Concise Review for Clinicians

Identifying and Counseling Women at Increased Risk for Breast Cancer

DEBORAH J. RHODES, MD

Women at increased risk for breast cancer should be identified and counseled about options for risk reduction. Identifying such women is simplified with use of the National Cancer Institute Risk Assessment tool, a computer-based tool that incorporates information on 6 risk factors for estimating an individual's risk of developing breast cancer. However, the tool does not incorporate all known or possible risk factors and may underestimate risk, particularly among women with a complex family history of breast cancer for whom alternative models of risk assessment are more appropriate. Women found to have an increased risk of breast cancer should be counseled about options for management, including close surveillance, lifestyle modifications, chemoprevention with tamoxifen, enrollment in a breast cancer prevention clinical trial, and prophylactic mastectomy and/or oophorectomy. In the absence of consensus about which risk level is best suited to which option, decisions about risk reduction depend as much on an individual's priorities and risk aversion as on numerical risk estimates.

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CI = confidence interval; DCIS = ductal carcinoma in situ; HRT = hormone replacement therapy; LCIS = lobular carcinoma in situ; NCI = National Cancer Institute; STAR = Study of Tamoxifen and Raloxifene

An estimated 192,200 women in the United States were diagnosed with invasive breast cancer in 2001.[1] Among American women, breast cancer is the most frequently diagnosed life-threatening cancer and the second leading cause of cancer death. Although improvements in adjuvant therapy and screening have resulted in a decline in breast cancer mortality, the incidence of breast cancer increased between 1940 and 1988 and has since plateaued. Because of new options for breast cancer risk reduction, a decrease in breast cancer incidence now seems within reach.

Informed decisions regarding risk reduction options depend on individualized breast cancer risk assessment. Because numerous studies suggest that many women substantially overestimate their individual breast cancer risk, often by a factor of 10 or more, discussions of risk reduction options must begin with a reasonable estimation of breast cancer risk.[2-4] This review summarizes the most widely used methods of breast cancer risk assessment and outlines the options for risk reduction.

BREAST CANCER RISK ASSESSMENT

Until recently, breast cancer risk assessment was the domain of breast cancer specialists and geneticists. However, the development of a computerized risk assessment tool by the National Cancer Institute (NCI) has simplified estimation of individual breast cancer risk. The NCI risk assessment tool is available online at http://bcra.nci.nih.gov/brc.

The tool is a modified version of a risk assessment model developed by Gail et al.[5] These investigators determined which factors were significant predictors of lifetime risk of breast cancer and then estimated the relative risks associated with each of these factors. In addition to age, factors found to be significant predictors of risk include age at menarche, age at first live birth, number of previous breast biopsies, presence of atypical hyperplasia, and number of first-degree relatives affected by breast cancer.

The relative risks associated with these factors, as determined in the original Gail model, are listed in Table 1. The NCI tool has incorporated these relative risks, included the additional factor of race, and replaced breast cancer rates used in the Gail model with more recent age-specific invasive breast cancer rates. The NCI tool prompts the clinician to answer 9 questions pertaining to these risk factors. Based on the answers to these questions, the tool estimates the woman's percentage risk of developing breast cancer over the next 5 years and for the remainder of her lifetime. A comparison risk is provided for a similarly aged woman with average risk factors. When the Web-based version of the NCI tool is used, the risk estimates can be printed to give to the patient, as can additional information on breast cancer risk factors, risk estimate interpretation, and risk reduction options.

Several validation studies have supported the predictive value of the NCI tool. One recent study using the NCI

From the Breast Clinic, Division of General Internal Medicine, Mayo Clinic, Rochester, Minn.

A question-and-answer section appears at the end of this article.

Address reprint requests and correspondence to Deborah J. Rhodes, MD, Division of General Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: rhodes.deborah@mayo.edu).

Table 1. **Risk Factors for Breast Cancer and Associated Relative Risks in the Gail Model**

Risk factor*	Relative risk
Age at menarche (y)	
≥14	1.00
12-13	1.10
<12	1.21
No. of biopsies	
Age <50 y	
0	1.00
1	1.70
≥2	2.88
Age ≥50 y	
0	1.00
1	1.27
≥2	1.62
No. of affected first-degree relatives	
Age at first live birth <20 y	
0	1.00
1	2.61
≥2	6.80
Age at first live birth 20-24 y	
0	1.24
1	2.68
≥2	5.78
Age at first live birth 25-29 y or nulliparous	
0	1.55
1	2.76
≥2	4.91
Age at first live birth ≥30 y	
0	1.93
1	2.83
≥2	4.17
Atypical hyperplasia	1.96†

