, Poole PS, Chikarmane SA, Sippo DA, Birdwell RL. Screening breast MRI in patients previously treated for breast cancer: diagnostic yield for cancer and abnormal interpretation rate. Acad Radiol. 2015; 22:1331–1337. [PubMed: 26142951]
51. Gweon HM, Cho N, Han W, et al. Breast MR imaging screening in women with a history of breast conservation therapy. Radiology. 2014; 272:366–373. [PubMed: 24635678]
52. Lehman CD, Lee JM, DeMartini WB, et al. Screening MRI in women with a personal history of breast cancer. J Natl Cancer Inst. 2016; 108:djv349. [PubMed: 26744477]
53. Schacht DV, Yamaguchi K, Lai J, Kulkarni K, Sennett CA, Abe H. Importance of a personal history of breast cancer as a risk factor for the development of subsequent breast cancer: results from screening breast MRI. AJR. 2014; 202:289–292. [PubMed: 24450667]

54. Weinstock C, Campassi C, Goloubeva O, et al. Breast magnetic resonance imaging (MRI) surveillance in breast cancer survivors. Springerplus. 2015; 4:459. [PubMed: 26322264]
55. Mainiero, MB., Bailey, L., D'orsi, C., et al. [Accessed June 26, 2016] Expert Panel on Breast Imaging. American College of Radiology: ACR appropriateness criteria—breast cancer screening. American College of Radiology website. acsearch.acr.org/docs/70910/Narrative/Published 2012
56. Scheel JR, Lee JM, Sprague BL, Lee CI, Lehman CD. Screening ultrasound as an adjunct to mammography in women with mammographically dense breasts. Am J Obstet Gynecol. 2015; 212:9–17. [PubMed: 24959654]
57. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. JAMA. 2012; 307:1394–1404. [PubMed: 22474203]
58. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008; 299:2151–2163. [PubMed: 18477782]
59. D'Orsi, CJ., Sickles, EA., Mendelson, EB., et al. ACR BI-RADS Atlas, Breast Imaging Reporting and Data System. 5. Reston, VA: American College of Radiology; 2013.
60. Ohuchi N, Suzuki A, Sobue T, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. Lancet. 2016; 387:341–348. [PubMed: 26547101]
61. Tagliafico AS, Calabrese M, Mariscotti G, et al. Adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts: interim report of a prospective comparative trial. J Clin Oncol. 2016 Mar 9. Epub ahead of print.
62. Houssami N, Ciatto S. The evolving role of new imaging methods in breast screening. Prev Med. 2011; 53:123–126. [PubMed: 21605590]
63. Ollendorf, DA., Loos, AM., Tice, JA., Lee, JM., Pearson, SD. Appropriate imaging for breast cancer screening in special populations: final appraisal document for the Washington State Health Care authority Health Technology Assessment Committee. Boston, MA: Institute for Clinical and Economic Review; 2014.
64. Berg WA, Blume JD, Cormack JB, Mendelson EB, Madsen EL. Lesion detection and characterization in a breast US phantom: results of the ACRIN 6666 Investigators. Radiology. 2006; 239:693–702. [PubMed: 16641344]
65. Berg WA, Blume JD, Cormack JB, Mendelson EB. Operator dependence of physician-performed whole-breast US: lesion detection and characterization. Radiology. 2006; 241:355–365. [PubMed: 17057064]
66. Henry NL, Hayes DF, Ramsey SD, Hortobagyi GN, Barlow WE, Gralow JR. Promoting quality and evidence-based care in early-stage breast cancer follow-up. J Natl Cancer Inst. 2014; 106:dju034. [PubMed: 24627271]
67. Roselli Del Turco MR, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. The efficacy of intensive follow-up testing in breast cancer cases. Ann Oncol. 1995; 6(suppl 2):S37–S39. [PubMed: 8616113]
68. Ghezzi P, Magnanini S, Rinaldini M, et al. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients: a multicenter randomized controlled trial—the GIVIO Investigators. JAMA. 1994; 271:1587–1592. [PubMed: 8182811]
69. Palli D, Russo A, Saieva C, et al. Intensive vs clinical follow-up after treatment of primary breast cancer: 10 year update of a randomized trial. JAMA. 1999; 281:1586. [PubMed: 10235147]
70. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors. Nature. 2012; 490:61–70. [PubMed: 23000897]
71. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000; 406:747–752. [PubMed: 10963602]
72. Sotiriou C, Neo SY, McShane LM, et al. Breast cancer classification and prognosis based on gene expression profiles from a population-based study. Proc Natl Acad Sci USA. 2003; 100:10393–10398. [PubMed: 12917485]
73. Alizart M, Saunus J, Cummings M, Lakhani SR. Molecular classification of breast carcinoma. Diagn Histopathol. 2012; 18:97–103.

