Evaluating the performance of the breast cancer genetic risk models BOADICEA, IBIS, BRCAPRO and Claus for predicting BRCA1/2 mutation carrier probabilities: a study based on 7352 families from the German Hereditary Breast and Ovarian Cancer Consortium.

Abstract:
Risk prediction models are widely used in clinical genetic counselling. Despite their frequent use, the genetic risk models BOADICEA, BRCAPRO, IBIS and extended Claus model (eCLAUS), used to estimate BRCA1/2 mutation carrier probabilities, have never been comparatively evaluated in a large sample from central Europe. Additionally, a novel version of BOADICEA that incorporates tumour pathology information has not yet been validated. Using data from 7352 German families we estimated BRCA1/2 carrier probabilities under each model and compared their discrimination and calibration. The incremental value of using pathology information in BOADICEA was assessed in a subsample of 4928 pedigrees with available data on breast tumour molecular markers oestrogen receptor, progesterone receptor and human epidermal growth
factor 2. BRCAPRO (area under receiver operating characteristic curve (AUC)=0.80 (95% CI 0.78 to 0.81)) and BOADICEA (AUC=0.79 (0.78-0.80)), had significantly higher diagnostic accuracy than IBIS and eCLAUSS (p<0.001). The AUC increased when pathology information was used in BOADICEA: AUC=0.81 (95% CI 0.80 to 0.83, p<0.001). At carrier thresholds of 10% and 15%, the net reclassification index was +3.9% and +5.4%, respectively, when pathology was included in the model. Overall, calibration was best for BOADICEA and worst for eCLAUSS. With eCLAUSS, twice as many mutation carriers were predicted than observed. Our results support the use of BRCAPRO and BOADICEA for decision making regarding genetic testing for BRCA1/2 mutations. However, model calibration has to be improved for this population. eCLAUSS should not be used for estimating mutation carrier probabilities in clinical settings. Whenever possible, breast tumour molecular marker information should be taken into account.