*Note that age is an important risk factor in the Gail model, but the effect of age is embedded in the baseline hazard rates. Data derived from Gail et al.[5]

†The relative risk assigned to atypical hyperplasia in the Gail model is lower than the relative risk of 4.0 to 5.0 cited in the consensus statement of the Cancer Committee of the College of American Pathologists.[6]

tool found that the ratio of observed to predicted breast cancers was 1.03 (95% confidence interval [CI], 0.88-1.21).[7]

Despite the ease of use and validity of the estimates within a population, the NCI risk tool has important limitations. Patient characteristics that are not incorporated in the NCI tool are listed in Table 2. Estimating breast cancer risk with the NCI tool for individuals with these characteristics may lead to inaccurate risk assessment.

The NCI tool is not designed to estimate risk for women younger than 20 years, and the Web-based version does not allow calculation of risk for women younger than 35 years (the minimum age at which women are eligible for NCI breast cancer prevention protocols).

The NCI tool was developed to predict the risk of invasive breast cancer in women with no history of invasive or noninvasive breast cancer. Therefore, the tool does not provide an accurate risk assessment for women with a history of lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS). Of note, however, women with a history of LCIS have a significantly increased risk of developing invasive breast cancer (relative risk, 8-10) and should be counseled about prevention options.

Although the NCI tool distinguishes between biopsy specimens showing atypical hyperplasia and all other benign breast histopathologic specimens, it makes no finer distinctions within the category of benign breast disease. Several studies have found that nonproliferative breast lesions (such as mild hyperplasia without atypia or ordinary cysts) confer no increased risk for breast cancer and that proliferative lesions (such as moderate to florid hyperplasia, complex fibroadenomas, papillomas, and radial scars) confer a moderately increased risk (relative risk, 1.5-2.0).[6] Despite this association between proliferative breast disease and subsequent breast cancer risk, the risk assessment tool will assign a higher risk to a woman who has had numerous biopsies showing ordinary cysts than to a woman who had 1 biopsy showing a radial scar.

Other risk factors for breast cancer have been identified or proposed but are not included in the tool either because evidence that these factors contribute to breast cancer risk is inconclusive or because the magnitude of additional risk conferred by these factors has not been determined precisely. These factors include age at menopause, density of breast tissue, use of oral contraceptives or hormone replacement therapy (HRT), dietary factors, obesity, exercise, prior radiation exposure, and environmental exposures.

The most important limitation of the NCI tool is that it may significantly underestimate risk in women whose predominant risk factor is a family history of breast cancer, particularly one that includes early-onset breast cancer, affected second-degree relatives, or inherited genetic mutations that increase the risk of breast cancer. The tool does not incorporate the age at diagnosis of affected first-degree relatives. Although a woman whose mother was diagnosed with breast cancer in her 30s has approximately twice the risk of developing breast cancer in her lifetime as the woman whose mother developed breast cancer in her 80s, the tool assigns the same increment of increased risk to both women. Because the tool does not incorporate a family history of breast cancer in maternal or paternal second-degree relatives, it underestimates risk in a woman who had 1 or more aunts or grandmothers with breast cancer.

For women whose predominant risk factor is a family history of breast cancer, alternative breast cancer risk as-

sessment models, such as the Claus model,[8] are more appropriate for assessing breast cancer risk. This model is applicable only to women with 1 or 2 first- or second-degree relatives (maternal or paternal) affected by breast cancer. Because the Claus model incorporates more detailed information on family history but excludes the nonfamilial risk factors represented in the Gail model, these models may provide significantly different risk estimates.[9]

Both the Claus and the Gail models generally underestimate breast cancer risk in women who are known or suspected carriers of breast cancer susceptibility genes, of which the most common are *BRCA1* and *BRCA2*. Women with inherited mutations in either *BRCA1* or *BRCA2* represent the highest known risk group, with lifetime risks of breast cancer approaching 55% to 80% (depending on the population studied) and have an increased risk of ovarian cancer that ranges from 10% to 44%. Features of a family history suggestive of *BRCA* involvement include multiple cases of early-onset breast cancer, cases of breast and ovarian cancer within the same individual or family, cases of breast cancer within a family of Ashkenazi Jewish heritage, bilateral breast cancer, and male breast cancer. Although testing for *BRCA* mutations refines risk estimates in women whose families have these characteristics or have members who are known carriers, only a small proportion of all breast cancers (about 5%-10%) is attributable to such germline mutations. Genetic testing is unlikely to yield useful information about risk in women without these familial characteristics.

