Breast density analysis using DENSITAS software on interval cancers from the Welsh breast screening programme

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Introduction

Increased breast density is a recognised risk factor for breast cancer, with denser tissue more likely to develop cancers and less likely that such cancers are identified on mammographic imaging. This can now be measured automatically with software eg DENSITAS 2.1.0 or later versions as well as from other providers eg Cumulus or Volpara.
Interval cancers (ICA) develop symptomatically following a normal screening episode and are inevitable aspect of any breast screening programme. Breast densities on consecutive ICA screened at the South East division of the Welsh breast screening programme (Breast Test Wales, BTW) between 2012 and 2016 were analysed, identifying densities more likely to develop ICA. The different ICA categories were also recorded.

Method

277 consecutive ICA were identified from the All Wales BTW database screened within the South East division between 2012 and 2016. All cases had undergone prior digital mammographic screening with Hologic or Sectra Philips equipment at static or mobile units. ICA cases are collected from the automatic monthly down loads from all pathology labs across Wales and the borders into the BTW ICA database. These identified processed, raw data screening images underwent area density and percentage density calculations using Densitas 2.1.0 software. These included the area and percentage amounts of dense tissue on the images with and without the pectoral area, skin and nipple being included for both sides and each image. The actual amount of non breast tissue is calculated also non breast and total breast areas, and a BIRADS 5 category was assigned (A,B,C or D.)
Each ICA case underwent formal ICA review of the prior screening images. This involved blinded double reading and arbitration to categorise into ICA group (True, False Negative,(FN), Minimal Signs, Occult and Unclassified) as per the standard BTW regimen. Time-to-cancer following the screening episode was also recorded. Histological details of the cancers are not included in this study.
The density groupings of the different ICA sub types were recorded and compared with other studies.

Results

Of the initial 277 ICA cohort, 7 cases were excluded from density analysis for incompleteness, (eg not all images having density assessment or an image missing) leaving 1104 mammo images in the remaining 270 studies. There was no difference in laterality of the images analysed with 563 MLO plus 541 CC views.
There were 5 cases in BIRADS A (1.7%) the least dense breasts, 84 in BIRADS B (31%), 171 in BIRADS C (63.3%) and 10 in BIRADS D (4%) the densest category.

TABLE 1 shows image area and breast density area distributions.
TABLE 2 shows study dense area and study breast area distributions.
GRAPH 1 is a histogram of percentage breast densities.
TABLE 3 shows the BIRADS groupings for the ICA cases.

Of the initial 277 cases, there were 272 with completed ICA subtyping and density analysis. 4 were cases excluded from the final analysis due to issues with density measurement (1 in each of the categories True, FN, Minimal signs and Unclassified) plus 1 with unavailable ICA category, leaving **138** *(50.5%)* True intervals, **47** *(17.2%)* FN, **36** *(13.3%)* Minimal Signs, **22** *(8.0%)* Occult. **29** *(10.6%)* were Unclassified due to mammograms not being performed at cancer diagnosis.

Graph 2 shows the range of BIRADS 5 densities against the ICA category type.
Graph 3 shows the proportion of ICA types

The majority of both True and FN groups had densities in the BIRADS group C. Overall there were few cases in BIRADS D but in the occult group most were in the highest density category D. Following the screening event, year 1 yielded 72 (26%) ICA cases, year 2 had 129 (46.6%) and year 3 had 76 (27.4%).

