Estimating the Long-Term Probability of Developing Breast Cancer

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Public awareness of breast cancer risk has increased during the 1980s, in part because of publicity highlighting recent increases in incidence rates and the occurrence of breast cancer in numerous public figures. This publicity, coupled with a trend toward increased patient participation in medical decision making, has led many women to seek information about their individual risks of developing breast cancer. Relative risk estimates for various individual risk factors are readily available from epidemiologic studies (1), but few authors have reported risks for combinations of factors. Even fewer have reported results in terms of the probability of disease occurrence, a form more easily interpretable by most patients. Geneticists have estimated the probability that a first-degree relative of a patient with breast cancer will also develop breast cancer (2,3). While a family history of breast cancer is a major risk factor, a recent genetic analysis of more than 200 families with bilateral breast cancer suggested the presence of important nongenetic risk factors as well (4), consistent with previous epidemiologic results. Obesity and the use of exogenous hormones are examples of modifiable factors that may affect lifetime breast cancer risk beyond an inherited predisposition.

Information regarding the absolute risk of breast cancer in the presence of combinations of both familial and environmental risk factors would permit physician and patient to make more informed cost-benefit decisions regarding screening schedules and other preventive measures. The ultimate preventive measure, prophylactic mastectomy, has been suggested most often for women with major risk indicators, such as the diagnosis of lobular neoplasia or a history of bilateral breast cancer in a premenopausal first-degree relative. The literature provides little guidance, however, in the more common situation of multiple moderate-level risk factors, which may or may not justify consideration of prophylactic mastectomy.

In this issue Gail et al. (5) present the results of an analysis of 2,852 white patients with breast cancer and 3,146 white controls who participated in the Breast Cancer Detection Demonstration Project (BCDDP). Using a model-based approach, they estimated long-term probabilities that a woman with a specified combination of risk factors would develop breast cancer. Important risk factors identified included age (<50 yr or ≥50 yr), age at menarche, age at first live birth, the number of previous breast biopsies, and the number of first-degree relatives with breast cancer. The tables in this article provide projected probabilities of developing breast cancer within 10, 20, or 30 years following an initial mammogram for combinations of initial age and relative risk.

How do these risk estimates compare with previously published data? The univariate relative risks presented for age at menarche and age at first live birth are consistent with those of other studies (1). These factors, along with age at menopause, determine an individual's "breast tissue age," which Pike et al. (6,7) found could accurately predict age-specific breast cancer incidence rates in both the United States and Japan. A recent extension of Pike's model to include parity and body mass index accurately predicted individuals' breast cancer risk as well (8).

The relative risk reported by Gail et al. (5) for having a mother and/or sister with breast cancer also appears similar to that reported in other studies (1,9). However, the failure of the authors to find an effect of menopausal status or bilaterality conflicts with most reports (2,3,7) but may be a result of the small numbers of BCDDP relatives reported to have premenopausal bilateral breast cancer (10). The interpretation of the predictive significance of the number of previous breast biopsies found by Gail et al. (5) is problematic, since biopsies are recommended more often in women with known preexisting risk factors for breast cancer. Even more puzzling is their failure to include postmenopausal estrogen use and moderate alcohol consumption in the model because of "limited numbers," even though they "appear to increase risk" in the BCDDP data. For example, the percentage of BCDDP women consuming one or more alcoholic drinks per day was reported to be 12%-15% (11), far greater than the proportion reporting multiple occurrences of breast cancer among first-degree relatives, a factor that was included in the model (10).

Gail et al. (5) used a combination of the estimated relative risks, baseline hazard rates by age, and an adjustment for competing risks to calculate probabilities of the future development of breast cancer from a large population of women being regularly screened for breast cancer. The few previously published studies providing probability estimates have focused on the familial risk of breast cancer. These analyses applied life-table methods to highly selected families with either multiple occurrences of breast cancer (9) or bilateral, premenopausal breast cancer (3) or extrapolated from relative to absolute risks by using tumor registry rates (12). None of these genetic studies incorporated nongenetic risk factors into the probability calculation.