Because the choice and interpretation of risk estimation models in this population is critical, women with a family history suggestive of *BRCA* involvement should be referred to a center with expertise in breast cancer genetics.

Table 2. **Patient Characteristics Not Included in the Gail Model or NCI Risk Assessment Tool***

Age <20 y
History of DCIS or LCIS
Distinction between prior breast biopsies showing nonproliferative vs proliferative lesions
Age at menopause
Density of breast tissue
Use of oral contraceptives or hormone replacement therapy
Dietary factors
Obesity/weight gain
Exercise
Prior radiation exposure
Environmental exposures
Second-degree relatives with a history of breast cancer
Paternal family history
Age at diagnosis of affected family members
Personal or family history of other cancers (such as ovarian cancer)

*DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ; NCI = National Cancer Institute.

MANAGEMENT OPTIONS FOR WOMEN AT INCREASED RISK

Once a woman has been identified as having an increased risk of breast cancer, numerous options exist for surveillance and risk reduction depending on her preferences and her level of risk. Because there is little consensus about what constitutes significantly increased risk or about which intervention is best suited to which level of risk, each woman must make her own informed decisions about risk management.

Close Surveillance

One option for women at increased risk is close surveillance. The intent of this option is to detect cancer at the earliest stage possible. A task force convened by the Cancer Genetics Studies Consortium issued surveillance recommendations for the management of women with *BRCA1* or *BRCA2* mutations.[10] The task force recommended monthly breast self-examination beginning at age 18 to 21 years, clinical breast examination every 6 to 12 months beginning at age 25 to 35 years, and annual mammography beginning at age 25 to 35 years. The task force also recommended performing annual transvaginal ultrasound studies and measuring serum cancer antigen 125 levels to screen for ovarian cancer. However, a recent study of women with *BRCA1* and *BRCA2* mutations found that this surveillance approach may be insufficient.[11] Further study is needed to determine whether this group of women would benefit from increasing the frequency of screening, combining mammography with additional imaging modalities, or possibly adding an alternative method of surveillance, such as breast ductal lavage.

For women with family histories of breast cancer that are not suggestive of an inherited mutation, annual screening mammography should be instituted 5 to 10 years before the age at which the youngest affected relative was diagnosed or at age 40 years, whichever is earlier.

Risk Reduction Options

Four options that may reduce the risk of breast cancer are lifestyle modification, chemoprevention, enrollment in clinical trials, and prophylactic surgery.

Lifestyle Modification.—Recent studies suggest a compelling role for lifestyle changes in breast cancer risk reduction. Obesity and weight gain appear to be associated with breast cancer risk.[12] One study from the Nurses' Health cohort found that weight gain after the age of 18 years was unrelated to breast cancer incidence before

menopause but was positively associated with incidence after menopause.[13] In this population, the percentage of postmenopausal breast cancer accounted for by weight gain alone was approximately 16%.

Regarding breast cancer risk and dietary intake, observational studies have often reached contradictory conclusions. A large randomized clinical trial being conducted by the Women's Health Initiative should clarify the association between breast cancer risk and consumption of fruits, vegetables, and fat.[14]

In a pooled analysis of cohort studies, alcohol intake was found to be associated with an increase in breast cancer incidence, with a relative risk of 1.41 (95% CI, 1.18-1.69) for women consuming 2 to 5 drinks per day compared with nondrinkers.[15]

Several studies have shown an association between exercise and breast cancer risk. One cohort study of 25,624 women found that the risk of breast cancer was lowest in lean women (body mass index, <22.8) who exercised at least 4 hours per week (relative risk, 0.28; 95% CI, 0.11-0.70).[16]

Although further study of these associations is certainly warranted, dietary and exercise changes that confer health benefits beyond the potential for breast cancer risk reduction can be recommended. Recommendations regarding use of exogenous hormones in women at increased risk of breast cancer are more complex. One study found that use of oral contraceptives was associated with a significantly increased risk of breast cancer among women with a first-degree relative with breast cancer. This risk was particularly high among women who had taken oral contraceptives during or before 1975 when formulations were likely to contain higher dosages of estrogen and progestins.[17] Another study found that oral contraceptives may increase the risk of breast cancer more in carriers of *BRCA1* or *BRCA2* mutations than in noncarriers.[18] Women with a family history of breast cancer in first-degree relatives and/or a *BRCA1* or *BRCA2* mutation should be counseled about these findings, and alternative methods of contraception should be considered.

