A preliminary retrospective study to determine early mammographic breast density reduction following treatment

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Authors: L. Metaxa¹, L. C. H. Leong², S. W Duffy¹, T. D. Suaris¹; ¹London/UK, ²Singapore/SG
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Purpose

The mammographic appearance of the breast is an established risk factor for breast cancer and a strong association between the percentage Mammographic Density (MD) with the breast cancer risk is known [1]. It is also well known that endocrine therapy with Tamoxifen and Aromatase Inhibitors, such as Arimidex, can affect breast tissue due to their anti-estrogen action [2] on the epithelial cells and so therefore reducing parenchymal density. However, it is unclear how early after the start of the treatment mammographic density change is seen, whether the age at which administration starts has an impact and if particular mammographic breast density types demonstrate better responses to therapy.
Methods and materials

Our study cohort consisted of patients diagnosed with breast cancer, both invasive and non-invasive types, both screen detected and symptomatic at St. Bartholomew’s Hospital, London, between January 2008 and January 2009. Our London service covers an area a culturally and economically diverse population.

For each patient the electronic patient record and patient archiving systems were reviewed and information regarding adjuvant therapy, surgery, radiotherapy was captured. Dates of all of these interventions were recorded. The type and date of commencement of endocrine therapy was documented.

**Mammographic breast density Estimation:**

The majority of the mammograms (MG) were digital (36 patients had film-screen MG as a baseline). Mammographic breast density (MD) was assessed visually twice independently and in cases with major differences (over 10%), there was a third reading. Prior to the study, the readers had undertaken two standardized density scoring tests to ensure density scoring uniformity. The tests contained 100 mammograms each, with the density calculated with a computer-assisted thresholding program.

The MD was scored from 0-100% in absolute numbers for both the baseline mammogram (the MG before treatment started), and the follow up mammograms after the start of treatment. The scoring was done both independently and in comparison with the previous MG and changes between successive mammograms measured.

MD changes were assessed in age subgroups and according to the type of endocrine therapy received.

The statistical analysis was performed using the $\chi^2$ test.
Results

Breast cancer cases (n=226) were women with age range from 31 to 85 (average age=60.1, SD= 9.86) and we included cases with primary invasive cancer or ductal carcinoma in situ. We excluded patients that had missing information (n=45) and the total number of cases with valid data were 181.

- **Age Groups**

The patients were separated in 4 age groups: 30-49.9, 50-59.9, 60-69.9 and 70-89. The Table 1 and Fig. 1 on page 9 demonstrate the distribution of the ages within our cohort (average age=60.1, SD= 9.86).

<table>
<thead>
<tr>
<th>Age Range Group</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-49</td>
<td>28 (15)</td>
</tr>
<tr>
<td>50-59</td>
<td>60 (33)</td>
</tr>
<tr>
<td>60-69</td>
<td>71 (39)</td>
</tr>
<tr>
<td>70-89</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
</tr>
</tbody>
</table>

*Table 1: Distribution of Ages*

- **Endocrine Treatment**

Of the 181 patients included, 75% had taken some form of endocrine treatment (Fig. 2 on page 9). #amoxilen treatment was seen in higher percentages in the younger patients, decreasing with age (#^2, p<0.001) (Table 2) while in contrast, Aromatase Inhibitors in older ages and increasing with age (Fig. 3 on page 10).

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tamoxifen (%)</td>
</tr>
<tr>
<td>30-49.9</td>
<td>18 (64)</td>
</tr>
<tr>
<td>50-59.9</td>
<td>17 (28)</td>
</tr>
<tr>
<td>60-69.9</td>
<td>17 (24)</td>
</tr>
<tr>
<td>70-89.9</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
</tr>
</tbody>
</table>
Table 2: Age Range Groups and the Type of Treatment

- **Menopause Status and HRT**

Analysis of patients taking hormone replacement therapy (HRT) identified that women in the pre- and peri-menopausal phase (n=22 and n=7 respectively) had no history of HRT uptake. 149 (82%) women were menopausal and from those, 107 (72%) women never used HRT, 33 (22%) were using HRT but stopped years to days prior to diagnosis, and only 9 (6%) continued in low dose during the trial, for treating menopausal symptoms and severe osteoporosis. In total, 171 (94%) patients did not take HRT or stopped prior to the diagnosis of breast cancer.

