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 mammography 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 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 a 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
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 beginning at age 40. July 20, 2011. Available at: http://www.acog.org/from_home/publications/press_releases/nr07–20–11–2.cfm. Accessed September 6, 2011.
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 has 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 and 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].

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].

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 (e.g., detection of indolent disease) are eloquently discussed in the Cochrane analysis [62].

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

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Primary Tumor (T)</th>
<th>Node (N)</th>
<th>Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis, N0, M0</td>
<td>N0, no regional lymph node metastases</td>
<td>M0, no clinical or radiographic evidence of distant metastases</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1* N0, M0</td>
<td>T1, tumor ≤ 20 mm in greatest dimension</td>
<td>M0, no clinical or radiographic evidence of distant metastases</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1*, N0, M0</td>
<td>T1, tumor ≤ 20 mm in greatest dimension</td>
<td>N0, no regional lymph node metastases</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T0, N1mi, M0</td>
<td>T0, no evidence of primary tumor</td>
<td>N1, metastases to movable ipsilateral level I, II axillary lymph node(s)</td>
</tr>
<tr>
<td></td>
<td>T1*, N1mi, M0</td>
<td>T1, tumor ≤ 20 mm in greatest dimension</td>
<td>N1mi, metastases to movable ipsilateral level I, II axillary lymph node(s)</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T0, N1, M0†</td>
<td>T0, no evidence of primary tumor</td>
<td>N1, metastases to movable ipsilateral level I, II axillary lymph node(s)</td>
</tr>
<tr>
<td></td>
<td>T1*, N1, M0†</td>
<td>T1, tumor ≤ 20 mm in greatest dimension</td>
<td>N1, metastases to movable ipsilateral level I, II axillary lymph node(s)</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T0, N0, M0</td>
<td>T0, no evidence of primary tumor</td>
<td>N0, no regional lymph node metastases</td>
</tr>
<tr>
<td></td>
<td>T2, N0, M0</td>
<td>T2, tumor &gt; 20 mm but ≤50 mm in greatest dimension</td>
<td>N0, no regional lymph node metastases</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T2, N1, M0</td>
<td>T2, tumor &gt; 20 mm but ≤50 mm in greatest dimension</td>
<td>N1, metastases to movable ipsilateral level I, II axillary lymph node(s)</td>
</tr>
<tr>
<td></td>
<td>T3, N0, M0</td>
<td>T3, tumor &gt; 50 mm in greatest dimension</td>
<td>N0, no regional lymph node metastases</td>
</tr>
</tbody>
</table>

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 100,000 women. In a meta-analysis of SEER and the US population-based mammography data, 25% of women undergoing screening mammography had a true negative examination, compared with 90% in the USPSTF model. Thus, 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.

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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 significant 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 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]

<table>
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<td>- Extremely dense breasts or unevenly dense breasts on mammogram</td>
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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]

<table>
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CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCES


85. The American Congress of Obstetricians and Gynecologists. Annual mammograms now recommended for women be-