Although women with proliferative benign breast disease (including atypical hyperplasia) are at increased risk for breast cancer compared to women with nonproliferative breast disease, use of HRT among women with proliferative breast disease does not appear to compound this increased risk.[19,20] Thus, HRT is not contraindicated in women with proliferative benign breast disease.

Whether women with a family history of breast cancer should be discouraged from using HRT is less clear. One meta-analysis found that the risk of breast cancer associated with HRT was elevated among women with no family history of breast cancer and was further elevated among women with a family history.[21] Conversely, another study found that HRT use in women with a family history of breast cancer was not associated with a statistically significant increased incidence of breast cancer but was associated with a significantly reduced total mortality rate.[22] Until further research clarifies the association between HRT use and family history of breast cancer, a sensible approach is to examine the individual's primary goal in considering HRT. If the primary goal is osteoporosis prevention, alternative medications (such as bisphosphonates or raloxifene) may achieve the same goal without increasing breast cancer risk. If the primary goal is vasomotor symptom alleviation, nonhormonal medications, such as venlafaxine, may provide acceptable relief. However, if the primary goal for taking HRT is an improved sense of well-being, this benefit may well outweigh the potential additional risk conferred by HRT use. Although there is no clear contraindication to HRT use in women with a family history of breast cancer, benefits must be weighed against potential risks as they pertain to the individual patient.

Chemoprevention.—Another option for women at increased risk of breast cancer is chemoprevention, an attempt to reduce the risk of breast cancer by means of drug therapy. Interest and controversy regarding chemoprevention soared in the wake of 3 studies,[23-25] all published in 1998, that examined the effect of tamoxifen on the incidence of breast cancer.

The largest of the studies was the Breast Cancer Prevention Trial[23] (also known as P-1) in which more than 13,000 women at increased risk for breast cancer were randomized to receive tamoxifen or placebo for 5 years. Increased risk was defined as: (1) age 60 years or older, (2) age 35 to 59 years with a 5-year predicted risk for breast cancer of at least 1.66% as determined by the risk assessment tool, or (3) a history of LCIS. Tamoxifen was associated with a 49% reduction in the risk of invasive cancer and a 50% reduction in the risk of noninvasive breast cancer (both DCIS and LCIS). The risk of developing breast cancer at 5 years was 1.3% in the tamoxifen group vs 2.6% in the placebo group, for an absolute risk reduction of 1.3% at 5 years. All age groups showed similar reductions in the incidence of breast cancer.

Although the other 2 trials,[24,25] both conducted in Europe, reported no effect of tamoxifen on the incidence of breast cancer, these studies were smaller, had fewer breast cancer events, allowed concurrent use of HRT, and had enrollment criteria that may have favored women less likely to benefit from tamoxifen. In contrast, the Breast Cancer Prevention Trial was adequately powered and methodologically sound. It confirmed that tamoxifen is effective in short-term breast cancer risk reduction among women whose estimated 5-year risk of breast cancer is 1.66% or higher. However, this does not mean that all

women with this degree of risk should take tamoxifen. A total of 120 women with this level of risk would need to take tamoxifen for 5 years to prevent 1 breast cancer.[26] Furthermore, tamoxifen is associated with an increased risk of endometrial cancer, deep venous thrombosis, pulmonary embolism, and stroke.

Many questions regarding the appropriate use of tamoxifen for breast cancer prevention remain. Will tamoxifen be as effective in the subgroup of women who are *BRCA1* and *BRCA2* carriers? What is the optimal age for and duration of tamoxifen administration in the prevention setting? Will the short-term reduction in breast cancer incidence translate into a reduction in breast cancer mortality? A woman's decision to take tamoxifen in the hope of reducing her risk of breast cancer should be based on her own level of risk aversion and a detailed understanding of these issues.

Clinical Trials.—Another option for women at increased risk is enrollment in a breast cancer prevention trial. The Study of Tamoxifen and Raloxifene (STAR) (also known as P-2) will determine whether raloxifene is as effective as tamoxifen in reducing the incidence of breast cancer in women at increased risk by using the same criteria for increased risk as the Breast Cancer Prevention Trial. Like tamoxifen, raloxifene is a selective estrogen receptor modulator that has estrogen-antagonist properties in breast tissue and estrogen-agonist properties in other tissues, such as bone (hence its approval for prevention and treatment of osteoporosis). The appeal of raloxifene is that, unlike tamoxifen, it is not associated with an increased risk of uterine cancer. Previous trials of raloxifene in postmenopausal women with osteoporosis have evaluated breast cancer incidence as a secondary end point and have found that raloxifene was associated with a decreased relative risk.[27] Despite these promising results, raloxifene should not be used primarily for breast cancer risk reduction outside of a clinical trial. Further information on STAR can be obtained at http://cancertrials.nci.nih.gov/types/breast/prevention/star/.