74. Trop I, LeBlanc SM, David J, et al. Molecular classification of infiltrating breast cancer: toward personalized therapy. RadioGraphics. 2014; 34:1178–1195. [PubMed: 25208275]
75. Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: classification, prognostication, and prediction. Lancet. 2011; 378:1812–1823. [PubMed: 22098854]
76. Eroles P, Bosch A, Alejandro Pérez-Fidalgo J, Lluch A. Molecular biology in breast cancer: intrinsic subtypes and signaling pathways. Cancer Treat Rev. 2012; 38:698–707. [PubMed: 22178455]
77. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA. 2001; 98:10869–10874. [PubMed: 11553815]
78. Çelebi F, Pilanci KN, Ordu Ç, et al. The role of ultrasonographic findings to predict molecular subtype, histologic grade, and hormone receptor status of breast cancer. Diagn Interv Radiol. 2015; 21:448–453. [PubMed: 26359880]
79. Uematsu T, Kasami M, Yuen S. Triple-negative breast cancer: correlation between MR imaging and pathologic findings. Radiology. 2009; 250:638–647. [PubMed: 19244039]
80. Voduc KD, Cheang MCU, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol. 2010; 28:1684–1691. [PubMed: 20194857]
81. Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol. 2011; 29:3885–3891. [PubMed: 21900114]
82. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975–2011; featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. J Natl Cancer Inst. 2015; 107:djv048. [PubMed: 25825511]
83. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies: improving the management of early breast cancer—St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015; 26:1533–1546. [PubMed: 25939896]
84. Perou CM. Molecular stratification of triple-negative breast cancers. Oncologist. 2011; 16(suppl 1): 61–70.
85. Ko ES, Lee BH, Kim HA, Noh WC, Kim MS, Lee SA. Triple-negative breast cancer: correlation between imaging and pathological findings. Eur Radiol. 2010; 20:1111–1117. [PubMed: 19898850]
86. Wang Y, Ikeda DM, Narasimhan B, et al. Estrogen receptor-negative invasive breast cancer: imaging features of tumors with and without human epidermal growth factor receptor type 2 overexpression. Radiology. 2008; 246:367–375. [PubMed: 18180338]
87. Collett K, Stefansson IM, Eide J, et al. A basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. Cancer Epidemiol Biomarkers Prev. 2005; 14:1108–1112. [PubMed: 15894660]
88. Caldarella A, Puliti D, Crocetti E, et al. Biological characteristics of interval cancers: a role for biomarkers in the breast cancer screening. J Cancer Res Clin Oncol. 2013; 139:181–185. [PubMed: 22961208]
89. Domingo L, Salas D, Zubizarreta R, et al. Tumor phenotype and breast density in distinct categories of interval cancer: results of population-based mammography screening in Spain. Breast Cancer Res. 2014; 16:R3. [PubMed: 24410848]
90. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007; 13:4429–4434. [PubMed: 17671126]
91. Dogan BE, Gonzalez-Angulo AM, Gilcrease M, Dryden MJ, Yang WT. Multimodality imaging of triple receptor-negative tumors with mammography, ultrasound, and MRI. AJR. 2010; 194:1160–1166. [PubMed: 20308526]
92. Krizmanich-Conniff KM, Paramagul C, Patterson SK, et al. Triple receptor-negative breast cancer: imaging and clinical characteristics. AJR. 2012; 199:458–464. [PubMed: 22826413]
93. Wojcinski S, Soliman AA, Schmidt J, Makowski L, Degenhardt F, Hillemanns P. Sonographic features of triple-negative and non-triple-negative breast cancer. J Ultrasound Med. 2012; 31:1531–1541. [PubMed: 23011616]

