Changes in breast density over time using automatic density measures. Preliminary analysis.

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ABSTRACT

Breast density is an important risk factor for the development of breast cancer. The aim of this paper is to evaluate temporal breast density changes using density maps, provided by the commercial software Volpara^{TM}. The dataset is composed of 563 mammograms from 55 patients (aged between 24 and 75 years old). The time frame between two acquisitions varies from less than one year to 4 years. Pairs of mammograms are registered using the morphons registration algorithm, in order to evaluate the structural similarity of the parenchymal distribution between the two acquisitions. To provide a fair comparison, the results are divided considering the patient age during the first mammographic acquisition and the time between the two studies. To evaluate the changes in breast density, local and global measures, such as the rate of change of the volumetric breast density, the histogram intersection between two density maps and the normalized cross-correlation after the registration, are considered. The results show significant differences in the statistics, mainly focused on patients younger than 30 years old and ranged between 56 and 65 years old with respect to those in the adulthood (between 30 and 55 years old). Similarly, the time between the two mammographic acquisitions shows a significant difference for patients older than 56 years old considering one and two year of difference between the two studies.

Keywords: Full-Field Digital Mammography, Changes in Breast Density, Local Breast Density

1. INTRODUCTION

Volumetric breast density (VBD) is one of the most important risk factors for developing breast cancer.[1] During liftime, the glandular tissue of the breast decreases, in particular around menopause. Moreover, the breast cancer incidence curve increases with the age[2] and, therefore, aging is a risk factor *per se*. Usually, VBD is determined by means of subjective visual measurements from the mammograms, and categorized using the BI-RADS (Breast Imaging Reporting and Data Systems) standard.[3] Several methods, such as feature-based,[4,5] area-based approaches[6,7] or physic-based models,[8,9] have been proposed to obtain an objective VBD value. In contrast, the physics-based model proposed by Highnam et al.,[10] available under commercial license as Volpara^{TM} Density Maps (Volpara Solutions[*]; Wellington, New Zealand), is able to provide the local (pixel-wise) information of the glandular tissue thickness within the mammogram.

In addition to global measures, such as the volumetric breast density and glandular tissue volume, the local density distribution can provide complementary information for risk assessment and disease development.[11,12] Lately, Volpara^{TM} Density Maps has shown the reliability of glandular tissue measurements using reacquired mammographic images.[13] In that work, 99 pairs of duplicated mammograms, acquired within a short time frame, just few minutes, were used to evaluate the parenchymal pattern similarity between the two acquisitions. In addition, the aim of this paper is to analyze the changes in local breast density over the time, extending the previous work.

Several factors need to be considered in a temporal analysis: aging, involution, hormone replacement therapy, oral contraceptive use, menstrual timing, diet, exercise, and general hormonal influences.[14] These factors may modify the appearance of the mammogram as well as the automatic density measures. The rate of involution may be the true variable associated with risk. The relationship between breast cancer and hormonal interactions and involution are suggested by the connection with high- and low- risk patterns.[14] In this case, we focus our

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[*]http://volparasolutions.com/

attention in aging. To achieve this goal, the mammographic studies are stratified considering the age of the patients, in order to provide a fair comparison among the pre-, post- and menopausal stages, and the time frame between the two studies. Volpara^{TM} Density Maps is used to extract the glandular tissue and global and local measures are used to evaluate the temporal changes.

This paper is organized as follows: Section 2 exposes the material and methods, which includes the basis of Volpara^{TM} and the evaluation methodology. Section 3 exposes the results obtained using local and global statistics. This paper concludes with Section 4, discussion, and a brief conclusion, Section 5.