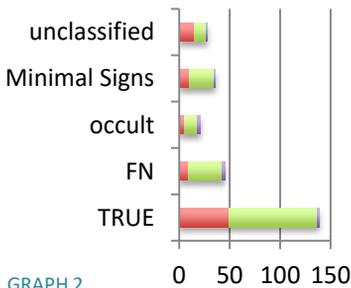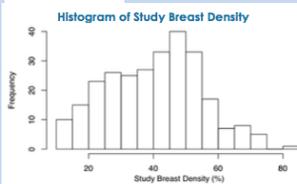### TABLE 1

Frequency Distribution - Image

	Image Dense Area (cm²)	Image Breast Area (cm²)	Image Breast Density (%)
Minimum	6.00	16.0	5.0
1st Quartile	32.00	90.0	28.0
Median	45.00	122.0	41.5
Mean	50.75	135.3	40.3
3rd Quartile	63.00	167.0	52.0
Maximum	212.00	434.0	89.0

TABLE 2

Frequency Distribution - Study

	Study Dense Area (cm²)	Study Breast Area (cm²)	Study Breast Density (%)
Minimum	12.00	33.0	12.00
1st Quartile	33.00	90.0	29.00
Median	45.00	121.0	42.00
Mean	50.98	133.8	40.75
3rd Quartile	62.00	166.0	51.00
Maximum	165.00	367.0	81.00

GRAPH 1

Histogram of Study Breast Density
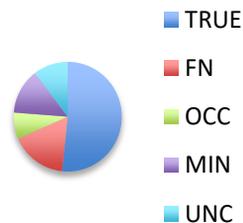
GRAPH 2

GRAPH 3

Discussion

Automated assessment of breast density with eg DENSITAS 2.1.0 prevents intra and inter observer error in density assessment and is readily reproducible. In many countries including most USA states, density measurements are mandatory in mammogram reporting. Within the overall population Sickles reports around 10% of breasts in groups A and D, the remaining fall equally into groups B and C with about 40% each. Women with cancer in a screening population tend to have denser breasts overall be they screen detected or ICA.
Around 40% of breast cancers in a screened population occur symptomatically as ICA following a normal screening result. This proportion remains similar with digital mammographic screening, despite high numbers of cancers being identified at the screen with many being higher grade, larger and more node positive tumours than the screen detected cancer cohort.
IN this study, the largest ICA subset (138) was the True category indicating there was no sign of cancer on the screening films with the majority falling in the BIRADS C group. Around 30% of ICA were either FN and minimal signs. These cancers are by definition present and visible on the screening images, yet not detected by readers. The majority (58/76) of these two groups combined were in denser breasts; BIRADS C and 4/76 in BIRADS D, suggesting that increased mammographic density may deter the recognition of these cancers. Yet Moshina et al found 51.3% of ICA in non dense breasts, with no difference in ICA category between dense and non dense groups although they report the odds of getting screen detected cancer as 1.37 versus 2.93. These data differ from ours but support the theory that higher breast density results in higher cancer incidence and ICA rates.
10.6% of our cases had no symptomatic images available (Unclassified) and were mostly in BIRADS B, which might suggest that the cancers were visible on screening films, thus clinicians did not require further imaging; the rigid classification system does not permit their classification otherwise.
Surprisingly the proportions of ICA in each of the 3 years following screening were different from previous film screen studies. NHSBSP expects around 50% to occur in the first 24 months post screen and the remaining in the 24-36 month period. This study shows that 72.6% occurred in the initial time frame. Further work is needed to consider why this has happened, aided with knowledge of the differences in the histology of the interval cancers themselves. This may be a new phenomenon due to digital screening or possibly a prevalent round effect for readers.

Learning points

Interval cancers continue to make up a significant proportion of all cancers in a screened population.
Increased breast density confers a risk for both screen detected and interval breast cancers.
Readers should be mindful to take care when reading BIRADS C type mammograms which contained overall by far the largest number of all ICA categories.
Almost a third of ICA were 'missed' (either false negative or minimal signs) on screening with the majority of these being in denser breasts with far fewer arising in the densest breast group BIRADS D
Despite the ease of obtaining digital mammograms for review over 10% were Unclassified as no images were performed at cancer presentation.

References Sickles E et al, ACR BI-RADS Mammography: American College of Radiology, 2013; 123–126
Moshina, Radiology 2018:288;343-352