ELSEVIER

European Journal of Radiology 52 (2004) 276–282

EJR
EUROPEAN JOURNAL OF RADIOLOGY

www.elsevier.com/locate/ejrad

A mammographic image analysis method to detect and measure changes in breast density

Kostas Marias [a,b,*], Christian Behrenbruch [c], Ralph Highnam [c], Santilal Parbhoo [d], Alexander Seifalian [d], Michael Brady [a]

[a] *Medical Vision Laboratory, Department of Engineering Science, Oxford University, Ewert House, Ewert Place, Summertown, Oxford OX2 7BZ, UK*
[b] *ICS-FORTH, Vassilika Vouton, P.O. Box 1385, Heraklion GR 711 10, Greece*
[c] *Mirada Solutions Limited, Oxford Centre for Innovation, Mill Street, Oxford OX2 0JX, UK*
[d] *Department of Surgery, Royal Free and University College Medical School, UCL, London NW3 2QG, UK*

Received 28 October 2003; received in revised form 13 February 2004; accepted 17 February 2004

Abstract

We present an image analysis method that can detect and measure breast density from digitised mammograms. We present initial results on applying our method to characterise breast changes, in particular, changes due to Hormone Replacement Therapy (HRT). It has been established that long-term use of certain hormone replacement therapies can increase the risk of breast cancer, a fact that encourages the notion that objective measures of tissue density can be an important development in breast cancer image analysis. A set of 59 temporal pairs of mammograms of patients undergoing HRT (two images per patient) were used. The clinician's assessment of density changes constituted the ground truth for evaluating the proposed quantitative measures of density change. The measures we developed are based on the Standard Mammogram Form (SMF) 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. The results clearly indicate that present methods for measuring mammographic density fail to characterise temporal changes while the proposed measures have the potential to aid the radiologist in assessing temporal density changes both on a global and a local basis.
© 2004 Elsevier Ireland Ltd. All rights reserved.

Keywords: Breast imaging; Computer aided diagnosis; Imaging approach; Mammography

1. Introduction

There is increasing evidence [1] linking breast cancer risk to mammographic patterns and to the amount of dense tissue in the breast. This was recognised by Wolfe as early as 1976 [2], who proposed a coarse classification of mammographic parenchymal patterns. The classification is qualitative in that it relies upon the perceptual judgement of the diagnostician rather than being based on measurements. Inevitably, diagnosticians differ in their assignment of a region of parenchymal tissue to one of Wolfe's four classes. Wolfe's scheme has been refined in a number of ways, for example in the Six Class Categorisation and the BIRADS classification scheme. Byng et al. have proposed a semi-automatic method for assessing breast density [3]. In a completely separate development, Highnam and co-workers [4,5] developed the "interesting tissue representation", more recently styled Standard Mammogram Form (SMF) as a quantitative measure of non-fat tissue at each location in a digitised mammogram image. The work reported in this paper begins to examine the proposition that SMF can be regarded as a fully automatic, quantitative method for measuring breast density, whether in localised regions or in the entire breast. Importantly, the SMF effectively removes from consideration the choice of mammogram formation parameters such as tube voltage and exposure time, which greatly affect the appearance of the mammogram; but which are independent of the breast anatomy. It is in this sense that SMF is said

* Corresponding author.
E-mail address: kmarias@ics.forth.gr (K. Marias).

0720-048X/$ – see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejrad.2004.02.014

to “normalise” or “standardise” a mammogram. This is discussed further in Section 2.2.

Our particular focus, introduced in the next paragraph, is on measuring changes in dense breast tissue, with particular application to monitoring the effects of HRT. Related work aims to characterise the texture patterns that arise in mammograms by learning texton descriptors [6]. Although it has been reported that certain types of hormones are potentially safe, the use of Hormone Replacement Therapy (HRT) in postmenopausal women remains controversial, especially as its effects are hard to characterise and quantify. According to [7], the risk of developing cancer increases with the duration of use, while it is reduced after cessation. It seems that the increased risk may be due to localised increases in breast density. Density (breast lobules, ducts and fibrous tissue) is known to be a major risk factor for breast cancer and this has been confirmed in studies using mammographic density measures [8]. In this paper, we use objective measures of breast density to characterise density changes with application to HRT temporal mammograms.

