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Image-Based Screening for Men at High Risk for Breast Cancer: Benefits and Drawbacks

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Abstract

Male breast cancer is a rare malignancy. Due to low prevalence and limited data to support male breast cancer screening, there are currently no recommendations for image-based screening in asymptomatic men and few recommendations for men at high risk for breast cancer. However, symptomatically diagnosed cancers in men are typically advanced, suggesting that earlier detection may improve outcomes. In this article we briefly review the risk factors for male breast cancer and discuss the potential benefits and possible drawbacks of routine image-based screening for men at high risk for breast cancer.

Keywords

male breast cancer; screening; risk factors; BRCA 1, 2; mammography

1. Background

Male breast cancer is a rare malignancy representing approximately 1% of all breast cancer cases [1], with an estimated 2670 new cases and 500 deaths attributable to the disease in 2019 in the United States [2,3]. The incidence of male breast cancer has risen over the past few decades [4–6]. The lifetime risk for female breast cancer is 1 in 8 (12%) while the lifetime risk for male breast cancer is 1 in 833 (0.12%) [7]. Men are overwhelmingly diagnosed with ductal carcinomas because lobules, the origination site of invasive lobular carcinomas, are not typically well developed in the male breast. The receptor status of male breast cancers is most commonly estrogen receptor (ER) and progesterone receptor (PR) positive and HER2 (human epidermal growth factor receptor 2) negative [1,6]. Men with breast cancer are older (median age of 63 years), present with a larger tumor size (> 2 cm),

more frequently have nodal involvement, exhibit more advanced stage, and have poorer stage for stage overall survival compared to women [6,8,9]. Approximately 40% of men present with stage III or IV disease [10]. Since the 1980s, mortality rates from breast cancer have decreased for women. This observation has been attributed to improvements in treatments as well as widespread adoption of screening mammography [11,12]. On the other hand, male breast cancer mortality rates have remained unchanged over the same period despite similar treatment algorithms [13].

Breast cancer in males is usually detected when symptomatic, typically presenting as a palpable lump, or less commonly as skin changes, nipple retraction, or nipple discharge [10,14,15] (Figure 1a-c). Due to anatomical differences in the male breast compared to females, breast masses may be more appreciable as they are closer to the skin, which may also explain the more frequent skin involvement and regional lymphatic involvement in male breast cancers [16]. Gynecomastia, a benign proliferation of breast tissue in men, is the most common differential diagnostic consideration, and is present in approximately half of male breast cancer cases [17]. Distinguishing gynecomastia from male breast cancer, however, is not usually a diagnostic challenge as male breast cancers usually present as an irregular mass with indistinct or spiculated margins sometimes with associated microcalcifications [18–20], while gynecomastia most often presents as a retroareolar flame-shaped focal asymmetry [16] (Figure 2a-b).

For men 25 years of age or older presenting with a palpable abnormality, bilateral diagnostic mammography [18,21] is the recommended initial imaging test. For men younger than 25 years, diagnostic ultrasound is recommended. Diagnostic mammography is highly sensitive (92–100%), and specific (90–96%) for male breast cancer, with a negative predictive value approaching 100% [17,18,20,22,23]. Diagnostic ultrasound can also be performed as an adjunct tool in the setting of indeterminate mammographic findings and for biopsy planning [18].

Due to the low prevalence of male breast cancer and limited data to support breast cancer screening in men [1,6,24], there are currently no recommendations for image-based screening in asymptomatic men [25]. The American Cancer Society states that “Screening men for breast cancer has not been studied to know if it is helpful, ...” [26]. Other organizations such as the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the American College of Radiology (ACR) do not directly address the question of breast cancer screening for asymptomatic men. Although the definition of women at “high risk” for breast cancer has been well established [27], a corollary definition for men has not yet been established, although one review paper considered men “high risk” if they had a lifetime risk greater than the male average risk [16]. This contrast is likely due to the large difference in “average” lifetime risk for breast cancer for each gender: approximately 1 in 833 for men, and 1 in 8 for women [28].

Little research has investigated screening for men at high risk for breast cancer resulting in few established guidelines for this population (Table 1). Men testing positive for a BRCA (Breast Cancer) 1 or 2 pathogenic or likely pathogenic variants have an increased lifetime risk for the development of breast cancer [29]. Thus, the NCCN recommends annual clinical

breast examination as well as training in monthly breast self-examination starting at age 35. The NCCN does not recommend routine screening mammography secondary to limited data [30]. For men with a personal history of breast malignancy, the NCCN recommends consideration of genetic testing. As a result of recent research [31], guidelines from the American Society of Breast Surgeons recommend that all patients diagnosed with breast cancer receive genetic testing for hereditary breast cancer [32].