94. Lamb PM, Perry NM, Vinnicombe SJ, Wells CA. Correlation between ultrasound characteristics, mammographic findings and histological grade in patients with invasive ductal carcinoma of the breast. Clin Radiol. 2000; 55:40–44. [PubMed: 10650109]

95. Youk JH, Son EJ, Chung J, Kim JA, Kim EK. Triple-negative invasive breast cancer on dynamic contrast-enhanced and diffusion-weighted MR imaging: comparison with other breast cancer subtypes. Eur Radiol. 2012; 22:1724–1734. [PubMed: 22527371]

96. Schrading S, Kuhl CK. Mammographic, US, and MR imaging phenotypes of familial breast cancer. Radiology. 2008; 246:58–70. [PubMed: 18096529]

97. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat. 2012; 133:831–841. [PubMed: 22147079]

98. Yang TJ, Yang Q, Haffty BG, Moran MS. Prognosis for mammographically occult, early-stage breast cancer patients treated with breast-conservation therapy. Int J Radiat Oncol Biol Phys. 2010; 76:79–84. [PubMed: 19619957]

99. Nguyen PL, Taghian AG, Katz MS, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol. 2008; 26:2373–2378. [PubMed: 18413639]

100. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010; 28:3271–3277. [PubMed: 20498394]

101. Oeffinger KC, Fontham ET, Etzioni R, et al. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA. 2015; 314:1599–1614. [PubMed: 26501536]

102. National Comprehensive Cancer Network (NCCN). [Accessed July 27, 2016] Clinical practice guidelines in oncology: breast cancer screening and diagnosis, version 1.2016. NCCN website. www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf

103. Ballard-Barbash R, Taplin SH, Yankaskas BC, et al. Breast Cancer Surveillance Consortium. A national mammography screening and outcomes database. AJR. 1997; 169:1001–1008. [PubMed: 9308451]

104. Miglioretti DL, Zhu W, Kerlikowske K, et al. Breast tumor prognostic characteristics and biennial vs annual mammography, age, and meno pausal status. JAMA Oncol. 2015; 1:1069–1077. [PubMed: 26501844]

105. Lee CS, Bhargavan-Chatfield M, Burnside ES, Nagy P, Sickles EA. The National Mammography Database: preliminary data. AJR. 2016; 206:883–890. [PubMed: 26866649]

106. Mandelblatt, J., Cronin, K., de Koning, H., Miglioretti, DL., Schechter, C., Stout, N. Writing Committee of the Breast Cancer Working Group; Cancer Intervention and Surveillance Modeling Network; Breast Cancer Surveillance Consortium. Collaborative modeling of U.S. breast cancer screening strategies: Agency for Healthcare Research and Quality publication no. 14-05201-EF-4. Rockville, MD: U.S. Department of Health and Human Services; 2015.

107. Mandelblatt JS, Stout NK, Schechter CB, et al. Collaborative modeling of the benefits and harms associated with different U.S. breast cancer screening strategies. Ann Intern Med. 2016; 164:215–225. [PubMed: 26756606]

108. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making. 1991; 11:88–94. [PubMed: 1907710]

109. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol. 2005; 23:8469–8476. [PubMed: 16293877]

110. Warner E, Plewes DB, Shumak RS, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. J Clin Oncol. 2001; 19:3524–3531. [PubMed: 11481359]

111. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA. 2004; 292:1317–1325. [PubMed: 15367553]

112. Lee, JM., Houssani, N. Imaging surveillance of women with a personal history of breast cancer. In: Houssami, N., Miglioretti, D., editors. Breast cancer screening: an examination of scientific evidence. London, UK: Elsevier; 2016. p. 299-322.

