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Screening and Follow-up of the Patient at High Risk for Breast Cancer

Shawna C. Willey, MD, and Costanza Cocilovo, MD

Accurately defining a patient's risk of developing breast cancer is a challenging endeavor. Many factors have been implicated in the causation of breast cancer and quantifying them is difficult. Risk stratification is performed using population models, such as the Gail model, as well as the patient's personal and family history and genetic testing. The clinician who is facile with these components will not only be able to identify those patients at highest risk for whom heightened surveillance is recommended, but also to allay the fears of the average-risk patient and provide them reassurance. Patients who are at very high risk of developing breast cancer are *BRCA1* or *BRCA2* gene mutation carriers, those with a personal history of atypical ductal hyperplasia or lobular carcinoma in situ with associated family history, those who have undergone therapeutic or similarly significant radiation exposure, and those with a history of a *BRCA1* or *BRCA2* gene mutation in the family of an untested individual. Patients with an elevated risk, but not in the very high risk category, are those with a family history of breast cancer, personal history of breast cancer, significantly dense breast tissue, hormone replacement therapy longer than 10 years, and a history of atypical ductal hyperplasia or lobular carcinoma in situ without family history of breast cancer. Risk-reducing strategies include chemoprevention with tamoxifen or raloxifene and surgical prophylaxis with bilateral prophylactic mastectomy and/or bilateral salpingo-oophorectomy. A high-risk surveillance regimen includes annual mammography, annual magnetic resonance imaging in selected individuals, and semiannual clinical breast exams.
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Practitioners who deal with women's health are routinely confronted with the inquiring patient who is anxious about her risk of developing breast cancer. This is a complex, data-rich topic, and yet accurately defining an individual's personal risk remains elusive. The risk for breast cancer lies along a continuum, and the distinction between various risk categories is arbitrary.

From the Division of Surgical Oncology, Georgetown University Hospital, Washington, DC.

Corresponding author: Shawna C. Willey, MD, FACS, Director, Betty Lou Ourisman Breast Health Center, Assistant Professor of Surgery, Division of Surgical Oncology, Georgetown University Hospital, 3800 Reservoir Road-PHC-4, Washington, DC 20007; e-mail: scw9@gunet.georgetown.edu.

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In America one in nine women, or 11%, will develop breast cancer. Eighty-five percent of these women have no family history of breast cancer, and 66% have no known risk factor.[1] It is common for a patient to overestimate her own risk, particularly if she has a family history of second-degree relatives (grandparents, aunts, nieces, and half siblings) diagnosed at a postmenopausal age. A knowledgeable practitioner can assess a patient's risk and provide reassurance to patients in an average risk category. For those patients with increased risk, an appropriate screening schedule can be established and risk-reducing strategies used. In this article we make a distinction between patients at very high risk of developing breast cancer and those at high risk, because the screening regimens and risk-reduction recommendations differ for these two groups of women.

DEFINING HIGH RISK AND THE MODELS THAT ARE AVAILABLE

There are myriad factors associated with breast cancer risk, and causation is probably multifactorial. Many of these factors are controversial, with conflicting studies. The classic risk factors for breast cancer are first-degree relative (parent, sibling, offspring) with breast cancer, history of benign breast biopsy, previous radiation treatment, age of menarche, and use of hormone replacement therapy. Study of the epidemiology of breast cancer is challenging. Exposure often occurs at a young age and is difficult to identify retrospectively. The disease manifests decades later.

Patients who are gene mutation carriers are clearly the highest-risk population. The additive effect of secondary risk factors and the degree to which risk can be reduced is difficult to quantify. Nonetheless, risk assessment helps the physician categorize patients into groups for which heightened surveillance is appropriate. It is frustrating to patients and practitioners alike that the risk factors placing the patient at highest risk are often not under the practitioner's or the patient's control and cannot be manipulated. For instance, we cannot control age (Fig. 1)[2] or family history.

Population Models

Several models have been used to assess risk for a particular patient. These are population-based models that allow for calculation of risk using specific, defined factors. An average-risk woman is one whose risk

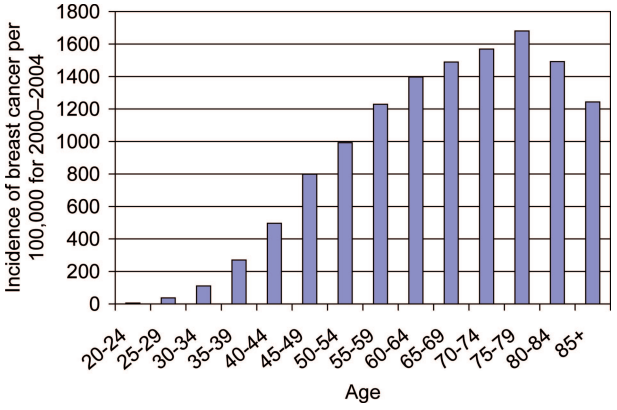

Fig. 1. Breast cancer incidence per decade of life. Data from Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 17 Regs Limited-Use, Nov 2006 Sub (2000–2004). National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission Nov 2006 Sub (2000–2004).

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factors confer no greater than a 1.5-fold increase in relative risk of developing breast cancer, such as a breast biopsy showing epithelial hyperplasia.

