



# *Breast Cancer and the Obstetrician- Gynecologist: A Focus on Screening, Risk Assessment and Treatment of Survivors With Genitourinary Syndrome of Menopause*

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**Abstract:** Because of conflicting guidelines, providing appropriate breast cancer screening recommendations to our patients has become challenging. Given the high prevalence of genitourinary syndrome of menopause (GSM) overall, and among breast cancer survivors, and the understandable reluctance of physicians to prescribe effective hormonal treatments to survivors with this

condition, addressing the needs of breast cancer survivors with bothersome GSM is both a common and controversial issue. In this review, we detail current breast cancer screening recommendations, breast cancer risk assessment, and management of GSM in breast cancer survivors.

**Key words:** breast cancer, genitourinary syndrome of menopause, menopause, breast neoplasms, mammography

## ***Introduction***

Given the conflicting recommendations as well as new technologies, it has become challenging to provide accurate recommendations to patients regarding breast cancer screening. As awareness of genetic testing with respect to risk of cancer grows, it is important for Obstetrician-Gynecologists (OB/GYNs) to remain up to date regarding risk assessment. Finally, the high prevalence of breast cancer along with improving survival have led to >3 million US breast cancer survivors.<sup>1</sup> This statistic underscores that OB/GYNs will regularly see breast cancer survivors in their practices. Given the high prevalence of genitourinary syndrome of menopause (GSM) overall, and among survivors, and the understandable reluctance of physicians to prescribe effective hormonal treatments for this condition, addressing the needs of breast cancer survivors with bothersome GSM is both a common and challenging issue. In this review, authored by 2 fellowship-trained breast surgeons and an OB/GYNs with a special interest in breast cancer and menopause, we detail current breast cancer screening recommendations and technology, review breast cancer risk assessment, and review management of GSM in breast cancer survivors.

### **SCREENING FOR BREAST CANCER**

Breast cancer is the most common cancer in women worldwide, and the second most common cause of cancer-related deaths in US women.<sup>2</sup> Over 230,000 cases are diagnosed annually, and an estimated 40,290 women die of breast cancer in the United States.<sup>3</sup> Although mortality from breast

cancer is declining, this malignancy represents the leading cause of premature deaths in women with an average of 19 years of life lost per death.<sup>4</sup> Women who are diagnosed at earlier stages have a better prognosis. The goal of screening mammography is to detect the disease early, when the lesion is small and before the development of symptoms. Patients with screen detected cancers are more likely to be at early stage, node negative, and less likely to require chemotherapy. The challenge is to facilitate the benefits of early diagnosis while minimizing harm associated with over diagnosis and overtreatment.

### ***Breast Cancer Screening Trials***

There has been controversy regarding benefits and harms of screening mammography. However, over the past 40 years, 8 randomized control trials have been conducted which included women age 40 to 70 years (5 in Europe, 2 in Canada, and 1 in the United States). All but 1 showed a statistically significant reduction in breast cancer mortality in the range of 23% to 30%. Three of these trials have reported long-term follow-up which demonstrated that the reduction in mortality has persisted.<sup>5-8</sup>

The Canadian study stands apart as it is the only trial on screening mammography which did not show a clear benefit among women screened in their 40's.<sup>9</sup> The Swedish Organized Service Screening Evaluation Group reported on 3 decades of follow-up, demonstrating a 43% reduction in breast cancer-related mortality in women invited for screening mammograms.<sup>10</sup> It is important to note that these randomized trials were all performed between 1963 and 1982 during the era of analogue imaging. Mammographic technology has improved significantly, but the data being used to determine its usefulness for population screening is based on outdated imaging modalities. A more recent prospective cohort study of Norwegian women aged 50 to 79 years who were biennially invited for screening mammography from 1986 to 2009 demonstrated

28% reduction in mortality from breast cancer. In this study, 386 women had to undergo screening to prevent one death from breast cancer.<sup>11</sup>

