IDENTIFYING WOMEN AT HIGH RISK OF DEVELOPING BREAST CANCER: IMPLICATIONS OF ADJUSTING FOR INTER-OBSERVER VARIABILITY IN VISUAL ANALOGUE SCALE ASSESSMENT OF PERCENTAGE BREAST DENSITY

Jamie C. Sergeant¹, Matthew Sperrin², Lawrence Bardwell³, Iain Buchan² Mary Wilson⁴, D. Gareth Evans⁴, Anthony Howell⁴, Susan M. Astley¹

¹Centre for Imaging Sciences, Institute for Population Health, University of Manchester, Manchester, UK
²Centre for Health Informatics, Institute for Population Health, University of Manchester, Manchester, UK
³Department of Mathematics and Statistics, University of Lancaster, Lancaster, UK
⁴Nightingale Centre and Genesis Prevention Centre, University Hospital of South Manchester, Manchester, UK

Aim

- Breast density is the relative amounts of fibroglandular and fatty tissue in a mammogram
- Measurement of percentage breast density using a visual analogue scale (VAS) has been strongly associated with risk of developing breast cancer [1]. However, VAS density assessment is subject to inter-observer variation
- Such variation may affect patient outcomes if VAS density is used in risk stratification
- We have developed a novel method of adjusting observers’ density estimates to make them directly comparable
- Our aim is to examine the implications of applying this method to data from the Predicting Risk Of Cancer At Screening (PROCAS) study [2, 3]

Method

The PROCAS Study: Predicting Risk Of Cancer At Screening:

- Aim: predict individual breast cancer risk at breast screening, with potential to facilitate preventative measures and tailor screening interval and modality based on risk
- Over 50,000 women recruited from routine breast screening in Greater Manchester, UK
- Questionnaire data used to compute 10-year risk using Tyer-Cuzick risk model
- Women classified as high risk if - Tyer-Cuzick risk ≥ 8% (following UK National Institute for Health and Care Excellence (NICE) guidelines) OR - Tyer-Cuzick risk ≥ 5% AND VAS breast density in top decile of densities (≥ 46% density)
- Consenting high risk women offered a consultation with a clinician to discuss their risk and entry into prevention trials

Data:

- 13,694 screening cases from the PROCAS study with GE Senographe Essential Full-Field Digital Mammography (FFDM) mammograms
- VAS breast density for each case estimated by two observers from a pool of 13 experienced mammographic readers
- Each reader estimated the density using a separate VAS for each view (mediolateral oblique (MLO) and craniocaudal (CC)) of each breast, which were later averaged:

![VAS assessment](image)

Method of adjustment [4]:

Stage 1 – transforming all readers onto the same distribution:

- Individual readers produce VAS density results on their own distribution
- Compute the empirical cumulative distribution function (ecdf) separately for each view by each reader
- Construct the overall ecdf by averaging the individual ecdfs, weighting each reader equally
- Transform an original “raw” VAS score by a reader to its position in the ecdf of the reader, then transform that position in the overall ecdf back to the 0-100% density scale

Stage 2 – case mix correction

- Different readers perform assessment on different sets of cases
- Each case is assessed by two readers
- Explore differences in pairwise assessment, after application of Stage 1
- Estimate a correction factor for each reader to correct for differences in case mix

Research question:

How many women are classified as high risk according to above criteria, before and after the adjustment of VAS breast density results?

Results

Bosplots of individual reader density distributions and scatterplot matrix of pairwise density assessments. Blank cells in the scatterplot matrix indicates readers who never assessed the same mammograms. All axes are scaled 0-100% and lines of perfect concordance are shown:

Of the 13,694 screening cases:

- 165 (1.2%) were classified as high risk due to Tyer-Cuzick risk ≥ 8%
- 1,125 (8.2%) had 5% ≤ Tyer-Cuzick risk < 8%, making them potential additional high risk women, depending on their VAS density

Of the 1,125 potential additional high risk women:

- Before density adjustment, 126 (11.2%) were high density and therefore high risk
- After density adjustment, 147 (13.1%) were high density and therefore high risk

Redeclaration table:

<table>
<thead>
<tr>
<th>Before adjustment</th>
<th>After adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>Non-high risk</td>
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<tr>
<td>Total</td>
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<td>1125</td>
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</tbody>
</table>

Conclusion

- We have presented a novel adjustment of VAS breast density estimates
- This adjustment accounts for inter-observer variation and makes estimates by different observers directly comparable
- Application of the method to PROCAS study data had a substantial impact on which women were identified as being at high risk of developing breast cancer
- The reclassifications seen highlight the need to account for inter-observer variation if VAS breast density assessment is used in risk stratification and personalised screening

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Contact: jamie.sergeant@manchester.ac.uk