Re: Multifactorial Analysis of Differences Between Sporadic Breast Cancers and Cancers Involving BRCA1 and BRCA2 Mutations

A number of multifactorial statistical models have been developed to estimate the chance that an individual carries a germline mutation in BRCA1 (1–3). These models are based principally on the cancer diagnoses in the family (particularly considering the type of cancer and age at diagnosis). We agree with Lakhani et al. (4) in their suggestion that histopathologic features of the breast cancers in a family could be used to increase the accuracy of predictions of the likelihood that a germline mutation in BRCA1 is involved. To this end, we note that perhaps the most distinctive and consistently reported features of breast cancers associated with BRCA1 mutations are the frequent absence of estrogen and progesterone receptors. Numerous investigators (5–7) have published reports comparing BRCA1 mutation-associated breast cancers with age-matched controls (e.g., either sporadic breast cancers or familial breast cancers lacking BRCA1 mutations), and all have reported statistically significant differences with regard to hormone receptor expression. Specifically, whereas only 25%–37% of the breast cancers not associated with BRCA1 mutation were estrogen receptor negative, 64%–92% of the cancers from BRCA1 mutation carriers were characterized as estrogen receptor negative (5–7). Progesterone receptor negativity was similarly a distinctive feature of BRCA1 mutation-associated breast cancers. Fewer data are available with regard to BRCA2 mutation-associated breast cancers.

An illustration of the potential value of incorporating hormone receptor status into pedigree-based estimations of mutation status can be provided using Bayes’ rule. For the purposes of these calculations, we will assume conservative estimates for estrogen receptor negativity rates of 33% for breast cancers not associated with BRCA1 mutation versus 67% for breast cancers in which BRCA1 mutation is involved. For a woman with an a priori risk of a BRCA1 germline mutation of 20%, conditioning upon estrogen receptor positivity in her breast cancer would serve to cut her predicted risk of a BRCA1 mutation almost in half (to 11%), as outlined in Table 1.

<table>
<thead>
<tr>
<th>Probability</th>
<th>BRCA1 mutation</th>
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<tbody>
<tr>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>A priori</td>
<td>0.20</td>
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<tr>
<td>Conditional (ER positive)</td>
<td>0.33</td>
</tr>
<tr>
<td>Joint</td>
<td>0.066</td>
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</table>

*This example is based on an a priori risk for a BRCA1 germline mutation of 20%, based on factors other than the person’s breast tumor ER status (which in this example is positive). For this calculation, we assume ER positive-to-negative ratios of 1 : 2 and 2 : 1 in BRCA1 mutation-associated tumors and sporadic tumors, respectively. The joint probability is calculated by multiplying the a priori and the conditional probabilities, and the posterior probability is the joint probability divided by the sum of the joint probabilities.
Table 1. On the other hand, if her breast cancer were negative for this receptor, her adjusted risk of being a carrier for a BRCA1 mutation would increase to 34%. Estrogen receptor status could be even more helpful if this information were available for other affected family members as well. For example, for an affected woman whose *a priori* risk estimate is 10%–14% because she has an affected mother, conditioning on estrogen receptor data from both her mother’s and her cancer could significantly refine the risk to as low as 3%–4% (if both cancers were receptor positive) or as high as 30%–40% (if both cancers were receptor negative). Note that these calculations apply only to the BRCA1 portion of heritable risk.

While Lakhani et al. (4) suggest adjusting BRCA1 mutation risk estimates by using such tumor-associated features as mitotic count or proportion of the tumor perimeter occupied by continuous pushing margins, clear advantages of using hormone receptor status are that this information is a standard component of nearly all breast cancer pathology reports and that interobserver agreement of receptor status is high. In short, tumor hormone receptor expression may be a readily available, reliable, and powerfully predictive piece of information that could be of considerable use in estimating the likelihood of a BRCA1 germline mutation. Although Bayesian calculations such as described above could be applied to risk estimates derived from currently available regression models, this approach is theoretical and is based on some assumptions (e.g., that hormone receptor expression in breast cancer is not otherwise heritable). We would therefore urge those groups that develop multifactorial prediction models for BRCA1 mutation status to, if possible, incorporate tumor hormone receptor status into their models.

**NOTES**

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**REFERENCES**


