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SPECIAL ISSUE ON BREAST CANCER

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STAGING, RISK ASSESSMENT AND SCREENING OF BREAST CANCER

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Breast cancer is the most common female malignant disease in the western countries where a woman's lifetime risk of developing the disease is more than 10%. Nulliparity or use of hormonal replacement therapy, strong family history, or a history of therapeutic thoracic radiation are considerable high risk factors for the development of breast cancer. Nowadays more new effective therapeutic agents have been developed for the intervention of the breast cancer, but prognosis is still remained poor in the metastatic disease. For the general population, screening mammography in women older than 40–45 years has been shown to be effective in identifying early-stage breast cancer and in decreasing the mortality rate. In randomized screening mammography trials for breast cancer, it has been established that screening mammograms reduced breast cancer mortality in women older than 50 years of age by 25 to 30%. This review article summarizes the risk factors for developing breast cancer, methods for risk assessment and the accepted screening guidelines.

***Key Words*: breast cancer, locally advanced, screening.**

INTRODUCTION

Breast cancer is the most common female malignant disease in the western countries where a woman's lifetime risk of developing the disease is more than 10% [1]. Nowadays more new effective therapeutic agents have been developed for the intervention of the breast cancer, but prognosis is still remained poor in the metastatic disease. To identify the cancers at an early stage is critical so that potentially curative therapy may be delivered. For the general population, screening mammography in women older than 40–45 years of age has been shown to be effective in identifying early-stage breast cancer and in decreasing the mortality rate [2]. However mammographic screening may be less effective to determine early cancers in women who are at high risk of breast cancer. So, newer radiologic technologies like magnetic resonance imaging (MRI) may be advocated in that setting. Nulliparity or use of hormonal replacement therapy, strong family history, or a history of therapeutic thoracic radiation are considerable high risk factors [3]. Here reviews the risk factors for developing breast cancer, methods for risk assessment and the accepted screening guidelines.

STAGING

Today, the determination of the disease stage is still remaining as the most important factor in evaluating prognosis and choosing the most appropriate treatment for patients with breast cancer. The staging procedure is based of combining several findings: whether the cancer has metastasized, the diameter of the primary tumor and whether it exhibits invasive characteristics, and the number of malignant lymph nodes. Using tools for disease staging are containing a physical exam and pathological exam of the tumor biopsy as well as imaging and laboratory blood tests.

For diagnostic or staging setting, chest x-ray, breast imaging (mammogram, ultrasound and/or MRI), bone scan, computed tomography, and positron emission tomography (PET) are used as imaging tools.

Routinely, chest x-ray for determining the presence of pulmonary metastases; mammogram for determining potentially malignant tissue in the breast; bone scanning for determining the presence of metastases to bone (using imaging agent for bone scan shows "hot spots" on the skeleton in presence of metastases); frequently used computed tomography either for determining metastatic regions or for using to guide needle biopsy placement; MRI for determining potentially malignant tissue in the breast and/or metastatic regions out of the breast; ultrasound for determining potentially malignant tissue in the breast and/or metastases in abdominal organs; PET for determining metastases especially in disease staging among patients with clinically locally advanced breast cancer, are commonly used.

After completed imaging procedures, patients are assigned a disease stage in terms of American Joint Committee on Cancer (AJCC) "TNM" system, most often using staging system (Table 1) [4].

