

Breast Cancer Risk Assessment: A Guide for Clinicians Using the NCCN Breast Cancer Risk Reduction Guidelines

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Key Words

Breast cancer, risk factors, risk assessment, epidemiologic models

Abstract

Breast cancer, a complex and heterogeneous disease, is the most common malignancy diagnosed in women in the United States, with over 180,000 new cases and approximately 44,000 deaths per year. Breast cancer risk is influenced by a large number of factors, including age, family history, reproductive and hormonal history, proliferative breast conditions, physical activity, diet, and environmental exposures. These factors all interact in a complex manner to contribute to the risk of developing breast cancer. Because the interactions between risk factors are poorly understood at the molecular level, it is difficult to accurately evaluate the breast cancer risk of a given person presenting with an individual constellation of factors. To better define the population at increased risk that may warrant specific intervention, several models exist to estimate a woman's risk for developing breast cancer and for harboring a germline mutation in a cancer susceptibility gene. This article summarizes these models and gives brief guidelines about which model may be preferable given a specific family history. (JNCCN 2003;1:297-301)

Breast cancer, a complex and heterogeneous disease, is the most common malignancy diagnosed in women in the United States, with over 180,000 new cases and approximately 44,000 deaths per year.^{1,2} The lifetime risks in the United States for invasive and in situ breast cancer are 12.6% and 14.4%, respectively.¹ Breast cancer risk

is influenced by many factors, including age, family history, reproductive and hormonal history, proliferative breast conditions, physical activity, diet, and environmental exposures.^{3,4} These factors all interact in a complex manner to contribute to a woman's risk of developing breast cancer. Because the interactions between risk factors are poorly understood at the molecular level, it is difficult to accurately evaluate the breast cancer risk of a given person presenting with an individual constellation of factors. However, as presymptomatic individuals at high risk are identified in increasing numbers, physicians must work on evaluating breast cancer risk with the best tools at hand. Mindful that this knowledge is incomplete at the present time, this article discusses the major breast cancer risk evaluation tools and the existing knowledge of how they may be used to estimate breast cancer risk.

Breast cancer is overwhelmingly a disease of women. The risk increases steadily with age after age 20, throughout the reproductive years and postreproductive years, until age 85. Mortality from breast cancer also increases with age in sporadic cases; the age-specific mortality trends in hereditary breast cancer are not known. After gender and age, family history is the most important predictor of breast cancer risk in an unaffected woman.⁵ Thirty-eight percent of patients with breast cancer have a family history of some type of cancer.⁶⁻¹⁰ However, it is important to emphasize that 80% of women with breast cancer have no first- or second-degree relatives with the disease.

Defining Risk

To better define the population at increased risk who may benefit from specific interventions, several models based on epidemiologic data are available to estimate a woman's risk for developing breast cancer and for harboring a

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germline mutation in a cancer susceptibility gene. This article summarizes these models and gives brief guidelines about which model may be preferable, given a specific family or personal history.

A detailed family history, comprising at least three generations, if available, is a highly desirable first step in cancer risk evaluation.¹¹ If possible, confirmation of cancer diagnosis should be made via medical records or pathology reports. If the patient has had a biopsy, medical records and pathology reports should be collected to confirm the outcome of the biopsy. This is especially important in cases of invasive breast cancer, ductal carcinoma in situ (DCIS), and nonmalignant proliferative breast disease as well as reported cases of ovarian cancer. Information on gynecologic malignancies affecting a family member can be especially unreliable, and obtaining pathology confirmation becomes quite important in these cases to prevent inaccurate risk calculations.

The Gail Model

In 1989, Gail et al¹² developed a mathematical model to calculate cumulative risk for developing breast cancer in white women over time. This model was based on data from 280,000 women recruited for the Breast Cancer Detection Demonstration Project (BCDDP) between 1973 and 1975. Using information from 2,800 new cases of breast cancer diagnosed in 5 years of annual mammographic screening and 3,100 controls, Gail et al¹² focused on five specific factors for their analytic model: age at evaluation, age at menarche, age at first live birth, number of breast biopsies and results, and number of first-degree relatives with breast cancer. They also calculated age-specific baseline incidence rate of breast cancer using women from the same cohort with no known increased risk of breast cancer as controls.

An absolute risk can then be estimated by combining the baseline incidence rates with the summary relative risk information. Risks using this model can be easily obtained using a computer, a calculator, or the Internet at www.bcra.nci.nih.gov/brc/start.htm.

