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Title: Genetic models for estimating age-specific risk of sporadic breast cancer

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Introduction: Accurately assessing individual risk of developing breast cancer is essential for early detection and prevention. The possibility exists to improve upon the widely used Gail model in predicting an individual's risk of developing breast cancer, by incorporating both genetic and lifestyle information. Methods: We have developed a model with data from ~7,000 Caucasian women (2,300 cases and 4,700 controls) enrolled in four geographically distinct regions of the US. Questionnaire-based information on clinical and lifestyle variables, including the Gail model questions, were collected. All samples were genotyped for 120 common, functional polymorphisms in candidate genes likely to influence breast carcinogenesis. The data were randomly divided into training (75%) and validation (25%) sets. Because of age-dependent genetic penetrance observed in the study, separate models were built for three age intervals (30-44, 45-54 and ≥55). Following assessment of Hardy-Weinberg equilibrium and linkage-disequilibrium, univariate and multivariate statistical analyses were performed to assess genetic main effects and epistatic interactions and define model terms. Models were evaluated by Receiver Operator Curve (ROC) analysis. Results: The risk prediction models developed for all three age intervals were informative with Area Under the Curve (AUC) that was consistently greater than expected by chance and exceeded the predictive power of the Gail model alone. No strong associations were found between scores derived from our models and the Gail model. The results suggest that the genetic markers examined contribute to breast cancer prediction independent of the Gail scores, and due to the improvement in the AUC, probably complement the Gail scores. The strongest genetic contributors to risk were identified in the youngest group where the AUC was 0.67 in the training set and 0.62 in the validation set. Estimated AUC values appear to be quite stable across 1,000 bootstrap samples of training and validation sets. Conclusions: The predictive power of these models integrating both genetic and epidemiological data provides an improved estimate of an individual's breast cancer risk.