In clinical practice, HRT is recommended for the relief of adverse symptoms related to the menopause, and to prevent osteoporosis. HRT is recommended in women who have had a hysterectomy. Over 60,000 hysterectomies are currently being performed in the United Kingdom each year [9]. A consequence of the operation is ovarian hormone deficiency, which often affects quality of life. There is also evidence that HRT can reduce the risk of heart disease; however, this still has to be confirmed by (ongoing) large-scale, controlled clinical trials. There are three main implications of HRT, discussed in the next subsections.

1.1. Increased risk for breast cancer

There is some disagreement in reports on whether HRT does or does not increase the risk of breast cancer. However, most studies agree that the risk of developing cancer increases for women that use HRT for more than 10 years. A study concerning women that participated in the breast screening programme in the West of Scotland [10], reports that 12.3% of women with screening detected cancers and 22.2% of women with interval cancers were using HRT. Perhaps the most interesting study, the Million Women Study in the UK investigated the relative risk of breast cancer between current HRT users and never-users [11]. 1,084,110 UK women aged 50–64 years participated in the study between 1996 and 2001 and the results indicate that HRT is indeed associated with an increased risk of incident and fatal breast cancer especially for combined oestrogen–progestagen therapy.

1.2. Changes in density and mammographic appearance

The response to HRT depends on the individual woman and is neither necessarily uniform nor global; in fact, it depends on the hormonal receptivity of the epithelial elements. As a result, HRT can lead to both an increase in the density and a change in the density distribution (pattern) of the breast tissue. Kaufman et al., reported that women using HRT were found to have higher risk parenchymal patterns (according to Wolfe’s criteria) than non-users [12]. A more recent study concludes that HRT users were more than twice as likely to have a high-risk pattern than never-users [13]. Several studies report that breast tissue density can increase in women who use HRT, sometimes causing cysts or fibroadenomas. Sterns and Zee [14] report that in a study of 1232 postmenopausal women, only 18% of the HRT group showed signs of continuing breast tissue involution, as opposed to 38% in the non-users group where density decrease (involution) was apparent.

In conclusion, there is a consistent belief that HRT can increase breast tissue density. The type and degree of change depends on the exogenous hormone receptivity of the individual, and also on the type of hormones used in the treatment [15]. An increase in tissue density can have an impact in screening mammography. This is discussed in the next section.

1.3. HRT changes decrease mammographic sensitivity

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. Several studies have reported a decrease in mammographic sensitivity due to HRT. Kavanagh et al. 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) [16]. For this reason, many researchers address the possible dangers related to the use of HRT and suggest measures for monitoring users more carefully. Sala et al., recommend careful clinical and mammographic follow-up for women on HRT, recognising the possible risks [13], while Berkowitz et al. [17] had previously suggested “serial” and “vigilant” monitoring of women that showed a positive response to HRT (density increase). As is reported in [13], the mammographic patterns induced by HRT usage can be a new baseline, and changes with respect to this new pattern should be monitored over time. Once a woman responds to treatment and the breast density increases, temporal comparison of mammograms becomes essential since an abnormality can be detected on the basis of significant difference with a baseline mammogram.

In all the studies cited above, it is evident that there is a lack of “objective” quantitative measures of dense tissue. From the image analysis standpoint, methods to detect and measure changes in breast density can potentially provide the clinician with a framework for assessing the individual risk of cancer and maximising the chances for early diagnosis. This is the key idea underlying our work in quantification of density changes in women that use HRT, as discussed in the next section.

2. Materials and methods

2.1. Mammographic measures of breast density

Several 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 localised changes on breast diagnosis. In addition, quantification of temporal changes has considerable clinical potential in supporting earlier, more reliable and reproducible diagnosis. For these reasons, the development of objective quantitative measures of density is potentially of importance for future research in assessing tissue density. In this paper we suggest mammogram density measures based on the SMF representation of digitised mammograms and test their agreement with the clinical assessment of changes in a dataset of temporal mammograms of women using HRT. In order to develop objective, mammographic measures of breast density, we need to normalise the mammogram image in order to account for the variability in imaging conditions. This is discussed in the next section where the proposed measures are presented, while in Section 2.3 we discuss an existing density measure proposed by Byng et al. [3].

2.2. The h_{int} (SMF) 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 density changes. After developing a method for the calculation and correction for the scattered radiation, Highnam and Brady [4] discovered a method for mammogram image normalisation. This was based in the following assumptions/observations:

- The X-ray attenuation coefficients of normal, healthy tissue and cancerous tissue are very nearly equal, but are quite different from that of fat.
- Fat is clinically uninteresting, so normal healthy and cancerous tissues are collectively referred to as “interesting”.