At first glance, the probabilities of breast cancer occurrence presented in table 4 of the article by Gail et al. (5) seem unusually high, ranging to 72.8%, a figure much higher than even the 50% predicted for the daughter of a breast cancer

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patient if one assumes a purely autosomal dominant mode of inheritance. Reasons for these apparently high estimates might include (a) overestimates of the relative risks because of the self-selection of women into the BCDDP screening program, (b) overestimates of the baseline hazard rates by age, (c) the additional effects of the nongenetic risk factors included in the model, or (d) extrapolation of multiplicative risk estimates to levels of relative risk that are extremely rare. Of these reasons, the first is unlikely, since the relative risk estimates seem to be in line with case-control results even when analyzed in more detail than is presented here (13). Second, the baseline incidence rates from the BCDDP population are shown in table 3 to be twice those estimated from National Cancer Institute data for premenopausal ages, perhaps as a result of earlier detection of disease by periodic screening, as suggested by the authors. Third, the probabilities of breast cancer development presented here may be correctly higher than the estimates from genetic studies, which did not include additional risk factors. Finally, the probabilities over 50% shown in table 4 are predominantly for women with a relative risk of 30, a level that cannot be achieved by even the highest combination of factors from table 1. Thus, the highest probability estimates, while initially alarming, will be attained by few if any individuals.

The proportional hazards model used by Gail et al. (5) has significant advantages over life-table methods because it permits estimates of multifactorial risk adjusted for confounding factors. A stratified analysis can also provide multifactorial risk estimates, but it does not provide a measure of the statistical significance of each factor. We would thus expect that use of the proportional hazards model has led to more accurate probability estimates than those published previously, if one assumes that the model assumptions hold.

Even with an optimal modeling technique, estimation of absolute rates of breast cancer requires long-term follow-up of thousands of individuals. In addition, the assessment of multifactorial risks requires large numbers of subjects to ensure sufficient numbers of most combinations of risk factors. With the recent early demise of the Women’s Health Trial, the BCDDP follow-up study of 285,000 women may be the only available dataset from which one can reasonably estimate the probability of developing breast cancer. How will these estimated probabilities be used? After assessment of a patient’s risk profile, knowledge of the future probability of developing breast cancer can assist both patient and clinician in deciding the best plan for follow-up. For women of low or average risk, recommendation of regular mammograms following the American Cancer Society’s or the National Cancer Institute’s guidelines is in order. Options for high-risk women are currently limited to more frequent examinations and prophylactic mastectomy, although recommendations might also include advice on oral contraceptive or postmenopausal estrogen use. The tables presented in the article by Gail et al. in this issue can be useful in quantifying the degree of change in risk attainable by possible modifications of these factors. However, quantification of risk must go hand in hand with a cost-benefit assessment. To become clinically useful, the publication of this risk assessment system calls for the timely specification of what probability level is sufficiently high to justify the extreme recommendation of prophylactic mastectomy.

With each advance in the science of risk analysis, pressure is generated to expand the range of interventions that prevent cancer and help the individual deal with the enhanced perception of risk. For example, if a 40-year-old woman is to be informed that her chances of developing breast cancer are 20% in the next 30 years, surely there is a need to offer something more protective than regular screening but less extreme than prophylactic mastectomy. In this regard, the risk projection system described by Gail et al. can potentially be of service in planning intervention trials designed to reduce breast cancer incidence. The utility of this article in study planning will depend on whether risk factors included in the model are related to the planned intervention. For this reason, it is unfortunate that the authors chose not to include factors such as alcohol and exogenous hormone use, which have a profound impact on the biochemical profile of the individual. It would seem that the risk model presented here is particularly suitable for planning studies based on endogenous hormone and familial factors.

It is often noted that about 75% of breast cancers occur in women who have no known risk factors; nevertheless, the study of preventive interventions in high-risk women is more likely to lead to the timely demonstration of desirable interventions. To the extent that this model will promote the use of breast screening services and facilitate research in breast cancer prevention, the results of Gail and colleagues represent a major step toward achieving breast cancer control.

References