Assessing the role of quantitative analysis of mammograms in describing breast density changes in women using HRT

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Abstract. We present an update of our investigations into the potential role of quantitative measures of breast density for characterising breast changes, and, in particular, changes due to Hormone Replacement Therapy (HRT). It has been established that long-term use of HRT can increase the risk of breast cancer, a fact that enforces the belief that objective measures of tissue density can be an important development in breast cancer image analysis. A set of 59 mammogram temporal HRT sequences (2 images per patient) were used in our experiments. The clinician's assessment of density changes constituted the ground truth for evaluating the proposed quantitative measures of density change. The measures are based on the h_{int} representation of interesting tissue and their performance (agreement with the expert's description) is also compared to the "interactive thresholding" method that has been used in the past to characterise mammographic density.

1. Introduction

The use of HRT (Hormone Replacement Therapy) in postmenopausal women has created a controversy, especially as its effects are hard to characterise and quantify [1]. Although HRT has several advantages (e.g. reduction of cardiovascular problems, reduction of discomfort during the menopause, prevention of osteoporosis), there is evidence of increased breast cancer risk, especially after long-term therapy. According to [1], the risk increases with the duration of use, while it is reduced after cessation. The increased risk may be due to localized increases in breast density. The breast lobules, ducts and fibrous tissue comprise the breast parenchyma (density).

Oestrogen is a powerful mitogen (for both normal breast epithelium and breast cancer cells) and the induced mitogenic signal is mediated by the hormone receptors [2]. Since there is a variable receptivity to exogenous hormones it can be expected that the density increase should not necessarily have a uniform distribution. An increase in tissue density can have an impact in screening mammography due to the fact that denser breast have a "brighter" mammographic appearance that can mask

abnormalities. Kavanagh et al [3] report a significant decrease in mammographic sensitivity and show that HRT users are more likely to have a false-negative report than non-users (odds ratio 1.60).

Clinical studies aim to correlate density changes to an increased risk of cancer or to the type of therapy used, and to assess the possible influence of such localized changes on breast diagnosis. In addition, quantification of temporal changes in women using HRT could be of great clinical value, assisting in a better prognosis for cancer. For these reasons, the development of *objective quantitative measures of density* is of great importance for future research in assessing tissue density. In this paper we suggest mammogram density measures based on a normalized representation of digitised mammograms (section 2) and then we evaluate their agreement with the clinical assessment of changes in a dataset of temporal mammograms of women using HRT (section 3) before concluding with a discussion (section 4).

2. Density Measures

In order to develop objective measures of breast density we need to normalize the mammogram image in order to account for the variability in imaging conditions. This is discussed in the next section (2.1) while in 2.2 we also consider the "area of dense tissue" measure proposed by Boyd et al. [4].

2.1 The h_{int} Representation of Interesting Tissue

Because of the relatively weak control over the image acquisition process, it is difficult to eliminate variability in image characteristics, such as contrast and brightness. Such differences in imaging conditions lead to a complicated functional relationship between the intensities of temporal pairs of mammograms that varies from patient to patient. For this reason, it becomes even more difficult to compare temporal mammograms, consequently to assess changes due to HRT.

The h_{int} representation of interesting tissue, introduced by Highnam and Brady [5], is a method to normalise mammograms, by calculating anatomical information from the mammogram image. In the resulting h_{int} image, each pixel represents the thickness of 'interesting' (non-fat) tissue of the compressed breast above that pixel during acquisition. This effectively provides objective quantitative information about the breast anatomy. Changes of fatty to glandular tissue are precisely changes in non-fatty – i.e. h_{int} – tissue. Hence, h_{int} is the natural representation to use for the quantitative approach needed. By using the h_{int} representation, we propose measures of "interesting" tissue change that reflect the underlying tissue changes due to HRT:

a) The sum of "interesting" tissue:

$$\Delta h_{\text{int}}\ (\%) = \frac{S_1(h_{\text{int}}) - S_2(h_{\text{int}})}{S_1(h_{\text{int}})} \cdot 100 \qquad (1)$$

b) The index volume of “interesting” tissue:

$$\Delta V_{\text{int}}\ (\%) = \left(V_1(h_{\text{int}}) - V_2(h_{\text{int}})\right) \cdot 100 \qquad \textbf{(2)}$$

Where,

$$S_i(h_{\text{int}}) = \sum_x \sum_y h_{\text{int}}(x_i, y_i) \qquad \text{and} \qquad V_i(h_{\text{int}}) = \frac{\sum_x \sum_y h_{\text{int}}(x_i, y_i)}{H_i \times A_i} \qquad \textbf{(3)}$$

for i=1,2

Where S_1, S_2 are the sum of interesting tissue values in each image, A_1, A_2 the area of the segmented breast region (number of pixels), H_1, H_2 are the heights of the compressed breast in each mammogram and Δh_{int}, ΔV_{int} are the suggested measures of density change.

