

THE ROLE OF “HIGH RISK CLINICS” IN SCREENING AND MANAGING BREAST CANCER

Gülün Tahan, Mohammed Firdos Ziauddin, Atilla Soran

Magee Womens Hospital The University of Pittsburgh, Department of Surgery, Pittsburgh, USA

ABSTRACT

Breast cancer is the most common cancer among women, and its prevalence and associated mortality rate is increasing significantly in developing countries. Early diagnosis and proper management are necessary to reduce breast cancer morbidity and mortality, as evidenced by the positive impact of breast cancer screening in the United States and elsewhere. The Breast Health Global Initiative set forth breast health care guidelines for early detection, diagnosis and treatment in countries with limited resources. Breast cancer screening guidelines include more rigorous schedules for women, at high-risk of developing this disease and for whom the general guidelines for screening are not adequate for early detection of breast cancer. Identification of women at high-risk is, therefore, important. For individual patients, breast cancer risk evaluation may include assessment of personal and family history, genetic testing if indicated, and estimation of risk using population-based models, such as the Gail-model. Patients may be at high-risk due to modifiable or non-modifiable risk factors, and risk scores may be assigned using the population-based models. Patients with non-modifiable risk factors and high-risk scores require heightened surveillance, and some groups benefit from chemoprevention or risk reduction surgery. The aim of this review is to emphasize the importance of high-risk breast cancer clinics in assessing breast cancer risk, screening high-risk patients, and managing the therapy and continued follow up of women who are at high-risk of developing breast cancer in developed and developing countries.

Keywords: High risk, breast cancer, clinics, screening, chemoprevention, tamoxifen, raloxifene, preventive surgery

MEME KANSERİ TARAMASI VE ÖNLENMESİNDE “YÜKSEK –RİSK KLİNİKLERİ”NİN ROLÜ

ÖZET

Meme kanseri kadınların en sık kanseri olup, gelişmekte olan ülkelerde prevalans ve mortalite oranları anlamlı olarak artmaktadır. Amerika Birleşik Devletleri ve gelişmiş başka ülkelerde de meme kanseri taramasının pozitif etkinliği kanıtlanmış olup, erken tanı ve uygun yaklaşım şekli meme kanserinin mortalite ve morbiditesinin düşürülmesi için gerekmektedir. “The Breast Health Global Initiative”ın yayınladığı dördüncü meme sađlığı ve bakımı rehberinde erken tanı, diağnoz ve tedavi sınırlı imkanlara sahip ülkeler için de önerilmektedir. Meme kanseri tarama rehberleri bu hastalığa yakalanmada “yüksek-riskli” kişiler için sıkı takip şeması önerirken, diğere taraftan erken tanı için tarama gerekmeyen kişileri de ortaya koyar. Bu yüzden “yüksek-risk” grubu hastaların tanımlanması önem taşır. Meme kanseri riskinin bireysel değerlendirilmesi kişisel ve ailesel anamnez, gereğinde genetik testler ve “Gail model” gibi toplum- tabanlı modellerle risk tahminini içerir. Bu toplumsal modellerle yüksek-risk hastalarının saptanması değiştirilebilir veya değiştirilemez risk faktörleri tanımlanmasına dayanmaktadır. Değıştirilemez risk faktörleri ve yüksek-risk skoru bulunan hastalarda sıkı takip gerekirken, bazı gruplar ilaçla koruma veya risk-düşürücü cerrahiden faydalanabilir. Bu derlemenin amacı gelişmiş ve gelişmekte olan ülkelerde meme kanseri riskinin değerlendirilmesinde “yüksek-risk klinikleri”nin önemi, yüksek-riskli hastaların taranması, meme kanseri gelişimi için “yüksek-riskli” kadınların sürekli takip ve tedavi gereğini vurgulamaktır.