**Mammographic breast density Estimation:**

- **Density measurements**

Categorising patients by BI-RADS classification system of MD, most of the patients (67%) had as baseline MG in Type I ACR, (Fig. 4 on page 11). The initial digital scores of the baseline MG (calculated from 181 patients) had a mean ± SD of 21 ± 19% and a range of 2-80%.

- **Density Reduction**

The patients had a surveillance MG in 4 to 26 months after the baseline MG (mean 11 months). As Fig. 5 on page 12 shows, 32% of patients had a surveillance MG within 6-8 months and 31% in 12-13 months. During that period, 135 patients (75%) started a type of treatment. 37% of the patients (n=67/181) had a reduction in the MD between the baseline and the first surveillance MG (Fig. 6 on page 12).

1. **Density Reduction-BI-RADS type of MD**

The MD score for the 1st surveillance MG had a mean of 19 (SD ± 17%) and a range of 1-80%. The possible connection between the type of the breast density and the possibility of changes in the MD was estimated by the $\chi^2$ test, which showed a strong trend between them ($\chi^2$, p<0.08).

<table>
<thead>
<tr>
<th>BI-RADS Types</th>
<th>Changes in MD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decrease</td>
<td>Same</td>
</tr>
<tr>
<td>ACR I</td>
<td>38</td>
<td>83</td>
</tr>
</tbody>
</table>


Table 3: BI-RADS density types and number of patients with changes in MD, between the baseline and the first Surveillance MG.

<table>
<thead>
<tr>
<th></th>
<th>ACR II</th>
<th>ACR III-IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>21</td>
<td>8</td>
<td>67</td>
</tr>
<tr>
<td>Treated (%)</td>
<td>21</td>
<td>10</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>18</td>
<td>181</td>
</tr>
</tbody>
</table>

### 2. Density Reduction-Age Range Groups

In the age group 30-49, 57% of patients within that group demonstrated a reduction in MD. The relationship between the age range group of the patients and the MD reduction was assessed using the $\chi^2$ test, which proved that there is statistically significant difference between them ($\chi^2$, $p<0.01$), showing a decrease in the possibility of MD reduction with age (Fig. 7 on page 13).

### 3. Density Reduction-Type of Treatment

In the first surveillance mammogram, 37% of patients had a reduction in the mammographic breast density compared with the baseline mammogram.

46% of patients treated with Tamoxifen had a reduction in density, which is significantly higher than the numbers of patients demonstrating MD reduction in other treatment groups (Table 4). $\chi^2$ test identified that MD reduction is significantly different in the different type of treatment groups ($\chi^2$, $p<0.01$).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>Patients with Reduction in MD based on the Type of Treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated (%)</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>56 (31)</td>
<td>26 (46)</td>
</tr>
<tr>
<td>Aromatase Inhibitors</td>
<td>79 (44)</td>
<td>25 (32)</td>
</tr>
<tr>
<td>No Treatment</td>
<td>46 (24)</td>
<td>16 (35)</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>64 (35)</td>
</tr>
</tbody>
</table>

Table 4: Type of Treatment and % possibility of MD reduction
The total number of patients satisfied the above criteria was 145 (80%) (Fig. 8 on page 14, Fig. 9 on page 15).

The number of patients that had treatment within 12 months (time between the starting date of Treatment and the 1st surveillance MG) was 115.

From that group of patients (n=145), 50 (34%) had a reduction in the MD (within 12 months). The earliest identifiable changes were seen at the 3rd-4th month after starting treatment (Fig. 10 on page 15 Fig. 11 on page 16).

