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**Introduction**

Available data show that women are anxious about their risk of developing breast cancer and that they tend to overestimate this risk. A large literature on the epidemiology of breast cancer has led to the development of validated, quantitative risk-assessment models. These models allow for the rapid identification of women who are at increased risk for breast cancer, along with an estimation of their probability of developing breast cancer over a period of years or by a certain age. Expressing the risk of developing breast cancer in quantitative terms facilitates the education of individual patients about their risk. It also permits the rational design of prospective interventional and management strategies and the selection of eligible participants for clinical prevention trials.

This article will describe currently available models for quantitative assessment of breast cancer risk and strategies for managing women shown to be at increased risk for this cancer. First, however, key terms will be defined and established risk factors reviewed.

**Definitions**

We evaluate risk of breast cancer both to identify women who require special management and to increase our understanding of the biologic processes that lead to this cancer. "Risk" is a relative term derived by comparing the incidence of a disease in a group having a particular risk factor or trait with the incidence of the same disease in a comparison group of individuals who do not carry the risk factor but who are otherwise the same.[1]

**Odds Ratio and Relative Risk**

Risk calculations derived from retrospective data are expressed as an odds ratio, or the ratio of the odds of having the disease in those with a trait of interest compared with those without the trait. Odds and probabilities are related mathematically in such a way that if either is known, the other can be calculated. In a prospective study, the risk of disease is expressed as the ratio of the incidence of the disease in those with a particular trait divided by its incidence in those without the trait. This ratio is known as the relative risk. A relative risk (or an odds ratio) of 1.5 means that a person with a given trait or characteristic is 1.5 times more likely to develop the disease than is someone without the trait. A trait associated with a relative risk of this magnitude can also be described as conferring a 50% increase in risk.

**Attributable Risk**

The presence of a risk factor does not guarantee the development of a disease, just as the absence of a risk factor does not afford absolute protection against the disease. The relationship between a risk factor and the proportion of cases of a disease that it may cause is known as the attributable risk. Determination of attributable risk requires that we know the prevalence of a particular risk factor in the population and the relative risk associated with that risk factor.[1] This so-called population attributable risk (PAR) is calculated according to the following formula: PAR = [prevalence ` relative risk] , {{(prevalence ` relative risk) - 1} + 1}. For example, a risk factor that is present in 20% of the population and that has an associated relative risk of 1.5 has an attributable risk of 0.09, or 9%; in other words, the presence of this risk factor explains 9% of the incidence of the disease in the population.

Common breast cancer risk factors and their associated relative risks, population prevalence, and attributable risks are presented in **Table 1**. Few breast cancer risk factors have a population prevalence more than 10% to 15%, although some (eg, mutated genes, cellular atypia) are associated with very large relative risks, making them important to consider in the clinical
management of breast cancer risk. Traits associated with large relative risks are rare; common risk factors are associated with relative risks less than 2.0 so that the attributable risk for any particular risk factor is small, as shown in Table 1.

In addition, because many women possess multiple risk factors for breast cancer and because of the epidemiologic confounding that may occur in evaluating both relative and attributable risks, it may not be possible to add up the known attributable risks to obtain a summary attributable risk. If the risk factors were independent and there were no interactions among them affecting the respective levels of risk associated with the individuals factors, the summary attributable risk would be as expressed according to the following formula: summary attributable risk = 1 - [P - (1 - PARi)], where P denotes the product of all individual risk terms; i, each specific risk factor included (ie, eight risk factors in Table 1); and PAR, population attributable risk.

Attributable risk does not establish causality, and it is clear that nearly half the attributable risk for breast cancer remains unexplained.[2] Nevertheless, it is instructive to examine briefly what is known about established risk factors for breast cancer.