BREAST CANCER RISK ASSESSMENT

Three decades ago, Gail et al. developed a multivariate logistic regression model for determining the probability that an individual woman would develop breast cancer [5]. Breast cancer risk is estimated as an overall score that describes the relative risk of developing breast cancer contributed individually by current age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, number of breast biopsies and presence of atypical ductal hyperplasia on biopsy. The probability of developing breast cancer at 5 years and the individual's lifetime risk are reported as percentages. Due

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Abbreviations used: AJCC – American Joint Committee on Cancer; HD – Hodgkin's disease; HR – hormone receptor; HER-2 – human epidermal growth factor 2; MRI – magnetic resonance imaging; NCCN – National Comprehensive Cancer Network; PET – positron emission tomography; SEER – Surveillance Epidemiology and End Results; USPSTF – US Preventive Services Task Force.

to the composition of the study population, the first Gail Model was only useful among white women. Then, the model was upgraded to the Gail Model-2 by including Surveillance Epidemiology and End Results (SEER) data regarding both race/ethnicity [6]. The validation studies of the second model have been completed and have been shown to predict cancer rates in population effectively [7–10]. The Gail risk model has been effectively used to determine eligibility for participation in chemoprevention trials. These trials enrolled healthy women whose risk of developing breast cancer was calculated by the Gail model to be 1.66% within 5 years

Table 1. Breast Cancer Staging according to AJCC "TNM" System [4]

Disease Stage	Primary Tumor (T)	Node (N)	Metastasis (M)
Stage 0			
Tis, N0, M0	Tis, carcinoma *in situ*	N0, no regional lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
Stage IA			
T1,* N0, M0	T1, tumor ⩽ 20 mm in greatest dimension	N0, no regional lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
Stage IB			
T0, N1mi, M0	T0, no evidence of primary tumor	N1, metastases to movable ipsilateral level I, II axillary lymph node(s)	M0, no clinical or radiographic evidence of distant metastases
T1, *N1mi, M0	T1, tumor ⩽ 20 mm in greatest dimension	N1mi N1, metastases to movable ipsilateral level I, II axillary lymph node(s)	M0, no clinical or radiographic evidence of distant metastases
Stage IIA			
T0, N1,† M0	T0, no evidence of primary tumor	N1, metastases to movable ipsilateral level I, II axillary lymph node(s)	M0, no clinical or radiographic evidence of distant metastases
T1*, N1,† M0	T1, tumor ⩽ 20 mm in greatest dimension	N1, metastases to movable ipsilateral level I, II axillary lymph node(s)	M0, no clinical or radiographic evidence of distant metastases
T2, N0, M0	T2, tumor > 20 mm but ⩽50 mm in greatest dimension	N0, no regional lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
Stage IIB			
T2, N1, M0	T2, tumor > 20 mm but ⩽50 mm in greatest dimension	N1, metastases to movable ipsilateral level I, II axillary lymph node(s)	M0, no clinical or radiographic evidence of distant metastases
T3, N0, M0	T3, tumor > 50 mm in greatest dimension	N0, no regional lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
Stage IIIA			
T0, N2, M0	T0, no evidence of primary tumor	N2, metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected‡ ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
T1,* N2, M0	T1, tumor ⩽ 20 mm in greatest dimension	N2, metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected‡ ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
T2, N2, M0	T2, tumor > 20 mm but ⩽50 mm in greatest dimension	N2, metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected† ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
T3, N1, M0	T3, tumor > 50 mm in greatest dimension	N1, metastases to movable ipsilateral level I, II axillary lymph node(s)	M0, no clinical or radiographic evidence of distant metastases
T3, N2, M0	T3, tumor > 50 mm in greatest dimension	N2, metastases in ipsilateral level I, II, axillary lymph nodes that are clinically fixed or matted; or in clinically detected‡ ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
Stage IIIB			
T4, N0, M0	T4, tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)	N0, no regional lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
T4, N1, M0	T4, tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)	N1, metastases to movable ipsilateral level I, II axillary lymph node(s)	M0, no clinical or radiographic evidence of distant metastases
T4, N2, M0	T4, tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)	N2, metastases in ipsilateral level I, II, axillary lymph nodes that are clinically fixed or matted; or in clinically detected‡ ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases	M0, no clinical or radiographic evidence of distant metastases
Stage IIIC			
Any T, N3, M0	Any size	N3, metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected‡ ipsilateral internal mammary lymph node(s) with clinically evident level I, II, axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	M0, no clinical or radiographic evidence of distant metastases
Stage IV			
Any T, N, M1	Any size	None or any lymph node involvement	M1, distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Tis – carcinoma in situ. *T1 includes T1mi. †T0 and T1 tumors with nodal micrometastases only are excluded from stage IIA and are classified stage IB. ‡Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macro metastasis based on fine needle aspiration biopsy with cytological examination.