### OVER DIAGNOSIS

Besides the disagreement in mortality reduction between the Canadian trials and the European and US trials, there is also concern regarding over diagnosis and harms of screening asymptomatic women. Implementation of an effective cancer screening program should reduce the incidence of stage IV disease (women presenting with metastasis at diagnosis). Screening and early detection should detect smaller asymptomatic tumors, thereby, reducing the number of women who present with stage IV disease. Unfortunately, this has not been the case. On the basis of the SEER data, the incidence of women presenting at stage IV has remained unchanged before and after the initiation of widespread screening mammography in the United States.<sup>12</sup> Explanations for this phenomenon appear to be multifactorial. New advances

in breast imaging allow us to detect and biopsy smaller lesions. Not all small mammographically detected lesions will progress to life-threatening cancers. Some small tumors may be more indolent without significant metastatic potential. Until recently, we did not have an accurate method to predict the biological behavior of various types of breast cancers. There is no data regarding the safety of nontreatment of any type of breast cancer; accordingly, almost all diagnosed invasive breast cancers are treated. Better risk stratification may determine which patients would benefit the most from screening mammography.

### Updated Guidelines on Screening Mammography

#### UNITED STATES PREVENTIVE SERVICES TASK FORCE (USPSTF)

The release of new mammographic screening guidelines by USPSTF in 2009 resulted in much controversy and media attention (Table 1). These guidelines

**TABLE 1. Screening Recommendation Guidelines for Average Risk Women in the United States**

	C.B.E. (Please Spell Out)	Mammogram Start Age	Interval	Mammogram Stop Age
USPSTF	Evidence insufficient to support exam for screening	50 (age 40-49 y: discuss with patient)	Every 2 y	< 75 y of age
ACS	Does not recommend	45 (discuss 40-45 y)	40-54 y—annual 55 and above Annual/biennial	Life expectancy <10 y
ACOG	25-39 may be offered 1-3 y 40 y and older annually	40-49 y initiate after discussion No later than 50 y of age	Annual or biennial	Continue until 75
ASBS		40-44 y—discuss with patient Start at age 45 y	45-54 y—annual > 55—annual/ biennial > 75—biennial	After age 75 discontinue based on women's health status Over age of 75 if estimated life expectancy is > 10 y

ACOG indicates American College of Obstetricians and Gynecologists; ACS, American Cancer Society; ASBS, American Society of Breast Surgeons; C.B.E., Clinical Breast Examination; USPSTF, United States Preventive Services Task Force.

recommended biennial screening for women aged 50 to 74 years, a shared decision-making process for screening women aged 40 to 49 years, and insufficient evidence to support screening women over the age of 75.<sup>13</sup> Most studies show a decrease in breast cancer mortality from screening starting at age 40. However, there is a higher false-positive rate as well as a higher risk of unnecessary biopsies in women aged 40 to 49 years. Biennial versus annual screening is also associated with fewer false-positive findings.<sup>14</sup>

#### **AMERICAN CANCER SOCIETY (ACS)**

The ACS published their updated guidelines for mammographic screening in 2015, which differed from the USPSTF and prior ACS recommendations. These guidelines represent a compromise between old recommendations of starting imaging at age 40 and those of USPSTF—initiating imaging at age 50. The 2015 ACS guidelines recommend annual screening for women aged 45 to 54 years, a shared decision-making process for women aged 40 to 44 years, and biennial screening for women over the age of 55. The ACS also advised continued screening for women with an estimated life expectancy of at least 10 years.<sup>15</sup>

#### **AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG)**

In 2017, ACOG published guidance regarding breast cancer risk assessment in average-risk women.<sup>16</sup> ACOG recommends that decisions regarding initiation, frequency, and duration of screening are best made with shared decision-making. ACOG suggests that average-risk women should be offered the opportunity to initiate screening at age 40. Women who choose not to initiate screening in their 40s should start no later than age 50. Screening should be performed every 1 or 2 years. Although biennial screening beginning after age 55 can reduce screening-related harms, less frequent screening is associated with

reduction in benefits. Screening should continue at least until age 75. Beyond age 75, decisions regarding continuing screening should into consideration the woman's health and estimated longevity. Screening is appropriate for women with a life expectancy of at least 10 years. An online tool to help determine longevity can be found at <https://eprognosis.ucsf.edu/>.

Because of the risk related to false-positive results and lack of evidence supporting benefits, ACOG does not recommend screening self-examination in women at average risk of breast cancer. Because more than half of all breast cancers are detected by women themselves, breast self-awareness should be promoted. Breast self-awareness encourages a woman's awareness of the normal appearance and feel of her breasts. Unlike breast self-examination, self-awareness does not include encouraging women to routinely examine their breasts in a systematic way. In average-risk women, ACOG recommends that clinicians may offer clinical breast examination within the context of shared decision-making, acknowledging the uncertainty of benefits and harms beyond screening mammography. If the patient desires, clinical breast examinations can be performed every 1 to 3 years for women aged 25 to 39 years and annually for women aged 40 years and older. Clinical breast examinations remain appropriate for high-risk women and those with symptoms or signs of breast disease.