**Established Risk Factors**

**Age**

All women are at risk for breast cancer, and the most important single risk factor is age. The risk of breast cancer increases throughout a woman's lifetime, and the annual incidence of breast cancer in US women 80 to 85 years old is 15 times higher than that in women 30 to 35 years old.[3] We do not yet know whether these observed differences are explained by the accumulation of a number of events that occur throughout a woman's lifetime or by a single event triggered with greater frequency in older than in younger women.

Race and ethnicity modify the effect of age on breast cancer risk. For example, African-American women under age 50 have a higher age-specific incidence of breast cancer than their white American counterparts, but older African-Americans have a lower age-specific incidence than older white Americans.[3] As yet, there is no adequate explanation for these differences. Furthermore, breast cancer incidence among Hispanic women living in North America is only 40% to 50% as great as that among non-Hispanic white women. Asian women born in Asia have an extremely low lifetime risk of breast cancer, but their daughters born in North America have the same lifetime risk of breast cancer as American white women.[4] No explanation, including dietary factors, yet accounts for these observed differences.

**Gynecologic Events**

Many breast cancer risk factors relate to gynecologic or endocrinologic events in a woman's life.[5-9] Both age at menarche and age at menopause are related to a woman's chance of developing breast cancer (Table 1). These data indicate that one way of expressing the risk of breast cancer in relation to gynecologic events is simply to count the number of ovulatory menstrual cycles that a woman experiences in her lifetime. Early menarche and late menopause lead to an increased total lifetime number of menstrual cycles and a corresponding 30% to 50% increase in breast cancer risk. Conversely, late menarche and early menopause lead to a reduction in breast cancer risk of similar magnitude. Consistent with this observation is the fact that oophorectomy before a woman reaches menopause (especially before age 40) lowers her risk of breast cancer by approximately two-thirds.[6]

Pregnancy at a young age, especially before age 20, markedly reduces the incidence of subsequent breast cancer.[6] Conversely, both nulliparity and age over 30 years at first live birth are associated with nearly a doubling of the risk of subsequent breast cancer.[10] Pregnancies not ending in the birth of a viable fetus do not reduce the risk of breast cancer.[10] For obvious technical, practical, and ethical reasons, there are no data from women that provide a histologic explanation for the protection from breast cancer afforded by an early pregnancy.

**Benign Breast Disease**

Symptomatic changes in the breast are observed quite commonly in clinical practice. Some studies show a correlation between risk factors for breast cancer and those for benign breast disease,[11] while other studies do not.[12] The latter studies raise the possibility that benign breast disease is not a precursor to breast cancer. Also, few benign lesions show amplification of the HER-2/neu oncogene or mutation of the p53 tumor-suppressor gene.[13]

Although there is some correlation between the presence of nodularity on physical examination and the appearance of the mammogram, benign breast disease is not more common in women with other risk factors for breast cancer, such as a family history of the disease. The signs and symptoms
of benign breast disease often resolve without treatment and usually do not require breast biopsy for definitive diagnosis; fewer than 20% of women in North America have undergone a biopsy for benign breast disease by age 50.[14] Benign breast disease that results in biopsy does increase the subsequent risk of developing breast cancer, however.[15]

**Proliferative vs Nonproliferative Disease**—Among women undergoing biopsy for benign breast disease, the risk of subsequent breast cancer is not uniform. The most informative classification scheme is based on histopathology: It divides benign disease into proliferative and nonproliferaive categories.[16] Proliferative disease includes lobular and ductal hyperplasia of the usual type; florid ductal or lobular hyperplasia; apocrine metaplasia, sclerosing adenosis, intraductal papilloma, and radial scar; and lobular or ductal hyperplasia with atypia. Nonproliferative lesions that do not increase risk include normal cysts, duct ectasia, mild hyperplasia, and fibroadenoma that has not been biopsied.