Prophylactic Surgery.—Prophylactic surgery is an option usually reserved for women with a significantly increased risk of breast cancer. A study by Hartmann et al[28] found that, among women with a family history of breast cancer, prophylactic mastectomy was associated with a 90% reduction in the incidence of breast cancer. The reduction in risk persisted throughout the median follow-up of 14 years. Prophylactic mastectomy is a reasonable option for high-risk women, but the potential gains in life expectancy must be weighed carefully against the personal costs.

Bilateral oophorectomy in women younger than 40 years is associated with a decrease in breast cancer risk of approximately 50% compared with women who have undergone a natural menopause. This risk reduction appears to apply not only to women with average breast cancer risk but also to women with *BRCA1* mutations.[29] Again, the potential gain in life expectancy must be weighed against the personal costs, including the adverse effects on bone and other organs after induction of premature menopause.

CONCLUSION

In light of the many options and the lack of consensus about which option is best suited to a particular level of risk, how can clinicians help the individual patient make such a complex decision? To begin, we must estimate her breast cancer risk, either by using the NCI risk assessment tool when appropriate or by referring her for genetic counseling.

We must then recognize that women with the same level of estimated risk may have markedly different perspectives on the importance of this risk. One woman may consider a 30% lifetime risk of developing breast cancer intolerable, while another with this same risk may consider her odds of not developing breast cancer favorable. Personal experiences may influence an individual's perception of risk. A woman who watched her mother die of breast cancer may feel very differently from another whose mother was successfully treated for a small breast cancer years earlier. A woman's age and body image may strongly influence her approach to prevention. A single 25-year-old woman with a *BRCA1* mutation may feel differently about prophylactic surgery than a 50-year-old *BRCA1* carrier whose priority is to raise her 4 children. Finally, no consensus exists on the age at which prevention interventions are no longer warranted. Although most clinicians agree that a 75-year-old woman who has not developed breast cancer should continue with surveillance only, what about a woman in her mid 60s who is a carrier of a *BRCA* gene?

These complex issues illustrate the importance of providing each patient with an assessment of her individual risk. Only then can we help each patient to understand the effect of this risk estimate on her life and to decide if her level of risk and concern are best addressed by routine screening, close surveillance, lifestyle modification, chemoprevention, enrollment in a clinical trial, or prophylactic surgery.

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Questions About Identifying and Counseling Women at Increased Risk for Breast Cancer

1. Which <u>*one*</u> of the following is <u>*included*</u> in the NCI Risk Assessment tool to estimate breast cancer risk in women?
   a. History of invasive breast cancer
   b. History of DCIS
   c. History of LCIS
   d. History of atypical hyperplasia
   e. History of bilateral prophylactic mastectomy
2. Which <u>*one*</u> of the following patient characteristics is <u>*incorporated*</u> into the NCI Risk Assessment tool?
   a. Family history of breast cancer in a sister
   b. Age at diagnosis of mother and/or sister affected by breast cancer
   c. Family history of breast cancer in a maternal aunt
   d. Family history of breast cancer in paternal relatives
   e. Family history of ovarian cancer
3. Which <u>*one*</u> of the following percentages is <u>*correct*</u> regarding the absolute breast cancer risk reduction after 5 years of tamoxifen administration in the Breast Cancer Prevention Trial?
   a. 1.3%
   b. 1.7%
   c. 2.6%
   d. 25%
   e. 50%

4. Which *one* of the following regarding raloxifene is *correct*?
   a. Is as effective as tamoxifen in short-term breast cancer risk reduction
   b. Acts as an estrogen antagonist at the level of bone
   c. Acts as an estrogen antagonist at the level of the breasts
   d. Is currently approved by the Food and Drug Administration for breast cancer risk reduction
   e. Is associated with an increased risk of uterine cancer
5. Which *one* of the following statements about breast cancer risk reduction options is *correct*?
   a. Tamoxifen should not be given as a chemopreventive agent to women older than 65 years
   b. Tamoxifen is the most effective means of breast cancer risk reduction in women with known *BRCA* mutations
   c. Close surveillance is not an appropriate option in women with *BRCA* mutations
   d. Prophylactic mastectomy is associated with a 90% reduction in the incidence of breast cancer
   e. Prophylactic oophorectomy is an effective means of breast cancer risk reduction in only women with *BRCA* mutations

Correct answers:
1. *d*, 2. *a*, 3. *a*, 4. *c*, 5. *d*