Anahtar sözcükler: Yüksek risk, meme kanseri, klinik, tarama, ilaçla önleme, tamoksifen, raloksifen, önleyici cerrahi.

Introduction

Breast cancer is the most common cancer among women and accounts for 23% of all cancer diagnoses in women worldwide. Despite its prevalence, it is the fifth most common cause of cancer death because of its relatively good prognosis when diagnosed early (1, 2). Although breast cancer incidence is lower in developing countries when compared with developed countries, the mortality is often much higher. The overall survival of breast cancer is improving with early diagnosis, and further improvement may be achievable by the optimization of screening and identification of women who are at high risk for breast cancer (3, 4). In this review,

we focus on the identification and management of patients who are at high risk of developing breast cancer, and we underline the importance of high risk breast cancer clinics in developed and developing countries.

High risk clinics for breast cancer are accessible in developed countries that have established extensive healthcare systems. Studies of these clinics have shown that chemoprevention with selective estrogen response modulator medications, such as tamoxifen and raloxifene, and risk-reducing surgeries for high risk breast cancer patients can decrease the risk of invasive breast can-

cer 50% and 90%, respectively (3, 4). 45% of new cases and >55% of deaths from breast cancer occur in developing countries (5, 6). By focusing on the special needs of women at high risk of breast cancer, high risk clinics can help to decrease this severe inequality in breast cancer mortality.

Identifying women at high risk of developing breast cancer

According to the 2009 National Comprehensive Cancer Network Guidelines, breast cancer risk assessment and counseling is indicated for women based on family history, known or suspected genetic predisposition, prior history of therapeutic dose thoracic radiation, personal history of lobular carcinoma in situ or atypical hyperplasia, or a 5-year risk score of $\geq 1.67\%$ by the Gail model risk calculator (7, 8). Several modifiable and non-modifiable risk factors for breast cancer have been identified (Tables 1 and 2), (8-27).

A family history of close relatives with breast and/or ovarian cancer suggests a possible heritable mutation predisposing to development of breast cancer. A personal or family history of breast cancer diagnosis at age younger than 50 years, diagnosis of breast cancer in a male family member, or Ashkenazi Jewish ancestry also suggest a hereditary cancer predisposition. However, available testing methods detect only 10% of mutations. Gene mutations associated with breast cancer include mutations in the BRCA 1/2, p53, and PTEN genes. The highest known risk is in women who carry a known mutation in BRCA 1 or 2. These women have a 50 to 80% lifetime risk of breast cancer, and a 15 to 45% lifetime risk of ovarian cancer (11, 12). At present, women with BRCA1 mutations account for 5% of all breast cancer patients. Some close communities, such as Ashkenazi Jewish women, have a relatively high prevalence of BRCA1 mutations.

A gene mutation probability program called BRCAPRO (UTSW Medical Center, Dallas, TX, USA) was developed using published data and assumes that genetic susceptibility to breast and ovarian cancer is due to mutations in BRCA1 and BRCA2. The program uses information about first-degree and second-degree relatives to compute the probability that an individual carries a mutation in these genes. This calculator is available at: <http://www4.utsouthwestern.edu/breasthealth/cagene/>.

Women who are found to have breast cancer risk factors in their personal or family histories may have their risk quantified using population-based risk calculators. The Gail model is the most commonly used risk calculator in the US and has been validated in other countries. The Gail model cannot be used for women who are known to have or LCIS or gene mutations predisposing to breast cancer. The risk score is based on known breast cancer risk factors (Table 3). This tool evaluates 5-year risk and lifetime risk to age 90. Patients with a 5-year risk value of 1.67 or greater may benefit from close surveillance and risk reduction strategies. (<http://www.cancer.gov/bcrisktool/>). The Claus model is another breast cancer risk calculator, and it is designed solely for estimating risk

for women with a family history of breast cancer. It employs variables such as the number of maternal and paternal first-degree and second-degree relatives with a history of breast cancer and their ages at the time of diagnosis. This model does not take into consideration other risk factors (28).

