Performance of BCRAT in high-risk patients with breast cancer

Authors' reply

We thank Mitchell Gail for his response to our Article on the 10-year prospective performance of four breast cancer risk models.[1] We agree that the Breast Cancer Risk Assessment Tool (BCRAT) performed similarly to the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) and the International Breast Cancer Intervention Study (IBIS) model in its discriminatory ability in women not known to have mutations in *BRCA1* or *BRCA2*. Although he has shown that, on average, our cohort has about three times the risk of breast cancer than the general population, the Breast Cancer Prospective Family Study Cohort (ProF-SC) covers a wide range of risk and still has a large proportion of women with a predicted absolute risk that is in the range of most average-risk cohorts.[2]

We stand by our conclusion that collecting pedigree information is preferable for estimating risk because it can improve model calibration. BCRAT underpredicted risk for women without known *BRCA1* or *BRCA2* mutations who were younger than 50 years (expected to observed risk 0·78, 95% CI 0·68–0·89; p=0·0003).[1] Further, when we investigated quantiles of risk, BCRAT underpredicted risk in the two lower quantiles (<3·4 for 10-year risk) and overpredicted risk in the top quantile. BOADICEA and IBIS gave the same pattern of overprediction and underprediction, but the differences were much smaller and not significantly different. Therefore, improvements in estimation of risk can be made by use of pedigree data, even for those at average risk.

The underprediction that we observed for BCRAT is not explained by the *BRCA1* and *BRCA2* mutation-carrying families. In sensitivity analyses, we excluded women who were not tested but who had at least one relative who was a known carrier (n=308), and we found that this exclusion had no effect on our overall conclusions. For example, in an additional analysis that we did in response to the Correspondence by Gail, BCRAT still underpredicted risk for women younger than 50 years who had no known *BRCA1* or *BRCA2* mutations (expected to observed risk 0·80, 95% CI 0·70–0·91; p=0·0008), and there was little change in quantile-specific estimates. Pedigree data aids model performance by capturing information on the intermediate and other risk variants that segregate within families.

We declare no competing interests.

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1 Terry MB, Liao Y, Whittemore AS, et al. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncol* 2019; **20:** 504–17.
2 Terry MB, Phillips KA, Daly MB, et al. Cohort profile: the breast cancer prospective family study cohort (ProF-SC). *Int J Epidemiol* 2016; **45:** 683–92.