Proliferative disease accounts for between one fourth and one third of all biopsies for benign disease, and 5% to 10% of the proliferative lesions show cellular atypia, the histologic change associated with the highest risk.[16-20] The atypical features are similar to some found in carcinoma in situ. Greater use of mammographic screening has led to increased identification of women with proliferative breast lesions.[21] Although early classification schemes for benign disease did not include sclerosing adenosis among the lesions that increase risk, recent data indicate that sclerosing adenosis increases the risk of breast cancer by approximately 70%, which justifies its inclusion among proliferative disease without atypia.[22]

A family history of breast cancer in a first-degree relative (mother, sister, or daughter) has an additive effect with proliferative changes or atypia on the subsequent risk of breast cancer.[16,19,20] Although fewer than 5% of women whose biopsy shows no proliferative changes develop breast cancer over the ensuing 25 years, nearly 40% of women with a family history of breast cancer and atypical hyperplasia subsequently develop breast cancer. Biopsy before the age of 50 to 55 years may be associated with a fivefold to sixfold increase in the risk of breast cancer, whereas biopsy at an older age is associated with only half this risk.[15]

**Family History of Breast Cancer**

Genetic factors contribute to approximately 5% of all breast cancers but to 25% of cases diagnosed before 30 years of age.[23] Early-onset breast cancer is that which occurs before age 50, at which point there is a flattening in the rate of increase in the age-specific incidence rates. Risk can be quantified rapidly and simply by assessing the number and degree of a woman's relatives affected with breast cancer and their ages at diagnosis (Table 2). Women without a diagnosis of breast cancer who have increased pretest probabilities of carrying a BRCA1 mutation can be identified on the basis of the number of relatives diagnosed with breast cancer and their ages at diagnosis.[23-27]

Having more relatives diagnosed with breast cancer before age 50 increases the cumulative lifetime risk of developing the disease to near 50%, indicating the autosomal-dominant behavior of some syndromes of genetically predisposed breast cancer.

**BRCA1 Mutation**—Mutation of one gene, BRCA1, appears to account for 45% of families with a significantly high incidence of breast cancer and at least 80% of families with an increased incidence of both early-onset breast cancer and ovarian cancer.[28,29] BRCA1 is located on chromosome 17q and appears to encode a tumor-suppressor protein that acts as a negative regulator of tumor growth.[30-32]

The presence of a mutated BRCA1 gene with a resultant truncated protein has important clinical consequences, as shown in Table 3. The relative risk of breast cancer associated with a BRCA1 mutation is more than 200 in individuals under age 40 but drops to 15 in the seventh decade of life.[33] Penetrance of the phenotype in carriers of mutated genes is estimated to be 87% for breast cancer and 44% for ovarian cancer by age 70. There is also evidence of allelic heterogeneity, with 29% of BRCA1 mutations conferring a high risk of ovarian cancer and 71% conferring a moderate risk. If these observations hold true, the average lifetime risk of ovarian cancer in BRCA1 mutation carriers is approximately 40%. Moderate-Risk and High-Risk

Families—Young women with a diagnosis of breast cancer who have multiple affected relatives have a higher likelihood of being mutation carriers, and approximately 45% of families with increased susceptibility to breast cancer carry mutations of BRCA1.[28] Hoskins and colleagues divide these women into two groups [24]: The first group, those from moderate-risk families, are characterized by a "less striking" family history, an absence of ovarian cancer, and an older average age at diagnosis. High-risk families are generally typified by at least three cases of breast cancer in close relatives that follow an autosomal-dominant pattern. Available data show that one-fourth of families with three affected members diagnosed before age 60 and 60% of families with four or more affected
members show BRCA1 mutations. The presence of even one case of ovarian cancer in the family makes a BRCA1 mutation more likely, whereas a case of male breast cancer makes this mutation less likely.

Because BRCA1 is an autosomal gene, it can be carried and transmitted by men in the affected families, although the risk of breast cancer in the male carriers appears to be negligible. A second breast cancer gene, BRCA2, which localizes to chromosome 13, confers risks for breast and ovarian cancer in women similar to those conferred by BRCA1; unlike BRCA1, BRCA2 is associated with an increased risk of breast cancer in male carriers.