Highnam and Brady’s method estimates—in millimetres—the amount of interesting tissue in each pixel column, as is illustrated in Fig. 1. This effectively provides objective quantitative information about the breast anatomy. If, for example, the separation between the Lucite plates is 6.5 cm, the amount of interesting tissue at a location (x, y) might be 4.75 cm, implying 1.75 cm of fat.

This way, the interesting tissue representation refers only to (projected) anatomical structures—the algorithm has estimated and then eliminated the particular parameters that were used to form this image. In short, the image can be regarded as standardised (hence, the more recent name

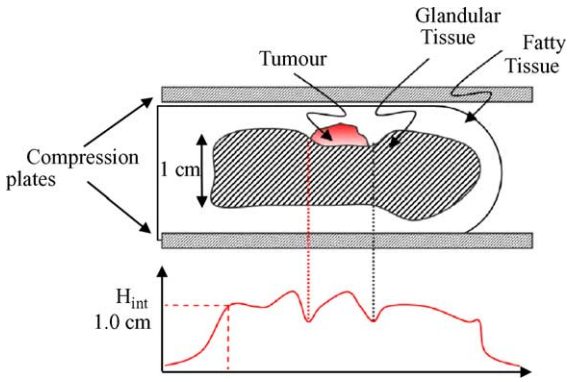


Fig. 1. A schematic of h_{int} calculation.

Standard Mammogram Form) and quantitative since the ‘normalised’ pixel values are measurements in millimetres, not in arbitrary shading (contrast) and they convey anatomical information. By using the h_{int} representation, we propose the following measures of “interesting” tissue change that are compression-invariant and reflect the underlying tissue changes due to HRT:

(a) The sum of “interesting” tissue:

$$\Delta h_{int}(\%) = \frac{S_1(h_{int}) - S_2(h_{int})}{S_1(h_{int})} \times 100 \quad (1)$$

(b) The index volume of “interesting” tissue:

$$\Delta V_{int}(\%) = [V_1(h_{int}) - V_2(h_{int})] \times 100 \quad (2)$$

where,

$$S_i(h_{int}) = \sum_x \sum_y h_{int}(x_i, y_i) \quad (3)$$

$$V_i(h_{int}) = \frac{\sum_x \sum_y h_{int}(x_i, y_i)}{H_i \times A_i} \quad (4)$$

S_i is the sum of interesting tissue values in each image, A_i the area of the segmented breast region, H_i the height of the compressed breast in each mammogram, $i = 1, 2$. Δh_{int} and ΔV_{int} are the suggested measures of density change. The first measure is the temporal difference of the sum of the normalised image values while the second is the difference of the approximate normalised volume indexes. These measures are compared to the “projected area” measure presented in the next section.

2.3. Projected area

The projected area of glandular tissue has previously been used as a measure of tissue density [3]. This measure is compression-dependant and is usually acquired by “interactive” thresholding, a method in which the clinician increases the image threshold until 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 at each location—hence, support a measure of breast density volume, rather it is restricted to measuring 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 for comparison to the suggested h_{int} measures and the experimental results are presented in the next section.

3. Results

3.1. Assessing the value of the proposed quantitative measures of density change

Similar to large-scale clinical studies (e.g. in [18]) 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 of the measures listed above, the agreement with the clinician was evaluated according to the sign of the difference of the measure between the two 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 well defined category because even if humans cannot perceive density changes in a mammogram sequence there is always an actual change in breast density.

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. 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 1
The rule to assess mammographic changes due to HRT-based on quantitative measures

Measurement of density change	Decision
If Δh_{int}% or ΔV_{int} or ΔArea% > 0	Density decrease (involution)
If Δh_{int}% or ΔV_{int} or ΔArea% < 0	Density increase (regeneration)

Fig. 2 shows 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. It is worth mentioning that according to the clinician, most of the pairs used in the experiment, exhibited significant changes in tissue content which are well described by the difference in the temporal curves of Fig. 2(right) but are not "captured" in Fig. 2(left). The most likely explanation is that the Area measure strongly depends on user interaction (user defines global threshold), and that the user tends to select equal area in temporal mammograms due to the similar tissue architecture appearance of a temporal mammogram pair. For this reason, we believe it is a weak measure of dense tissue, and especially in measuring density changes. We argue that any other measure not based on a normalised representation of image intensities (like SMF-based on h_{int} values) cannot be the basis of a robust image analysis tool for the objective description of density changes in mammogram sequences. In the following section we investigate the idea of characterising HRT tissue density changes locally.