Managing high risk patients

Patients who are identified as being at high risk for development of breast cancer need more frequent screening compared to patients at average risk. Furthermore, high risk patients may be offered risk reduction therapy in the form of chemoprevention or risk reduction surgery.

Screening methods

Breast Examination

Physical examination can include breast self examination, in which a patient palpates her own breasts and axillae for any alterations in size, shape, and texture. The patient needs to be aware of normal changes during her menstrual cycle, pregnancy, or menopause. Any unusual or concerning finding needs to be brought to her physician's attention. Unfortunately, studies show that breast self-exams alone do not reduce the risk of deaths from breast cancer. Therefore, breast self-exams cannot be replaced by clinical breast exams and regular imaging studies (27, 29).

Many physicians include a clinical breast exam as a component of the annual physical examination for women. Approximately 5% of breast cancers are diagnosed only by clinical breast examination, with pooled data estimating 54% sensitivity and 94% specificity, based on nationwide screening data from the Health Insurance Plan of New York Study (30).

Screening Mammograms

Mammograms are the primary breast imaging modality for breast cancer screening. Signs of cancer on mammogram, such as calcifications or architectural distortion, may be found before there is any palpable abnormality in the breast. European guidelines for quality assurance in breast cancer screening and diagnosis in fourth edition confirmed that mammography remains the cornerstone of population-based breast cancer screening and could reduce mortality from this disease in women aged 50 years and over (31). Current U.S. guideline recommends that women at average risk should have screening mammograms every one to two years beginning at age 40 (32). Although a previous meta-analysis of mammographic screening showed 15% reduction in breast cancer mortality in women aged 40-49 years (33). In a recent the largest up-to-date trial, Moss et al studied the effect of mammographic screening on breast cancer mortality in women from age 40 years compared with women from 50 age years in the Great Britain. They revealed no significant reduction in breast cancer mortality in the annual screening group of women ages 40-48 years. (34). Breast cancer in Turkish women between 41-50 and 51-70 years of age were reported as 31% and 40.7% respectively (35). In a recent prospectively conducted survey by Ozmen

Table 1. Risk factors for breast cancer

Age	As a woman ages the risk of breast cancer increases. About 75% of women with breast cancer are over age 50 at the diagnosis.
Race and ethnicity	Asian women have a lower risk of breast cancer. Caucasians have slightly higher risk than African women (9). However African women tend to have more aggressive tumors (10).
Genetics	BRCA1 or BRCA2 gene mutations have approximately 80% risk of breast cancer (11, 12).
Personal and family cancer history	Women who had breast cancer history are five times more likely to develop breast cancer again than the population average (13). A first-degree relative with breast cancer doubles the risk (14). Two or more relatives with breast, ovarian cancer, breast cancer before age 50 in a relative, relatives with both breast and ovarian cancer, a male relative with breast cancer, an Ashkenazi Jewish heritage and hereditary breast cancer history can increase the risk (15).
Menstrual periods	Experiencing menarche before age 12 and menopause after age 55 increases the risk of breast cancer approximately 30% and 50% respectively (16).
Delayed childbirth	Women who do not have a child or who have their first child after age 30 have two times increased risk of breast cancer (17).
Previous breast biopsy conditions	Atypical hyperplasia has 4.5 fold increased risk. Additional family history increases the risk 11-fold. Ductal carcinoma in situ and lobular carcinoma in situ confer a similar risk for developing invasive breast cancer (14).
Number of breast biopsies	The number of breast biopsy >1 reveals higher risk in the Gail risk calculation.
Previous radiation therapy	Radiation exposure increases the risk from 1.2 to 2.4-fold related with total dose and the age at exposure (18).
Hormone replacement therapy	The use of hormone replacement therapy 35% increases the risk of breast cancer (19). A decrease in the use of combined estrogen plus progestin has recently been reported to decrease by 28-43% in the incidence of breast cancer among certain age groups (20).
Not breast-feeding	Lactation for 2 or more years decreases the breast cancer risk by at least 50% (21, 22).
Weight (BMI)	Fat tissue produces estrogen after menopause. Overweight women (BMI>25) who take hormone replacement therapy have additional greater risk of developing breast cancer (23).
Diet	High fat diets with polyunsaturated fats are associated with a higher risk of breast cancer. High-fat diets can cause to obesity, which also increase the risk (24).
Alcohol / Smoking	The consumption of 2 to 5 drinks per day has a 41% high risk of invasive breast cancer (12). Even 10 g/day of consumption has a 9% risk (8). There is suggestive but not sufficient evidence for avoiding smoking and secondhand smoke (25).
Lack of physical activity	Sixty minutes of physical activity per week reduces the risk by 30% (26, 27).

