Indicators of Future Breast Cancer Risk at Prevalent Round Screen

Poster No.: C-1401
Congress: ECR 2015
Type: Scientific Exhibit
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Keywords: Cancer, Screening, Mammography, Breast
DOI: 10.1594/ecr2015/C-1401

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Aims and objectives

This study aims to evaluate possible risk factors for future development of breast cancer which may be identified at the time of first (prevalent round) screen. While there are multiple factors which are known to affect breast cancer risk, including parity, age at menarche, hormone replacement therapy use, etc., and while risk modelling may be invoked to create an individual's risk profile (1-3), it is not always feasible to collect and interpret this information in the context of a large screening programme. Breast density and a history of high risk or atypical lesions are both known to confer increased risk and are easily identified via mammographic assessment and national screening database records. The purpose of this study was therefore to evaluate both breast density and high risk lesion history in the prevalent screen population with implications for predicting future risk of breast cancer.
Methods and materials

Study Population

This retrospective study adheres to local patient confidentiality requirements. Our regional screening programme assessment activity was reviewed over a one year period (April 2013-March 2014). The study cohort included women in the standard screening age (50-70), as well as those older than 70 who had the option of self-referral for screening. Prevalent round screen group was defined as women presenting for first screen without history of previous screening episodes. Incident screen was defined as a screening exam occurring in a woman with a history of previous prevalent screen.

Data Collection

Our local screening national breast screening service (NBSS) database was reviewed to identify total numbers of prevalent and incident screens performed during the study period. Number of women assessed as well as number of biopsies during the study period were recorded for prevalent and incident groups. If a biopsy was performed, we recorded resultant pathology according to standard United Kingdom breast pathology categories: benign (B2), lesion of uncertain malignant potential (B3), in situ malignancy (B5a) or invasive disease (B5b).

B3 lesion pathology

B3 lesion pathology was identified through the patient records and compared between prevalent and incident groups. Lesion types included atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), in situ lobular neoplasia (ISLN, also including atypical lobular hyperplasia and lobular carcinoma in situ), papillary lesions, radial scars, and mucocele-like lesions. All women whose worst core biopsy result of any lesion at assessment showed cancer were excluded. B3 lesions with atypia (ADH, ISLN including ALH and LCIS, FEA) were identified and Pearson's Chi-squared test was used to evaluate significant difference in the number of cases of atypia in prevalent versus incident round screens.

Density

Breast density data was obtained from a subset of screening mammograms (approximately half of the study population) based on availability of raw data transfer.
Density was quantitatively measured using Volpara Density software (VolparaSolutions Wellington, NZ), an automated volumetric means of assessing density which has recently been validated against other methods of measuring density (4). Average density scores were calculated using the Volpara algorithm (the Macro) using all the available views (CC and MLO) and averaged right and left breast densities. Prevalent versus incident round data with cancers detected was drawn from national database and analysed with respect to %Volumetric Density (%VD) and Absolute Fibroglandular Volume (cm$^3$) (FGV). Mann Whitney U test was used to evaluate significance.
Results

39,491 women were screened over the study period (including self-referred women and excluding high risk or moderate risk women). The age profile of the group assessed is shown in Figure 1. Of the study population, 7181 women had prevalent screens and 694 of these women were referred for assessment. There were 370 biopsies and 73 cancers. 32311 women had incident screens and 1427 were referred for assessment. There were 743 biopsies and 309 cancers. This information was obtained from the NBSS KC62 report.

High Risk Lesions

78 biopsy proven B3 lesions were identified in the cohort over the study period. Atypia was found in 63.6% (14/22) prevalent round B3 biopsies and in 50% (28/56) incident round B3 biopsies, but this difference was not significant (p=0.277). However, when the rate of atypia diagnosis for the entire screening cohort is considered, more atypia is diagnosed in the prevalent round than the incident round (prevalent 0.19% [14/7181] and incident 0.09% [28/32311], (p=0.019). (Table 1.)

Density subset analysis

Over the study period, 22,885 screening records were analysed for density using Volpara volumetric software. 4283 women were prevalent screens (mean age 52.8) and 18,602 women were incident screens (mean age 61.7). 164 cancers were identified in the incident group and 42 cancers were found in the prevalent group. This subset is similar in distribution to the overall screening cohort (Table 2.).

Figure 2 shows the SABC (screen, assessment, biopsy, cancer) analysis by prevalent and incident cohorts categorized by Volpara Density Grade. The upper two charts show that for all densities, more women are recalled in the prevalent round than in the incident round. The lower two charts demonstrate that the likelihood of biopsy in women attending assessment is similar in all groups whether incident or prevalent (approximately 50%). However, the PPV of biopsy is less in the prevalent round. As well, in this data set, the number of incident women with dense breasts is low, but there are disproportionately few cancers (Figure 2 and Table 2).

The violin plots in Figure 3 show the approximate distributions of Volpara breast density for women attending in the prevalent and incident screening rounds. The black circles
indicate the median value, and the orange markers show the upper and lower quartiles. The varying width of the plot reflects the numbers of women at each density. **Figure 3** demonstrates that the median breast density for women with cancer in the prevalent round is higher than the median density in all other groups.
Fig. 1: Study population (breast density cases) by age and round.

