Volumetric Breast Density Improves Breast Cancer Risk Prediction

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P6-09-04

Background:

There is increasing interest in implementing personalized breast cancer screening strategies rather than relying on population based guidelines. Most risk models do not include breast density and two models that do rely on subjective BI-RADS categories; all have limited discriminatory ability (C-statistics ranging from 0.60-0.74). Our aim was to develop a model that includes an automated objective and numeric volumetric measurement of breast density combined with other known risk factors to improve risk prediction.

Methods:

This study was approved by our IRB and was HIPAA compliant. A case-control study design was used to evaluate the association between risk factors and breast cancer diagnosis. All women diagnosed with breast cancer during 2003-13 with a digital contralateral mammogram at the University of Virginia at the time of diagnosis were eligible as cases. All women without a breast cancer diagnosis but with a digital mammogram at UVA during 2003-2008 were eligible as controls. Risk factor information was collected using a self-reported electronic questionnaire. Mean automated volumetric breast density (Volpara, NZ) was calculated for each patient as a percentage. Controls were matched to cases in a 2:1 ratio based on age group, race, and education, using the GREEDY algorithm. Case-control selections were made using the weighted sum of the absolute differences between the case and control matching factors. Conditional logistic regression using the partial likelihood function from Cox proportional hazard's regression was used to fit risk prediction equations to the matched case-control study dataset, with stratification for each case matched set.

A full model was estimated including all available covariates for use as a model performance reference standard. Reduced Models were then estimated including covariates in the full model that had a Wald Chi-Square/degrees of freedom ratio > 1.0 (A) and then again including covariates with p value < 0.10 (B) . A Minimal Model was then estimated including covariates from Model B with Wald/Chi-square/DF >5.0). The performance of the full, reduced, and minimal models was measured using the C index and the maximum R-Square statistic.

Results:

The study enrolled 3,445 women; 839 cases and 2,606 controls. Multivariable analysis was conducted using 860 cases and 1,683 controls with 1 or more breast studies reported for the surveyed population. The matching process yielded balanced matching factor values between cases and controls, with no significant differences in age group ($p = 0.95$), race ($p = 0.13$), or education ($p = 0.86$).

Model Development Results

Model	Number of Covariates	Maximum Adjusted R^2	C Statistic
Full Model (All available covariates)	62	0.62	0.86
Reduced Model A: (Full Model with Wald Chi-Square/DF > 1.0)	34	0.59	0.85
Reduced Model B: (Reduced A with Wald Chi-Square p value < 0.10)	21	0.56	0.84
Minimal Model: (Reduced Model B covariates with Wald Chi-Square/DF > 5.0)	13	0.54	0.82

The full prediction model (with 97df) yielded a C index of 0.86, and an R-Square of 0.62. The reduced model (with 15 df) had a C index of 0.83 and an R-Square of 0.54. Variables in the reduced model included: mean breast density; biopsy showing ADH, ALH/LCIS; BMI; use of HRT, contraceptives, NSAIDS; smoking; exercise; parity; diabetes; family history of breast cancer, HBOC, Li-Fraumeni or Cowden Syndromes and/or BRCA mutation. Mean volumetric breast density was a leading independent predictor of case status in the full ($p<0.0001$), reduced models (A: $p=0.0212$, B: $p=0.0011$), and minimal model ($p=0.0046$).

Discussion:

The addition of volumetric breast density improved breast cancer risk discrimination. Our model uses an automated measurement of breast density used as a continuous variable that proved to be one of the top five predictors of breast cancer risk in our population. Discrimination is key in model development if screening recommendations are to be individualized. Even the minimal model that includes only 13 covariates demonstrates improved discrimination (0.82) compared with the Tyrer-Cuzick (IBIS) model (0.74).

This study was supported by CDMRP BC100474