I would like to thank the editors for the invitation to comment on “Projecting Individualized Probabilities of Developing Breast Cancer for White Females Who Are Being Examined Annually” (1) and to recognize coauthors of that article, Louise A. Brinton, David P. Byar, Donald K. Corle, Sylvan B. Green, Catherine Schairer, and John J. Mulvihill, who contributed key insights and analyses.

Several features may explain the frequent citations to this paper. 1) It focused on a clinically crucial quantity, absolute risk, namely the probability that a woman with specific risk factors will develop breast cancer over a defined age interval, with allowance for competing risks. 2) Breast cancer is a common cancer for which preventive interventions have been developed. Risk models are most useful in connection with interventions because the absolute risk of breast cancer can be compared with that of other health outcomes in the presence and absence of intervention. 3) The model is simple: only age and answers to five questions about reproductive, family, and medical history are needed. 4) The model (sometimes called the “Gail model”) has been taken up by practitioners and is available at [http://www.cancer.gov/bcrisktool/](http://www.cancer.gov/bcrisktool/) as the National Cancer Institute’s (NCI’s) Breast Cancer Risk Assessment Tool (BCRAT). Currently this site is visited over three million times a year. I shall elaborate on the first two points, mention alternative models, and discuss prospects for improving risk models and other applications of absolute risk.

**Absolute Risk**

Absolute risk is the probability that a woman with specific risk factors but without breast cancer at age \( a \) will be diagnosed with breast cancer in the age interval \( a < T \leq a + \tau \), where \( \tau \) is the duration of the risk projection interval. Consider a 40-year-old white woman who began menstruating at age 12 years, whose first live birth was at age 25 years, who has had no biopsies, and whose mother developed breast cancer. From BCRAT, her absolute risk of breast cancer in five years is 1.1% and her risk to age 90 years (“lifetime risk”) is 18.8%. In contrast, the average absolute risk for a 40-year-old white woman in the NCI’s Surveillance, Epidemiology and End Results (SEER) Program are, respectively, 0.6% and 12.4%. These absolute risk estimates are reduced by the chance that the woman might die from a competing cause of mortality before breast cancer develops. In the competing risks literature, the terms “crude risk” (2) and “cumulative incidence” (3) are sometimes used instead of absolute risk.

Absolute risk is not the same as the “pure” cumulative risk that is often used for risk models, such as genetic models of breast cancer risk (4,5). Pure risk is the hypothetical risk of developing breast cancer over a defined time interval if there were no competing causes of mortality. Pure risk is therefore higher than absolute risk. For example, based on SEER rates in white women from 2007 to 2011, the absolute risk to age 90 years is 12.28%, but the pure risk is 15.74%, which is 28% higher. For short projection intervals, such as five years, competing mortality typically has little effect and pure risks are only slightly higher than absolute risks. But for longer intervals, absolute risk is the relevant quantity, because in fact women are subject to competing mortality risk. One minus the Kaplan-Meier estimate of the probability of remaining breast cancer–free estimates pure risk. Special calculations (1,6) are needed to estimate absolute risk.

**Uses of Absolute Risk Models in Counseling and Public Health**

Risk models are used for counseling individual women and for developing and implementing public health prevention strategies.

**Counseling**

One of the most valuable uses of risk models is to give a woman a realistic risk estimate and perspective on how large this risk is in comparison with other risks. Indeed, BCRAT was initially
developed for this purpose. Dr. Mulvihill, one of the authors of the 1989 article, thought that many of the women he was advising in a high-risk breast cancer clinic had unrealistically high perceptions of risk that could lead to ill-advised procedures, such as prophylactic mastectomy.

Such perspective can also affect less drastic but nonetheless important management decisions. There has been disagreement over whether women in their forties should have routine mammographic screening. The American Cancer Society recommended it (7), whereas the US Preventive Services Task Force (USPSTF) wrote (8), “USPSTF recommends against routine screening mammography in women aged 40 to 49 years. The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into account patient context, including the patient’s values regarding specific benefits and harms.” This report disregarded risk assessment based on “demographic, physical, or historical risk factors,” stating that, “none conveys clinically important absolute increased risk for cancer” (8). Risk assessment can help women who are confused by these conflicting recommendations. Although age is the most important risk factor over wide age ranges, many women in their forties with elevated risk factors in BCRAT have higher risks than a 50-year-old woman without such risk factors. Gail and Rimer (9) and Gail and Schairer (10) argued that such women should consider screening, because they have a similar benefit-to-risk ratio as the 50-year-old women for whom screening mammography has been widely recommended. Indeed, 73.6% of non-Hispanic white US women in their forties and 30.9% of non-Hispanic black US women have risks above the 50-year-old baseline risk (11).