et al., being greater than or equal to age 35 years old was found as a breast cancer risk factor in Turkey (36). One may assume that starting screening of breast cancer in developing countries such as Turkey at the age of 40 instead of 50 a) helps diagnosis more early stage breast cancer, b) detects more noninvasive breast cancers and atypia, and c) reduces the need of adjuvant therapies to surgery. On the other hand, if a woman is diagnosed with breast cancer before she reaches age 50, it is recommended that her

first degree relatives begin screening mammography at an age 10 years younger than her age at diagnosis. Women who are assessed to be at high risk for development of breast cancer should have annual mammograms. The sensitivity of mammography for the detection of cancer is between 60 and 90% (37). Digital mammography maximizes image acquisition and is more sensitive than film screen mammography in women younger than 50 years, pre- or perimenopausal women, and women with radiographical-

Table 2. A woman's chances of breast cancer increases with age

From age 30 to age 39	0.44% (1 in 227)
From age 40 to age 49	1.49% (1 in 67)
From age 50 to age 59	2.79% (1 in 36)
From age 60 to age 70	3.38% (1 in 26)

Source: National Cancer Institute, <http://www.cancer.gov>.

ly dense breasts (38). Findings on screening mammogram those are suspicious for malignancy may prompt clinicians to proceed with a biopsy or to order further imaging of the breast with diagnostic mammography, which may include magnification or compression views. However, the Breast Health Global Initiative (BHGI) guideline suggested that when resources are lacking in low- and middle-income countries, diagnostic mammography is not mandatory for preoperative diagnostic assessment (39).

Breast Ultrasonography

Because the density of breast tissue in young women decreases the sensitivity of mammography, screening in young women at high risk is often supplemented with breast ultrasound. Ultrasound is not commonly recommended as a stand-alone screening tool. There is a role for ultrasonography in the evaluation of lesions from dense tissue to palpable mass (40). Berg, et al, recently reported that although breast ultrasound can increase the number of false positive findings, adding screening ultrasound to mammography can yield an additional 1.1 to 7.2 breast cancer diagnoses per 1000 high-risk women. The addition of a single ultrasonographic examination to mammography for women at high risk of breast cancer results in higher detection of breast cancer (41).

Magnetic Resonance Imaging

MRI in high-risk women is significantly more sensitive than mammography with or without ultrasonography (42, 43). MRI integrated into screening programs may lead to earlier diagnosis of breast cancer in these patients (44, 45). MRI is expensive, however, and carries a higher false positive rate than other breast imaging modalities (46, 47). The combination of MRI and mammogram is better than either alone (48). MRI has not been studied in the general population as a screening tool.

The American Cancer Society recommends that women at high risk of breast cancer undergo annual MRI screening as an adjunct to mammogram. This screening is to begin at age 30 for women with known gene mutations predisposing to breast cancer or for women who have not had genetic testing but who are first-degree relatives of mutation carriers. Screening with MRI and mammogram is also recommended for women who have a lifetime risk of breast cancer of 20-25% or higher according to the BRCAPRO calculator or the Claus model (43, 49).