34% of the patients were treated with Tamoxifen, the 46% with Aromatase Inhibitors and the rest 27% had not treatment (Table 5, Fig. 12 on page 17).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients Treated (%)</th>
<th>No. of Patients with Reduction in MD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>49 (34)</td>
<td>22 (45)</td>
</tr>
<tr>
<td>Aromatase Inh.</td>
<td>66 (46)</td>
<td>10 (18)</td>
</tr>
<tr>
<td>No Treatment</td>
<td>30 (21)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td>50 (34)</td>
</tr>
</tbody>
</table>

*Table 5: Type of Treatment, number of patients treated and MD reduction within 12 months*

This group of 145 patients were separated into two groups, based on the treatment or not with Tamoxifen (A. Treatment with Tamoxifen n=49 and B. no treatment with Tamoxifen n=96) (Table 6). 45% of patients treated with Tamoxifen had a reduction in density while the percentage decreased (29%) in the patient set that did not have Tamoxifen (Fig. 13 on page 18).

The relationship between treatment or not with Tamoxifen and the MD reduction was assessed using the \#^2 test, which proved that there is statistically significant difference between them (\#^2, p<0.05).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MD Changes</th>
<th>No. of Patients</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients with Reduction in MD (%)</td>
<td>No. of Patients with No Reduction in MD (%)</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>22 (45)</td>
<td>27 (55)</td>
<td>49</td>
</tr>
</tbody>
</table>
Table 6: Type of Treatment and changes in MD within 12 months

<table>
<thead>
<tr>
<th>No Tamoxifen</th>
<th>28 (29)</th>
<th>68 (71)</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>50</td>
<td>95</td>
<td>145</td>
</tr>
</tbody>
</table>

5. Rate of MD change

In a 12 month period of treatment the **average MD reduction** that was observed in all patients (n=145) that had a surveillance MG within that interval, was 1.7%, while among the patients that had reduction (n=50) the mean reduction in MD was 5%.

The **average reduction in the MD per month** among all the patients (n=145) is 0.36units/month for Tamoxifen which is higher than the 0.22units/month and the 0.14units/month for Aromatase Inhibitors and for the no treatment group, respectively.

Additionally, when we assess only those patients that demonstrate a reduction in MD (n=50) within the 12 months, that rate increased and corresponds to 0.8units/month for Tamoxifen, 0.78units/month for Aromatase Inhibitors and 0.52units/month for no treatment (Fig. 14 on page 18).
**Fig. 1**: Distribution of the ages within our cohort (average age=60.1, SD= 9.86)

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**Fig. 2:** Distribution of the Age Range Groups and the Treatment effects

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Fig. 3: Age Range Groups and The Type of Treatment. Younger patients treated with Tamoxifen (65% in the age range group 30-49) while older more often with Aromatase Inhibitors (51% in the age range group 60-69)

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**Fig. 4:** Mammographic Breast Density - BI-RADS ACR types

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![Graph showing time interval until first surveillance mammogram](image)

**Fig. 5:** Time Interval between the Baseline and the first surveillance MG

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**Fig. 6:** Time Interval between the Baseline and the first surveillance MG and the changes in MD

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Fig. 7: MD changes in the 1st surveillance MG and comparison with the different Age range groups

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Fig. 8: Timeline

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**Fig. 9:** Distribution in time of the 1st Surveillance MG, within 12 months of treatment

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**Fig. 10:** Distribution of the changes in the MD of the 1st surveillance MG, within 12 months of treatment

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Fig. 11: Percentage of the patients with a reduction in the MD within 12 months of treatment

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Fig. 12: Percentage of the patients with changes in the MD within 12 months and the different type of Treatment

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Fig. 13: Number of patients that had changes in the MD in correlation with treatment or not with Tamoxifen

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Fig. 14: Average reduction in % MD per Month and Type of Treatment, within 12 months of treatment

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Conclusion

The mammographic appearance of the breast is an established risk factor for breast cancer and there is a strong association between the percentage MD with the breast cancer risk [1].

As cancers develop within the epithelial and stromal tissue, the denser areas in the breast parenchyma are at higher risk [2]. There is a huge body of literature that provides evidence for the association between the Wolfe grade or percentage breast density (BI-RADS categorisation of breast density) and an increased risk of developing cancer. Additionally, Hartmaan et al. [3] in a large cohort study for benign lesions suggest that involution of the breast parenchyma is associated with reduction in the risk of developing cancer. Following that, the American College of Radiology (ACR) suggests in the Mammographic reports always to include the type of the breast composition, depending the percentage of the density of the glandular tissue (Type I: 0-24%, Type II: 24-49%, Type III: 50-74%, Type IV: 75-100%).