More formal risk-benefit analyses based on absolute risk can help a woman decide whether to take a preventive intervention, such as tamoxifen, that has both favorable and adverse health effects (12). These analyses require estimates of the absolute risks not only of breast cancer but also of the other events affected by the intervention, both in the presence and absence of the intervention. Suppose a 40-year-old woman has a projected five-year invasive breast cancer absolute risk of 2% and that she has a uterus. Table 1 presents the numbers of events of various types expected in five years in a population of 10 000 such women who do not take tamoxifen and who do take tamoxifen, as well as the numbers of various types of events that would be expected to be prevented (or caused if a minus number is shown) by tamoxifen. These calculations are based on the randomized placebo-controlled Breast Cancer Prevention Trial that estimated the various effects of tamoxifen (13). Among “life-threatening events,” tamoxifen is expected to reduce the number of invasive breast cancers by 97 and to eliminate one hip fracture but to cause an additional 16 endometrial cancers, 13 strokes, and 15 pulmonary emboli. Tamoxifen is also expected to reduce in situ breast cancers by 53 but to increase deep vein thrombosis by 15 (“serious events”). Overall tamoxifen is expected to eliminate 54 life-threatening events and 38 serious events. By assigning life-threatening events a weight of 1 and serious events a weight of 0.5, one can calculate a net benefit index of 54 +0.5 x 38 = 73, which favors the use of tamoxifen in this woman. Using this index, one can show that younger women with high breast cancer risk tend to benefit most (12). Moreover, there is no single five-year breast cancer risk threshold (such as ≥1.67% on the Food and Drug Administration indication label) above which tamoxifen has a net benefit. The required benefit threshold depends on the absolute risks of the other factors, such as stroke and endometrial cancer, which increase with age (12). A recent extension for women aged 50 years or older showed that raloxifene had a more favorable net benefit index profile than tamoxifen among women with a uterus, but a similar profile among women without a uterus (14).

### Public Health

Absolute risk models have several potential applications in public health. One is designing preventive intervention trials. For example, BCRAT was used to design the Breast Cancer Prevention Trial. The statistical power depends on the number of breast cancers that develop during the trial, which is proportional to the average absolute risk of trial participants. BCRAT accurately predicted the number of breast cancers that developed in the Breast Cancer Prevention Trial (13) and in the Study of Tamoxifen and Raloxifene Trial (15). Risk models are also useful for determining who has a high enough risk to be likely to benefit from the trial intervention and therefore be eligible for the trial. For example, women younger than 60 years old who have a projected five-year risk of at least 1.67% (the risk of an average 60-year-old woman) to enter the Breast Cancer Prevention Trial.

Another potential use of models of absolute risk is assessing the effects of a preventive intervention on absolute risk in the population. For example, Petracci and others (16) developed a model for absolute breast cancer risk in Italian women that included modifiable risk factors (alcohol consumption, lack of exercise, and body mass index [BMI] > 25 kg/m²) in addition to risk factors in BCRAT. Assuming that these modifiable factors could be set to baseline levels in the population and that the associations from observational studies would translate into absolute risk reductions, Petracci et al. calculated that the absolute 20-year risk among 55-year-old women would fall from 6.5% to 4.9%. This is a relative reduction of 24%, but the reduction in absolute risk is only 1.6%. (One should not forget, however, that a

### Table 1. Numbers of events expected in five years with and without tamoxifen in a population of 10 000 white 40-year-old women with uterus and with a projected breast cancer risk of 2%

<table>
<thead>
<tr>
<th>Health events</th>
<th>No tamoxifen</th>
<th>All get tamoxifen</th>
<th>Prevented by tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive breast cancer</td>
<td>200</td>
<td>103</td>
<td>97</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>10</td>
<td>26</td>
<td>-16</td>
</tr>
<tr>
<td>Stroke</td>
<td>22</td>
<td>35</td>
<td>-13</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>7</td>
<td>22</td>
<td>-15</td>
</tr>
<tr>
<td>Net life-threatening events</td>
<td>241</td>
<td>187</td>
<td>54</td>
</tr>
<tr>
<td>In situ breast cancer</td>
<td>106</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>24</td>
<td>39</td>
<td>-15</td>
</tr>
<tr>
<td>Net serious events</td>
<td>130</td>
<td>92</td>
<td>38</td>
</tr>
</tbody>
</table>

* A negative number means that tamoxifen increases the number of events.
1.6% reduction in absolute 20-year risk in one million women amounts to 16 000 breast cancers.) For women with a positive family history of breast cancer, the absolute risk is reduced from 13.7% to 10.5%, which is a relative reduction of 23% but a reduction in absolute risk of 3.2%. Epidemiologists often calculate the population attributable risk, which is a measure of relative risk reduction. As these examples illustrate, estimates of the reduction in absolute risk give a different perspective on the potential benefit of the intervention.