Table 3. Gail risk calculator for breast cancer

1. Does the woman have a medical history of any breast cancer or of ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)?	Yes No
2. What is the woman's age? This tool only calculates risk for women 35 years of age or older.	35-90
3. What was the woman's age at the time of her first menstrual period?	Unknown 7 to 11 12 to 13 ≥14
4. What was the woman's age at the time of her first live birth of a child?	Unknown No births <20 20 to 24 25 to 29 ≥30
5. How many of the woman's first-degree relatives - mother, sisters, daughters - have had breast cancer?	Unknown 0 1 >1
6. Has the woman ever had a breast biopsy?	Unknown No Yes
6a. How many breast biopsies (positive or negative) has the woman had?	1 >1
6b. Has the woman had at least one breast biopsy with atypical hyperplasia?	Unknown No Yes
7. What is the woman's race/ethnicity?	Unknown White Black Hispanic Asian or Pacific Islander American Indian or Alaskan native

Calculate Risk

Source: <http://www.cancer.gov/bcrisktool/>

Ductal lavage

It is a minimally invasive procedure to access ductal epithelial cells. However, some small studies reported the sensitivity of ductal lavage to be around 20% in women with known breast cancer. Therefore, it is not recommended for routine screening, yet (50, 51). It has potential for screening in the future in this patient population but needs to be studied extensively.

Strategies for risk reduction

The goal of preventing breast cancer can be achieved by eliminating modifiable risk factors and identifying the high-risk individuals who would benefit most from preventive therapies. Changeable risk factors are related with personal behaviors, such as smoking, drinking. To predict how much of these factors may cause invasive breast cancer, some risk calculators have also been developed. If a person has one or more non-modifiable risk factors she can be followed-up as a high risk breast cancer patient and guided for preventive approaches (8). Breast cancer risk reduction may be achieved by eliminating modifiable risk factors. Women at high risk may benefit from chemoprevention or risk reduction surgery.

A) Reducing the number of modifiable risk factors

Limit alcohol consumption. Use should be limited to less than one drink per day. Complete avoidance is preferable (8).

Maintain a healthy weight. Postmenopausal weight gain especially increases the risk (52). Fresh fruits, vegetables, whole grains, high fiber foods and vitamins C, E and folate may reduce the risk (53, 54).

Stay physically active. For any age group, moderate physical activities on most days are recommended. This activity also can help prevent obesity, heart disease, and many other types of cancers (55).

Consider not using long-term hormone replacement therapy. Hormone replacement therapy for greater than 5 years is associated with increased risk of breast cancer (56). The decision to use hormone replacement therapy should be determined judiciously based on a careful discussion of risks and benefits.

Avoid exposure to chemicals. Some environmental chemicals such as pesticides and industrial chemicals mimic the structure of estrogen and aside from their inherent toxicity, can contribute to breast cancer risk (57).

B) Chemoprevention

Selective estrogen receptor modulators (SERM) are the main drugs used for breast cancer prevention in women at high risk. It is hypothesized that estrogen-mediated events are integral in the development of hormone receptor positive breast cancer. Oophorectomy or radiation-induced ovarian ablation can reduce the incidence of breast cancer by up to 75% (58).

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) drug. It blocks estrogen uptake in the breast. There have been 4 published, prospective studies of breast cancer risk reduction by tamoxifen. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT, P-1) is the largest of these studies (n=13,388) (59, 60). The other studies are the Royal Marsden Hospital Tamoxifen Chemoprevention Trial (61, 62), the Italian Tamoxifen Prevention Study (63, 64), and the

