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EDITORIALS

Comparing Breast Cancer Risk Assessment Models

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In this issue of the Journal, Amir et al. (1) review models for estimating the probability of carrying a mutation in the *BRCA1* or *BRCA2* genes and models for estimating the risk of developing breast cancer. The aim of the review was "to distill the diverse literature and provide practicing clinicians with an overview of the available risk assessment methods." The authors have provided a useful survey of the literature and have presented an informative summary of the risk factors used in various models. A careful reading of the article and its references can promote the proper use of these models. We are concerned, however, that some readers will skip the details and rely mainly on the flowcharts in figures 2 and 3 in Amir et al. (1), which, in our opinion, may be misleading.

Amir et al. (1) categorize models that estimate the probability of carrying a mutation as "empirical models" or "genetic risk models." Examples of empirical models are Myriad II (2), which was derived from 10 000 samples, and the Manchester model (3). Genetic risk models assume a pattern of genetic inheritance of breast cancer risk. For example, the BRCAPRO model assumes that excess risk is conferred only by carrying an autosomal dominant mutation in *BRCA1* or *BRCA2* (4,5). The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model (6) includes a polygene, which allows for familial correlation that is not captured by mutations in *BRCA1* or *BRCA2*. The International Breast Cancer Intervention Study (IBIS) model (7) accommodates such residual familial correlation by incorporating a latent common autosomal dominant gene that confers low risk.

A study in the United Kingdom (8) compared the performance of BOADICEA, BRCAPRO, and IBIS for predicting the likelihood of carrying a *BRCA1* or *BRCA2* mutation. Such a model is said to be "well calibrated" if the observed number of mutations in a given risk category is close to the number of mutations predicted by the model. BOADICEA was well calibrated overall, with 358.6 mutations expected and 365 mutations observed. BRCAPRO overestimated the number of mutations overall (expected number of mutations was 399.3 [$P = .086$] or 468.4 [$P < 3 \times 10^{-5}$] depending on assumed mutation frequencies), and IBIS underestimated the number of mutations (expected number was 301.1 [$P < 3 \times 10^{-4}$]). All of these models, but especially BRCAPRO and IBIS, underestimated the number of observed mutations among subjects who were classified as having a mutation carrier probability below 10%. For example, IBIS predicted 20.1 mutation carriers below this probability threshold, whereas 72 were observed. This finding is troubling because 10% is often taken as the threshold above which mutation testing is recommended [figure 2 in (1)].

Discriminatory accuracy, measured as the area under the receiver operating characteristic curve (AUC), is another performance criterion that was compared in the UK study. For predicting mutation status, the AUC values for BOADICEA, BRCAPRO, IBIS, Myriad II, and the Manchester model were 0.77, 0.76, 0.74, 0.75, and 0.72, respectively (8). In commenting on the flowchart in figure 2, Amir et al. (1) warn that one must think carefully about the patient population when applying the 10% risk threshold for mutation testing. One should also think critically before applying the 1.67% 5-year risk [figure 2 in (1)] to initiate preventive interventions. For example, a young (<50-year-old) woman with a 1.67% risk stands to benefit from tamoxifen, whereas a woman in her sixties needs a higher breast cancer risk to outweigh the adverse risks of stroke, pulmonary emboli, and endometrial cancer that are associated with tamoxifen chemoprevention (9).