2. MATERIAL AND METHODS

2.1 Volpara^{TM} Density Maps

The basis of Volpara software can be found in the work of Highnam et al.[10] Briefly, Volpara^{TM} starts by looking for an entirely adipose area within the mammogram. The mean intensity value of this area (P_{fat}) is subsequently used as a reference to estimate the density map $DM(x, y)$, i.e. the thickness of the glandular tissue at each pixel of the mammogram, using the equation:

$$DM(x,y) = \frac{ln(P(x,y))/P_{fat}}{\mu_{fat} - \mu_{dense}},\tag{1}$$

where $P(x, y)$ corresponds to the gray level intensity at pixel (x, y) in the raw mammogram, which is proportional to the x-ray energy absorbed at the image receptor. Key acquisition parameters from the meta-data of the image (e.g. kVp, x-ray tube anode material, filter material, compressed breast thickness) are read from the DICOM header to use the appropriate x-ray linear attenuation coefficients (μ_{fat} and μ_{dense}). This approach provides us the spatial distribution of breast glandular tissue from Full Field Digital Mammograms (FFDM). Integrating $DM(x, y)$ over the whole mammogram, Volpara^{TM} computes the Volume of Glandular Tissue (VGT). Furthermore, by taking into account the area of the projected breast on the mammogram and the recorded compressed breast thickness, Volpara^{TM} also computes the Breast Volume (BV). Finally, the ratio between VGT and BV represents the Volumetric Breast Density (VBD).

2.2 Density maps registration

Mammograms are two-dimensional projections of the internal tissues of the breast. However, the reproduction of exact image acquisition conditions during repeated mammograms is not possible in practice. This is due to small variations in patient positioning, differences in breast compression, or even different image acquisition parameters that are selected by an automatic exposure control software (e.g. anode/filter material, beam quality). In order to minimize these misalignments when comparing the local density maps, we perform a two-dimensional registration step. In this case, the morphons registration algorithm was used to align the two temporal density maps, because it obtained the best performance in previous work.[13]

Briefly, morphons[15] is a non-rigid registration method performed in three steps. Firstly, it estimates the local displacement using quadrature phase differences, which are invariant to image intensities and weak gradients, and are used as a measure of the local structures. Afterwards, the local displacement is estimated as a function of the local phase along each direction. Finally, the displacement is accumulated into a total displacement field and regularized, allowing to morph the source image into the target image.

2.3 Evaluation

Global and local measures are used to evaluate the appreciable change of the glandular tissue computed by Volpara^{TM}. In particular, we focus our attention in the rate of change (RC) of the volume of the breast density, the histogram intersection (HI) between the information contained in two density maps and the normalized cross-correlation (NCC) between the two images in order to perform a structural analysis of the glandular distribution.

Table 1. Dataset composed of 613 pairs of temporal mammograms, divided considering the patient age in the first acquisition and the time frame, in years, between the two acquisitions.

Time frame	Age									
	24-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70	71-75
0	2	0	0	4	1	4	4	4	0	0
1	20	28	102	56	73	34	22	26	0	8
2	16	20	56	28	14	16	7	8	0	4
3	6	0	20	12	0	4	0	2	0	0
4	0	4	4	4	0	0	0	0	0	0

2.3.1 Rate Of Change (RC)

The rate of change is used to mathematically describe the percentage change in value over a defined period of time. RC represents the change of a variable with respect to the value from the former period. Usually, the value is multiplied by 100 in order to obtain a percentage representation.

Formally, the RC is defined as follows:

$$RC = \frac{VBD_t - VBD_{t-1}}{VBD_{t-1}} \cdot 100. \tag{2}$$

where VBD_t and VBD_{t-1} represent the volumetric breast density value at time t and $t-1$ respectively.

2.3.2 Histogram intersection (HI)

Histogram Intersection[16] computes the similarity between the intensity (i.e the glandular tissue thickness) distributions of the two images. Usually the intersection value is normalized to obtain a result between 0 (no overlap) and 1 (identical distributions), and is defined as follows:

$$H(I_A, I_B) = \sum_i min(h_{I_A,i}, h_{I_B,i}) \tag{3}$$

where $h_{I_A,i}$ and $h_{I_B,i}$ represent the value of the bin i in the histograms corresponding to the image I_A and I_B.