International Breast Intervention Study I (IBIS I) (65, 66). The primary aim of BCPT was to evaluate the effectiveness of tamoxifen, vs placebo, taken orally for five years for the prevention of invasive breast cancer in a study group of high risk women. Secondary aims of the trial were to assess osteoporotic fractures and cardiovascular disease in women on tamoxifen compare to those on placebo. This study showed a 49% ($P < 0.00001$) risk reduction in breast cancer associated with tamoxifen chemoprevention. The overall relative risks for invasive breast cancer were 0.56 for women less than 50 years of age; 0.49 for women 50 to 59 years of age; and 0.45 for women 60 years of age and older (67). Overall, a total of 264 cases of invasive breast cancer were documented; 175 cases occurred in the placebo group, compared with 89 cases in the tamoxifen group (risk ratio 0.51; 95% confidence interval [CI] 0.39-0.66; $p < 0.00001$).

The metaanalysis of data from these four studies showed that tamoxifen decreased breast cancer incidence by 38% ($P < 0.0001$) (68). The risk reduction for development of estrogen receptor-positive breast cancer was 48% ($P < 0.0001$); however, no significant risk reduction was seen in the incidence of estrogen receptor negative breast cancers (69). The regimen suggested by the studies is a 5-year course of tamoxifen at 20 mg per day. On the basis of the results of BCPT, the Food and Drug Administration (FDA) approved tamoxifen for reduction of breast cancer risk in women whose calculated risk is 1.67% or greater according to the Gail model (70). Candidates for chemoprevention with tamoxifen include women with atypical ductal or lobular hyperplasia, ductal or lobular carcinoma in situ, premenopausal women with BRCA1 or BRCA2 gene mutations, and women aged ≥ 35 years with a Gail model 5-year probability of breast cancer $\geq 1.67\%$ (68). Tamoxifen protects against contralateral breast cancer for carriers of BRCA1 mutations. Women who used tamoxifen for 2-4 years had a 75% decreased incidence of contralateral breast cancer. Perhaps the same risk reduction would be seen for primary breast cancer. However larger prospective studies are necessary to prove the benefit of tamoxifen in women with these mutations.

The potential benefits of tamoxifen need to be weighed against its potential serious complications. In the four prospective tamoxifen studies, venous thromboembolic events were nearly doubled in women using tamoxifen. To avoid thromboembolism among women receiving SERMs for breast cancer risk, concurrent low-dose aspirin can be used. Rates of endometrial cancer were also found to be increased in association with tamoxifen, with a reduction in this risk seen by excluding women at increased risk of endometrial cancer. Women in the tamoxifen arm of the trial were found to have a 3.3 times greater risk of developing invasive endometrial carcinoma than women in the placebo arm. Nearly all of these endometrial cancers were caught at an early stage. Of the 70 cases of endometrial cancer (17 in the placebo group and 53 in the tamoxifen group) 67 cases were International Federation of Gynecology and Obstetrics (FIGO) stages 0 or I and thus had excellent clinical prognoses with treatment (59, 60). In the BCPT, endometrial hyperplasia and cancer incidence were higher

among women taking tamoxifen; however, these risks were not elevated in women younger than 50. Postmenopausal women are at increased risk of adverse events, thus alternate therapy such as raloxifene has to be considered. Annual cervical cytology and pelvic examinations are proposed in women receiving tamoxifen. Women should be advised against becoming pregnant since tamoxifen is a teratogen. Because of the modest increase in risk of cataracts women should be questioned about symptoms of cataracts or a personal history of cataract surgery. These women need periodic eye examinations. If the patient needs any surgery, tamoxifen can be discontinued in the preoperative setting and early ambulation is stressed in the postoperative period (70). Absolute contraindications to the use of tamoxifen are any history of severe thromboembolic disease, uncontrolled atrial fibrillation, diabetes or hypertension, pregnancy, cataracts, and current use of oral contraceptives or warfarin.