Amir et al. (1) describe the risk factors that are used in various models for predicting breast cancer risk [table 1 in (1)]. Other differences among these models are also important (Table 1). The National Cancer Institute's Breast Cancer Risk Assessment Tool is abbreviated as BCRAT in Table 1. The model for white women in BCRAT is otherwise known as "Gail model 2" (10), which was used in the validation studies in Table 1. Some models, such as BCRAT, are calibrated to breast cancer rates in the United States, whereas others are calibrated to rates in England and Wales; 5-year age-specific rates in England and Wales are 5%–25% lower than those in the United States for women older than 55 years. Some models predict the risk of invasive breast cancer and ductal carcinoma in situ (DCIS) combined, whereas others predict only the risk of invasive breast cancer (Table 1). In the United States in 2000–2004, DCIS accounted for 18% of diagnoses in women older than 49 years and for 22% of diagnoses in younger women (16). It may be appropriate to exclude some women from risk projections with a particular model. For example, BCRAT does not make a risk projection for women with a history of lobular carcinoma in situ (LCIS) (see http://www.cancer.gov/bcrisktool/); instead, the high rate of 6.5% has been recommended as the projected 5-year risk of invasive breast cancer (9), based on data from the Breast Cancer Prevention Trial (17). Unlike the other models in Table 1, BCRAT accounts for competing mortality from non–breast cancer causes, which reduces the absolute risk of breast cancer, especially over long prediction intervals. These differences can be important in deciding which model to use and in interpreting studies to assess model validity.

Many practitioners counsel women who have few risk factors for breast cancer as well as women with strong family histories. Although the title of the review by Amir et al. (1) highlights "women at high risk of breast cancer," the flowchart in figure 3 of the review includes model recommendations for women with no

Table 1. Features of models for projecting breast cancer risk*

Model (reference)	Calibrated to	Breast cancer outcome predicted	Conditions that preclude use of model (exclusions)	Accounts for competing risks of mortality other than breast cancer	References for studies done to assess model calibration	
					General population	High-risk clinic
BCRAT (10)	US SEER	Invasive	LCIS	Yes	(10,11,12)	(13,14)
Claus (15)	US SEER	Invasive and DCIS†	No affected first-degree relatives	No	NA	(13)
BRCAPRO (4,5)	Meta-analysis for carriers (5); US SEER for noncarriers	Invasive for noncarriers	None	No	NA	(13)
BOADICEA (6)	England and Wales	Invasive	None	No	NA	(13)
IBIS (7)	England and Wales	Invasive and DCIS	None	No	NA	(13)

* BCRAT incorporates Gail model 2 (10). BCRAT = Breast Cancer Risk Assessment Tool; BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; DCIS = ductal carcinoma in situ; IBIS = International Breast Cancer Intervention Study; LCIS = lobular carcinoma in situ; NA = none available; SEER = Surveillance, Epidemiology, and End Results.

† DCIS was rare in this study, which accrued women with breast cancer from 1980 to 1982.

family history of breast or ovarian cancer. Unlike the other models in Table 1, only BCRAT has been assessed for calibration in general populations (Table 1). Data from the Nurses' Health Study (11) showed that BCRAT slightly underestimated invasive breast cancer risk (expected/observed = 1273.4/1354 = 0.94, 95% confidence interval [CI] = 0.89 to 0.99). However, BCRAT fit very well in women with a 5-year risk of invasive breast cancer of at least 1.67% (expected/observed = 622.7/601 = 1.04, 95% CI = 0.96 to 1.12). For women with a positive family history, the expected to observed ratio was 237.7/207 or 1.15 (95% CI = 1.00 to 1.32). Thus, BCRAT slightly overestimated risk in women at increased risk because of family history. Data from the placebo arm of the Breast Cancer Prevention Trial showed excellent overall calibration of BCRAT (10) (expected/observed = 159.0/155 = 1.03, 95% CI = 0.88 to 1.21). The fit was also good in women with a positive family history (expected/observed = 137.8/131 = 1.05, 95% CI = 0.89 to 1.25). In data from the Women's Health Initiative (12), BCRAT underestimated risk overall (expected/observed = 2562/3236 = 0.79, 95% CI = 0.76 to 0.82) but was better calibrated in women with a 5-year risk greater than 1.68% (expected/observed = 1494/1676 = 0.89, 95% CI = 0.85 to 0.94). Together, these large studies indicate good calibration of BCRAT in women at elevated risk and, except for the Women's Health Initiative data, good calibration in the general population, which most practitioners face.