The Gail model has been validated in three independent projects. An important validation occurred in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 clinical trial of tamoxifen versus placebo, which showed that tamoxifen significantly reduced the risk of developing breast cancer in women

whose 5-year risk was greater than 1.7. In the NSABP P-1 cohort, the number of breast cases ascertained at 5 years was in close agreement with the Gail model prediction.¹³

In 2001, Rockhill et al¹⁴ published another validation of the Gail model. Their study evaluated the goodness of fit of the Gail model and the discriminatory accuracy at the individual level in the Nurses' Health Study. They evaluated a cohort of 82,109 white women aged 45 to 71 years in 1992 and applied the Gail model to estimate a 5-year risk of invasive breast cancer. Again, the Gail model was robust in predicting the number of breast cancer cases, and had modest discriminatory accuracy at the individual level. It is at the individual level that the Gail model is used for day-to-day calculations in breast cancer risk evaluation clinics.

The Gail model is especially useful in calculating breast cancer risk in white women who are screened regularly and who do not have a strong family history of breast cancer defined by a pattern of apparent autosomal dominant transmission of a cancer susceptibility gene or a family history of ovarian cancer (Table 1). The model may be used cautiously for individuals of other ethnic backgrounds. The NSABP recently issued a modified version of the Gail model that accommodates breast cancer risk data for Hispanic and African-American women. This version should be employed with patients of those ethnicities, with the cautionary note that much less independent validation has been performed in these populations to date.¹⁵

In contrast, for individuals with a significant family history of breast cancer, a family history of ovarian cancer, paternal family history of breast or ovarian

Table 1 Patient and Family Characteristics That Would Favor Use of the Gail Model for Breast Cancer Risk Estimation

- Small family size
- Previous breast biopsy revealing proliferative breast condition (ie, atypical hyperplasia)
- Family history of cancer in the maternal lineage only
- One first-degree relative with breast cancer
- No history of ovarian cancer in first-degree relatives
- Early menarche
- Late childbirth

Web site: www.bcra.nci.nih.gov/brc/start.htm

cancer, a constellation of characteristics pointing to a specific syndrome not associated with the BRCA genes (such as Cowden's disease or Li-Fraumeni syndrome), or multiple associated cancers, the Gail model is likely to give inaccurate estimates of risk and thus should be avoided.

The Claus Model

In 1994, Claus et al^{9,10} developed an empiric model using segregation analysis to assess the age-specific risk of developing breast cancer in women who have at least one female relative with breast cancer. The Claus model was derived from data collected in the Cancer and Steroid Hormone Study (CASH), a case-control study. This model was created under the generally accepted principle that women have a two- to threefold increase in risk for developing breast cancer if they have a first-degree relative with breast cancer. This model also assumes that age of onset and susceptibility to breast cancer are controlled by the same single gene and that the gene is inherited in an autosomal dominant manner.^{9,10} Tables were constructed that show predicted cumulative probabilities for occurrence of breast cancer at different ages, depending on both the presence of breast cancer in various combinations of first- and second-degree relatives and the age of onset of these cancers in the relatives. The Claus model allows estimation of absolute lifetime risk or risk over defined time intervals, such as 10, 20, and 30 years. The Claus model has not been systematically validated in other cohorts, however. In spite of these potential limitations, the Claus model has proven exceptionally helpful in risk calculations for individuals with more involved family histories of cancer for whom the Gail model would not be suitable.

The Claus model, however, does not incorporate other risk factors, such as reproductive history and history of atypical hyperplasia or other cancers, and it may not be accurate for women who have both an affected mother and maternal grandmother. This model also is likely to underestimate the risk for an individual who has a small family or a small number of female relatives

The Breast Cancer Risk Assessment Tool

Most recently, the Breast Cancer Risk Assessment Tool (BRISK) was developed by Dr. Suzanne O'Neill at the University of Pittsburgh. This is a Microsoft

Excel-based (Redmond, WA) risk assessment tool that estimates breast cancer risk based on both the Gail and Claus models. It was designed as a screening method to identify patients who would be considered at high risk for developing breast cancer based on either the Gail or Claus model. This interfacing risk assessment tool allows the clinician to see estimates of the patient's risk of developing breast cancer from both the Gail and Claus models side by side, along with a comparison of the patient's risk compared with risk in the general population. BRISK can be obtained by contacting O'Neill (Table 2). We encourage practitioners who serve a population of women at possible high risk for breast cancer to use this program, because it greatly facilitates and expedites breast cancer risk estimates in an office setting, provided a computer is available.