2.3.3 Normalized Cross-Correlation (NCC)

Normalized Cross-Correlation[17] is a standard statistical measure used to calculate whether two datasets are linearly related, and represents the 2D version of the Pearson's correlation coefficient. NCC is defined as follows:

$$NCC = \frac{\sum_{(i,j)}(I_A(i,j) - \bar{I}_A)(I_B(i,j) - \bar{I}_B)}{\sqrt{\sum_{(i,j)}(I_A(i,j) - \bar{I}_A)^2}\sqrt{\sum_{(i,j)}(I_B(i,j) - \bar{I}_B)^2}} \tag{4}$$

where $I_A(i,j)$ and $I_B(i,j)$ represent the intensity value (i.e. thickness of glandular tissue) of the pixel (i,j) and $\bar{I}_A$ and $\bar{I}_B$ are the mean intensity values of the images I_A and I_B, respectively.

3. EXPERIMENTAL RESULTS

The dataset was composed of 563 images, including both CC and MLO mammograms, from 55 different patients, yielding 613 temporal pairs of mammograms within time frames between 0 and 4 years. Images were acquired at the Radboud University Medical Center (Nijmegen, The Netherlands) between January, 2005, and May, 2011, using either a GE Senographe 2000D or a GE Senographe DS. These FFDMs were acquired for screening purposes of women at high-risk breast cancer (high familiar or genetic risk), according to the standard clinical settings. Patients aged between 24 and 75 (44.09 ± 10.16) years old during the first acquisition.

The dataset was divided, considering: i) the patient age in the first acquisition, and ii) the interval between the two acquisitions. Table 1 summarizes the dataset division and the number of images for each interval. The
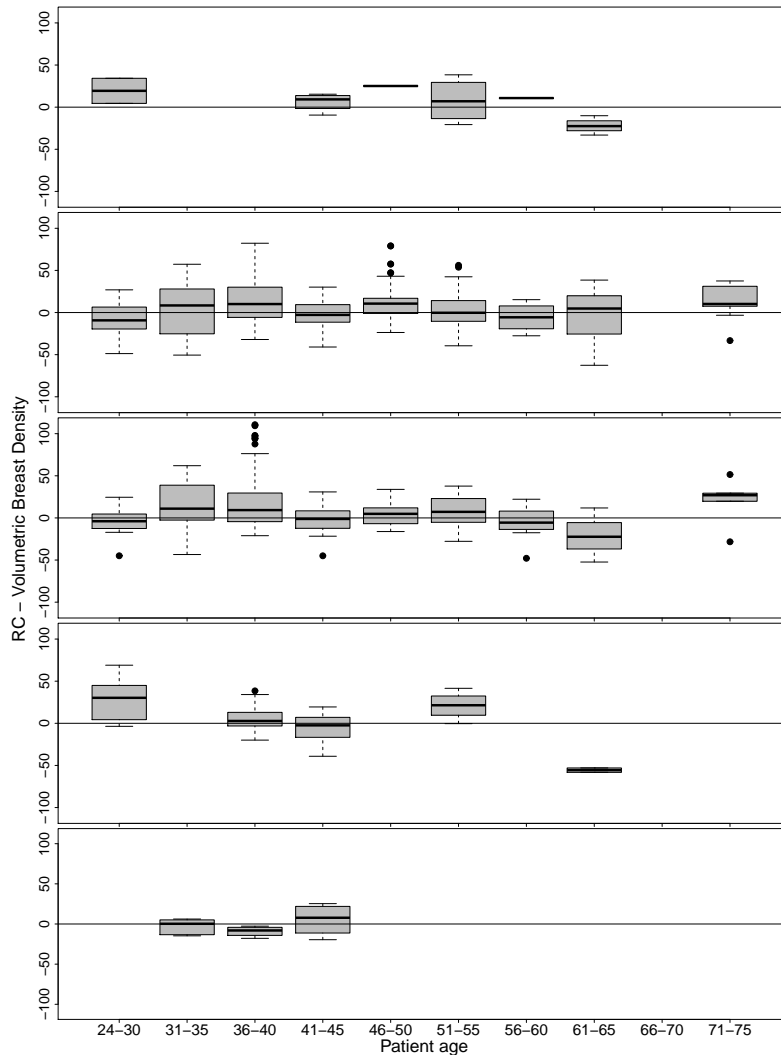
Figure 1. Rate of change, in percentage, of the volumetric breast density, computed between two temporal density maps, with respect to the patient age, in years. Each row corresponds to an increasing time frame between the two acquisitions, from 0 to 4 years. Negative RC values represent that the software reports a higher VBD value in the first acquisition.