In constructing the flowchart in figure 3, Amir et al. (1) appear to consider which risk factors are in the models and to rely on a few selected studies, such as that by Pankratz et al. (18), and especially on an article by Amir et al. (13) that compared BCRAT, the Claus model (15), BRCAPRO, and IBIS in 3150 women assessed in the Family History Clinic of South Manchester. All but 29 of the 3150 women had a family history of breast cancer. Only 64 incident breast cancers were observed in this comparatively small study. The expected/observed ratios for the BCRAT, Claus, BRCAPRO, and IBIS models were 0.69 (95% CI = 0.54 to 0.90), 0.76 (95% CI = 0.59 to 0.99), 0.66 (95% CI = 0.52 to 0.86), and 1.09 (95% CI = 0.85 to 1.41), respectively. Amir et al. (13) did not specify how many of these women had a history of LCIS; women with LCIS are not eligible for risk estimation by BCRAT, as discussed previously. Another small study in a high-risk clinic (14) indicated that BCRAT was adequately calibrated among women who were screened annually (expected/observed = 25.9/29 = 0.89, 95% CI = 0.62 to 1.28). Thus, four of the five validation studies in Table 1 indicate that BCRAT is adequately calibrated in women at elevated or high risk, and some of the discrepancy in Amir et al. (13) may be explained by inclusion of patients with a history of LCIS at study entry. In our opinion, the flowchart in figure 3 of Amir et al. (1) should only be regarded as a preliminary attempt to synthesize a complex literature and should not be used as a true guide to action. In fact, the lack of independent assessments of calibration of these models (Table 1) is a serious deficiency in the confirmatory research needed to show that these models yield reliable risk estimates. We strongly agree with Amir et al. (1) about the need for such calibration studies, which could provide data to support future guidelines.

In the meantime, how should the practitioner proceed? We believe that good calibration is the key requirement for using a particular risk assessment model to weigh the risks and benefits of an intervention (9,19–21) and to design intervention trials (17). BCRAT has been tested for calibration in general populations, in subgroups at elevated risk, and in high-risk clinic populations. Table 2 shows the 10-year risks and risks to age 80 years for various risk models and risk factor scenarios for a healthy 35-year-old woman. Among women with affected relatives, risk estimates tend to be higher for BCRAT and IBIS than for the other models and lowest for BCRAPRO. Euhus et al. (22) previously noted that the Claus model and BRCAPRO usually gave lower risk estimates than BCRAT in a high-risk clinic population. As the inconsistencies in Table 2 illustrate, all of these models cannot be well calibrated.

Even if BCRAT is adequately calibrated in many settings, some situations are not covered. For families with many affected members or members affected at early ages, it may be informative to try several risk assessment models. If a woman comes from a family that is known to have a *BRAC1* or *BRCA2* mutation, models such as BOADICEA, BRCAPRO, or IBIS are preferred. If the

Table 2. Breast cancer risks (%) estimated from five models for 16 scenarios for a healthy 35-year-old woman with menarche at age 11 years, first live birth at age 25 years, no biopsies, and unknown atypical hyperplasia (AH) status unless otherwise indicated*