Men commonly have advanced disease at the time of initial presentation suggesting that earlier detection may improve outcomes and introduces the potential value of image-based screening in high risk populations. Recent American Society of Clinical Oncology Multidisciplinary Meeting recommendations suggest consideration of baseline and annual mammography for BRCA 1 or 2 positive men with gynecomastia or glandular breast density on the baseline study [24]. Male patients proposed for annual image-based screening may include men with a personal history of breast cancer or BRCA mutation carriers [33]. In this article, we briefly review the risk factors for male breast cancer, and discuss the potential benefits and possible drawbacks of routine image-based screening for men at high risk for breast cancer.

2. Risk Factors for Male Breast Cancer

There are multiple factors that increase the risk of breast cancer in men beyond increased age, including genetic, demographic, hormonal, and environmental influences (Table 2). As with women, deleterious genetic mutations increase the risk for male breast cancer and are found in approximately 10% of men diagnosed with breast cancer [31]. Studies demonstrate that up to 4% of men with breast cancer have BRCA1 mutations, while 4 to 16% have BRCA2 mutations [1,34–36]. The absolute lifetime risk for male BRCA 1 carriers is 1.2–2%, while the risk for BRCA 2 carriers is 6.8–8% [16,29]. Although the absolute risk is low given the low incidence of the disease, the relative increase in risk from baseline is higher for men than women: BRCA1 carriers have a 20-fold increase in risk, while BRCA 2 carriers have an 80-fold increase in risk (there is an approximately 7-fold increase in risk for BRCA1 or 2 female carriers) [16,37]. In addition, as more women with breast cancer are identified as carriers of a genetic mutation through the increased adoption of multigene testing and recommendations such as those from the American Society of Breast Surgeons, male relatives will be increasingly identified as carriers thus expanding the pool of men known to have an increased risk of malignancy. In addition, mutations in CHEK2 (checkpoint kinase 2), PALB2 (partner and localizer of BRCA2), CYP17A1 (cytochrome P450 family 17 subfamily A member 1), and PTEN (phosphatase and tensin homolog) genes are established risk factors for male breast cancer, albeit with much lower penetrance than BRCA 1 or 2 mutations.

Family history is one of the strongest risk factors for female breast cancer [38–40] and a family history of breast cancer increases the risk for male breast cancer depending on the number and family member(s) affected. Men with a first-degree relative have a relative risk of 1.9, and those men with both an affected mother and sister have nearly 10 times the risk of men without a family history [41]. There is a 30- to 112-fold risk for recurrence or a second primary breast malignancy in men previously treated for breast cancer [42–44]. This

level of risk is far greater than for women with a personal history of breast cancer (2- to 4-fold) [43]. There is also evidence for a racial predilection for male breast cancer with black men disproportionately affected, and diagnosed at an earlier age with poorer outcomes as compared to non-Hispanic white men [45,46]. Like their female counterparts, men of Ashkenazi Jewish descent also have an increased risk for breast cancer [47,48].

A relative excess of estrogen in relation to androgens secondary to a variety of causes has also been shown to increase the risk for male breast cancer. Exogenous estrogen exposure, Klinefelter syndrome, liver disease, testicular abnormalities, and obesity have all been implicated in the development of male breast cancer [1,49]. In particular, Klinefelter syndrome (excess X chromosomes, usually 47-XXY karyotype) confers a 16- to 19-fold increased risk for breast carcinoma [49–51]. Gynecomastia, an important imaging finding to distinguish from male breast cancer and related to a relative estrogen excess in males, increases the risk of male breast cancer approximately 5- to 10-fold in some studies [49,51]. Interestingly, in a recent study by Coopey and colleagues, atypical ductal hyperplasia identified on excision or mastectomy specimens for gynecomastia did not appear to elevate the risk for male breast cancer as it does in women [52]; the authors note that the reasoning behind this result was uncertain.

A few environmental exposures have been linked to the incidence of male breast cancer. Radiation exposure, a known risk factor for many types of cancers, has been shown to increase the risk for male breast cancer. This finding was demonstrated in studies of atomic bomb survivors [53,54], but also for diagnostic and therapeutic ionizing radiation [55]. Much smaller effects have been demonstrated for exposure to high temperature environments and exhaust fumes (polycyclic aromatic hydrocarbons), and electromagnetic fields [10].