patients age were divided into 5-years frames, in order to provide a fair comparison of the changes among pre-, post- and menopausal stages. The commercial software Volpara^{TM} (v. 1.5.11) was used to extract the glandular tissue distribution while the data analysis and statistical tests were performed using the software R-studio (R v.3.0.3).[18]

Figure 1 shows the RC of the volumetric breast density computed by Volpara^{TM}. Notice that, while equation 2 represent the first acquisition as $t - 1$, in this analysis, the time frame between two acquisitions varies from 0 (less than one year) to 4 years. Negative RC values represent that the software reports a higher VBD value in the first acquisition.

RC values vary from -62.62%, when patients are between 61 and 65 year old in the time frame of 1 years between the two acquisitions, to 110% in age ranged between 36 and 40 years in the frame of 2 years between the two acquisitions. In the adulthood (patients younger than 45 years old) and the perimenopausal stage (between 46 and 55 years old) the median of the RC distributions are ranged between -16.9, with 3 years of difference between the two mammographic studies, and 25.11, with less than one year. While in the menopausal stage (between 56 and 65 years old) the median values vary from -22.49, less than one year, to 14.00, one year.
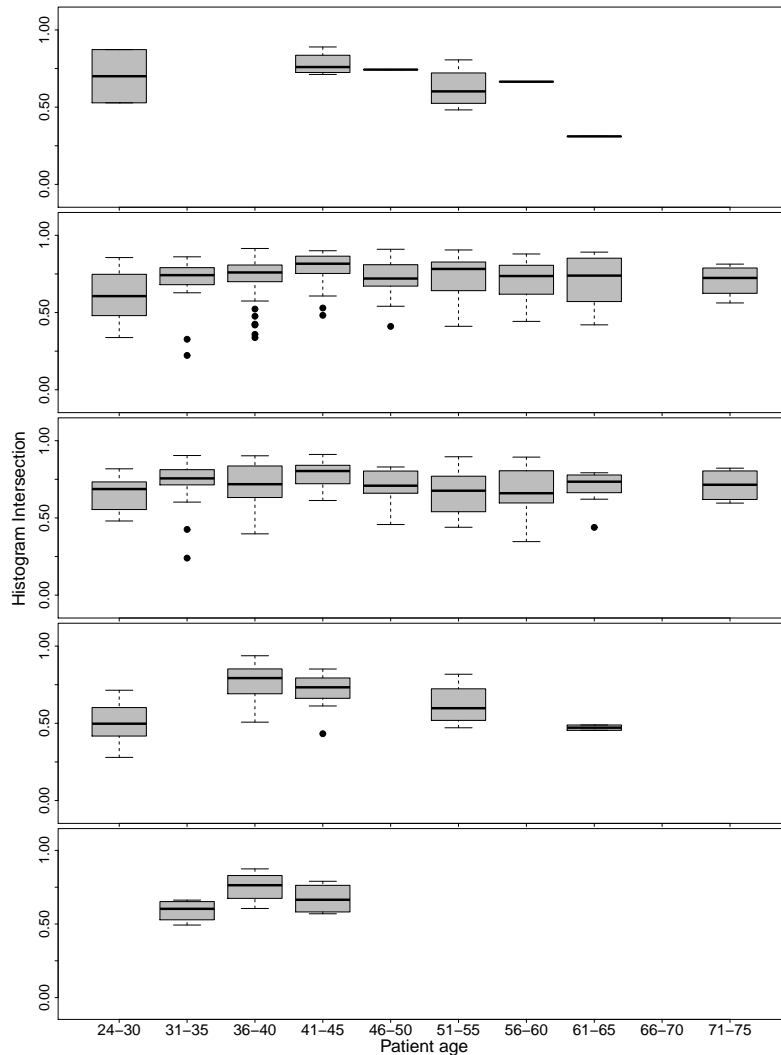
Figure 2. Histogram intersection between two temporal density maps, with respect to the patient age, in years. Each row corresponds to an increasing time frame between the two acquisitions, from 0 to 4 years. The higher the histogram intersection, the higher the shared information between the images.