The four previously discussed applications of risk models require that the models be well calibrated, which means that the number of breast cancers predicted for women with certain combinations of risk factors is close to the number of breast cancers observed in such women in independent validation cohorts. The following two applications require, in addition to good calibration, that the risks among women destined to become cases be higher and well separated from the risks among women not destined to develop breast cancer. This feature, called “discriminatory accuracy,” is often measured by the area under the receiver operator characteristic curve (AUC) (17,18).

Risk models are needed to implement a “high risk” prevention strategy in which women with high breast cancer risk, who might benefit from the intervention, are identified and treated. It is preferable to find an intervention with few adverse effects that could be applied to the entire population, rather than to treat a high-risk subset (19). For example, if one could lower salt consumption in the general population and thereby reduce diastolic blood pressure by 1 mmHg throughout the population, one could prevent more heart attacks than by identifying and treating “high-risk” people with very high blood pressure. However, this “general population” strategy cannot be used if the intervention has serious adverse effects, like tamoxifen. Instead, one is forced to intervene only for those with high enough breast cancer risk that the benefits of intervention outweigh the risks. Consider life-threatening events in one year (Table 2) among 100 000 white women age 50 to 59 years (20). In the absence of tamoxifen, one expects 589.6 life-threatening events (246.6 invasive breast cancers, 101.6 hip fractures, 81.4 endometrial cancers, 110.0 strokes, and 50.0 pulmonary embolisms). If all women get tamoxifen, breast cancers and hip fractures are reduced, but the increases in stroke, endometrial cancer, and pulmonary embolisms are so great that there is a net increase of 243.9 life-threatening events. The five-year invasive breast cancer risk must exceed 3.80% for tamoxifen to have a net benefit in this age group, and only about 1% of the population has a risk this high (20). It is not surprising that restricting intervention to this small high-risk subset limits the potential for prevention. If only those with BCRAT risk greater than 3.80% are given tamoxifen, there is a net reduction of 1.4 events in one year (Table 2). Using a slightly more discriminating model that also includes seven breast cancer–associated single nucleotide polymorphisms (SNPs) only prevents 1.8 life-threatening events. If one had a perfectly discriminating model that could pick out all 246.6 women destined to develop breast cancer without error, one could give the tamoxifen only to them, thereby reducing breast cancer by about half but incurring few adverse events, and leading to a net reduction of 119.9 events. It is, however, very difficult to increase the discriminatory accuracy of breast cancer risk models. A more promising approach is to find interventions with fewer side effects. Modest improvements might also be made by modeling the risks of other events, such as stroke, in addition to breast cancer (21).

Risk models can also be used to allocate scarce prevention resources. The American Cancer Society recommended breast cancer screening with magnetic resonance imaging (MRI) for women with certain genetic disorders and women with a projected lifetime breast cancer risk of at least 20% (7). The recommendation was based on an assessment of risks and benefits rather than cost considerations, although it was noted that the cost per detected case was lower in high-risk women. For interventions such as MRI for which medical facilities are limited or where funds for prevention are limited, more health benefits can be derived by directing the intervention to those at highest risk. This approach can be beneficial if the cost of risk assessment is much smaller than the cost of the intervention. Suppose there were enough money to provide mammographic screening to half the female population. If mammograms were allocated at random, only 50% of the mortality reduction from screening would be achieved compared with screening all women. However, if the women’s risks were first assessed with BCRAT, if the risk assessment cost 2% as much as mammography, and if those at highest risk were given mammography in decreasing order of risk until the money ran out, then 63.2% of the maximal mortality benefit could be achieved (22). More discriminating risk models do even better. A model that adds seven SNPs to BCRAT achieves 66.7% of the maximal mortality reduction, provided the cost of the risk assessment is 2% of the cost of mammography, which is currently unrealistic (22). Pashayan et al. (23) argue that risk assessment based on age and breast cancer–associated SNPs is superior to guidelines based on age alone, because risk assessment can identify younger women who benefit from mammography and reduce the total number of women requiring mammography with little reduction in the total number of cases detected.