The Gail model incorporates the number of first-degree relatives with breast cancer (0, 1 or 2 or more), age at menarche (younger than 12 years, 12–13 years, or 14 years or older), age at first live birth (24 years or younger, 25–29 years, 30 years or older or nulliparous), number of breast biopsies, and the presence of atypical hyperplasia on breast biopsy.[3] The model was first validated in whites and has been modified for different ethnicities. It is available on the National Cancer Institute Web site and can be downloaded to a personal digital assistant.[4] Omission of other risk factors (mammographic density, more detailed data on family history of breast and ovarian cancer, reproductive history, levels of plasma estrogen, and genetic or other markers) limits the accuracy of the Gail model. It should not be used in women who have a personal, prior history of breast cancer or women who are known gene mutation carriers. Even with the modifications, it underestimates the risk in African-American women and overestimates the risk in Asian women and women aged younger than 40 years.[5] Nonetheless, it is the most commonly used risk assessment tool. A 5-year risk of 1.67 or higher as calculated by the Gail model is the inclusion criterion for many prevention studies.

Other models, such as the Claus model, include the number of maternal and paternal first-degree and second-degree relatives with a history of breast cancer as well as the age of diagnosis of these relatives. Elizabeth Claus published her article entitled "Autosomal Dominant Inheritance of Early Onset Breast Cancer"[6] in 1994, the same year that *BRCA1* was sequenced. The Claus model established that risk depends on which relatives are affected and also their age at onset. The goal of the Claus model was to address risk calculation for the subset of women who are at potentially high risk of breast cancer based solely on family history. The Claus model, however, does not take into account any other risk factors.

The following table summarizes many risk factors and divides them into categories of risk factors that increase risk, are potential risk factors, and those that decrease risk (Table 1). For comparison's sake, we have tried, when possible, to use relative risk (RR) to express the increase or decrease in risk. Relative risk is defined as the ratio of the incidence of a disease among individuals exposed to a specific risk factor to the incidence among unexposed individuals. Assum-

Table 1. Breast Cancer Risk Factors

Factor	Risk
Gender (female:male)	135:1
Age	There is a progressive increase in risk with increasing age. From 35 years to 65 years there is a sixfold increase.
Hormonal factors	Uninterrupted menstrual cycles
Menses	Early menarche Regular menses Late menopause
Reproductive history	Nulliparity increased risk by 30%. Childbirth aged older than 30 years carries a twofold increased risk compared with women aged younger than 20 years. Transient increased risk after childbirth
DES use in pregnancy	Relative risk increase is 2.5-fold.[7]
Oral contraceptive	No association; (use prior to 1975 may have an effect)
Hormone replacement therapy	The use of unopposed estrogen after menopause is estimated to increase the breast cancer risk 2.1% per year above that of women not using it.[8] Combination of estrogen and progesterone conferred an increase in relative risk of 1.4 after a mean use of 3.6 years; after 10 years of therapy there was a 2.86 increase in relative risk.[9]
Mammographic density	Dense tissue in greater than 60% of the breast confers a fourfold increased relative risk.
Atypical hyperplasia	Fourfold increased relative risk Eightfold to 12-fold increased relative risk if patient has a first-degree relative with breast cancer[10] Moderate to florid hyperplasia twofold increased relative risk[11]
Previous history of cancer	History of endometrial or ovarian cancer twofold increased risk Some association with melanoma, salivary gland tumors, colon cancer
Previous breast cancer	Fivefold increased risk[12]
Ionizing radiation	Increase risk if exposure prior to age 30 years Atomic bomb threefold increased risk Dose related[13,14]
Alcohol	Dose related with increased risk directly proportional to intake[15]
Family history	85% of cases do NOT have a family history. One first-degree relative twofold increased risk Two first-degree relatives fourfold to sixfold increased risk
Hereditary breast cancer	*BRCA1* 30-40% of all inherited breast cancers *BRCA2* gene
Potential risk factors	
IGF-1	Higher circulating levels in premenopausal women; twofold increased risk
Diet	No association with total dietary fat intake[16]
Obesity	Risk factor in postmenopausal women
Abortion	Weak or no association
Organochlorine exposure	No correlation with plasma/serum level Tissue levels have not been studied.
Occupational	Exposure to light at night may increase risk by suppressing normal melatonin production.[1]
Factors that decrease risk	
Early age at first full term pregnancy	Birth of first child before age 18 years
Menopause before age 35 years	Early oophorectomy
Lactation	Slight reduction in risk in premenopausal women associated with younger age at first lactation and increased cumulative time
Physical activity	37% decreased risk of developing breast cancer Relative risk of death from breast cancer was decreased at every level of physical activity compared with being sedentary.
Vitamins	Not proven[16]

(*continued*)

Table 1. Breast Cancer Risk Factors (*continued*)

Factor	Risk
Diet	Olive oil and fish oil may be protective. Fiber: not protective[16] Phytoestrogens: converted to estrogen in the gut (example: soybeans); not associated with breast cancer risk[1] Low-fat diets (less than 25% of calories from fat) lead to a statistically significant drop in estradiol levels.[17]
Chemoprevention	Tamoxifen reduces risk by 50%.[18]

ing a baseline risk of 10%, someone with a RR of 1.7 has a 17% risk of developing breast cancer.

Who then is high risk? According to the NCCN (National Comprehensive Cancer Network) guidelines there are several criteria that qualify a patient as high risk. These include:

- Prior therapeutic dose thoracic radiation
- 5-year risk of invasive breast cancer >1.7% in women over age 35 per the Gail model
- Strong family history or genetic predisposition
- Lobular carcinoma in situ/atypical ducal hyperplasia
- Prior history of breast cancer.[19]

We will elaborate on each of these risks.