The Claus and Gail models address the risk for developing breast cancer for women with a family history breast cancer. They do not address the probability that a woman carries a mutation in *BRCA1* and/or *BRCA2*. Several investigators have published summary tables of estimated probabilities of carrying a *BRCA* mutation,^{16,17} given certain characteristics of the family. In assessing a family's risk for *BRCA1* and/or *BRCA2*, it is important to evaluate the number of affected individuals relative to the total number of first- and second-degree relatives and the types and ages of onset of all cancers, seeking associations that may hint at a known syndrome. Reliable assignment of clinical diagnoses is paramount for an accurate risk evaluation. Therefore, the importance of the physical examination and confirming the diagnosis by reviewing the original pathology reports cannot be overemphasized.

The BRCAPRO Model

In 1998, Parmigiani et al¹⁸ developed a model called BRCAPRO based on Bayesian principles, which was

Table 2 Information for Obtaining the Breast Cancer Risk Assessment Tool

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designed to provide the probability that a family carries mutations in the breast cancer susceptibility genes *BRCA1* or *BRCA2*.¹⁸ BRCAPRO incorporates all relevant family history, up to second-degree relatives. For each family member, information is gathered regarding previous breast cancer diagnoses, age at diagnosis, or, if cancer free, the current age or age at death. If the family member is female, information regarding ovarian cancer status is also considered. This model can incorporate uncertainty of cancer status in the input. The model computes a likelihood ratio of a mutation for the observed family history. Estimates of mutation frequency in the population provide the probability of a mutation in the individual being counseled, before ascertaining family history. Bayes' rule is then applied to the determination of the probability of a mutation for a specific individual, given the known family history. This probability is after family history but before genetic testing. For applications in the clinic, calculation of the likelihood of a mutation is easily computed by specific software.¹⁸

In 2002, Berry et al¹⁹ published data on BRCAPRO validation, revealing that this program is effective in predicting risk of testing positive for a deleterious mutation in *BRCA1/2*, especially when the carrier probability is less than 70%. Larger carrier probabilities overestimate the frequency of a mutation in approximately 15% of cases. The risk of breast cancer can be inferred for unaffected patients by multiplying the BRCAPRO carrier probability by the penetrance of the gene.

A limitation of this model is that only *BRCA1* and *BRCA2* are considered to be possible predisposing genes, and all non-BCRA breast cancers are considered sporadic. However, significant scientific evidence suggests that other breast cancer susceptibility genes, such as *TP53*, *PTEN*, and others yet to be discovered, are involved with hereditary breast cancer. Thus, this model tends to mildly overestimate the probability of a *BRCA* mutation in a family. However, based on existing data on large family collections, those authors believe that any undiscovered breast cancer genes will probably have low prevalence or penetrance. If this scenario is true, then genes with penetrance similar to *BRCA1/2* would be very rare. BRCAPRO is meant to be used as a guide rather than a rigid algorithm for the counselor and patient to tailor risk evaluation and management strategies. These constraints and limitations notwithstanding, BRCAPRO is the most sophisticated model presently

available to evaluate the probability of a *BRCA1/2* mutation given a particular family history.

BRCAPRO is available for PC users at <http://www3.utsouthwestern.edu/cancergene/>, and for Progeny users at <http://progeny2000.com/utilities.html>.

An Example of a Risk Evaluation Work-up

As an illustration, we provide a clinical case that highlights the importance of using the risk evaluation models appropriately. A patient with both a proliferative nonmalignant breast condition and also a strong family history of breast or ovarian cancer presents an especially challenging case of risk estimation. For such a patient, who is often encountered in practice, we recommend the following approach:

If a patient has a breast tissue diagnosis such as atypical hyperplasia, the clinician may use the Gail model as a starting point for risk assessment, even if the family history is suggestive of inherited susceptibility. The risk estimate from the Gail model, which takes into account the diagnosed proliferative breast condition, could be used as a lower limit of the true risk range. The Claus tables or the BRCAPRO model could be used to produce realistic estimates of the upper limit to the patient's lifetime risk of breast cancer.

In the future, as these and other models are refined, we hope that the detailed risk factor profile of every patient will be adequately taken into account. As a guideline, it seems appropriate to refer patients with a 10% or greater probability of having a positive *BRCA1/2* test result by the BRCAPRO model for specialized counseling services.

Conclusions

Several interesting and user-friendly models exist to calculate age-specific breast cancer risk. As detailed in this article, however, the models differ substantially in their assumptions and thus in their applicability for specific patients. Because they do not incorporate all of the known risk factors, the estimates of risk that they yield should be considered as guides rather than absolute criteria for genetic testing, chemoprevention, or cancer risk management. We believe that practitioners with female patients may benefit from establishing a collaborative referral or consultative relationship with a specialized breast and ovarian

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cancer risk evaluation clinic in a comprehensive cancer center in their region.

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