2. 2 Projected Area

The projected area of glandular tissue has previously been used as a measure of tissue density. This measure is usually acquired by “interactive” thresholding where the clinician increases the image threshold until only the dense part of the mammogram is isolated. Subsequently, the Area % measure is calculated as the ratio of the dense area over the total area of the segmented mammogram (in pixels).

As a measure of breast density, the area of the projected glandular tissue has two basic flaws:

1. It does not calculate the “depth” of the dense tissue, only the 2D area of the projection of the breast parenchyma.

2. The interactive segmentation of the “dense tissue” is a subjective procedure and therefore the measure obtained is not consistent.

In this paper, the Area % is used in conjunction to the suggested h_{int} measures and the experimental results are presented in the next section.

3. Experimental results

Similar to large-scale clinical studies (e.g. in [6]), an experienced clinician described the changes in each HRT temporal mammogram pair. The 59 HRT mammogram sequences were classified into one of three categories by the clinician: involution (density decrease) in 21 sequences, regeneration (density increase) in 21 sequences and no significant change in the remaining 17 sequences.

For each measure, the agreement with the clinician was evaluated according to the sign of the difference of the measure between the 2 mammograms of each sequence, as is described in Table 1. The “no change” category was not considered since it is not clinically useful (only density changes can be related to cancer) and it is not a clear category since there is always a certain degree of change in the breast.

By using this description as the gold standard we evaluated our measures according to the rule presented in Table 1. The results on the agreement between classification based on measures and the clinician are presented in Table 2.

Table 1. The rule to assess mammographic changes due to HRT

Measure change in each mammogram sequence	Physiological change indicated
If $\%\Delta h_{int}$ or ΔV_{int} or $\%\Delta$Area >0	Density Decrease (Involution)
If $\%\Delta h_{int}$ or ΔV_{int} or $\%\Delta$Area <0	Density Increase (Regeneration)

Overall, the measure that performed the best is the Δh_{int} measure, as it gave consistently good results (agreement with clinical "ground truth") in both cases (involution, tissue regeneration pairs). This experiment agrees with the hypothesis that h_{int} is the right representation to use for the quantitative comparison of temporal mammograms.

Table 2. Results on the agreement between the quantitative measures used and the clinician, concerning tissue changes

Density change measure	$\%\Delta h_{int}$	ΔV_{int}	$\%\Delta$Area
Agreement with clinician in "tissue regeneration" pairs	71%	60%	71%
Agreement with clinician in "involution" pairs	81%	86%	57%

In Figure 1, we can see the V_{int} and Area % measures calculated both for the previous and current mammograms of each sequence. It is noticeable that the Area measure tends to be very similar in the "previous" and "recent" curves while the V_{int} captures more efficiently the temporal changes due to HRT. A possible explanation is that the Area measure is only a 2D measure of area, depends on user interaction (user defines global threshold) and does not capture the anatomical changes in dense tissue due to the use of HRT, or equivalently the changes in brightness due to increased or decreased density (that can be confined in the same mammographic area).

4. Discussion

We have developed a method for quantitative description of density changes in mammogram sequences and evaluated the performance of 3 measures by assessing their agreement with a clinician. Although there remains much validation work to do, it is clear from these results that measures based on the h_{int} representation can play the role of objective quantitative descriptors of mammographic density and that measures based on the area of dense tissue alone (e.g. [4]) can fail to capture temporal

variations in breast density caused by physiological processes (involution) or due to the use of HRT.

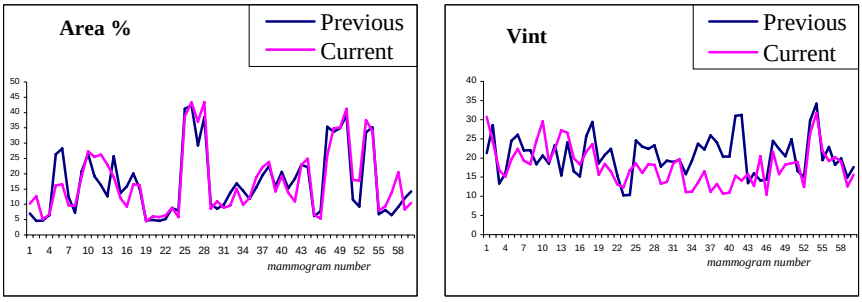


Fig. 1. Quantitative measures of breast density (Area% and V_{int}) over all the mammogram sequences examined. For each sequence there are two mammograms (previous and recent) and the V_{int} measure captures more efficiently the temporal variations in density while the Area % appears to be more "static" probably because it can't capture the changes in tissue density (or the changes of "brightness" in mammogram sequences).

Acknowledgements

The authors would like to acknowledge the Cancer Research UK for supporting this work and Mirada Solutions (http://www.mirada-solutions.com/) for providing the SMF generation software.

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