Regarding the latest, the RC values tends to decrease which represents the acceleration of the loose of glandular tissue. Significant differences in the RC distributions are shown at this stage when the two mammograms are acquired between 56 and 65 years old ($p < 0.05$ and $p < 0.001$ considering each interval independently) with respect to the adulthood stage.

Considering each age interval independently, women between 24 and 30 years old, as well as between 36 and 40 years old and between 60 and 65 years old show significant changes ($p < 0.05$, $p < 0.05$ and $p < 0.01$ respectively) in the RC distributions considering the time frame between the two acquisitions.

Figure 2 shows the histogram intersection between two density maps acquired within the corresponding time frame. During this analysis, each bin in the histogram represents 1 mm of glandular tissue. Furthermore, notice that, so far, the registration has not been performed and these values correspond to the density maps directly obtained from the FFDMs. The HI values vary from 0.44, where patients are aged between 24 and 30 years old in the time frame of 3 years between the two acquisitions, to 0.97 in age ranged between 36 and 40 years in the frame of 3 years between the two acquisitions. Significant differences are shown when the mammograms are acquired with one and three years of difference. In the first case, patient aged between 24 and 30 years old ($p < 0.01$)
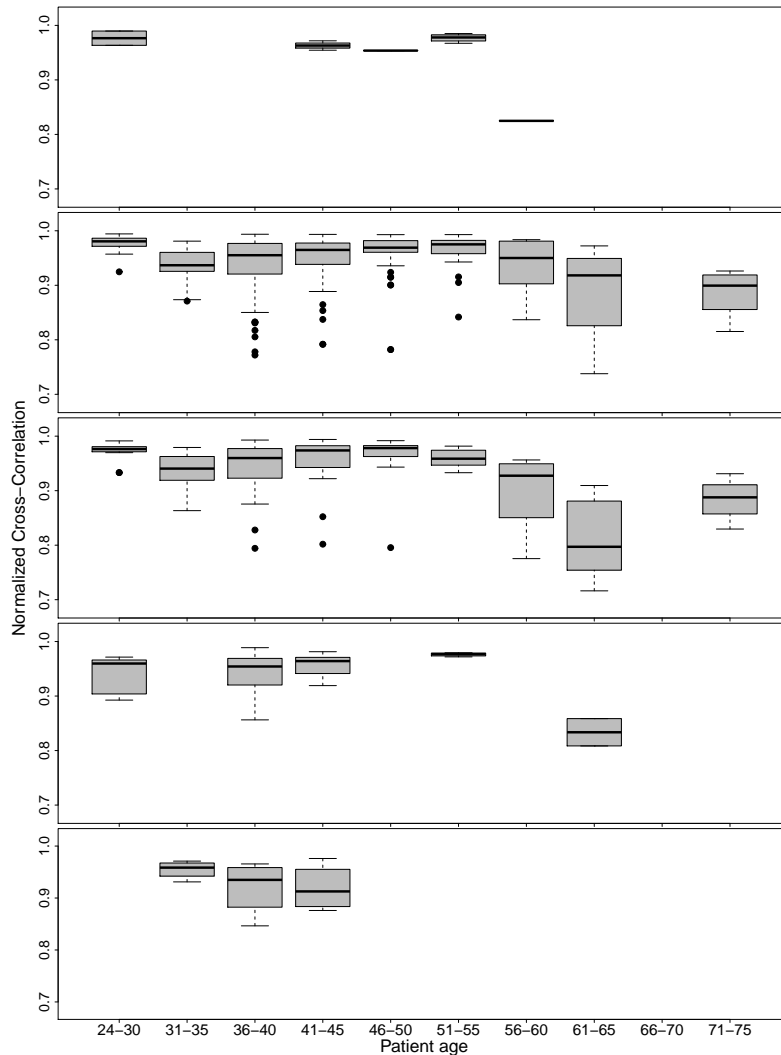
Figure 3. Normalized Cross-Correlation after morphons registration, with respect to the patient age, in years. Each row corresponds to an increasing time frame between the two acquisitions, from 0 to 4 years. The higher the NCC value, the higher the parenchymal pattern similarity.

and between 40 and 45 years old show a significant difference ($p < 0.01$) while, using the mammograms acquired with 3 years of difference, this effect occurs when patient are ranged between 60 and 65 years old ($p < 0.001$) with respect to the rest of the age intervals. Considering the patient age, there is not a significant difference when two acquisitions are performed with different time frames, with the exception of the interval between 61 and 65 years old where the values obtained with 3 years of difference show a significant difference ($p < 0.05$) with respect to the rest.