A description of the genetic evaluation of moderate- and high-risk families is beyond the scope of this review. The reader is referred to the appropriate quantitative models and reviews for guidance in this area.

Quantitative Risk Assessment

Some patients who have unique characteristics in their risk-factor profiles or well-characterized predisposition syndromes can be readily identified and referred to a either genetics counselor or an experienced clinician for thorough evaluation and management. Patients with the following risk factors should be considered candidates for referral:

- More than two first-degree relatives with breast, ovarian, or other cancers;
- Two or more generations affected;
- First-degree relatives with bilateral breast cancer;
- Multiple primary tumors, including breast and other sites;
- Early-onset cancer (younger than 45 years);
- Relatives with sarcomas, adrenocortical carcinomas, or other rare cancers;
- Relatives with ataxia-telangiectasia; and
- Relatives with a known mutation in a susceptibility gene.

A referral may also be appropriate for women considering prophylactic mastectomy or oophorectomy.

Having identified and appropriately referred women with a high likelihood of having a genetic syndrome or predisposition to breast cancer, the clinician can identify additional women who are at increased risk for breast cancer using individual risk factors one at a time. However, this approach does not permit one to combine risk factors, nor does it readily lend itself to calculating a woman's lifetime probability of developing breast cancer.

Multivariate risk models allow for the determination of composite relative risks for breast cancer along with a cumulative lifetime risk, adjusted both for all risk factors taken together and for competing causes of mortality. Risk is then expressed as the percentage chance that a woman will ever develop breast cancer. Published data are derived largely from studies of white women, and the generalizability of these data to other racial and ethnic groups is uncertain.

The Gail Model

A model developed by Gail and colleagues is a widely used method of quantifying a woman's risk of developing breast cancer. It is being used for risk evaluation in the Breast Cancer Prevention Trial, a clinical study aimed at determining the worth of tamoxifen (Nolvadex) in preventing breast cancer in women at increased risk. The model allows one to estimate the likelihood that a woman of a given age with certain risk factors will develop breast cancer over a specified time interval.

The model was derived using 4,496 matched pairs of breast cancer cases and controls from the Breast Cancer Detection and Demonstration Project, a mammography screening project carried out between 1973 and 1980, which involved more than 280,000 women. Using logistic regression techniques, Gail and colleagues examined a number of possible risk factors for breast cancer, among them, the use of various medications, including hormones; cigarette smoking and alcohol consumption; height; gynecologic history, including a woman's ages at menarche and first childbirth; history of breast biopsy; and family history of breast cancer in first-degree relatives. The risk factors were adjusted simultaneously for the presence of the other risk factors, and only five factors were shown to be significant predictors of the lifetime risk of breast cancer: current age; age at menarche; number of breast biopsies; age at first live birth; and family history of breast cancer in first-degree relatives.

Each risk factor is grouped into categories, as shown in Table 4, and the procedure to determine a
Assessing Women's Potential Risk of Developing Breast Cancer
Published on OBGYN.Net (http://www.obgyn.net)

woman's risk is straightforward. Age at menarche is considered alone, and its associated relative risk is obtained from the table. Next, a woman's age and the number of breast biopsies (incisional, excisional, or fine-needle aspirations but not cyst aspirations) for benign breast disease are then considered together, and a second relative risk is derived from the table. A breast biopsy showing atypical hyperplasia doubles the risk estimate shown in the table. To obtain the final relative risk for the model, a woman's age at first live birth is considered together with the number of first-degree relatives with breast cancer. To obtain a summary relative risk, these three relative risks are multiplied together (see sample calculation shown in Table 5).