Models of absolute risk estimate the chance that disease will develop in the future. For many screening applications, one needs a model that predicts the prevalence of detectable disease toward which an intervention can be directed. In the preceding paragraph, the “intervention” was screening mammography, which can identify detectable breast cancer and lead to further treatment. Provided the prevalence of breast cancer

Table 2. Life-threatening events prevented in one year among 100 000 white women based on high-risk prevention strategies with tamoxifen

<table>
<thead>
<tr>
<th>Prevention strategy</th>
<th>Expected life-threatening events</th>
<th>Events prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>No tamoxifen</td>
<td>589.6</td>
<td></td>
</tr>
<tr>
<td>All get tamoxifen</td>
<td>833.5</td>
<td>-243.9</td>
</tr>
<tr>
<td>Give tamoxifen if BCRAT risk &gt;3.80%*</td>
<td>588.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Give tamoxifen if BCRAT+7SNPs risk &gt;3.80%*</td>
<td>587.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Perfect model: give tamoxifen only to the 246.6 women who will develop invasive breast cancer</td>
<td>469.7</td>
<td>119.9</td>
</tr>
</tbody>
</table>

* “BCRAT risk” is the five-year risk of breast cancer from National Cancer Institute’s Breast Cancer Risk Assessment Tool (BCRAT), and “BCRAT+7SNPs risk” is the five-year risk from a model that also includes seven single nucleotide polymorphisms (20). BCRAT = National Cancer Institute’s Breast Cancer Risk Assessment Tool.
is nearly proportional to short-term absolute risk, absolute risk models can be used as noted in the preceding paragraph (20). One typically requires high discriminatory accuracy to screen a population for people with prevalent disease. A valuable measure of such discriminatory accuracy is the "proportion of cases followed," $PCF(q)$, which is the proportion of prevalent cases detected among the proportion $q$ of the population at highest risk (24). For example, if the $100q = 10\%$ of the population at highest risk contains $100 \times PCF(0.1) = 90\%$ of the cases, the model is very discriminating. BCRAT approximately has $100 \times PCF(0.1) = 18\%$ (24). Thus $82\%$ of cases would be missed by restriction to women in the top $10\%$ of BCRAT risks.

Other Breast Cancer Risk Models and Prospects for Improved Models

Types of Available Breast Cancer Risk Models

Empirical estimates of pure cumulative breast cancer risk were obtained from life-tables for relatives of family members with breast cancer (25,26). BCRAT is called an “empirical model” because relative risks were estimated from case-control data by logistic regression without preconceived theory concerning the risk factors. These relative risks were then combined with an estimate of attributable risk from the case-control data and with data on breast cancer incidence rates from the NCI’s SEER program to estimate absolute risk. Another recent empirical model used estimates of relative risks from large cohorts and also included potentially modifiable risk factors, such as alcohol consumption, BMI, and menopausal hormone use (27). Four commonly used models are based on genetic theories of breast cancer risk. The models by Claus (28) and BRCAPRO (29,30) assume that breast cancer is an autosomal dominant disease. Two other genetically-based models, BOADICEA (4) and IBIS (5), also allow for other genetic effects to account for the considerable residual familial correlation that is not explained by autosomal dominance. These genetically based models rely on extensive data on the family history of breast cancer, but only IBIS includes reproductive risk factors or data from biopsies (31,32). BRCAPRO, BOADICEA, and IBIS use information on mutations in the BRCA1 and BRCA2 genes to estimate risk, which is an important advantage when this information is available.

Other differences among these models are important. BCRAT and the model in Pfeiffer et al. (27) take competing risks into account to compute absolute risk, whereas the genetically-based models compute pure risk. BOADICEA and IBIS are calibrated to data from England and Wales, whereas the other models are calibrated to the US. The Claus and IBIS models project the risk of invasive breast cancer and ductal carcinoma in situ, whereas the other models project invasive cancer risk only. Each of these analytic choices impacts estimates of risk. The website for BCRAT warns that the model is not appropriate for women with a personal history of breast cancer or lobular carcinoma in situ and for several other conditions, such as previous chest irradiation for Hodgkin’s lymphoma, for which other risk models are more appropriate (33).