Finally, Figure 3 shows the normalized cross-correlation after the morphons registration step. Notice that NCC introduces a structural analysis, since the statistics are computed using pixelwise considerations. NCC values vary from 0.48, when patients are between 61 and 65 year old in the time frame of less than one year between the two acquisitions, to 0.99 in age ranged between 24 and 30 years in the frame of one year between the two acquisitions. In a pre-menopausal stage (women younger than 56 years old) the median of distributions are ranged between 0.94 and 0.99, while in the menopausal and post-menopausal stages the median of the distributions vary from 0.81 to 0.96. Notice that, in the menopausal stage, the NCC values tend to decrease along time. Patients older than 55 years old show a significant difference ($p < 0.05$) in the NCC obtained between the two mammograms of different acquisitions in all the cases, with respect to the rest of patients. Similarly,

the youngest group, between 24 and 30 years old, show a significant difference ($p < 0.05$) with respect to the adulthood stage, between 30 and 55 years old, in most of cases.

Considering each age interval independently, for patients younger than 56 years old, there is not a significant difference among the different interval acquisition frames. However, between 56 and 65 years old, in most of the cases there is a significance ($p < 0.05$). This significance does not appear in older patients.

4. DISCUSSION

The aim of this paper was to analyze the changes in breast density and parenchymal distribution over the time, using the commercial software Volpara^{TM} Density Maps in order to locally extract the glandular tissue directly from Full-Field Digital Mammograms. Changes in the glandular tissue were evaluated using global and local statistical measures such as the rate of change of breast density and the histogram intersection and normalized cross-correlation between two density maps.

The results show several significant differences. Two main groups need to be considered. Patients younger than 30 years old show a significant variation with respect to those in the adulthood (between 30 and 55 years old) in all the statistics. Similarly, the group composed of women between 61 and 65 years old show a significant different behavior with respect to the rest of cases. While using global measures, in this case the RC of the glandularity, may not be clearly visible, using structural statistics, such as the NCC, show a clearly different behavior for patients older than 56 years old. Furthermore, these statistics differ depending on the time interval between two mammographic studies. Most of the measures show this behavior when the time between the two acquisitions is two years.

The main limitation of this work is related to the histopathology of the patients. The FFDMs used in this study have not been analyzed previously to this work. Therefore, we cannot assure that all the images belong to healthy patients. While the breast density should decrease over the time, developing breast cancer may affect automatic breast density measures because, usually, these softwares do not include an automatic diagnostic system to discriminate between healthy and unhealthy tissues. Thus, the growing of the cancer may compensate the loss of glandular tissue. Furthermore, changes in the breast thickness have not been considered. This factor may affect the local distribution of glandular tissue[13] and, therefore, the values directly obtained from the density maps, such as the histogram intersection metric and NCC. Similarly, breast volume, breast glandularity, including BI-RADS rating and glandular tissue percentage, and other factors regarding the mammographic acquisition have not been analyzed.

5. CONCLUSIONS

The aim of this paper was to analyze the temporal changes in local breast density using Volpara^{TM} Density Maps. Using the measures provided by the software, we evaluated both global and local changes in the glandular tissue. In order to compensate the different patient position between two temporal acquisition, the morphons registration algorithm was used to align the mammograms.

Results showed significant variations with respect to the age and, for patients older than 56 years old, the time between the two mammographic studies. While using global measures this fact may not be clearly visible, the use of local and structural statistics allows to show a clearly different behavior. Therefore, statistical measures directly computed from the density maps can improve the evaluation of temporal changes in glandular tissue. This fact could help to provide newest approaches to evaluate risk breast cancer with a high likelihood of developing breast cancer.