3.2. Can we assess local density changes in HRT mammograms?

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. Since there is a variable receptivity to exogenous hormones it can be expected that the density increase would not necessarily be uniformly distributed throughout the breast. In the

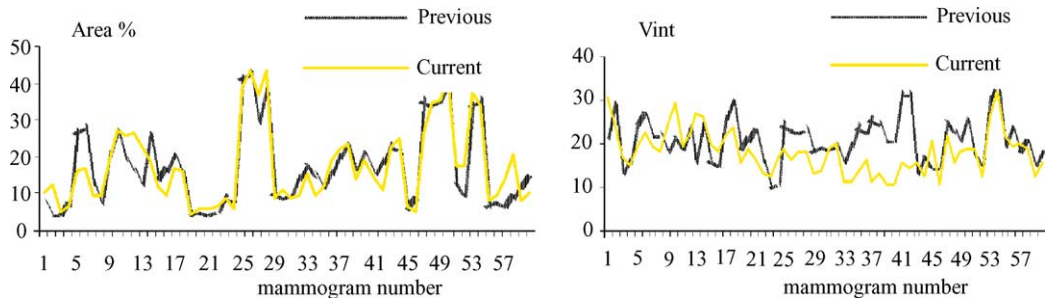


Fig. 2. Quantitative measures of breast density (Area% and V_{int}) over all the mammogram sequences examined. For each mammogram number there are two mammograms (previous and current). The V_{int} measure captures more efficiently the temporal variations in density than the Area%.

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

Density change measure	Δh_{int}%	ΔV_{int} (%)	ΔArea%
Correctly classified "tissue regeneration" pairs	71	60	71
Correctly classified "involution" pairs	81	86	57

previous section, we suggested measures of global changes in tissue composition. Our ultimate goal is to be able to assess significant local changes in tissue density. However, it is most often the case that different breast compression is exerted at the breast between successive mammograms. For this reason, to achieve local quantitative comparison of mammographic density it is necessary to geometrically align the mammograms we wish to compare. The registration algorithm that we use is described in [19] and it is based on aligning mammogram pairs using consistent landmarks that are calculated on the breast outline as well as internal regions that reflect the architectural similarity of the temporal mammogram pair.

The framework that we propose for the assessment of local density changes, combines registration and normalisation, so that the clinician can locally compare temporal mammogram pairs. Fig. 3(a) and (b), shows a registered and normalised mammogram sequence of a woman on HRT. It is obvious in the second image that there is a "global" increase in glandular tissue. Using the Δh_{int} measure the change was calculated to be 35% increase in glandular tissue. The line-intensity profile after registration in Fig. 3(c) shows that there is indeed an increase in the overall intensity with some "larger" local variations (numbered 1, 2, 3) that correspond to the three areas of glandular tissue regeneration indicated in Fig. 3(b). Although this is a preliminary result, it clearly shapes a vision for its several potential clinical applications in prompting the clinician into regions of "high" density change (potential abnormalities). In this context, automatic density measures should be used on a local basis, and after the mammograms have been geometrically aligned, so that they can detect regions of subtle density change.

4. Discussion

We have developed a method for quantitative description of density changes in mammogram sequences and evaluated the performance of three 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 an important role in developing objective quantitative descriptors of mammographic density. In addition, it is clear that measures based on the mammographic area of dense tissue alone (e.g. [3,8]) fail to capture temporal variations in breast density caused by physiological processes (involution) or due to the use of HRT. Part of the reason is that the mammographic area is a 2D representative of the 3D dense tissue. However, the most important drawback of such methods is that they compare measures calculated in mammograms sequences that have not been intensity-normalised so that they can convey reliable, quantitative information.

