Log Odds of Carrying an Ancestral Mutation in BRCA1 or BRCA2 for a Defined Personal and Family History in an Ashkenazi Jewish Woman (LAMBDA)

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Abstract

Introduction: Ancestral mutations in BRCA1 and BRCA2 are common in people of Ashkenazi Jewish descent, and associated with a substantially increased risk of breast and ovarian cancer. Women considering mutation testing usually have several personal and family cancer characteristics, so predicting mutation status from one factor alone could be misleading. The aim of this study was to develop a simple algorithm to estimate the probability an Ashkenazi Jewish woman carries an ancestral mutation based on multiple predictive factors.

Methods: We studied Ashkenazi Jewish women with a personal or family history of breast or ovarian cancer and living in Melbourne or Sydney, Australia, or with a previous diagnosis of breast or ovarian cancer and living in the United Kingdom. DNA samples were tested for the germline mutations 185delAG and 5382insC in BRCA1, and 6174delT in BRCA2. Logistic regression was used to identify, and to estimate the predictive strength of, major determinants.

Results: A mutation was detected in 64 of 424 women. An algorithm was developed by combining our findings with those from similar analyses of a large study of unaffected Jewish women in Washington. Starting with a baseline score, a multiple of 0.5 (based on the logistic regression estimates) is added for each predictive feature. The sum is the estimated log odds ratio that a woman is a carrier, and is converted to a probability using a table. There was good internal consistency.

Conclusions: This simple algorithm may be useful in the clinical and genetic counseling setting. Validation in other settings should be sought