Number of affected first-degree relatives†	Age(s) at breast cancer onset in relative(s)‡ and/or other characteristics of the patient	BCRAT	Claus	BRCAPRO	BOADICEA	IBIS
0	No special features	1.0, 10.7	N/A	0.9, 11.1	0.8, 8.7	0.9, 9.6
0	1 biopsy	1.7, 14.2	N/A	0.9, 11.1	0.8, 8.7	0.9, 9.6
0	1 biopsy with AH	3.2, 24.2	N/A	0.9, 11.1	0.8, 8.7	3.7, 33.6
0	LCIS	N/A	N/A	0.9, 11.2	0.8, 8.7	7.2, 55.8
1	60 y	1.8, 18.2	0.9, 9.2	0.9, 11.3	1.5, 13.4	1.9, 18.8
1	60 y; LCIS	N/A	0.9, 9.2	0.9, 11.3	1.5, 13.4	14.2, 81.2
1	30 y	1.8, 18.2	2.1, 15.5	1.2, 12.1	2.0, 16.2	2.5, 20.2
1	40 y	1.8, 18.2	1.6, 12.5	1.1, 11.7	1.9, 15.4	2.2, 19.6
1	60 y; 1 biopsy	3.1, 23.8	0.9, 9.2	0.9, 11.3	1.5, 13.4	1.9, 18.8
2	40 y, 60 y	3.2, 30.0	3.6, 22.9	1.3, 12.6	3.2, 21.5	2.7, 24.2
2	40 y, 60 y; 1 biopsy	5.4, 38.0	3.6, 22.9	1.3, 12.6	3.2, 21.5	2.7, 24.2
2	40 y, 60 y; 1 biopsy with AH	9.6, 57.5	3.6, 22.9	1.3, 12.6	3.2, 21.5	10.5, 66.9
3	40 y, 50 y, 60 y	3.2, 30.0	4.6, 28.0	2.5, 16.1	4.8, 28.3	3.4, 27.0
3	30 y, 40 y, 50 y; 1 biopsy	3.2, 30.0	6.5, 37.4	5.2, 24.4	6.6, 33.0	8.4, 34.8
3	40 y, 50 y, 60 y; 1 biopsy	5.4, 38.0	4.6, 28.0	2.5, 16.1	4.8, 28.3	3.4, 27.0
3	40 y, 50 y, 60 y; 1 biopsy with AH	9.6, 57.5	4.6, 28.0	2.5, 16.1	4.8, 28.3	12.7, 71.7

* The left number is the projected risk to age 45 years, and the right number is the projected risk to age 80 years. BCRAT incorporates Gail model 2 (10). BCRAT = Breast Cancer Risk Assessment Tool; BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; IBIS = International Breast Cancer Intervention Study; LCIS = lobular carcinoma in situ; N/A = not applicable.

† For no affected first-degree relatives and for one affected first-degree relative, the pedigree includes the mother and the proband. For two affected first-degree relatives, the pedigree includes the mother, sister, and the proband. For three affected first-degree relatives, the pedigree includes the mother, two sisters, and the proband. These pedigree structures are held constant as other risk factors, including ages at breast cancer onset, vary in the table.

‡ The mother has the oldest age at onset in all scenarios with affected relatives.

counselee is known to carry a mutation, these models can be used to estimate her risk. If the woman has a genetic syndrome that predisposes her to breast cancer, such as the Cowden syndrome or the Li–Fraumeni syndrome, standard risk models are not applicable, and risk assessment should be based on the relevant literature. If a woman has had previous radiation for treatment of Hodgkin lymphoma, special methods for risk projection are needed (23). A history of LCIS in the counselee increases risk dramatically [(9,24); Table 2]. If a woman comes from a region such as rural China, where the risk of breast cancer is low, none of the models discussed by Amir et al. (1) will be well calibrated. Variations in breast cancer risk that can affect calibration are considerable even among Western countries. Ethnic and racial subgroups may have different risks, even within the same country. A woman who is not getting periodic mammograms has a lower age-specific risk of having a breast cancer diagnosis compared with a woman who is getting regular screening mammograms. If DCIS is counted as breast cancer, the risk of having a breast cancer diagnosis will be higher. Breast cancer rates can change over time, as indicated in a forthcoming report showing that BCRAT underestimated risk by about 13% in two US cohorts from about 1993 to 2002 but not from 2003 to 2006 (25). Thus, the practitioner needs to be aware of factors that affect calibration but are not in the model, and models should be updated to account for temporal trends.

Some applications, such as deciding who should receive screening mammography or allocating prevention resources to women at highest risk, require a risk assessment model with good discriminatory power (20,26). None of the models discussed by Amir et al. (1) has good discriminatory power, and the authors indicate possible ways to improve it. Promising directions include incorporating mammographic density, information on genotypes or regulation of gene expression [although initial studies have found only modest improvements in discriminatory accuracy from adding single-nucleotide polymorphisms to models (27–30)], and more refined use of pathology data and biomarker data from biopsy samples. Thus, continuing efforts are needed to improve and assess risk models so that they can play a useful role, in concert with preventive interventions, in reducing the burden of breast cancer.

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