Assessing Breast Cancer Risk: Evolution of the Gail Model

Melissa L. Bondy, Lisa A. Newman

This issue of the Journal contains two articles refining and advancing the breast cancer risk assessment model known as the Gail Model (1). This model has been shown to be well calibrated with respect to predicting the number of cancers likely to develop within cohorts of white American women with specific risk factors (2–4). As needs of the chemoprevention trials (for determining eligibility) and clinicians (in counseling patients) have grown, the Gail Model has been modified to account for history of atypia and race or ethnicity, but until now it has included only non-modifiable risk factors (i.e., age, reproductive history, and biopsy history). It is readily available to practitioners as a user-friendly program (http://bcra.nci.nih.gov/brc/start.htm).

Chen et al. (5) modified the Gail Model to estimate the absolute risk of invasive breast cancer on the basis of breast density, weight, age at birth of first live child, and the number of first-degree relatives with breast cancer. The Breast Cancer Detection and Demonstration Project (BCDDP) served as the dataset for the model of Chen et al. and the original Gail Model (1). For the current model, women who developed breast cancer, had a biopsy, or were recommended for biopsy and a subset of women remaining normal during the screening phase were followed through December 31, 1995. Breast density measurements for 7200 women were obtained from baseline mammograms from the screening phase of the BCDDP (1973–1979).

The importance of breast density as an indicator of breast cancer risk is emphasized in the more ethnically diverse multi-institutional study by Barlow et al. (6). They used prospective data from the Breast Cancer Surveillance Consortium (BCSC) to evaluate risk in a cohort of more than 1 million women undergoing screening mammography. They constructed separate risk models for pre- and postmenopausal women. Risk factors for premenopausal women were age, breast density, family history of breast cancer, and a prior breast procedure. Risk factors for postmenopausal women were age, breast density, race or ethnicity, family history of breast cancer, a prior breast procedure, body mass index, natural menopause, hormone therapy, and a prior false-positive mammogram. This model is more complex than the conventional Gail Model, but key findings are related to the inclusion of risk factors that are amenable to modification (body mass index, hormone therapy, and possibly breast density) and reinforcement of the message of Chen et al. (5) that breast density is a strong predictor of breast cancer risk. The rich BCSC dataset would serve as an excellent source of validation for the revised model described by Chen et al. (5).

Suggested modifications of the Gail Model are in no way a criticism of its aims or rejection of its approach. Rather, they demonstrate ongoing collaborative efforts of oncologists, epidemiologists, and biostatisticians to introduce chemoprevention into clinical practice as a viable and safe option for high-risk women. Gail et al. embarked upon their biostatistical journey with great care, thoughtfulness, and respect for the women who did or did not have representation in the BCDDP study, and for these reasons Gail et al. have been quite specific about the primary applicability of their model to white women undergoing screening mammography. Studies of the Gail Model’s accuracy in multiethnic populations thus far have been preliminary and speculative in nature (7–9). Current efforts to incorporate breast density into the Gail Model offer tripartite benefits: 1) breast density appears to represent a truly individualized risk factor that increases the discriminatory accuracy of prediction models to more than 0.6 (5,6), 2) breast density may be more uniformly predictive of breast cancer risk in multiethnic populations (10,11), and 3) breast density may also represent a modifiable risk factor that can monitor responsiveness to lifestyle and/or medical prevention strategies. Interestingly, in both studies, breast density was more predictive of risk than family history of breast cancer, despite the fact that two different measures of breast density were used.

In its present form, the calibration strength of the Gail Model substantiates the fulfillment of its goal to identify cohorts of high-risk patients who are appropriate participants for chemoprevention trials. However, the diagnostic accuracy of the Gail Model at 0.5–0.6 suggests that it is only slightly better than chance in generating a higher risk estimate for a woman with versus without a diagnosis of breast cancer (12). Furthermore, the medical community has defaulted to generalizing the Gail Model, the best available risk prediction model for white women, to women of all racial or ethnic backgrounds. Although the model is quite valuable for defining chemoprevention trial eligibility, it is somewhat less able to assist in counseling the individual patient who visits a clinician’s office and desires advice regarding whether she should face the morbidity of a chemoprevention medication. Risk assessment that uses an anatomic-based or tissue-based biomarker would be a more rational tool, but the ability to retrieve evaluable tissue from the general population is an obvious obstacle. Assessment of an individual woman’s breast density may be the next-best option, as shown by Chen et al. and by Barlow et al.

Despite the potential for breast density to improve the precision of the Gail Model, it is incumbent upon the medical community to consider the feasibility of its widespread use by looking at contemporary mammography-reporting practices. Mammography facilities in the United States are accredited through the Food and Drug Administration through their adherence to the Mammography Quality Standards Act (MQSA) of 1994. MQSA inspections monitor mammogram reports to ensure presentation of clear, final impressions as “negative,” “benign,” “probably benign,” “suspicious,” or “highly suggestive of malignancy.” MQSA descriptors correlate with the numbered categories as defined by the American College of Radiology (ACR)
in the Breast Imaging Reporting and Data System (BI-RADS). The ACR has also developed the following set of fibroglandular density descriptors that may be used within the text of a mammogram report: “almost entirely fat” (<25% density), “scattered fibroglandular densities” (25%–50%), “heterogeneously dense” (51%–75%), and “extremely dense” (>75%). The prospective clinical trial of digital versus film-screen mammograms (13) found that breast density is a useful indicator of women that benefit from digital mammography, and this result has motivated many mammographers to routinely incorporate the BI-RADS density descriptors into their reports. However, it must be noted that mammography facilities currently have no MQSA mandate to include breast density into their reporting mechanism. Furthermore, one meta-analysis of breast density and breast cancer risk (10) found that the correlation is strongest when density is reported as percentage density as opposed to qualitative categories, such as the BI-RADS descriptors. Barlow et al. used the ACR descriptors to stratify breast density; however, Chen et al. used a five-category stratification of percentage density measurements. Standardization of breast density reporting must be achieved before breast density can be adapted into a clinically useful risk assessment model.

Inclusion of breast density, and perhaps other modifiable risk factors, is indeed exciting in the ongoing evolution of breast cancer prediction tools and our quest for accurate, individualized estimates. However, we must continue to exercise caution with these adjustments; a perfectly predictive model will be of minimal value if its component factors are unavailable, misunderstood, or inappropriately assigned.

REFERENCES


