How Reliable Are BRCA1/2 Mutation Estimates?

In Response:

We read with interest the letter from McClain et al. (1). Although our article (2) focused primarily on the prevalence of mutations in cases and the relative importance of predictors of mutation carriership, we appreciate the interest in the population carrier frequency estimates we included. Applying an algorithm (3) that relies on the interrelationship of population carrier frequency, penetrance, cumulative disease incidence, and mutation prevalence in cases, McClain et al. examined the plausibility of our estimate of population carrier frequency.

The methods we used for generating a rough estimate of population carrier prevalence were presented in our article (2). Briefly, we calculated a weighted average, assuming our cases were representative of prevalent cases and our controls representative of those without breast cancer.

We do not question their previously published algorithm, but, in applying it to our data, the authors do not seem to have made the necessary adjustments to accommodate the Women’s Contraceptive and Reproductive Experiences (CARE) Study population structure. McClain et al. (1) applied our estimates of case mutation frequency and population carrier frequency directly to a hypothetical population of women age 65 with an expected cumulative breast cancer incidence of 5.8%. However, our case mutation frequencies were derived from a study of women ages 35 to 64, who by definition had a lower cumulative incidence of breast cancer.

To illustrate, we estimated the proportion of the catchment area population underlying the CARE Study that fell into 12 categories based on age (5-year groups: 35–39 to 60–64) and race (Caucasian, African-American). From DevCan,1 we obtained the proportion of women expected to develop breast cancer by race and age according to prespecified 5-year groups. Because DevCan only provides estimates “as of” every 5 years, our incidence estimates for each age group were either too high (i.e., using age 40 estimates for the 35–39-year age group) or too low (i.e., using age 35 estimates). Therefore, we computed three estimates: one using the overestimates, one using the underestimates, and one averaging these two. These approaches, respectively, yielded cumulative incidences of 2.3%, 1.4%, and 1.8%, which better reflect the true cumulative incidence of breast cancer among women ages 35 to 64, the population we studied. Using the formula of McClain et al., in conjunction with the case mutation prevalences (2.4% and 2.3%) and estimated carrier frequencies in women ages 35 to 64 (0.06% and 0.4%) reported for the CARE Study, we show the distribution of penetrance estimates observed for four cumulative incidence estimates: the one used by McClain et al. that assumes the entire population has aged out to age 65 (5.8%) and the other three described above. These varying estimates of cumulative incidence translate into very different penetrance estimates. All penetrance estimates associated with the three lower cumulative incidence estimates fall below 100% (Table 1).

The above explanation addresses the application of their formula to the CARE Study underlying population of Caucasian and African-American women ages 35 to 64. Alternatively, if the CARE Study population was aged out to age 65 along the lines of the example in the letter and experienced the cumulative breast cancer incidence that would be expected (i.e., 5.8% cited by McClain), the required adjustment to the case mutation prevalence estimate would result in a much lower case mutation prevalence than we reported because the mutation frequency in the subsequently accruing cases would be much smaller. It is not clear to us that McClain et al. made any such adjustments in their calculations.

We have computed confidence intervals for our carrier frequency estimates using a weighted average of the SE of the proportion estimates for each age-race stratum. These intervals, which reflect the power limitations faced even by a study of this size, show the general compatibility of our carrier frequency estimates with those from prior studies (Table 2).

Several factors could influence our rough estimate of carrier frequencies. As suggested in our article, the inclusion of African-American women could account in part for the higher BRCA2 mutation frequency estimates observed (2). In addition, we included in our calculation of population carrier frequencies the results of direct testing of control women, an underpowered component of our study that could insert instability in our estimates. Although we have not identified other sources of bias or miscalculation, we certainly cannot rule out these possibilities. It seems clear that given the absence of large-scale testing of unaffected women, we continue to be constrained by the assumptions, extrapolations, and limitations of indirect estimates of population carrier frequencies.

Table 1. BRCA1/BRCA2 mutation penetrance estimates for varying scenarios of cumulative breast cancer incidence in women ages 35-64

<table>
<thead>
<tr>
<th>Estimate of cumulative incidence of breast cancer (% CI)</th>
<th>Estimate of penetrance of BRCA1 mutations using the McClain method (%)</th>
<th>Estimate of penetrance of BRCA2 mutations using the McClain method (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.8</td>
<td>232.0</td>
<td>33.4</td>
</tr>
<tr>
<td>2.3</td>
<td>95.2</td>
<td>13.1</td>
</tr>
<tr>
<td>1.4</td>
<td>59.8</td>
<td>8.3</td>
</tr>
<tr>
<td>1.8</td>
<td>77.5</td>
<td>10.7</td>
</tr>
</tbody>
</table>

1 http://srh.cancer.gov/devcan/

Table 2. Confidence intervals for BRCA1/BRCA2 population mutation carrier frequency estimates

<table>
<thead>
<tr>
<th>Gene</th>
<th>Estimated carrier frequency in the general population of women ages 35–64</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>0.057% (1 in 1,749)</td>
<td>0–0.156%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>0.397% (1 in 252)</td>
<td>0–0.972%</td>
</tr>
</tbody>
</table>
References

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