Lifetime Probabilities of Developing Breast Cancer—A lifetime relative risk of developing breast cancer denotes the chance that a given woman will develop the disease compared with a woman of the same age who does not have any of her risk factors. A relative risk is not very useful for providing information about an individual's risk of breast cancer, however. Recognizing this, Gail and colleagues calculated lifetime probabilities of developing breast cancer with a given relative risk and adjusting for competing causes of death. (A woman cannot develop breast cancer if she first dies of another disease.) These probabilities are listed in Table 6, which contains estimates of developing breast cancer during 10, 20, or 30 years of follow-up.

Table 6 shows an "initial relative risk" and a "later relative risk." The initial relative risk corresponds to the initial age, ie, the woman's age at evaluation. If the initial age is less than 50 years and the initial age plus the specified follow-up is more than 50, a later relative risk at age 50 should also be specified. If the initial age is 50 or more, only the initial relative risk is required. For example, the hypothetical 45-year-old woman illustrated in Table 5 has an initial relative risk of 5.0, but she becomes older than 50 years during the first follow-up interval of 10 years, indicating that we must calculate a later relative risk. From Table 4, we see that the associated relative risk for a woman older than 50 years with one biopsy is 2.77. The later relative risk then becomes 1.099 ’ 1.273 ’ 2.756 = 3.85.

The probabilities in Table 6 are approximations, at best. For our 45-year-old patient, we begin in the initial relative risk column labeled 5.0. Looking down the column to the line that corresponds to an initial age of 40 years and 10 years of follow-up, we find that her 10-year probability of developing breast cancer is 6.1%. For 20 years of follow-up, we have calculated a later relative risk of 3.85, which is between 2.0 and 5.0. The 20-year probability of breast cancer with an initial relative risk of 5.0 and a later relative risk of 2.0 is 8.9%, and that for an initial relative risk of 5.0 and a later relative risk of 3.8 is 13.1%. Therefore, this woman's 20-year probability of developing breast cancer is approximately 12%. Finally, her 30-year probability of developing breast cancer is between 11.9% and 20%, or about 17%.

Some clinicians may find the use of Table 6, with its required interpolations and estimations, to be overly cumbersome. Gail and colleagues have addressed this problem through the use of graphical methods to estimate absolute risks of developing breast cancer once a relative risk is calculated using the model.[39] The published graphs simplify the task of calculating the probability of developing breast cancer, and the estimates derived from the graphs correlate closely with the calculations derived using the tables.

Limitations of the Model—There are limitations to the use of the Gail model. Investigators who have attempted to validate the model found that it overpredicted absolute breast cancer risk by 33% among women 25 to 61 years old who did not receive annual mammographic screening.[40] Most of the overprediction was confined to premenopausal women who do not adhere to guidelines for annual screening[41] and women with extensive family histories of breast cancer in whom other risk models may be more appropriate.

Critics of the Gail model also suggest that there are ethical questions regarding the value of individual breast cancer risk prediction in the absence of safe and effective preventive regimens. Conversely, it may be unethical to withhold counseling from women who overestimate their risk and live with inappropriate anxiety or elect unnecessary procedures, such as prophylactic mastectomy.

Alternative Models

Alternatives to the Gail model are available. The most useful of these models was developed by Claus and colleagues using case-control methodology applied to data from the Cancer and Steroid Hormone Study conducted by the Centers for Disease Control.[26] This model offers the advantage of counting the number of first- or second-degree relatives affected with breast cancer and considering their ages at diagnosis. Both of these factors are known to affect a woman's risk of developing breast cancer and are not considered in the Gail model.

Using the tables published by Claus et al, it is possible to estimate either the cumulative probability that a woman with a given risk profile will develop breast cancer by a given age, or, similarly, the
probability that a woman will develop the disease between her current age and a given age attained in the future. These probabilities can be adjusted further based on the ages at diagnosis of the affected first- and second-degree relatives. This approach allows for the incorporation of data not available when one uses the Gail model, which considers only affected first-degree relatives.