Raloxifene

Raloxifene is a second generation SERM that has antiestrogenic effects on breast and endometrial tissue and estrogenic effects on bone, lipid metabolism, and blood clotting (69). Raloxifene has been studied in four prospective trials. The Multiple Outcomes of Raloxifene Evaluation (MORE) (71, 72), and The Continuing Outcomes Relevant to Evista (CORE) (73) studies evaluated the effect of raloxifene on vertebral fracture incidence in postmenopausal women with osteoporosis. The Raloxifene Use for the Heart (RUTH) trial evaluated the effect of raloxifene on the reduction of coronary heart disease in postmenopausal women (74). During the 8 years of the concomitant MORE and CORE studies, the group taking raloxifene had a 58% reduction in the overall incidence of invasive or noninvasive breast cancer compared to the group taking placebo. The reduction in the incidence of invasive cancer was 66%. Interestingly, this reduction in breast cancer incidence was due to reduction in the incidence of estrogen-receptor positive breast cancer, which was 76% less in the raloxifene group compared with the placebo group. There was no statistically significant difference between these groups in the incidence of estrogen-receptor negative breast cancer (71-73). None of these three studies specifically examined women at high risk of breast cancer; however, they concluded that raloxifene decreased the incidence of breast cancer as a secondary outcome.

On the other hand, the NSABP study of tamoxifen and raloxifene (STAR) trial has been unique in studying raloxifene as a breast cancer prevention drug. Eligible women were at least 35 years old and postmenopausal, and had either lobular carcinoma in situ or a 5-year risk of invasive breast cancer of at least 1.67% as determined by the Gail model. Women participating in the study were randomly assigned to receive either a tamoxifen dose of 20 mg/day or a raloxifene dose of 60 mg/day for five years with a double-blind study design (75, 76). The overall study results showed that raloxifene reduced the incidence of invasive breast cancer by 44-76% in postmenopausal women. This decreased incidence was completely attributable to a 90% reduction in the incidence of estrogen receptor positive breast cancer. There was no decrease seen in the incidence

of estrogen receptor negative breast cancer. The authors concluded that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women at high risk. A difference was seen between the two drugs, however, in the reduction of the incidence of in situ carcinoma. While tamoxifen reduced the incidence of in situ carcinoma, raloxifene did not.

Raloxifene was found to have a safer side effect profile compared to tamoxifen. There were 25% fewer cases of uterine cancer and endometrial hyperplasia in the raloxifene group compared to the tamoxifen group. The number of thromboembolic events was 30% lower in the raloxifene group. There was no significant difference in the number of cerebrovascular events. Women on raloxifene also had a lower incidence of cataracts compared to those taking tamoxifen. The investigators concluded that raloxifene is as effective as tamoxifen in decreasing the incidence of invasive breast cancer in younger, postmenopausal women at high risk, and that raloxifene has a lower associated incidence of adverse side effects (70-77). In September, 2007, the USA, FDA approved raloxifene for prevention of invasive breast cancer in postmenopausal high risk women. Raloxifene has not been studied as a chemopreventive drug in premenopausal women at high risk; therefore, tamoxifen remains the chemopreventive drug of choice for this group.

Aromatase Inhibitors

Aromatase is found in fat, muscle and also breast tissue. Aromatase inhibitors block the peripheral conversion of androstenedione to estrone and testosterone to estradiol. Aromatase inhibitors such as anastrozole, exemestane, and letrozole are being investigated in randomized trials of chemoprevention in postmenopausal women. Data from these studies may clarify the possible role of aromatase inhibitors in breast cancer chemoprevention (<http://www.Clinicaltrials.gov/>).