[11–14]. However the Gail model is an effective tool for determining cancer risk it is not as useful in predicting second primary cancers in women having history of invasive or noninvasive breast cancers.

INHERITED FORMS OF BREAST CANCER

The probability of family history of breast cancer is approximately 25% of women with newly diagnosed disease. The suspicion of hereditary breast cancer is increased in individuals whose family histories include at least one of the following factors: multiple cases of breast cancer, breast cancer occurring at younger than 50 years of age; bilateral breast cancer; breast cancer in male relatives; ovarian, fallopian tube, primary peritoneal cancers in female relatives; and Ashkenazi Jewish heritage. Studies of twins suggest that as many as one quarter of breast cancer cases are hereditary [15]. Many genes will likely be identified related on breast cancer in the future but mutations in 4 genes are currently recognized and responsible for 5 to 10% of all new breast cancer diagnoses — *BRCA1*, *BRCA2*, *TP53*, and *PTEN* which are tumor suppressor genes and associated with autosomal dominant disorders [16]. Genetic testing should be considered for women, who have been diagnosed with breast cancer at an early age or who are from Ashkenazi Jewish ancestry [17].

MUTATIONS IN *BRCA1* AND/OR *BRCA2*

Mutations in *BRCA1* and/or *BRCA2* account for the majority of inherited breast cancers and are the most common in individuals of Ashkenazi Jewish ancestry. The incidence of a *BRCA1/2* mutation in the general white population is 1 in 800, whereas in the Ashkenazi Jewish population the rate is 1 in 50 [18].

It has been reported that the risk of developing breast and ovarian cancers have increased among women with mutations in *BRCA1* [19]. In these women population, the risk of developing breast cancer by 40 years of age and a lifetime risk is 20 and 82%, respectively. Similarly the risk of ovarian cancer is 17% by 40 years of age and 54% by 80 years of age. The primary breast cancers related on *BRCA1* mutations often have similar characteristics, including high-grade histology; estrogen/progesterone receptor negative (–), and human epidermal growth factor 2-negative status ("triple negativity"); p53 positivity; and epidermal growth factor receptor overexpression [20–22]. Although medullary breast cancer is seen as an uncommon histology it is accounts for 20% of primary breast cancers diagnosed in *BRCA1* mutation carriers. Despite of poor prognosis in triple-negative phenotype associated with medullary carcinomas, the presence of *BRCA1* mutation in these tumors is associated with a more favorable prognosis [23–25]. However the breast cancers developing in women with *BRCA1* mutations are associated with poor prognosis is consistent with the "basal-like" intrinsic subtype [26]. The *BRCA1* pathway is very important for homologous repair of breaks in double-stranded DNA. It has been indicated that this pathway is inactivated by mutations in *BRCA1* and is diminished in sporadic triple-negative breast cancers [27]. But, it has not shown that the presence of the *BRCA1* mutations is predictive in choosing of therapeutic tools [28–30].

Breast cancers in both male and female relatives, ovarian cancer, and a higher incidence of cancers of the prostate, stomach, skin (melanoma), and pancreas are the most important features of family history of individuals with *BRCA2* mutations includes [31]. For these women, a lifetime risk for developing breast cancer and for ovarian cancer is 45 and 11%, respectively [19]. By contrast to *BRCA1* mutations, primary cancers that develop in *BRCA2* mutation carriers are most often hormone receptor positive and have a more favorable prognosis [28, 29].