Gene Mutation Carriers

Patients suspected of carrying a genetic mutation (about 2% of all patients diagnosed with breast cancer) should be referred for genetic counseling. Early onset of disease is a hallmark in mutation carriers (Table 2).[20]

Factors that are suggestive of carrying a *BRCA* mutation include:

- A known *BRCA1* or *BRCA2* mutation in the family
- Breast and ovarian cancer in the same family
- Two or more family members aged younger than 50 years with breast cancer
- Male breast cancer
- One or more members diagnosed with breast cancer aged younger than 50 years and Ashkenazi ancestry

Table 2. Breast and Ovarian Cancer Risk by Age 70 Years in Gene Mutation Carriers

Mutation	Breast Cancer Risk	Ovarian Cancer Risk
BRCA1	55–85	16–60
BRCA2	37–85	11–27

Data are %.

Data from Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies [published erratum appears in Am J Hum Genet 2003; 73:709]. Am J Hum Genet 2003;72:1117–30.[20]

- Ovarian cancer plus Ashkenazi ancestry

Anyone in these categories has an approximately 10% or greater risk of being a gene mutation carrier.[21] Those of Ashkenazi Jewish descent have been intensely studied because of their high rate of breast cancer and have been found to carry a 2.3% risk of being a gene mutation carrier.

The BRCAPRO (UTSW Medical Center, Dallas, TX) program calculates the probability of carrying a mutation or developing breast or ovarian cancer by a given age using a family pedigree. The Web site is http://www4.utsouthwestern.edu/breasthealth/cagene/. One can enter the family history of breast or ovarian cancer, ages of affected relatives, and male relatives with breast cancer and estimate the likelihood that a family carries a mutation.

Atypical Ductal Hyperplasia and Lobular Carcinoma in Situ

Patients who have been diagnosed with atypical ductal hyperplasia or lobular carcinoma in situ (LCIS) are also at high risk. Ninety-five percent of all breast cancers originate in the lobular or ductal cells of the breast. Epithelial hyperplasia of the breast is an increased number of cells relative to the basement membrane. The increased risk from mild or moderate hyperplasia is so slight that it does not change a woman's risk category. Women with proliferative lesions and no atypia have a slightly increased risk; however, it is not a great enough elevation to place them in the high-risk category. Proliferative lesions include papillomatosis, moderate or florid hyperplasia, and sclerosing adenosis (Fig. 1).

When the alterations begin to approach patterns seen in carcinoma they are termed atypical ductal hyperplasia, atypical lobular hyperplasia or LCIS. Atypical ductal hyperplasia shares features with ductal carcinoma in situ (DCIS) but does not meet the criteria of DCIS (Fig. 2). Lobular carcinoma in situ is a solid proliferation of cells in the lobule that is the last step in a continuum of lobular neoplasia. Both atypical ductal hyperplasia and LCIS are considered pre-

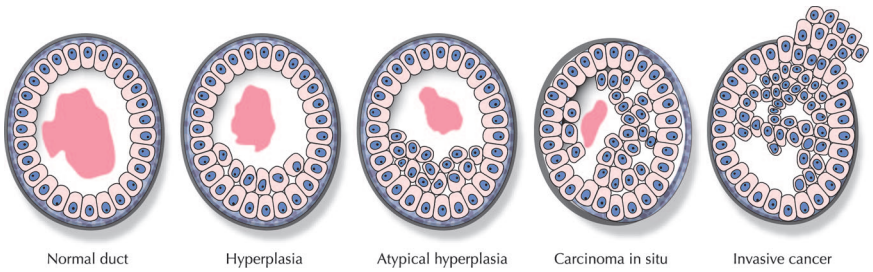

Fig. 2. Histologic changes of the breast. Illustration: John Yanson.
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cursor lesions and confer a similar risk for developing invasive breast cancer.

In two large landmark studies published in 1985, pathologists Dupont and Page[10] reported on a retrospective review of 10,366 consecutive breast biopsies, for which follow-up information was obtained in 4,419 cases. They found that patients with atypical ductal hyperplasia had a 4.1-fold to 4.5-fold increased RR of developing breast cancer. The risk increased even further to 11 times that of someone who did not have proliferative lesions when a patient with atypia also had a positive family history.

Wrensch et al[22] reported similar findings in relation to nipple aspirate fluid cytology that they examined in 2,701 volunteers. Atypical hyperplasia on cytology conferred a 4.9-fold increase in RR of developing breast cancer. Atypical hyperplasia and a first-degree relative increased the RR 8.9-fold. In 2005 Fabian et al[23] published a review of breast tissue sampling for risk assessment and prevention. They reported that nipple aspirate fluid, random periareolar fine needle aspiration, and ductal lavage were all being used as primary or response end points in breast cancer prevention studies, and it was not clear at that time which method would be most cost-effective. Although there was much initial enthusiasm that ductal lavage would be valuable for risk stratification, its clinical usefulness is not well established. These techniques and their possible role in determining which patients are at high risk remain under study.

Radiation Exposure

The effect of radiation exposure on breast cancer risk has been examined in several different patient populations. Understanding this risk is important not only to identify those patients who should be placed on increased surveillance, but also to reassure those patients who have concerns about the possible carcinogenesis of radiation from mammograms. Radiation can cause chromosomal deletions and translocations leading to genomic instability. If radiation occurs at a young age, genetic damage to epithelial stem cells may be passed to daughter cells. The evidence for the effect on breast cancer risk comes from follow-up studies of three groups of patients: atomic bomb survivors, patients receiving therapeutic mantle radiation, and patients in tuberculosis sanitaria in Canada treated with fluoroscopy.