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Table 1: Lesions without cancer showing atypia at biopsy by screening round. About half of women with a B3 biopsy opinion have atypia, regardless of screening round; but as a proportion of all women screened, there is more atypia in the prevalent round (p=0.019).
**Fig. 2:** Numbers of women screened, assessed and biopsied by round and Volpara density grade, to show the comparative proportions

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<table>
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<th>Volpara Grade</th>
<th>Prevalent round</th>
<th>Incident round</th>
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<tr>
<td></td>
<td>Screened</td>
<td>Assessed</td>
</tr>
<tr>
<td>1</td>
<td>1018</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>1316</td>
<td>134</td>
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<td>3</td>
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<td>135</td>
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<tr>
<td>4</td>
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<tr>
<td>KC62</td>
<td>7181</td>
<td>694</td>
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</table>

**Table 2:** Numbers of women screened, assessed and biopsied by round and Volpara density grade. The bottom line shows the equivalent numbers from the matching KC62 report.
**Fig. 3:** These plots show the approximate distributions of Volpara breast density for women attending in the prevalent and incident screening rounds. The black circles indicate the median value, the orange markers show the upper and lower quartiles. The varying width of the plot reflects the numbers of women at each density. Screened=mammogram but not assessed. Assessed=assessed but not biopsied. Biopsied=biopsied but no cancer.
Conclusion

Multiple studies have shown that a history of a high risk lesion, in particular a history of atypia, confers increased risk of developing breast cancer. In their seminal work, Dupont and Page found a 5.3 times greater risk of developing cancer in women with atypical hyperplasia compared to women with nonproliferative breast changes (5). More recently, Hartmann and colleagues found that 143/698 (20%) of women with a history of either ALH or ADH followed for a mean of 12.5 years developed cancer (6,7). Although it is difficult to determine frequency of atypical lesions in a normal population, one autopsy study identified atypia in as many as 17% of cases (8). In our study we identified 14/22 cases of atypia in the prevalent screen group out of all B3 lesions and 28/56 in the incident screen group. There is a significantly higher detection of atypia in the prevalent round compared to the incident round. However, in both rounds, approximately 7% of all biopsies were B3; this is concordant with national UK data (National Pathology Audit 2010-2013). In our unit, approximately half of all B3 lesions show atypia.

Likewise, mammographic density has also been shown to identify increased cancer risk (9,10). The Predicting Cancer Risk at Screening (PROCAS) trial (cohort of 50,000 women) has estimated that approximately 5.2% of the population will have a high (>60%) visually assessed breast density with a relative risk of developing cancer of 2.9 over the next decade for the most dense group compared to the least dense group (11). We have evaluated breast density across this cohort of women; in our cohort, 15% of prevalent round women have very dense breasts (Volpara Grade 4). We note that the cancer detection rate in these women was 40% higher than average prevalent round detection rate.

It should also be remembered that a personal history of breast cancer is a key indicator of future risk (12).

One of the questions raised by our study is whether women will choose to be informed of an increased risk of breast cancer. There is evidence to suggest that women will in fact opt to find out and act upon risk assessment data (13). Interestingly, a recent survey of screening-eligible women has suggested that women are not only interested in knowing their personal risk of breast cancer, but also may find such information particularly meaningful when associated with a breast screening episode. Women indicated that the screening visit would act as a catalyst to inspire lifestyle changes to decrease their personal risk (14).

The prevalent screen may offer a particularly key opportunity to select women for more careful scrutiny over time and to make women aware of their risk. A look at recall rates
(RR) in our prevalent versus incident populations shows that RR is nearly three times as high in the prevalent group as in the incident group (Table 3). In fact, it may well be that those women recalled for assessment at the prevalent screen are at higher risk for later cancer occurrence, possibly due to comparatively increased breast disease at baseline (15-17).

Limitations of the study are as follows: all women did not have breast density Volpara analysis as raw data transfer was not available at all of our facilities. As well, the recent nature of our study period (2013-2014) does not allow for follow-up and identification of interval cancers which could affect our conclusions. Despite these limitations, our study suggests that prevalent round factors (atypia on biopsy, breast density on mammogram and actual cancer diagnosis) are readily identifiable and therefore may be a practical means of assessing future risk.

We were surprised and interested to find that while women with cancer at prevalent round screen had higher mean breast density than other prevalent round women, women with cancer detected in incident screening round had similar breast density compared to their peers. Although our study is a limited observational study, this finding may suggest that there is low yield in selecting women for incident screening based on breast density. The number of women with very high breast density (Volpara 4) in the incident round is low and our observation of only 6 cancers in this group may be spurious. On the other hand, it may indicate that mammography is not the optimal screening test for women with very dense breasts. Analysis of interval cancers in this cohort is therefore critical.

Statistical analysis performed by Toby Thurston, Thurston Information Ltd, info@thurston.eml.cc.
<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalent round</th>
<th>Incident round</th>
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<tbody>
<tr>
<td>1998–1999</td>
<td>5.52%</td>
<td>2.83%</td>
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<td>1999–2000</td>
<td>5.76%</td>
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<td>2000–2001</td>
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<td>2001–2002</td>
<td>7.11%</td>
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<td>10.24%</td>
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<td>2011–2012</td>
<td>9.44%</td>
<td>3.48%</td>
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</table>

Table 3: Recall Rate % Over Time by Prevalent and Incident Screen (Adapted from London QARC data)

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Personal information

The authors would like to acknowledge VolparaSolutions and Philips for their support.
References