A greater lifetime risk of cancer is associated with *BRCA1* mutation among women, whereas a higher breast cancer risk with *BRCA2* mutation among men [32]. Although incidence of breast cancer is only 1% of all cancers diagnosed among men, the risk of breast cancer is increased up to 100-fold with a breast cancer incidence of 1.3 to 6.3% in male *BRCA2* mutation carriers [33, 34].

A population-based analysis demonstrated the BRCAPRO tool, a computer-based Bayesian probability model, accurately predicted the number of *BRCA1/2* carriers in women aged 30 years or younger. Genetic testing remains the gold standard tool [35–37].

INHERITED SYNDROMES

Li-Fraumeni syndrome and Cowden's syndrome is very important inherited diseases related to high risk of breast-cancer, and indicated P53 mutations and *PTEN* mutations which are tumor suppressor genes. So, multiple cancers may develop including bone and soft tissue sarcomas, leukemias, primary brain tumors, and adrenocortical cancer in individuals with Li-Fraumeni syndrome [38–40]. Cowden's syndrome is known as tricholemmomas (hamartomas of the infundibulum of hair follicles) and an increased incidence of thyroid and breast cancers. Lifetime risk of breast cancer in women with this syndrome has been reported as 25 to 30% [41–43].

BREAST CANCER RISK AFTER CANCER TREATMENT

Hodgkin's disease (HD) is known as a curable malignancy with effective chemotherapy and radiation therapy. Because these patients have an increased long-term survival, the development of secondary cancers following curative treatment for HD is well recognized. Swerdlow et al. has been reported that the incidence of secondary cancers which are lung, breast, and gastrointestinal cancers, is 5.8% in a series of 5519 individuals treated for HD. In this report, the greatest risk of second malignancy was associated with a younger age at diagnosis of HD [44]. Initial reports suggested a 5–17-fold increased incidence of breast cancer in female patients treated for HD at the age of 30 years or younger [45–48]. Then, the risk

of breast cancer (hormone receptor-positive or -negative) has been reported that it is increased up to 10-fold in survivors of HD, compared with the general population. Another population-based cohort study of HD survivors has been demonstrated that younger age before 30 at diagnosis of HD and presence of radiation therapy is associated with an increasing in the absolute cumulative risk of breast-cancer [48, 49]. So, it has been shown that the reduction of the radiation volume is associated with a decreased risk of breast cancer after HD [50].

The efforts which are changing of chemotherapy regimen and lowering of radiation doses and fields have been continued for minimizing long-term complications due to treatment for HD. The impact of these modifications instead of conventional therapeutic tools (ABVD regimen for MOPP) on secondary breast cancer is unknown [51]. Therefore all HD survivors should be considered to be at high risk of secondary breast cancer, and more stringent screening procedures are recommended on these population.

SCREENING MAMMOGRAPHY

The aim of screening mammography is to identify breast cancer at an early stage when treatment may be curative. Many national guidelines for screening mammography recommend an annual mammogram beginning at age 40 years [52, 53]. A Cochrane analysis consisting of 7 randomized clinical trials [54–61], assessing mammography in women who had no breast cancer history and for whom mortality was endpoint, was published in 2006 [62]. In this analysis, total of 500,000 women from 7 trials were included, and the summary of studies is depicted in Table 2.

As seen, all trials in Cochrane analysis have significant limitations and heterogeneity in study design and/or methods (see Table 2). First of all, the potential implications of lead-time (early diagnosis) and length-time biases (detection of indolent disease) are eloquently discussed in the Cochrane analysis [62]. In total, 6 of the 7 trials invited women to participate in one or the other study arms; only the Canadian trial consented women for trial before randomization. Many of the trials included women with a history of breast cancer and these women were excluded from the study only after they had been randomized. All 7 screening studies were conducted before genetic testing was available and may have included women who would now be considered high risk and for whom screening mammography alone may not be adequate. Second, no consistent method of screening was used in these trials in terms of screening intervals and screening views. For example, baseline imaging was generally with 2 views, but follow-up mammography often employed a single view. The Malmö study employed a single view unless the woman had dense breasts, in which case 2 views were performed. Screening intervals also varied from an annual exam to an exam every 2 years. Participant compliance in the screening arms varied significantly. A baseline mammogram was obtained in only two thirds of women in the screening arm of the Edinburgh trial, and only 50% of women underwent mammography at last follow-up. For Malmö trial, 24% of women who were enrolled in the control arm often underwent screening mammography. The methods used to verify a diagnosis of breast cancer in the study participants also varied from review of the pathology and autopsy data to registry reports. Finally, all studies were statistically underpowered to demonstrate a decrease in breast cancer mortality.