Land and Tokunga[14] provided an update in 2003 of their data of atomic bomb survivors. They found that exposure before age 20 years was associated with higher RR and that there was a significant decline in risk if the exposure was after age 35 years.

Clemons et al[13] performed a review of retrospective clinical data on breast cancer after irradiation for Hodgkin's disease. They found that women irradiated between puberty and age 30 years, when breast tissue is most active and most susceptible to the carcinogenic effects of radiation, were at highest risk (Table 3). The mean time from radiation exposure to diagnosis of breast cancer was 15 years, and the increased risk was dose related.

A case–control study from the Netherlands of 770 women reported on women who had been diagnosed with Hodgkin's disease before age 41 years. Forty-eight of these patients developed breast cancer. They found that breast cancer risk increased with increasing doses of radiation in patients who received radiation alone. Patients who received more than 38.5 Gy had a 4.47-fold increased RR. Patients who received chemotherapy in combination with radiation had a lower risk, likely because of the ovarian suppression effect of the chemotherapy. Reaching menopause before age 36 years reduced the risk of breast cancer. The median interval between radiation and

Table 3. Breast Cancer Risk in Patients Irradiated for Hodgkin's Disease

Age of Radiation Exposure (y)	Relative Risk
Younger than 19	56
20–29	7.0
Older than 30	0.9

Data from Clemons M, Loijens L, Goss P. Breast cancer risk following irradiation for Hodgkin's disease. Cancer Treat Rev 2000;26:291–302.[13]

diagnosis was 18.7 years and the median age at diagnosis was 44 years.[24]

Therefore, any patient who has had significant radiation exposure or therapeutic radiation exposure before age 30 years should be in a high-risk surveillance program. Because the risk of breast cancer in women who are exposed to radiation after age 35 years, the usual age of the first mammogram, approximates that of the average risk population, practitioners can confidently reassure their patients that the radiation exposure from mammograms is very low and does not have a significant effect on risk.

Prior Breast Cancer

Another high-risk group is patients who have previously had breast cancer. Santiago et al[12] report on 15-year follow-up results of 937 women with stage 1 and 2 breast cancer who had breast conservation surgery and radiation. The median follow-up time was 10 years. At 15 years, there was a 19% local failure rate and a breast cancer incidence of 12% in the contralateral breast. Of ipsilateral cancer events after breast-conserving surgery, approximately 38% were new primary tumors and 62% were true recurrences. Women with new primary tumors had a longer mean time to relapse than actual recurrences. Most ipsilateral breast cancer diagnoses that occur after 5 years are outside the primary tumor bed.

Hormone Replacement Therapy

Hormone replacement therapy is a controversial topic. In 2004, the Women's Health Initiative published an update of its two randomized placebo-controlled disease prevention trials. The Women's Health Initiative estrogen plus progesterone trial was stopped prematurely in July 2002 because health risks exceeded benefits. Coronary heart disease, stroke, and venous thromboembolic disease were all increased. The breast cancer risk increased by 24%, whereas colorectal cancer and hip fracture rates decreased.[25] The estrogen-only arm continued until February 2004, but it was also terminated because of the increased risk of stroke. It showed a significant decrease in the risk of hip fractures. The risk of breast cancer was slightly lower, but not significant; nor was any other rate of cancer occurrence.[26]

A Finnish study[27] using the national medical reimbursement register looked at all women age 50 or over using oral or transdermal estradiol (E2), oral estriol, or vaginal estrogens for at least 6 months from 1994 to 2001. They found that E2 for 5 or more years, either orally or transdermally, meant 2–3 extra cases of breast cancer per 1,000 women who were followed for 10 years.

Similarly, a British study by Kendall et al[28] confirmed that even low levels of vaginal E2 raises serum levels. Serum E2 levels were a mean of 81 pmol/L with the 25 mcg dose of estradiol (Vagifem, Novo Nordisk FemCare AG, Bagsværd, Denmark) and 40 pmol/L for the 10 mcg dose compared with a level of 3 pmol/L in women who are taking aromatase inhibitors. The average level in a postmenopausal woman is 20 pmol/L. The use of estrogen is contraindicated in women using aromatase inhibitors to treat breast cancer.

Breast Density

Breast density has been shown to affect breast cancer risk. Byrne et al[29] showed in a nested case–control study with 16 years of follow-up that women who had a breast density of 75% or greater had an almost fivefold increased risk of breast cancer compared with women with no breast density. These effects persisted for 10 or more years and were noted for premenopausal and postmenopausal women of all ages.

A recently published study from Tamimi et al[30] showed that endogenous hormone levels and mammographic density were independent risk factors for breast cancer. This was a nested case–control study within the Nurses' Health Study cohort, with 253 case subjects with breast cancer and 520 control subjects. Levels of circulating sex steroid hormones were associated with a twofold increased risk of breast cancer, comparing the highest and lowest risk categories, and mammographic density was associated with an approximate fourfold increased risk of breast cancer. High levels of both were associated with a particularly high risk of breast cancer.

Patients who are at the highest risk of developing breast cancer, those with atypia, lobular carcinoma in situ, prior breast cancer, factors conferring a 1.7 times increase in RR, significant radiation exposure, and gene mutation carriers, should be offered options to reduce their risk (Fig. 3). Risk-reducing strategies include chemoprevention and prophylactic surgery. Enhanced surveillance is recommended for all patients in the high-risk group regardless of other risk reduction strategies.