6. ACKNOWLEDGEMENT

REFERENCES

[1] Boyd, N., Martin, L., Yaffe, M., and Minkin, S., "Mammographic density and breast cancer risk: current understanding and future prospects," *Breast Cancer Res.* **13**(6), 223 (2011).

[2] Powell, K. A., Obuchowski, N. A., Davros, W. J., and Chilcote, W. A., "Quantitative analysis of breast parenchymal density: correlation with women's age," *Academic radiology* **6**(12), 742–747 (1999).

[3] D 'Orsi, C., Sickles, E., Mendelson, E., Morris, E., and et al., [*Breast Imaging Reporting and Data System ACR BI-RADS^{TM} Atlas*], American College of Radiology (2013).

[4] Kallenberg, M. G., Lokate, M., van Gils, C. H., and Karssemeijer, N., "Automatic breast density segmentation: an integration of different approaches," *Physics in Medicine and Biology* **56**, 2715 (2011).

[5] Oliver, A., Freixenet, J., Marti, R., Pont, J., Pérez, E., Denton, E. R., and Zwiggelaar, R., "A novel breast tissue density classification methodology," *IEEE Transactions on Information Technology in Biomedicine* **12**(1), 55–65 (2008).

[6] Byng, J. W., Boyd, N., Fishell, E., Jong, R., and Yaffe, M. J., "The quantitative analysis of mammographic densities," *Physics in Medicine and Biology* **39**(10), 1629 (1994).

[7] Oliver, A., Tortajada, M., Lladó, X., Freixenet, J., Ganau, S., Tortajada, L., Vilagran, M., Sentís, M., and Martí, R., "Breast density analysis using an automatic density segmentation algorithm," *Journal of Digital Imaging* **28**(5), 604–612 (2015).

[8] van Engeland, S., Snoeren, P. R., Huisman, H., Boetes, C., and Karssemeijer, N., "Volumetric breast density estimation from full-field digital mammograms," *IEEE Transactions on Medical Imaging* **25**(3), 273–282 (2006).

[9] Shepherd, J. A., Kerlikowske, K. M., Smith-Bindman, R., Genant, H. K., and Cummings, S. R., "Measurement of breast density with dual X-ray absorptiometry: Feasibility 1," *Radiology* **223**, 554–557 (2002).

[10] Highnam, R., Brady, M., Yaffe, M. J., Karssemeijer, N., and Harvey, J., "Robust breast composition measurement - Volpara^{TM}," *Lecture Notes in Computer Science (IWDM 2010)* **6136**, 342–349 (2010).

[11] Sala, E., Warren, R., McCann, J., Duffy, S., Day, N., and Luben, R., "Mammographic parenchymal patterns and mode of detection: implications for the breast screening programme," *Journal of medical screening* **5**(4), 207–212 (1998).

[12] Wolfe, J. N., "Risk for breast cancer development determined by mammographic parenchymal pattern," *Cancer* **37**, 2486–2492 (1976).

[13] García, E., Diaz, O., Martí, R., Diez, Y., Gubern-Mérida, A., Sentís, M., Martí, J., and Oliver, A., "Local breast density assessment using reacquired mammographic images.," *European Journal of Radiology* **93**, 121–127 (2017).

[14] Heine, J. J. and Malhotra, P., "Mammographic tissue, breast cancer risk, serial image analysis, and digital mammography: Part 2. serial breast tissue chage and related temporal influences," *Academic radiology* **9**(3), 317–335 (2002).

[15] Wrangsjö, A., Pettersson, J., and Knutsson, H., "Non-rigid registration using morphons," *Image Analysis* , 501–510 (2005).

[16] Swain, M. J. and Ballard, D. H., "Color indexing," *International Journal of Computer Vision* **7**(1), 11–32 (1991).

[17] Lewis, J., "Fast normalized cross-correlation," in [*Vision interface*], **10**, 120–123 (1995).

[18] R Core Team, *R: A Language and Enviroment for Statistical Computing.* R Foundation for Statistical Computing., Viena, Austria (2014).