How Reliable Are BRCA1/2 Mutation Estimates?

To the Editor:

Malone et al. (1) recently reported the clinical sensitivity (prevalence) for BRCA1 and BRCA2 mutation testing in a population-based cohort of Caucasian and African-American women with breast cancer. The carrier rates of BRCA1 and BRCA2 mutations in the general population were reported as well. We have developed an approach that integrates these two epidemiologic parameters with two others: cumulative incidence of breast cancer in the general population and penetrance of BRCA1 and BRCA2 mutations (2, 3). We applied this approach to their data to test the plausibility of their parameter estimates.

They report a clinical sensitivity and carrier frequency for BRCA1 mutations of 2.4% and 0.06% (1 in 1,667), respectively. We estimated the cumulative incidence of breast cancer in all women by age 65 (5.8%), taking into account the racial distribution of their cases (DevCan 6.1.1). Together, these three parameters can be used to derive the fourth parameter: penetrance of BRCA1 mutations (penetrance was not reported by Malone et al.). Our calculated penetrance of >200% is not plausible and indicates that one or more of the other three parameters are not correct. Using the same approach, the penetrance estimate for BRCA2 mutations is 33%, a plausible, but lower, estimate than found in our report (2).

Their methodology for estimating the mutation carrier frequencies is not described, nor are confidence intervals provided. We question their statement that these carrier frequencies are compatible with earlier estimates. The BRCA1 mutation carrier rate of 1 in 1,667 is considerably lower than the 1 in 800 to 1 in 1,400 contained in the literature (2), whereas the BRCA2 mutation carrier rate is higher (1 in 250 versus 1 in 300 to 1 in 450). These inconsistencies suggest two possibilities for Malone’s findings: (a) existing estimates for BRCA1 and BRCA2 mutation carrier frequencies should be revised, or (b) one or more biases are present (e.g., sampling bias or weighting bias). More information is needed from the authors to document the need for the first. Until then, the findings should be interpreted with caution.

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