Lastly, the US Preventive Services Task Force (USPSTF), incorporating 2 models using data from SEER and the US population-based mammography outcomes from the Breast Cancer Surveillance Consortium, updated their recommendations on screening mammography [63, 64]. Three recommendations of the USPSTF include: 1) Screening mammography should begin at 50 years of age — not 40. According to the statistical modeling used by the USPSTF, screening mammography prevents 1 death for every

Table 2. Summary of trials included in the Cochrane analysis [62]

Trials	Year	Site	Age, yrs	Sample size screen/ control, n	Randomization	Mammography view	Screen interval	Screens, n	Additional screening	Compliance with screening	Relative risk reduction in breast cancer
HIP	1963	New York	40–69	31,000/ 31,000	Invitation	2 views	Annual	3	Physical exam	Yr 1: 80% Yr 2: 74% Yr 3: 69%	0.78
Malmö	1976	Sweden	>45	21,088/ 21,195	Invitation	First: 2 views Follow-up: 1–2 views	18–24 months	6	-	Yr 1: 74% Thereafter: 70%	0.78
Edinburgh	1978	Scotland	45–64	26,026/ 28,628	Invitation	NS	24 months	4	Offered physical exam	Yr 1: 66% Final yr: 50%	0.78
Stockholm	1981	Sweden	40–64	40,318/ 19,343	Invitation	Oblique	Single view	2 in 5 yrs	-	Yr 1: 81%	0.90
Swedish	1978	Sweden	40–74	77,080/ 55,985	Invitation	Single view	50–74 yrs: 33 months 40–49 yrs: 24 months	Up to 7	-	89,00%	0.68
Gothenburg	1982	Sweden	39–59	21,650/ 29,961	Invitation	First: 2 views Follow-up: 1 view	18 months	6	-	Yr 1: 69%	0.79
Canadian 1&2	1980	Canada	1) 40–49 2) 50–59	1) 25,214/ 25,216 2) 19,711/ 19,694	Consent before randomization	2 views	Annual	5	Physical exam; taught BSE	-	1) 0.97 2) 1.02

HIP – Health Insurance Plan; BSE – breast self exam; NS – not specified.

1900 women aged 40–49 years who are screened for 10 years. That ratio improves to 1 in 1300 for women aged 50–59 years and 1 in 400 in women aged 60–69 years. 2) Screening should be performed every 2 years for those aged 50–69 years. The increased duration between mammography increases the risk-benefit ratio [65]. 3) Women should undergo screening up to 74 years of age. According to statistical modeling, 1 death is prevented for every 500 screened. The last USPSTF recommendations for screening have resulted in significant criticism and debate. These debates are likely to continue until a safer and more effective screening test is developed.

Despite these limitations, the Cochrane analysis concludes that screening mammography does reduce breast cancer mortality by 20%, which translates to an absolute risk reduction of 0.05% [62]. After now on, it is unlikely that additional screening studies will be performed because women would likely feel uncomfortable giving consent to a new randomized trial that included a "no imaging" arm. As the Cochrane study concluded, "for every 2000 women participated for screening through 10 years, 1 will have her life prolonged, and 10 healthy women who would not have had breast cancer diagnosed if there had not been screening will be diagnosed as cancer patients and will be treated unnecessarily. In addition, it is likely that more than 200 women will experience important psychological distress for many months because of false-positive findings". Also, it is estimated that 30% of abnormalities identified on screening mammography lead to overdiagnosis and overtreatments [66].