#### **AMERICAN SOCIETY OF BREAST SURGEONS (ASBrS)**

ASBrS recommends women aged 40 to 44 consider screening mammography based on a balanced discussion of risks and benefits. Most studies show a decrease in breast cancer mortality from screening starting at age 40 but in the group 40 to 49 there is a higher false-positive rate. Annual screening is recommended for women ages 45 to 54 which is concordant with the new ACS guidelines. ASBrS recommends annual or biennial screening for women 55 and older

based on a shared decision-making discussion. Biennial screening is recommended for women over the age of 75 if an estimated life expectancy is > 10 years. For asymptomatic intermediate risk women, consider use of a risk assessment tool to determine an estimated life time risk for breast cancer. Consider annual screening mammography for women with greater than an estimated 15% lifetime risk for breast cancer or recommend entry into clinical trials evaluating risk-based screening. For asymptomatic high-risk women (20% to 25% or greater estimated lifetime risk), discuss use of a risk assessment tool to determine estimated life time risk for breast cancer, and risk of a germ-line mutation associated with a markedly elevated lifetime risk of breast cancer. Also, discuss annual screening with both mammography and breast magnetic resonance imaging (MRI) in compliance with ACS and NCCN Guidelines.<sup>17,18</sup>

### ***Breast Cancer Screening in Special Populations***

**Older woman:** breast cancer is more prevalent, but also can be more indolent in older women. Accordingly, mammographic screening in an older compared to a younger population would be expected to have a lower rate of false positives and unnecessary biopsies but a higher risk for detected tumors representing overdiagnosis. Over treatment may be more of a concern in women with competing comorbidities leading some experts to recommend mammographic screening only in women with at least a 5-year life expectancy.<sup>19</sup> None of the randomized prospective trials included women older than 74 years of age; therefore, the USPSTF has not recommended screening mammography in this age group.<sup>20</sup> The ACS however recommends screening if women have a life expectancy of 10 or more years. Twenty-six percent of breast cancer deaths are in women over the age of 75 and yet 50% of women over age 80 are expected

to live another 10 years. In this group, the ACS recommends individualized decisions for mammography.<sup>15,21</sup> Three observational studies show a benefit in women older than age 75 provided that the women do not have severe comorbidities. Two studies found a survival benefit for screening women with mild comorbidities and no benefit for women with severe comorbidities.<sup>19,22</sup> Another study found that when older women were screened, cancers were detected at an earlier stage.<sup>19</sup>

**Younger woman:** for women under 39 there is no data supporting routine screening. Because of more breast density in this population, mam screening as well as diagnostic mammography is less accurate in premenopausal women age under 45.<sup>23</sup> For women with average lifetime risk of breast cancer screening is not recommended by USPSTF under the age of 39 whereas the ACS does not recommend screening before age 40.

**Breast cancer survivor:** in the past it was common practice to perform every 6-month breast imaging to establish a new baseline after breast surgery and evaluate for stability after radiation therapy. However, studies have shown that the yield on 6 month interval breast imaging is quite low.<sup>24,25</sup> Less than 10% of local breast cancer recurrences occur in the first 5 years after treatment. Majority of local recurrences occur 6 to 20 years after initial diagnosis. Therefore, the American College of Radiology and the American Society of Clinical Oncology recommend obtaining a bilateral mammogram 12 months after the initial mammogram, which should be at least 6 months following completion of radiotherapy. Bilateral annual screening mammography is recommended thereafter.<sup>26</sup>

### ***Risk Stratification and Screening for Breast Cancer Based on Risk Assessment***

Although lifetime risk of breast cancer in average risk women is 1 in 8 to 1 in 12, the