We believe that SMF-based quantitative measures should be the basis for quantitative analysis in mammography, especially for large-scale epidemiological studies aiming to define the relationship of breast cancer incidence and mammographic density. Moreover, we consider the results of our work to be very encouraging for developing computer tools that will automatically monitor important changes in mammographic density in successive scans. This is illustrated in Fig. 4, where two different ways of examining changes in mammographic density are suggested; first a 3D surface visualisation of a geometrically aligned SMF mammogram pair (Fig. 4(a) and (b)) allows us to have a better feeling of the areas where the h_{int} measures indicate maximum density

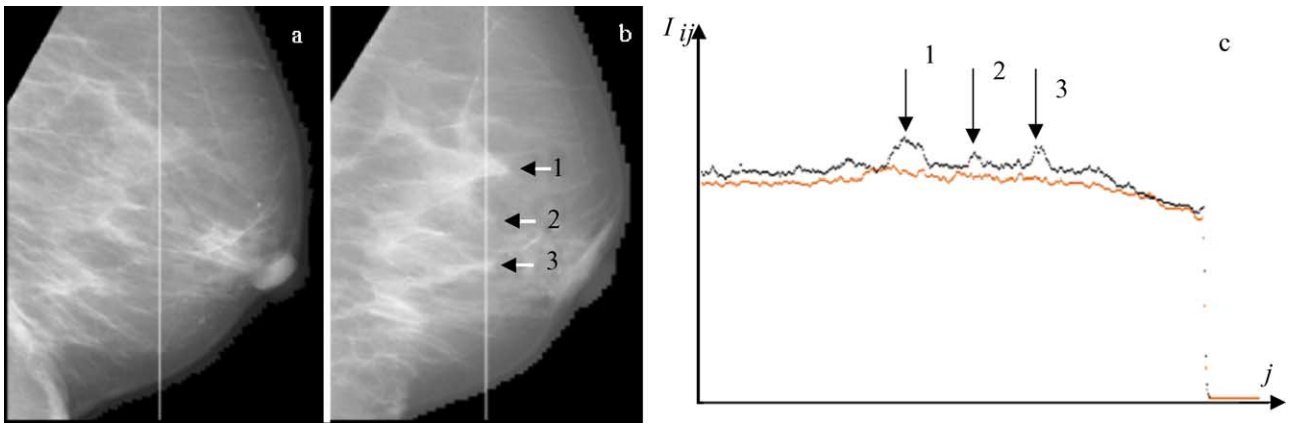


Fig. 3. (a and b) A normalised, aligned mammogram pair, where, in (b) density is increased due to HRT. (c) "Larger" local variations (numbered 1, 2, 3) along the same bright line indicated in (a) and (b) correspond to the three areas of glandular tissue regeneration marked in (b).

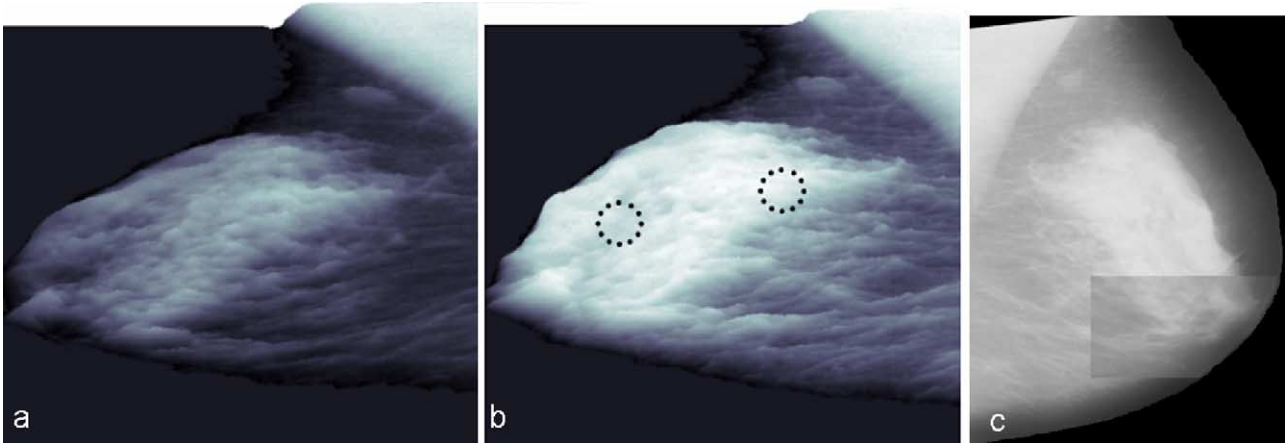


Fig. 4. (a and b) Automatic HRT local density change assessment shown in 3D. The two circles (right image), indicate the areas of maximum density increase due to hormones, as suggested by the computer, (c) illustrates a proposed method for viewing local changes in registered images.

change. Alternatively, as is shown in Fig. 4(c), the clinician can read the most recent mammogram moving an image tile that corresponds to the previous registered and normalised mammogram, in order to visually detect and focus in areas of significant density change.