The treatment for breast cancer has evolved from a surgical disease to one that requires a multidisciplinary team approach including surgeons, radiation oncologists, and medical oncologists. Adding systemic adjuvant therapy regimens to surgery is largely credited with the recent decline in deaths from breast cancer [67]. On one hand, the multidisciplinary treatment of early-stage breast cancer results in increasing numbers of long-term survivors and individuals who are likely cured. The impact of early detection may be little. On the other hand, more therapies (chemotherapy and endocrine) come with the potential for increased complications related to those therapies. The Cochrane analysis incorporated unfavorable effects of radiation therapy such as an increased risk of heart disease and lung cancer [68, 69]. Radiation therapy techniques have improved so that the dose of radiation to the heart and lung are negligible. The long-term complications of adjuvant chemotherapy and endocrine therapy are increasingly being defined. Finally, according to Cochrane analysis an annual 2-view mammogram is recommended for all women at average risk of breast cancer, beginning at age 40 years [53, 70, 71]

MAMMOGRAPHY FOR OLDER WOMEN

Age is the most common risk factor for breast cancer for women; the median age at diagnosis is 61 years [72]. Breast cancers that arise in older women tend to have more favorable pathologic features. In general, the primary tumor is most often hormone receptor positive (HR-positive), human epidermal growth factor 2 negative (HER2-negative), and node negative in women older than 60 years of age. Although age defines a high risk group, data from screening mammography in this population are limited as the eligibility criteria of the mammography trials frequently excluded women older than 70 years of age. A cohort study of 2011 older women than 80 years of age who were screened between 1994 and 2004 concluded that the rate of diagnosis of breast cancers, stage, and death rate were not affected by screening [73]. Individual patient preferences and life expectancy should be considered in the decision to offer screening mammography to elder patients [74].

MAGNETIC RESONANCE IMAGING FOR SCREENING

In women with *BRCA* mutations, it has been emphasized that the risk of developing breast cancer increases after 25 years of age, with a peak incidence between 30 and 50 years of age [75]. As known, conventional screening mammography may not be the optimal screening procedure for these predominantly young, high-risk individuals. Also, the sensitivity of mammography is lowest in young women who have dense breasts [76, 77]. Because the *BRCA* genes play an important role in homologous repair of DNA damage, a theoretical concern is that the ionizing radiation from radiographies may increase local tissue damage and result in predisposition to cancer. In a case control study compared 1600 women with breast cancer with 1600 age-matched women without cancer, adjusting for known endocrine-associated risk factors and ethnicity, the investigators found no increase in incidence of breast cancer among mutation carriers, suggesting that mammography was safe in this population [78]. More importantly, conventional screening mammography in women with *BRCA* mutations may not be effective in identifying early cancers. Some observational studies in this population suggest that only half of new breast cancers are identified by screening mammography and the remaining are "interval cancers" — cancers diagnosed between screening mammograms [79, 80].

Comparing mammography, MRI has a high sensitivity for breast cancer regardless of breast density and avoids the patient being exposed to radiation. But, MRI is associated with 35% of the false-positive findings and lacking in identifying microcalcifications associated with ductal carcinoma *in situ* [81, 82]. In addition, it has been notified that screening MRI in younger women with dense breast tissue is associated with a 3-fold increase in the number of benign biopsies, comparing mammography [83]. So, these data support the use of both an annual mammogram and MRI in women aged 25 years and older with *BRCA* mutations despite of high rate of false-positive results.