Chemoprevention

The first drug approved for chemoprevention of breast cancer is tamoxifen (Nolvadex, AstraZeneca, Wilmington, DE), It is administered orally for 5 years and reduces breast cancer incidence overall by 50%. Other promising drugs such as raloxifene (Evista, Eli

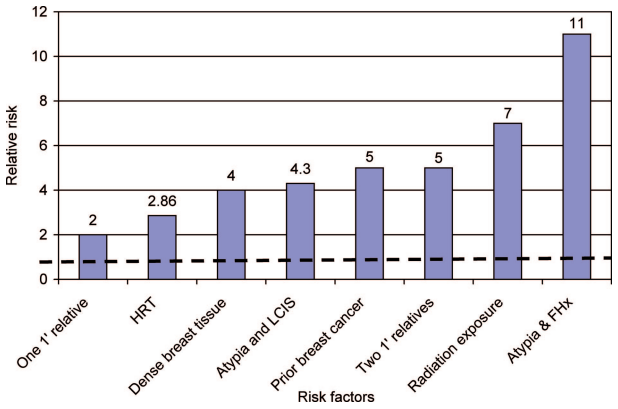

Fig. 3. Highest risk categories for breast cancer (excluding gene mutation carriers who have an absolute risk as high as 85%).

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Lilly and Company, Indianapolis, IN) and the aromatase inhibitors are under investigation for chemoprevention and may well prove more effective than tamoxifen. Tamoxifen is a triphenylethylene selective estrogen receptor modulator. It has either estrogenic or antiestrogenic effects depending on the tissue. In premenopausal women it can cause a paradoxical increase in estrogen. Fifty percent of premenopausal patients develop amenorrhea or oligomenorrhea.[1] It binds to estrogen receptors in the breast, thus blocking estrogen uptake. Complications include an increase in the development of endometrial carcinoma and thromboembolic events, and accelerated cataract formation. These adverse effects occur in the over-50-year age group.

Tamoxifen as a chemopreventive agent has been studied in several large trials. Between 1992 and 1997 the National Surgical Adjuvant Breast and Bowel Project (NSABP P-1) trial included 13,388 high-risk women randomly assigned to receive either placebo or tamoxifen for 5 years. Inclusion criteria were age 60 years or older, 35–59 years old with a 5-year predicted risk of breast cancer of at least 1.66% using the Gail model, or a history of LCIS. After median follow-up time of 7 years, the rate of invasive breast cancer was reduced by 50% overall. The greatest reduction was seen in the subset of women who had previously had atypical ductal hyperplasia in whom there was an 87% reduction in invasive breast cancers (Table 4).

The patients who received tamoxifen had a 32% reduction in osteoporotic fractures compared with placebo. There was no evidence that tamoxifen increased ischemic heart disease. There was a statistically significant increased risk of endometrial cancer (from .91/1,000 to 2.3/1,000), although 67 of 70 patients were stage 1. The slightly increased risk of stroke, pulmonary embolism, and cataracts was not statistically significant. These adverse effects are similar to those found in women taking hormone replacement therapy. The National Surgical Adjuvant Breast and Bowel Project B-14 established that the recurrence-free survival benefit from 5 years of tamoxifen continued to increase through 15 years of follow-up. The net benefit derived from tamoxifen increases as the predicted level of breast cancer risk increases.[18]

Table 4. The National Surgical Adjuvant Breast and Bowel Project P-1 Trial: Incidence of Breast Cancer per 1,000 Women

Type of Cancer	Placebo	Tamoxifen
Invasive breast cancer	42.5	24.8
Noninvasive breast cancer	15.2	10.2

Data from Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97:1652–62.[18]

The use of tamoxifen as an effective chemopreventive option in gene mutation carriers is controversial; however, for women who have not had prophylactic surgery, it is commonly prescribed. In the 10 years after diagnosis of breast cancer in a *BRCA1* or *BRCA2* mutation carrier, the risk of contralateral breast cancer is about 35%.[31] Narod et al[32] found that the risk of contralateral breast cancer is reduced by 50% in carriers of *BRCA1* and *BRCA2* when tamoxifen is used, even though the majority of *BRCA1* carriers who develop breast cancer have estrogen receptor–negative tumors. The NSABP P-1 trial showed a benefit only for *BRCA2* carriers; however, the number of patients enrolled was extremely small.

Raloxifene is a benzothiophene selective estrogen receptor modulator. It has estrogen agonist effects on bone and has been approved for the prevention and treatment of postmenopausal osteoporosis. Raloxifene has no estrogen agonist effects on the endometrium, and is therefore not associated with an increased risk of endometrial cancer. Its possible estrogenic effect on lipids is being investigated. It is not indicated for the treatment of breast cancer; however, it can be used for chemoprevention.