5. Conclusion

There is global awareness of the possible risks associated with HRT. Although there are still disagreements about whether or not there is a statistically significant increase of the risk of breast cancer in women using HRT, all studies seem to agree that more frequent and careful screening should be introduced for women receiving treatment. These increased concerns about HRT users would inevitably increase the recall rate for incident screening, hence, an increased cost and anxiety in the screening population [20]. However, the cost should not be a significant factor in the decision of whether or not to use HRT, especially since computer assisted radiology has the potential to assist the clinician to determine changes (e.g. due to HRT). In this work we argued that the use of mammogram image analysis could improve the early detection of abnormalities by providing the clinician with both quantitative information concerning temporal density and information relative to the region where these changes take place. Our future work aims to perform more validation work on automatic density measures and develop robust clinical tools, able to provide reliable mammographic information for both the monitoring of density in HRT users and for epidemiological studies.

References

[1] Day N, Warren R. Mammographic screening and mammographic patterns. Breast Cancer Res 2000;2(4):247–51.
[2] Wolfe JN. Breast pattern as an index for developing breast cancer. Am J Roentgenol 1976;126:1130–9.
[3] Byng JW, Yaffe MJ, Jong RA, et al. Analysis of mammographic density and breast cancer risk from digitised mammograms. Radiographics 1998;18(6):1587–98.
[4] Highnam RP, Brady JM. Mammographic image processing. Kluwer Academic Press; 1999.
[5] Brady M, Gavaghan D, Simpson A, Parada MM, Highnam R. eDiamond: a grid-enabled federated database of annotated mammograms. In: Bearman, Fran, Fox, Geoffrey, Hey, Tony, editors. Grid computing: making the global infrastructure a reality. Wiley; 2003.
[6] Marias K, Petroudi S, English R, Adams R, Brady M. Subjective and computer-based characterisation of mammographic patterns. International Workshop on Digital Mammography, Lecture Notes in Computer Science. Berlin Heidelberg: Springer Verlag; 2002.
[7] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative analysis of data from 51 epidemiological studies of 52705 women with breast cancer and 108411 women without breast cancer, Lancet 1997;350 (9084):1047–59.
[8] Boyd NF, Lockwood GA, Byng JW, et al. Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers 1998;7:1133–44.
[9] Khastgir G, Studd J. Hysterectomy and HRT. London: Martin Dunitz Ltd.; 1998.
[10] Litherland JC, Stallard S, Hole D, Cordiner C. The effect of hormone replacement therapy on the sensitivity of screening mammograms. Clin Radiol 1999;54(5):285–8.
[11] Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. Lancet 2003; 362:419–27.
[12] Kaufman Z, Garstin WI, Hayes R, Michell MJ, Baum M. The mammographic parenchymal patterns of women on hormonal replacement therapy. Clin Radiol 1991;43(6):389–92.
[13] Sala E, Warren R, McCann J, et al. High-risk mammographic parenchymal patterns, hormone replacement therapy and other risk factors: a case-control study. Int J Epidemiol 2000;29(4):–36.
[14] Sterns EE, Zee B. Mammographic density changes in perimenopausal and postmenopausal women: is effect of hormone replacement therapy predictable? Breast Cancer Res Treat 2000;59(2):125–32.
[15] Ozdemir A, Konus O, Nas T, et al. Mammographic and ultrasonographic study of changes in the breast related to HRT. Int J Gynaecol Obstet 1999;67(1):23–32.

[16] Kavanagh AM, Mitchell H, Giles GG. Hormone replacement therapy and accuracy of mammographic screening. Lancet 2000;355(9200):270–4.
[17] Berkowitz JE, Gatewood OM, Goldblum LE, Gayler BW. Hormonal replacement therapy: mammographic manifestations. Radiology 1990;174(1):199–201.
[18] Persson I, Thurfjell E, Holmberg L. Effect of oestrogen and oestrogen–progestin replacement regimens on mammographic breast parenchymal density. J Clin Oncol 1997;15:3201–7.
[19] Marias K, Behrenbruch CP, Brady M, Parbhoo S, Seifalian A. Multi-scale landmark selection for improved registration of temporal mammograms. Proceedings of the International Workshop in Digital Mammography. Toronto: Medical Physics Publishing; 2000.
[20] Litherland JC, Evans AJ, Wilson AR. The effect of hormone replacement therapy on recall rate in the National Health Service Breast Screening Programme. Clin Radiol 1997;52(4):276–9.