OVERVIEW OF CURRENT SCREENING RECOMMENDATIONS

In randomized screening mammography trials for breast cancer, it has been established that screening mammograms reduced breast cancer mortality in women older than 50 years of age by 25 to 30% [84]. According to the American Cancer Society recommendations mammogram should be performed in women aged 40 years and older for breast cancer screening and should be continued every year in women who remain in good health [85]. Mammograms should be performed on the basis of whether comorbidities exist for older women. If female individuals are between 20 and 40 years of age, clinical breast exams should be done at least once every 3 years. A clinical breast exam should be given once per year, beginning at the 40 years of age. According to the American Cancer Society, clinical breast exam when performed by a health professional represents a teaching opportunity and a chance to discuss any medical history that may put a woman at increased risk of breast cancer. At this time, women 20 years of age or older can also be instructed to perform breast self exam [85]. In addition, the National Comprehensive Cancer Network (NCCN) guidelines are accepted that mammography and ultrasound is complementary imaging methods used to diagnose breast cancer (Table 3) [70].

Table 3. NCCN Guidelines for Screening of Women at High Risk (NCCN Breast Screening 2011) [70]

Factor Contributing to High-Risk Status	NCCN recommendations for screening
Personal history of LCIS or atypical hyperplasia	• Annual mammogram • Consider annual MRI (for women with LCIS) • CBE every 6–12 mos by healthcare professional • Periodic BSE • Risk-reduction strategies, including surgical and medication interventions considered
Family history or hereditary (genetic) syndrome	*Younger than 25 yrs of age:* Annual CBE and periodic BSE *25 yrs of age or older:* • Annual mammogram and CBE every 6–12 mos *Begin at age 25 for hereditary breast and ovarian cancer syndromes* *Others begin 5–10 yrs before youngest family cancer case (breast cancer or related cancer)* • Periodic BSE • Breast MRI in conjunction with mammogram considered • Risk-reduction strategies, including surgical and medication interventions considered
Aged 35 yrs or older and Gail Model risk ⩾ 1.7%	• Annual mammogram and CBE every 6–12 mos • Periodic BSE encouraged • Risk-reduction strategies, including surgery and pharmacologic agents considered
Personal history of mantle radiation for HD	*Younger than 25 yrs of age:* Annual CBE and periodic BSE *25 yrs of age or older:* • Annual mammogram and CBE every 6–12 mos *Begin 8–10 yrs after radiation therapy or at 25 yrs of age, whichever occurs last* • Periodic BSE encouraged
Previous diagnosis of breast cancer	• Mammogram every 12 mos • Clinician exam every 4–6 mos for 5 yrs, then every 12 mos

BSE – breast self-exam; CBE – clinical breast exam; LCIS – lobular carcinoma *in situ*.

Also, the American Cancer Society recommends that women with high risk who have a 20% or higher lifetime risk should undergo MRI and a mammogram every year. Women at moderately increased risk, between 15 and 20%, should consult with their healthcare professional about whether they should undergo MRI in addition to a yearly mammogram (Table 4). MRI is not indicated for women at low increased risk who have less than 15% lifetime risk [85].

Table 4. High and moderately high risk of developing breast cancer, as defined by the American Cancer Society (ACS 2011) [85]

Degree of risk	Risk factors
Women at high risk (> 20% lifetime risk)	• Known *BRCA1* or *BRCA2* gene mutation • First-degree relative (parent, brother, sister, or child) with a *BRCA1* or *BRCA2* gene mutation, and have not had genetic testing themselves • Li-Fraumeni syndrome, Cowden syndrome, Bannayan –Riley – Ruvalcaba syndrome, or hereditary diffuse gastric cancer (or have a first-degree relative with one of these syndromes) • Radiation therapy to the chest between 10 and 30 years of age
Moderately increased risk (15% to 20%)	• Extremely dense breasts or unevenly dense breasts on mammogram • Personal history of breast cancer, ductal carcinoma *in situ*, lobular carcinoma *in situ*, atypical ductal hyperplasia, or atypical lobular hyperplasia

CONFLICT OF INTEREST

There is no conflict of interest.

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