The *M*ultiple *O*utcomes of *R*aloxifene *E*valuation (MORE) trial, a 4-year multicenter, randomized, double-blind trial to evaluate the effect of raloxifene on bone mineral density and vertebral fracture incidence in postmenopausal women with osteoporosis, exam-

ined breast cancer reduction as a secondary end point. In this trial, raloxifene decreased the incidence of all breast cancers by 62% and invasive breast cancer by 72%. There was an 84% reduction in estrogen receptor–positive tumors. It had no effect on estrogen receptor–negative breast cancer. The risk of venous thrombosis and pulmonary emboli is similar to that of tamoxifen and estrogen.[33] The *C*ontinuing *O*utcomes *R*elevent to *E*vista (CORE) trial was an extension of the MORE trial. Women continued either placebo or raloxifene for 4 more years, according to their initial randomization. The CORE trial demonstrated continuation of a lower annual incidence of breast cancer; however, many of these women had been off the study drug for many years and some had taken hormone replacement during that time. Neither the MORE nor CORE trial specifically examined women who were high risk for breast cancer, so it is not known if the result would be the same in that group. The authors concluded that tamoxifen remains the standard for risk reduction.[34]

The second prevention trial, NSABP P-2, was the *S*tudy of *T*amoxifen and *R*aloxifene (STAR). Enrollment criteria were women 35 years of age or older with LCIS or a risk of invasive breast cancer of at least 1.67%, or women who were postmenopausal. The trial opened in July 1999, and after nearly 3 years, 13,416 women had been randomly assigned. The median age was 58 years, and the median breast cancer risk was 3.3%. Preliminary results reported in April 2006 showed that, like tamoxifen, raloxifene reduced the risk of invasive breast cancer by 50%. Women on raloxifene had fewer uterine cancers and blood clots. Whereas tamoxifen decreased the incidence of DCIS and LCIS by 50%, raloxifene did not.[35] The final results of the Study of Tamoxifen and Raloxifene trial are due out in 2008. The FDA approved raloxifene on September 14, 2007, for prevention of invasive breast cancer in postmenopausal women at high risk.

Studies are underway to evaluate aromatase inhibitors (anastrozole, letrozole, exemestane) for chemoprevention. The interest for using aromatase inhibitors for chemoprevention arose out of the findings of the *A*nastrazole, *T*amoxifen, *A*lone and in *C*ombination trial (ATAC). This was a multicenter, international, double-blind randomized trial that enrolled 9,366 postmenopausal women with early stage breast cancer to receive tamoxifen alone, anastrazole alone, or a combination of the two. After 33 months there was a statistically significant 58% reduction in contralateral primary invasive breast cancers in the anastrazole alone group. Although this group fared better in regard to thromboembolic events and endometrial cancer, there was an excess of bone fractures related to osteoporosis compared with the tamoxifen group. Aromatase inhibitors block the peripheral conversion of androstenedione to estrone and testosterone to E2. Aromatase exists within tissues such as fat and muscle and also within breast tissue. Breast tissue aromatase can synthesize estrogen in situ. Aromatase inhibitors are not used in premenopausal women because they may cause a gonadotropin surge and subsequent increase in E2 levels, which would be detrimental to breast cancer patients. Aromatase inhibitors have been found to be more effective than tamoxifen as treatment for breast cancer, with different side effects. There are currently numerous studies ongoing to see if there is a similar result in the prevention of breast cancer. In the MA-17 trial, letrozole given after 5 years of tamoxifen in early breast cancer was compared with placebo. There was a 39% reduction in the incidence of developing contralateral breast cancer in those patients receiving letrozole. The ongoing MAP-3 study randomly assigns women to exemestane or placebo. More data will be required before a recommendation for the prophylactic use of an aromatase inhibitor can be made.[36]

The use of any agent given in a group of healthy women for a period of time to prevent a disease that may not occur must be scrutinized. Tamoxifen has the potential for serious side effects and a risk-benefit analysis must be considered. Women on aromatase inhibitors exhibit the effects of estrogen depletion, which include osteoporosis, myalgias, joint pain, and increased cholesterol levels.

Surgical Prophylaxis

Prophylactic mastectomy is an effective risk-reducing strategy. A Mayo Clinic retrospective review of 639 women who underwent bilateral prophylactic mastectomy from 1960 to 1993 was performed. Two hundred fourteen women were classified as high risk if family history was suggestive of an autosomal dominant predisposition to breast cancer. The control group included 403 sisters of the patients who had the prophylactic mastectomies. There was a 90% reduction in the incidence of breast cancer. The reduction in the risk of death was 81% to 94% among the prophylactic mastectomy group.[37] When *BRCA* testing became available, the high-risk group had genetic testing. Eighteen women were found to have a known mutation; eight had a mutation of unknown significance. None of these 26 women developed breast cancer after 13.4 years of follow-up, which translates into a breast cancer risk reduction of 89.5–100%. In

the moderate risk group, the reduction in the risk of death was 100%.[37] Prophylactic mastectomy is effective in reducing breast cancer death in gene mutation carriers or other high-risk individuals.[38]

Many factors lead a woman to choose prophylactic mastectomy. The role of the clinician is to ascertain that the woman is not overestimating her risk, that she understands the permanence of her decision, and that she fully understands the effects on body image that the decision may cause. Better breast reconstruction outcomes have made this option more palatable for many women facing this decision (Fig. 4).

Rebbeck et al[39] identified 551 women who had a *BRCA1* or *BRCA2* mutation and had undergone prophylactic oophorectomy. Eligible controls were randomly selected. The incidence of breast cancer was studied in a subgroup of 241 subjects followed for an average of 10.7 years after surgery. The risk of ovarian cancer was reduced by 96%, and the risk of breast cancer was reduced by 53%. Even with a more conservative analysis of the data, the breast cancer risk reduction after oophorectomy was 25%. The greatest benefit is seen in younger patients undergoing the procedure. Bilateral salpingo-oophorectomy is the single most beneficial intervention for gene mutation carriers who are premenopausal because of the reduction in both ovarian and breast cancer. Any patient who is considering prophylactic mastectomy because of her gene mutation status, should also be counseled on the 50% breast cancer risk reduction from oophorectomy alone. Certainly there are serious side effects to oophorectomy, such as hot flushes, vaginal dryness, decreased libido, sleep disturbances, weight gain, and memory loss, and these must be balanced against the possible benefits.