3. Potential Benefits of Image-Based Screening of High Risk Men

There are several potential benefits for screening men at an elevated risk for male breast cancer (Table 3). First, the sensitivity of mammographic screening for men is expected to be high secondary to the predominantly fatty male breast tissue. The detection of malignancy in females is hampered by denser and more diffuse fibroglandular tissue [56,57]. In males, however, the diagnostic performance in the setting of clinical symptoms demonstrates mammography to be highly sensitive and specific, with a high negative predictive value [17,18,20,22,23].

Second, there may be subpopulations of men with particularly high risk who may benefit more from routine mammographic screening. For example, men with known BRCA genetic mutations, particularly BRCA2 mutations, have a lifetime risk as high as 8% [16]. This level of risk approaches the lifetime risk for average women of 12%, and some authors have proposed that these men undergo mammographic screening [33,58]. The subpopulation of men with the next highest risk for breast cancer are those with a personal history of male breast cancer. The estimated risk for a subsequent male breast cancer is just under 2% [42–44,59]. It is likely that this particular group of men, given the heightened awareness surrounding their diagnosis are already being screened with mammography. There is

increasing evidence [60,61] to show that screening is increasingly being utilized and that it confers a high cancer detection rate (CDR) for men with a known BRCA genetic mutation, Ashkenazi Jewish ancestry, a strong family history, or a personal history of breast cancer. For example, Marino, et al. found a CDR of 4.9/1000 while Gao, et al. found a CDR of 18/1000. The reason for the variability in CDR is unknown, however, the studies differed in the proportion of men in each high-risk category.

Finally, screening asymptomatic high-risk men introduces the potential for earlier detection of a disease that is often locally advanced when detected clinically. Recent research based on data from 2004 to 2014 [9] demonstrates that there is a persistent disparity in survival rate for men with breast cancer even after accounting for age, race, clinical and treatment factors, and access to care. Earlier detection could result in down staging at diagnosis and subsequently decrease mortality, both of which are known to be elevated in male breast cancer. In addition, earlier detection may allow patients to decrease rates of locoregional disease, providing patients with the option of breast conserving therapy as opposed to mastectomy for the standard of surgical care [62,63]. Although mastectomy has been the mainstay for surgical treatment of male breast cancer, breast conservation is increasingly being considered as a therapeutic option [64–66]. In addition, males do not typically have lobules, and present with masses (sometimes with associated calcifications [19,67]; Figure 3a-c) on mammography. One review has suggested that mammographic screening earlier in the development of male breast cancer may more frequently demonstrate calcifications [16] as ductal carcinoma in situ is the predominant precursor lesion present in almost half of male patients with invasive carcinoma [68].

There is currently no published evidence for screening with ultrasound or MRI in men, although as adjunct to mammographic screening these modalities have demonstrated a benefit for women [69–72]. However, the benefit of supplemental screening may be dependent on the level of risk [73], which would be particularly low for asymptomatic, average-risk men. Breast density may also impact the value of supplemental screening as men have breast tissue that is primarily fatty.

4. Possible Drawbacks of Screening High Risk Men

There is no established screening regimen for males, and no research has been conducted to determine the optimal screening strategy in this population as men are not typically screened. Although there is interest in improving research to inform prevention, early detection and management of male breast cancer [24], there have been no studies evaluating the impact of image-based screening on survival or disease-specific mortality. In regards to mammography, one potential confounder of mammographic screening in men is the presence of gynecomastia, seen in approximately 50% of asymptomatic males, and in up to 60% of men presenting with a symptom [16,74–76]; however, this is not typically a diagnostic challenge. The presence of gynecomastia may, however, increase rate of false positives, a known limitation of screening in women. In addition, when considering any screening program, which utilizes ionizing radiation, the potential risks associated with increased radiation exposure must be considered.

Finally, there are costs associated with establishing and maintaining a screening program for this population. This is especially pertinent when considering non-mammographic imaging tools for screening. For example, screening with MRI would be very costly as has been demonstrated in women [77]. Diagnostic performance in relation to the pathology of male breast cancer should also be considered. For example, screening with ultrasound would likely fail to diagnose the nearly 2% of male breast cancers that present solely as calcifications [19].

5. Conclusion

Male breast cancer is a rare malignancy comprising a small proportion of the total number of new breast malignancies diagnosed annually. There are currently no guidelines or data supporting screening men of average risk for male breast cancer. Although clinical breast exam is promoted as a screening tool for men with BRCA mutations, there are no recommendations from any organization for routine image-based screening for high-risk men.