TABLE 1

Evidence-Based Guidelines for Imaging Surveillance After Treatment of Primary Breast Cancer

Organization, Imaging Modality	Routine Imaging Surveillance Recommendation
American Cancer Society and American Society of Clinical Oncology (ASCO), 2015 [16]: general survivorship guidelines after primary breast cancer treatment	
Mammography	Initiation, not specified; frequency, annual
Breast MRI	If patient meets high-risk criteria (> 20% lifetime risk for primary cancer per American Cancer Society guidelines)
Ultrasound	Not specified
ASCO, 2013 [17]: women who have undergone breast-conserving surgery and chemotherapy	
Mammography	Initiation, 1 year after initial mammogram and at least 6 months after completion of radiation therapy; frequency, annual
Breast MRI	Not recommended
Ultrasound	Not specified
National Comprehensive Cancer Network (NCCN), 2016 [18]	
Mammography	Initiation, 6–12 months after completion of radiation therapy; frequency, annual
Breast MRI	Not specified
Ultrasound	Not specified
American College of Radiology (ACR), 2014 [19]: stage I breast cancer after breast-conserving therapy	
Mammography	Initiation and frequency per local institutional protocol
Breast MRI	Based on risk assessment
Ultrasound	Based on risk assessment if breast MRI is contraindicated
European Society for Medical Oncology (ESMO), 2015 [21]: women with personal history of breast cancer	
Mammography	Initiation, not specified; frequency, annual
Breast MRI	May be indicated for young patients with dense breasts and genetic or family history
Ultrasound	Annual
National Institute for Health and Care Excellence (United Kingdom), 2014 [22]	
Mammography	Initiation, not specified; frequency, annual mammography for the first 5 years after breast cancer therapy, then based on patient risk category
Breast MRI	Not recommended
Ultrasound	Not recommended

Note—This table is modified from Lee and Houssami [112] with permission from Elsevier.

TABLE 2

Breast MRI Surveillance in Women With a Personal History of Breast Cancer

Reference	Year	No. of Women With Personal History of Breast Cancer	Age (y), Mean (Range)	No. of MRI Examinations	No. of MRI-Detected Cancers	Cancer Detection Rate (No. of Cancers/1000 Examinations)
Elmore and Margenthaler [49]	2010	141[a]	51 (24–73)	202	2	9.9
Brennan et al. [48]	2010	144	49 (22–73)	NR (1–11 examinations/woman)	18[b]	10.6[c]
Schacht et al. [53]	2014	208	52 (NR)	NR	6	28.8[c]
Gweon et al. [51]	2014	607	48[d] (20–72)	932	13	13.9[e]
Giess et al. [50]	2015	691[f]	52[d] (26–86)	1194	12	10.1
Weinstock et al. [54]	2015	249	46[d] (25–64)	571	11	19.3
Lehman et al. [52]	2016	915	NR (< 40 to ≥ 70)	915	18	19.7

Note—NR = not reported.

[a] Includes eight women with known genetic mutation.

[b] Includes one woman with two metachronous cancers.

[c] Number of cancers per 1000 women, because the number of examinations was not reported.

[d] Median age.

[e] Cancer detection rate over three rounds of surveillance. Cancer detection rate for first round was 11/607, or 18.1 per 1000 examinations.

[f] Includes 172 women with additional family history of breast cancer.

TABLE 3

Major Breast Cancer Molecular Subtypes

Subtype[a]	Hormone Receptors and Genes			Clinical Associations
	ER and PR	HER2	Proliferation[b]	
Luminal A	High expression	Low expression	Low expression	Frequency, 50–60%; prognosis, favorable; grade, low to intermediate
Luminal B	High expression	High expression	Low expression	Frequency, 10–20%; prognosis, intermediate to poor; grade, intermediate to high
	High expression	Low expression	High expression	
HER2 enriched (nonluminal HER2)	Low expression	High expression	Any	Frequency, 10–15%; prognosis, traditionally poor before HER2-targeted therapies and variable after HER2-targeted therapies; grade, high
Basal (high expression of basal cytokeratin)	Low expression	Low expression	High expression	Frequency, 10–20%; Prognosis, poor; grade, high; associated with *BRCA1* mutation carriers

Note—ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2.

[a]Other subtypes (normal breast–like, claudin-low, and molecular apocrine) are not included in this table.

[b]Proliferation genes include Ki-67 and epidermal growth factor receptor.