Mammographic Density and Treatment Types

Tamoxifen is a selective estrogen receptor modulator (SERM), and in breast acts blocking the estrogen receptors in cancer cells, preventing them from growing and division. Several articles have been publish in the last 15 years suggesting the risk reduction for breast cancer in the group of patients that treated with Tamoxifen [4]. Recently Cuzick J. et al, in an extended analysis of the IBIS-I trial provided important evidence showing 5 years of Tamoxifen treatment reduces the evidence of breast cancer for at least 20 years [5].

Tamoxifen has been found by several investigators [6-9] to reduce the MD after 1-5 years of use. Prophylactic treatment with Tamoxifen could be beneficial in women at high risk for breast cancer with dense breast parenchyma, as well as in increasing the effectiveness of the mammographic breast screening [9] in cases with very dense breasts (ACR III, IV) which by fact (ACR) reduce the sensitivity of the MG.

This study comprised the MG of patients that were diagnosed with cancer from January to December of 2008, observed and calculated the changes in the MD between the baseline and the first surveillance MG and tried to find the correlation of those changes with the age of the patients, the type and duration of treatment and estimate how early we can identify those changes in the mammogram.

The benefit of Tamoxifen is generally proved to be seen in women who are not using HRT during the treatment period, indicating the clear loss of efficacy of tamoxifen when
HRT therapy is used concomitantly [5, 10]. In our study 94% of the women did not have treatment with HRT and so that factor didn’t influence our measurements in the MD.

Our sample were women (n=181) with age range from 31 to 85 (average age=60.1, SD=9.86), diagnosed with breast cancer during 2008. 65% had a MD in ACR Type I (BI-RADS), a pattern well recognised in a British population. The initial MD scores of the baseline MG (calculated from 181 patients) had a mean of 21 (SD ± 19%) and a range of 2-80%. 75% of the patients had taken some form of endocrine treatment (Tamoxifen, Aromatase Inhibitors).

Our study showed that 37% of the patients (n=181) had a reduction in the MD between the baseline and the surveillance MG. MD reduction was noticed to have shown a strong trend in denser breasts (#2, p<0.08), with women with the most dense breasts demonstrating the biggest MD reduction. Clear evidence of an association with the age of the patients (#2, p<0.01), with younger patients having a higher probability of MD reduction rather than older women.

Differences in the extent of MD reduction were seen between the treatment groups. MD reduction is associated with the type of Treatment (Tamoxifen, Aromatase Inhibitors, No Treatment) (#2, p<0.01) and appears to be greatest in the groups of patients treated with Tamoxifen rather than no Tamoxifen (#2, p<0.05). Additionally, the rate of MD reduction per month is highest in patients treated with Tamoxifen (0.36%/month) in comparison with the other treatment protocols. Based on the rate of reduction in MD, we can reject the hypothesis that we can identify changes in the MD in patients treated with Tamoxifen earlier than 3 months (mean reduction 1%) as very small incremental reductions in density are difficult for the human eye to discern. As in our study the minimum change in MD that was measured based on the experience of the readers and the direct comparison with the baseline MG, was 2%, we can suggest that if a patient starts treatment with Tamoxifen, we should expect to identify minimum changes in the surveillance MG after 5.5-6months of treatment. Very small changes in density can be measured accurately using automated breast density software, but we were not able to access this for our study.

We have yet to identify if those who demonstrate early MD reduction, continue to see a reduction in subsequent years, and also if the risk of breast cancer recurrence is reduced in those women who demonstrated the earliest reductions. This will require us to continue to follow up our cohort.
Personal information

Dr L. Metaxa: Radiologist, St Bartholomew's Hospital, London

Dr L. Leong: Radiologist, Singapore General Hospital, Singapore

Prof. S. W. Duffy: Statistician, Wolfson Institute for Epidemiology, London

Dr T. Suaris: Consultant Radiologist, St Bartholomew's Hospital, London