Imaging

According to the American Cancer Society, all women should be screened with an annual mammogram beginning at age 40 years.[40] The American College of Obstetricians and Gynecologists recommends that mammography be performed every 1–2 years from ages 40 years to 49 years and then annually.[41] A key component to increased survival after a diagnosis of breast cancer is early detection (Figs. 5–7). The questions are 1) which patients would benefit from additional screening, 2) what should that additional screening be, and 3) what is the proper interval of the screening? Magnetic resonance imaging (MRI) has higher sensitivity than mammography and moderate specificity.[42] The higher sensitivity may prompt additional biopsies and follow-up studies and increase patient anxiety. It is expensive and labor intensive for the reading radiologist. It is not a replacement for mammography, because the detection rate of the two modalities used together is higher than the detection rate of either by itself.

Plevritis et al[43] examined the cost-effectiveness of screening *BRCA* mutation carriers. For both *BRCA1* and *BRCA2* carriers, MRI reduces mortality by 23% when compared with mammography alone. The cost per quality of life year of an annual MRI from ages 25 years to 69 years is $88,651 for *BRCA1* and $188,034 for *BRCA2* mutation carriers. They concluded that MRI screening was more cost-effective in *BRCA1* and

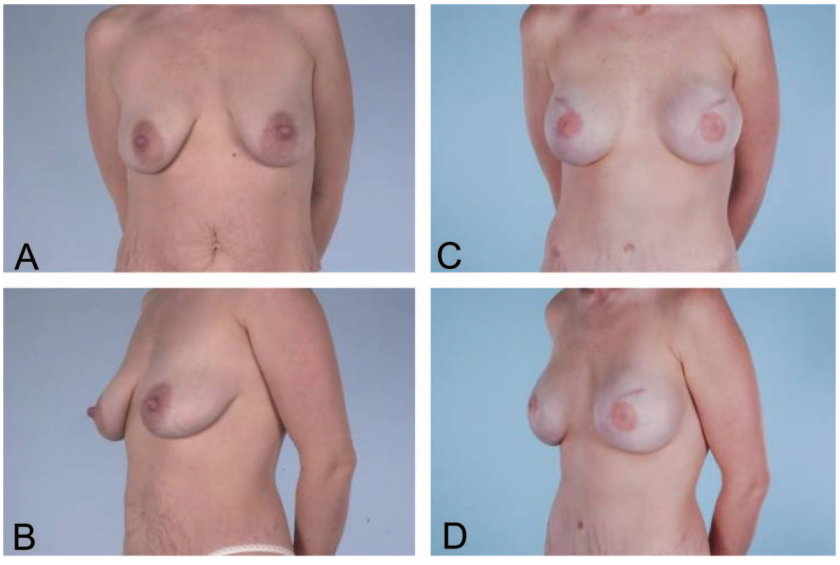

Fig. 4. Bilateral prophylactic mastectomies. Preoperative **(A and B)** and postoperative **(C and D)** views. Images are courtesy of Scott Spear, MD.
Willey. Management of High-Risk Breast Patients. Obstet Gynecol 2007.

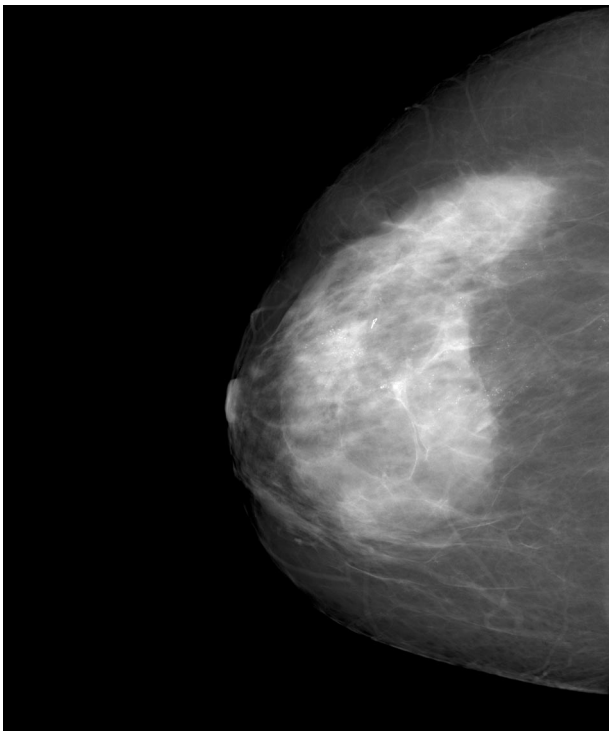

Fig. 5. Mammographic demonstration of breast cancer.
Willey. Management of High-Risk Breast Patients. Obstet Gynecol 2007.