An important step in the validation of a risk model is to determine whether it is well calibrated, namely, whether it accurately predicts number of breast cancers that will develop in a cohort of women overall and in women with specific risk factor combinations. BCRAT was shown to be well calibrated in the Nurse’s Health Study cohort (34), but needs to be monitored for calibration when US breast cancer incidence rates change (35) and may underpredict risk in women recruited as relatives of a woman with breast cancer (36). Partly to achieve good calibration, special models have been developed and incorporated into BCRAT for African American women (37) and Asian American women (38), and BCRAT projections for Hispanic women are based on Hispanic SEER rates, which are lower than for non-Hispanic white women in the United States. There is comparatively little data on the calibration of genetically based models in high-risk clinics, where they are most in demand (31,32).

Prospects for Improving Risk Models

BCRAT has modest discriminatory accuracy (AUC near 0.60 for women of the same age but higher for women of various ages), as do the other available breast cancer risk models. In order to increase discriminatory accuracy, other strong risk factors need to be found. In women who have breast biopsies, potentially useful prognostic features include atypical hyperplasia (39), lobular area, and acini-count per lobule (40). Moreover, mammographic density, measured by BI-RADS (almost entirely fat, scattered fibro glandular densities, heterogeneously dense, extremely dense), and biopsy features (nonproliferative, proliferative without atypia, atypical hyperplasia) act multiplicatively on risk (41), suggesting that AUC values near 0.7 will be achievable in women with biopsies. There may even be useful pathologic information from reduction mammoplasties (42).

For women without biopsies, mammographic density and SNPs will be useful. Indeed, models have already been developed that include mammographic density (43) or BI-RADS data (44) in addition to other risk factors. These models have AUCs near 0.65. Earlier work had estimated the potential for combining SNPs with BCRAT to improve discriminatory accuracy at a time when only seven SNPs had been proven to be associated with breast cancer (45). Recently, such methods were used to assess the usefulness of 76 such SNPs that have been identified from very large genome-wide association studies (46). Garcia-Closas et al. estimated that elaborate questionnaire data plus mammographic density data plus these SNPs would yield an AUC of 0.68. The authors note that such a model has not yet been built from women with data on all these risk factors, however. Although this AUC represents a substantial improvement compared with BCRAT, the more elaborate questionnaire and the mammographic density and SNP data would require more expense and effort. Moreover, while such a model could improve performance with respect to some applications mentioned above, such as directing the use of public health resources more efficiently, it does not achieve the high discriminatory accuracy needed to screen for prevalent breast cancer or to identify a small high-risk portion of the population containing most of the breast cancer risk.

These calculations indicate how difficult it is to improve discriminatory accuracy. Much stronger risk factors need to be discovered.

Discussion

This commentary focused on models to project the risk of breast cancer incidence and their applications. All the applications require good calibration. Some applications, like screening for prevalent disease and identifying high-risk subsets that contain most of the population’s breast cancer risk require high discriminatory accuracy. Although improvements in discriminatory accuracy are coming, they are unlikely to meet the needs
of a “high-risk” prevention strategy in the foreseeable future. They can be effective, however, in conjunction with improved interventions with fewer side effects that can be given safely to broad segments of the population. Certain lifestyle changes, such as reducing alcohol consumption, have promise but have yet to be tested in breast cancer prevention trials. Development of an agent like raloxifene, but with smaller risk of stroke and pulmonary embolism (14), or a drug like anastrozole (47), but with fewer side effects such as arthrosis and arthralgia, could lead to wider chemoprevention. Risk modeling would still have a role, but the requirement for high discriminatory accuracy would be reduced because a larger portion of the population could be safely treated.

Absolute risk models can be useful not only in conjunction with preventive interventions but also as part of a program to screen for prevalent disease. Although short-term projections of absolute risk are likely to be nearly proportional to the prevalence of screen-detectable and therefore useful for ranking women most likely to benefit from mammographic screening, it would be useful to develop and validate models to predict the prevalence of screen-detectable breast cancer. Age, family history (48), mammographic density (49), and history of previous screening results (50) predict the probability of a screen-detectable breast cancer, but no multivariable model for screen-detectable prevalence is available. Such a model could also be used to test the assumption that prevalence is proportional to short-term absolute risk of breast cancer incidence.

Absolute risk also plays a key role in disease management following diagnosis. The absolute risk of dying of breast cancer is reduced by competing mortality from non-breast cancer causes (51). Thus it may be wise to treat some older women less aggressively than younger women. As another example, trastuzumab treatment has adverse side effects and is only indicated for women with metastastic disease or with a substantial risk of recurrence.

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**Notes**

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**References**