10-year risk in any given decade of life in this population is never  $> 1$  in 25.<sup>27</sup> In addition to this population risk of breast cancer, other factors impact risk (Box 1). Therefore, a personal and family history covering these factors is important for individualized risk assessment. Family history associated with increased risk of pathogenic BRCA or other mutations include breast cancer diagnosis before age 50 years, bilateral breast cancer, presence of breast and ovarian cancer, presence of breast cancer in 1 or more male family members, multiple cases of breast cancer in the family, 1 or more family members with 2 primary types of BRCA-related cancer, and Ashkenazi Jewish ethnicity. A Referral Screening Tool (an updated version, the B-RST, is available at: [www.breastcancergenescreeen.org](http://www.breastcancergenescreeen.org)) ([www.breastcancergenescreeen.org/default.aspx](http://www.breastcancergenescreeen.org/default.aspx))

**BOX 1. List of known breast cancer risk factors**

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- Age
- Hormonal factors
    - Early menarche
    - Late menopause
    - Nulliparity
    - Late first pregnancy
    - Hormone therapy with estrogen and progestin in postmenopausal women (decreased risk with estrogen alone)
    - Not breastfeeding
  - Host factors
    - Higher body mass index
    - Alcohol intake
    - Smoking
    - Mammogram showing dense breasts
    - High risk breast pathology
      - Atypical ductal or lobular hyperplasia
      - Lobular carcinoma in situ
    - Radiation exposure to chest at a young age
  - Genetic factors
    - Ashkenazi Jewish ethnicity
    - Family history of breast cancer, ovarian cancer or other hereditary breast and ovarian syndrome-associated cancer
    - Pathogenic breast cancer-related genetic mutations
- 

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can be used to identify women who will benefit from referral for genetic counselling.<sup>28</sup> On the other hand, for women without significant genetic/hereditary risk factors for breast cancer, risk assessment models which incorporate host risk factors should be used. On the basis of the assessment of lifetime risk of breast cancer, women can be classified as average risk ( $< 15\%$ ), intermediate risk ( $15\%$  to  $20\%$ ), and high risk ( $> 20\%$  to  $25\%$ ).<sup>17</sup> Women identified as high risk should be offered enhanced surveillance, lifestyle, pharmacological, or surgical interventions for risk reduction.

### ***Other Screening Modalities for Women With Mammographically Dense Breasts***

Dense breast tissue is a common finding which is associated with increased risk of breast cancer and which reduces sensitivity of screening mammography by masking potential cancer.<sup>29,30</sup> At present 31 states have enacted dense breast notification legislation to provide patients with mammographically dense breasts information about their breast density, the limitations of mammography, and their increased risk of breast cancer. This has led to increased use of supplemental breast ultrasound and MRI after a negative screening mammogram. Supplemental imaging may help in early detection of otherwise occult breast cancer, but it also leads to an increase in false-positive findings, unnecessary biopsies, anxiety, and increased overall cost of care. Cost of supplemental imaging for women with dense breast may not be covered by individual health plan except in Connecticut, Illinois, Indiana, and New Jersey where it is mandatory. Health care providers should order supplemental imaging selectively for women with dense breast based on comprehensive understanding of their breast cancer risk factors.<sup>31</sup>

### DIGITAL BREAST TOMOSYNTHESIS

Many centers are offering digital breast tomosynthesis to patients with radiologically dense breasts or those at higher risk for breast cancer. Digital breast tomosynthesis is a modification of digital mammography that allows for the acquisition of 3-dimensional (3D) thin section data of the breast. Approximately 10 to 15 one millimeter thickness slices are acquired through each breast and reconstructed using algorithms like those used with computed tomography.<sup>32</sup> A tomogram reduces the visualization of overlapping structures by blurring tissue above and below the slice of interest. Both conventional 2-dimensional (2D) mammography and 3D images can be acquired on the same tomosynthesis unit. Studies suggest screening using tomosynthesis may enhance screening sensitivity and reduce false positives, thereby, avoiding over diagnosis.<sup>33</sup> Currently, insurance coverage for screening with tomosynthesis remains inconsistent. Neither the USPSTF nor ACS guidelines provide specific recommendations for type of mammogram.