Management of High-Risk Women

All women in whom quantitative risk assessment is performed should undergo counseling. Counseling is necessary to educate these patients about risk, assess and manage anxiety and other psychopathology, and review clinical management options.[42,43] Management options for women who are at increased risk include mammographic screening, prophylactic mastectomy, and participation in investigational chemoprevention trials.

Annual Mammographic Screening

If a woman is older than 30 years of age and her estimated odds ratio for developing breast cancer is 5 or greater, consideration can be given to initiating annual mammographic screening. This strategy is based on the assumption that the positive predictive value of a screening mammogram in a 30-year-old woman with a fivefold increase in risk should be identical to the positive predictive value of a screening mammogram in a 40-year-old woman at usual risk.[42] It should be recognized that this strategy has not yet been validated in a prospective clinical trial, however.

Prophylactic Mastectomy

Some women may desire to use the projected probabilities of developing breast cancer to assist them in making decisions about prophylactic mastectomy. The optimal time to provide risk quantification and assessment may be at the time of diagnosis in an affected relative when the unaffected woman is most concerned about her risk. Because women tend to overestimate their risk by an order of magnitude or more[44], the use of quantitative risk assessment can help the patient arrive at an informed decision.

Some women undergoing quantitative risk assessment will be identified as having a high pretest probability of carrying a mutation in the BRCA1 gene. Such a woman should be referred for counseling and consideration of genetic testing before a decision is made about prophylactic mastectomy if the woman agrees that a negative test would provide a strong argument against having prophylactic surgery.

Clinical Prevention Trials

Women at increased risk should be encouraged to enter clinical prevention trials studying tamoxifen, dietary fat reduction, luteinizing hormone-releasing hormone agonists, retinoids, or other preventive strategies. Information obtained in quantitative risk assessment can also be used as a component of a decision strategy to evaluate the relative risks and benefits of taking estrogen replacement therapy after menopause either for the relief of symptoms or to manage the risks of heart disease and osteoporosis.

Psychological Issues

Any valid estimate of a woman's lifetime probability of developing breast cancer can be used for counseling purposes and for making decisions about clinical management of risk. Positive recommendations should accompany clear messages about risk management, emphasizing that risk calculations should be used only to estimate the probability of developing the disease and not the risk of dying of breast cancer.[24] Previous research suggests that quantifying risk without providing a management plan may have unwanted psychological effects.[45] Because a substantial proportion of women who have abnormal mammograms but not cancer report significant impairments in mood and daily functioning[46,47] and may have clinically elevated levels of psychological distress,[48] mammographic screening encounters may be the ideal time to offer risk assessment and counseling. Although our preliminary studies showed a greater likelihood of having prior mammograms among women with higher self-perceived risks of breast cancer, [49] psychological distress may interfere with adherence to recommended breast screening[47,48,50-52] or other preventive behaviors. More research is needed to define at what level risk perception becomes inhibitory rather than motivating. Because of these recognized concerns about psychological issues, it is important to explore a woman's fears about breast cancer, and the clinician should ask each patient if her worries about breast cancer impede her daily functioning. If simple reassurance and encouragement do not relieve anxiety or the patient cannot participate in making clinical decisions because of her anxiety, psychological consultation is warranted.

Conclusions
Quantitative risk assessment is a practical tool that can now be regarded as a valuable adjunct in managing the risk of breast cancer. Risk assessment is the starting point for counseling women about risk, and it facilitates rational decision-making about prophylactic surgery, initiation of screening at an early age, and designing preventive interventions. The availability of published tables and graphs permits rapid risk calculation during routine clinical encounters, and risk profiles can be easily updated at subsequent clinical visits. Clinicians can now incorporate risk assessments into their routine screening and health maintenance appointments. Over time, this process permits risk profiling for entire populations at risk, allowing for planning and resource allocation. Additional prospective clinical evaluations should be conducted to define the optimal use of existing instruments, develop refined instruments that incorporate additional risk-factor information, and evaluate populations for whom validated risk-assessment instruments do not yet exist.

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