C) Risk reduction surgery

Prophylactic mastectomy is removal of the breast to avoid cancer. This measure may seem drastic to some patients and clinicians, but it may have significant benefit for some groups of patients at high risk of breast cancer. Breast cancer risk can be reduced by 90% in patients with family histories strongly suggestive of a hereditary predisposition to breast cancer development, or in patients with known gene mutations predisposing to breast cancer. A Mayo Clinic retrospective study examined 639 women who underwent prophylactic mastectomy. Of these patients, 214 were categorized as the high-risk group and 403 individuals were sisters of these high risk patients. The overall reduction in incidence of breast cancer was 90%. The decrease in the incidence of death was 81% to 94% in the prophylactic mastectomy group (78). The decision for risk reduction surgery needs to be individualized for each patient with consideration given to the high risk condition and its associated breast cancer risk. Paramount to this decision are the patient's preferences and level of comfort with the options of screening, chemoprevention, and prophylactic mastectomy. Prophylactic mastectomy was reported also effective in decreasing breast cancer death in BRCA gene mutation carriers (79).

Prophylactic bilateral salpingo-oophorectomy is removal of the ovaries to prevent ovarian and/or breast cancer. It eliminates the body's primary source of estrogen, which can feed a breast tumor. It is not effective at preventing breast cancer in postmenopausal women, whose ovarian function has naturally declined. In women with BRCA1 or BRCA2 gene mutations, prophylactic oophorectomy decreases the risk of ovarian cancer by 96% and the risk of breast cancer by 53% (80). In a recent study, Rebbeck et al. revealed a meta-analysis of risk reduction with risk-reducing salpingo-oophorectomy (RRSO) in BRCA1 or BRCA2 mutation carriers. They reported that RRSO was associated with 80% reduction in ovarian/fallopian tube cancer risk and 50% reduction in breast cancer risk in BRCA1 or BRCA2 carriers (81). In the premenopausal period this surgery results in infertility, which is an important consideration for women who desire to bear children.

The importance of high risk breast cancer clinics

The incidence and prevalence of breast cancer are increasing, especially in developing countries such as Turkey and other Eastern European countries, where these parameters have increased threefold in the past few decades. Breast cancer incidence in Turkish women between ages 41-50, 51-70, and ≥ 70 years of age is 31%, 40.7%, and 8.2%, respectively, and most of these women were diagnosed with stage 2 breast cancer (35). A breast cancer screening program which includes periodic clinician physical examination and mammography may allow earlier detection of breast cancer in the general population. Screening and risk factor assessment may also allow identification of women at high risk of developing breast cancer. These high risk patients have special needs beyond the screening recommended for women at average risk. Risk assessment, more intense screening, education regarding risk reduction, standardization and specialized management, such as chemoprophylaxis, are important components of

the care of women at high risk for breast cancer development. The clinician's tasks in identifying candidates for chemoprophylaxis include a detailed evaluation of family history, ordering genetic testing when appropriate, and complete quantitative risk estimation (82). The time needed for this special care is difficult, if not impossible, to find in a busy oncology practice that is not dedicated solely to the evaluation and management of high risk patients.

Establishment of high risk clinics also facilitates scientific evaluations of issues such as screening and chemoprevention that are of importance to high risk patients. These clinics may also be a rich source of data for study of high risk pathologies and hereditary breast cancer.

Conclusions

Breast cancer is the most common malignancy of women. There are subsets of women who are at greater-than-average risk of developing breast cancer. These women at high risk have special needs for screening and management. High risk breast cancer clinics are staffed by professional teams well-versed and equipped for the needs of these women at high risk. They counsel these patients regarding screening, chemoprevention, and risk reduction surgery. They also provide services such as screening breast physical examinations and imaging. The organization of high risk breast cancer clinics is not only needed in developed countries but is also becoming more important for developing countries in which breast cancer awareness and incidence is increasing. BHGI in its 3rd meeting on October 2007 addressed the accomplishment of breast health care guidelines for early detection, diagnosis and treatment in low-and middle-income countries. In the near future, studies of high risk breast cancer clinics can establish national guidelines for screening, prevention, and treatment of women at high risk for development of breast cancer.

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Correspondence

Gülgün Tahan
Tel : 001 412 2457163
E-mail : tahang@mail.magee.edu