Based on this review of the current literature we believe that the potential benefits of screening mammography (high sensitivity, elevated risk in certain subpopulations, and earlier detection) outweigh the potential drawbacks of false positives, cost, and radiation exposure. Screening mammography is increasingly being utilized and it confers a high cancer detection rate (CDR) for men with a known BRCA genetic mutation, Ashkenazi Jewish ancestry, a strong family history, or a personal history of breast cancer. At a minimum, the CDR for screening in high risk men is on par with the CDR for screening in average risk women, or potentially higher.

We believe that a screening program for these subpopulations of high-risk men offers the best chances for early detection of a disease that disproportionately presents with advanced or metastatic disease. Further research, potentially including data from large national or international registries or meta-analyses of large single institutional studies, may further support and establish a mortality benefit from image-based screening in high risk men and would most powerfully support the widespread adoption of high-risk screening.

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Figure 1a-c.

60-year-old male presents with a palpable mass. Craniocaudal (a) and mediolateral oblique (b) views from diagnostic mammography demonstrates a 1.7 cm irregular, high-density mass with a few calcifications in the subareolar location. Ultrasound (c) demonstrates a corresponding hypoechoic irregular mass with angular and microlobulated margins. Ultrasound-guided core needle biopsy revealed grade 2 ER positive, PR positive, HER2 negative invasive ductal carcinoma. At surgery, 1 of 6 axillary lymph nodes were positive for malignancy.

Figure 2a-b. Left breast craniocaudal (a) and mediolateral oblique diagnostic mammograms demonstrate the typical flame-shaped appearance of retroareolar breast tissue in a male patient consistent with gynecomastia.

Figure 3a-c.

63-year-old male presents with a non-tender palpable right breast mass that was noticed for several months. Right cropped magnified craniocaudal (a) and mediolateral oblique (b) mammograms demonstrate Mammographically, there is a 24 mm oval subareolar mass with indistinct margins containing fine pleomorphic calcifications underlying a radioopaque BB marker. Ultrasound (c) demonstrates a corresponding hypoechoic mass with circumscribed and indistinct margins with extension into the subareolar region. Ultrasound guided core

needle biopsy revealed grade 3, ER positive, PR positive, HER2 positive invasive ductal carcinoma.

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Table 1.

Current national organization recommendations for screening men at high risk of breast cancer.

Organization	Recommendations
American Cancer Society	<ul style="list-style-type: none"> Careful breast exams might be useful for screening men with a strong family history of breast cancer, or with BRCA mutations Screening men for breast cancer has not been studied to know if it is helpful
American College of Radiology	<ul style="list-style-type: none"> None
American Society of Breast Surgeons	<ul style="list-style-type: none"> None
American Society of Clinical Oncology	<ul style="list-style-type: none"> None
National Comprehensive Cancer Network	For BRCA positive men: <ul style="list-style-type: none"> Education regarding signs and symptoms of cancer Breast self-exam training and education starting at age 35 years Clinical breast exam, every 12 months, starting at age 35 years Limited data support imaging in men

Table 2.

Risk factors for male breast cancer

Risk Factor		Relative Risk of Malignancy
Genetic	BRCA1 mutation	20x [16,29]
	BRCA2 mutation	80x [16,29,78]
	CHEK2*1100delC mutation	4–10x [79,80]
	PALB2 mutation	Minimal [36]
Demographic	Age	Average age = 67 years [6]
	Family history of breast cancer	First degree relative: 1.9x Mother and sister: 10x [41]
	Personal history of male breast cancer	30–112x [42–44]
	Black race	1.3x [45]
	Ashkenazi Jewish	1.8x [47]
Hormonal	Klinefelter syndrome, XXY	16–19x [49–51]
	Gynecomastia	5–10x [49,51]
	Obesity	1.4–2x [41,49]
	Increased serum estradiol	2.5x [81]
Environmental	Radiation exposure	1–2x (diagnostic/therapeutic radiation) [55] 15x (atomic bomb survivors) [54]

Table 3.

Benefits and drawbacks of image-based screening for men at high-risk for breast cancer

Benefits	Drawbacks
<ul style="list-style-type: none">• Mammography in males confers a high sensitivity, specificity, and negative predictive value• Lifetime risk for specific populations of males may approach the average risk for women• Earlier detection of a disease that frequently presents as locally advanced	<ul style="list-style-type: none">• No established screening regimen• No current data to support the practice of routine screening• Increased costs associated with screening for a low prevalence disease• Radiation exposure