### BREAST ULTRASOUND

Screening breast ultrasound in women with dense breast tissue is effective in detecting mammographically occult breast cancer. Sensitivity for breast cancer detection with screening mammogram and physical examination is 74.7% which can be increased to 97.3% with addition of screening ultrasound. However positive predictive value of screening ultrasound was only 20.5% when compared with 35.8% with mammography. Also, the increased time required for the performance of bilateral handheld ultrasound makes it a challenge for use of this technology in screening. In order to make ultrasound screening time-efficient, automated breast ultrasound was developed. This has allowed whole-breast ultrasound to be widely integrated into clinical practice and more experience with its use in the screening environment may prove it to be beneficial. Health care providers may selectively use screening

ultrasound in addition to screening mammography for intermediate-risk women with dense breast tissue for whom mammography may not be sufficiently sensitive and MRI not warranted.<sup>34</sup>

### MRI

Sensitivity of screening MRI ranges between 81% and 100%, in women with various risk profiles, which is approximately twice as high as the sensitivity of mammography. The specificity ranges between 83% and 98%, with positive predictive values for biopsy in the same range as for mammography (11% to 40%). After a screening MRI, mammography may yield ~5% additional cancers, mostly ductal carcinoma in situ. For this reason, screening MRI is performed in addition to but not in lieu of mammography in high risk women. Also, MRI has a higher sensitivity for all types of breast cancer, including low-grade ductal carcinoma in situ, and may therefore also increase overdiagnosis.<sup>35</sup> ACS recommends MRI screening for all women with a lifetime risk for the development of breast cancer of 20% to 25% or higher based on family history or genetic predisposition. Screening MRI is not recommended for average risk women (lifetime risk <15%). However, for women with intermediate risk (lifetime risk of between 15% and 20%) evidence is insufficient to recommend for or against screening.<sup>17</sup> While indications for screening breast MRI screening are expanding, it is difficult to integrate this technology into clinical practice due to limited availability of MRI scanners and high costs, along with the need for contrast administration. Application of abbreviated breast MRI protocols may alleviate these issues except for administration of intravenous contrast.<sup>35</sup>

### SUPPLEMENTAL IMAGING WITH BREAST MRI AND ULTRASOUND AND DIGITAL TOMOSYNTHESIS

A systematic review of literature was performed for the USPSTF comparing various supplemental imaging (MRI, ultrasound,

and digital tomosynthesis) in women with dense breasts and negative mammograms. It was noted that 13% to 19% of women were recategorized between “dense” and “nondense” upon subsequent screening mammography. Supplemental imaging was associated with increased sensitivity but there was also increased false-positive rate. However, use of digital tomosynthesis reduced recall rates.<sup>36</sup>

#### MOLECULAR BREAST IMAGING (MBI) AND FDG-PEM

Use of in women with dense breasts increases the cancer detection rate; however, there are no large population studies of MBI for screening, and the whole-body radiation dose with this technique is concerning. Positron emission mammography with fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG-PEM) is similarly limited by lack of evidence in large screening populations and radiation dose.<sup>37</sup>

### *Management of GSM in Breast Cancer Survivors*

GSM represents a highly prevalent progressive condition that can impair the health, sexuality, and quality of life in menopausal women. Breast cancer survivors experience an increased symptom burden from GSM for iatrogenic reasons and because there is a reluctance to use conventional treatments for this condition.

Package labeling for all estrogens, including local low-dose vaginal estrogen formulations, lists a history of breast cancer as a contraindication to use. Chemotherapy-induced menopause commonly incurs as part of treatment of breast cancer in premenopausal women. Likewise, bilateral salpingo-oophorectomy or use of GnRH agonists induce menopausal symptoms, including GSM. Finally, the use of aromatase inhibitors (AIs) leads to exacerbation of GSM.

In 2018, a consensus statement<sup>38</sup> prepared by menopause specialists, medical oncologists

focusing on breast cancer, and others was published and made recommendations including the following:

- Sexual function and quality of life should routinely be assessed in all women with breast cancer.
- Management of GSM should be individualized, based on shared decision-making incorporating the perspectives of the patient and her oncologist.
- Initial nonhormonal management of GSM should include lubricants and moisturizers as well as dilator therapy and referral to specialized pelvic floor physical therapists when applicable.
- Low-dose vaginal estrogen therapy may be appropriate for women at relatively low risk for recurrence, those using tamoxifen, as well as those particularly concerned regarding quality of life. Because their use is associated with minimal if any long-term elevation in serum estradiol levels, use of the vaginal ring (Estring), tablets (Vagifem or Uvafem) or inserts (Imvexxy) is preferred, rather than use of estrogen creams. The newer agents for GSM vaginal prasterone (DHEA) as well as the selective estrogen receptor modulator ospemifene have not been studied in breast cancer survivors. Given that AIs prevent recurrence by lowering estrogen levels, oncologists may be reluctant to support use of vaginal estrogen among women using AIs.

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