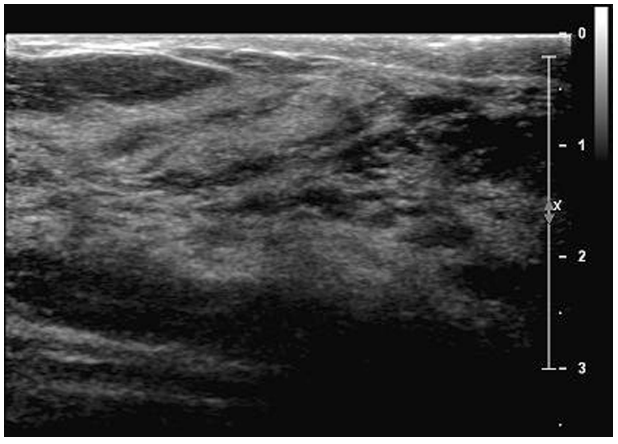

Fig. 6. Ultrasonographic demonstration of breast cancer.
Willey. Management of High-Risk Breast Patients. Obstet Gynecol 2007.

the most cost-effective years to screen are between ages 34 years and 55 years.

A recent retrospective review from Memorial Sloan-Kettering Cancer Center examined the results of MRI screening for breast cancer in patients with LCIS and atypical hyperplasia. Their data demonstrated no added value of MRI screening in patients with atypical hyperplasia and a small benefit, of approximately 4%, in women with LCIS. Patients who underwent MRI screening had a significantly greater number of biopsies. Even in this closely screened group, two cancers were detected only on physical examination,[44] thus emphasizing the importance of continued clinical examinations.

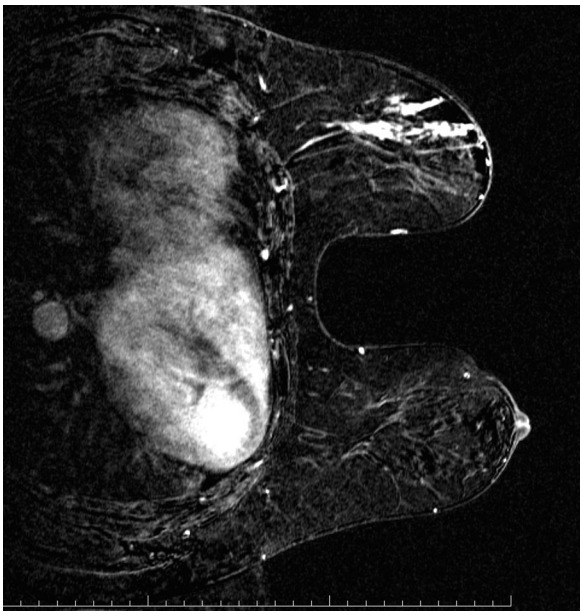

Fig. 7. Magnetic resonance imaging demonstrating breast cancer in the right breast.
Willey. Management of High-Risk Breast Patients. Obstet Gynecol 2007.

The American Cancer Society has issued guidelines for breast screening with MRI as an adjunct to mammography. They divided their recommendations into several categories:

Annual MRI is recommended based on evidence only for patients with a 1) *BRCA* mutation, 2) first-degree relative of a mutation carrier, but who is personally untested 3) lifetime risk of approximately 20–25% or greater based on BRCAPRO or other models that are largely dependent on family history.

Annual MRI is recommended based on expert consensus in patients who have 1) undergone radiation to chest between age 10 years and 30 years, 2) are carriers of Li Fraumeni syndrome and first-degree relatives of these patients, or 3) are carriers of Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives.

At this time there is insufficient evidence to recommend for or against MRI screening for pa-

tients with a 1) lifetime risk of 15–20% as defined by BRCAPRO or other models that are largely dependent on family history, 2) lobular carcinoma in situ, and atypical lobular hyperplasia, 3) atypical ductal hyperplasia, 4) heterogeneously or extremely dense breast on mammography, 5) personal history of breast cancer or DCIS.

The expert panel recommended against MRI for any woman with a less than 15% lifetime risk of developing breast cancer.[45] There are other modalities being tested, such as breast-specific gamma imaging, a molecular breast imaging technique that detects abnormalities after injection of a radioisotope and positron emission mammography. These may have a future role in screening. Thermal scans are also being tested; however, it is as yet not clear what abnormal thermal tests mean or how they should be used clinically.

CONCLUSION

These patients should be followed in a comprehensive breast care or high-risk clinic:

Very high-risk patients:

Gene mutation carriers

Personal history of atypical ductal hyperplasia or LCIS with associated family history

Therapeutic or similarly significant radiation exposure

History of a gene mutation in the family in an untested individual

They should have a physical examination every 6 months and consider MRI screening and additional imaging as technology becomes available. There should be consideration for chemical risk reduction, despite the potential side effects. Confirmed gene mutation carriers should be counseled about surgical prophylaxis and it should be strongly considered once they have completed child bearing or feel they are prepared to make such a permanent decision.

A practitioner who reassesses risk and performs a breast examination during 6-month follow-up visits should follow these patients:

High-risk patients:

Two or more primary relatives, a relative diagnosed at a young age, or multiple second-degree relatives

Prior breast cancer

Significantly dense breast tissue

Hormone replacement therapy greater than 10 years

History of atypical ductal hyperplasia or LCIS without family history of breast cancer

In the absence of symptoms or mammographic abnormalities, there is no need to recommend imaging other than an annual mammogram. For patients with a family history or histologic abnormalities, the recommendation for chemoprophylaxis should be based on a 5-year Gail model risk assessment of 1.7% or greater.

All patients should be encouraged to have annual mammograms after age 40 years, maintain a normal postmenopausal weight, and make lifestyle changes that could help decrease their breast cancer risk, such as increasing physical activity, decreasing alcohol intake, and eating a healthy diet. We hope this review will help clinicians not only identify and manage high-risk patients, but also identify and reassure the average-risk patient.

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