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Computing mammographic density from a multiple regression model constructed with image-acquisition parameters from a full-field digital mammographic unit

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Abstract

Breast density (the percentage of fibroglandular tissue in the breast) has been suggested to be a useful surrogate marker for breast cancer risk. It is conventionally measured using screen-film mammographic images by a labor intensive histogram segmentation method (HSM). We have adapted and modified the HSM for measuring breast density from raw digital mammograms acquired by full-field digital mammography. Multiple regression model analyses showed that many of the instrument parameters for acquiring the screening mammograms (e.g. breast compression thickness, radiological thickness, radiation dose, compression force, etc) and image pixel intensity statistics of the imaged breasts were strong predictors of the observed threshold values (model $R^2=0.93$) and % density ($R^2=0.84$). The intra-class correlation coefficient of the %-density for duplicate images was estimated to be 0.80, using the regression model-derived threshold values, and 0.94 if estimated directly from the parameter estimates of the %-density prediction regression model. Therefore, with additional research, these mathematical models could be used to compute breast density objectively, automatically bypassing the HSM step, and could greatly facilitate breast cancer research studies.

Keywords

breast density; mammographic density; breast parenchymal pattern; full-field digital mammography; digital mammogram; models; breast cancer; biomarker

Introduction

Breast cancer is one of the most common cancers among women and one of the leading causes of cancer-related death in women. The American Cancer Society (ACS, 2006) estimated that in 2006 over 212,920 women in the United States would be diagnosed with invasive breast

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cancer and about 40,970 of these women would probably die from the disease. Mammography is currently the standard screening modality for early detection of breast cancer. In 1976, two studies by Wolfe (Wolfe, 1976a;Wolfe, 1976b) first indicated that elevated breast density, as measured by mammography, is a risk factor for the development of breast cancer. Several other studies have subsequently confirmed this association (Brisson et al., 2003;Saftlas, Szklo, 1987;Boyd et al., 1995;Byrne et al., 1995;Kato et al., 1995).

The radiographic appearance of the breast depends greatly on the relative composition of adipose tissue and connective and fibroglandular tissue (Wolfe, 1976a;Feig, 1992). Adipose tissue has a slightly lower physical density than fibroglandular tissue and is thus more radiolucent. In conventional screen-film mammography, areas that are bright correspond to fibroglandular tissue, while darker areas correspond to adipose tissue. These variations in mammographic density are commonly referred to as the breast parenchymal pattern. There are several classifications of the parenchymal pattern, depending on the relative amount of adipose/fibroglandular tissue in the breast as well as the distribution of these tissues within the breast (Wolfe, 1976a;BIRADS, 1995;Gram et al., 1997).

Because increased mammographic breast density is one of the strongest risk factors for breast cancer, an objective and automated method for measuring changes in breast density has been suggested as a useful development for breast cancer research (Wolfe et al., 1987;Heine et al., 2002;Oza, Boyd, 1993;Byng et al., 1996).

Various techniques aimed at automation and improved objectivity in tissue segmentation have been devised to calculate mammographic density and classify parenchymal patterns. Karssemeijer (Karssemeijer, 1998) developed an automated classification technique based on the Hough transform and feature-extraction methods. Zhou et al. (Zhou et al., 2001) developed semiautomatic image analysis tools, based upon a discriminant analysis method and the Maximum Entropy Principle, for estimating mammographic density, with results similar to the visual estimates from five radiologists. Saha et al. (Saha et al., 2001) developed a procedure for quantifying breast density based on scale-based fuzzy connectivity methods. Sivaramakrishna et al. (Sivaramakrishna et al., 2001) segmented the dense breast area by a modified Kittler's optimal threshold procedure. Breitenstein and Shaw (Breitenstein, Shaw, 1998) measured breast tissue composition using a single-energy hybrid technique. Heine and Velthuisen utilized a chi-square probability analysis method to discriminate radiolucent tissue (fat) from radiographic densities (fibroglandular tissue) in digitized mammograms (Heine, Velthuisen, 2000). Byng, et al. (Byng et al., 1996;Byng et al., 1997) used an automated analysis routine that measured the skewness of the image brightness histogram and the image texture, characterized by the fractal dimension, and found that these two measures correlated well with the subjective classification by radiologists of mammographic parenchyma. Currently, the most widely used technique for measuring breast density is based on a histogram segmentation method (HSM), an algorithm developed by Byng et al., (Byng et al., 1996). Computer programs have been developed to assist in the determination of mammographic density [Cumulus at the University of Toronto (Byng et al., 1996); and Madena at the University of Southern California (Ursin et al., 1998)]. All of the above-mentioned techniques utilized conventional screen-film mammograms, which need to be scanned and digitized to perform the analyses. Digital mammography is a newer modality for acquiring mammograms, and several types of full-field digital mammographic (FFDM) machines have been approved by the FDA since 2000 (Fischer et al. 2006). Its wide-spread use is expected in the future. Digital mammograms store all instrument parameters for the proper acquisition of mammograms electronically. Many of these instrument parameters are engineered to allow FFDM to perform automatic exposure control and to equalize image intensities across a wide range of breast density and, therefore, may be indices of breast tissue glandularity. This paper describes a statistics-based approach for constructing mathematical models that could be used to objectively compute %-breast density,

thus eliminating the histogram segmentation procedure. The %-breast density computed from these mathematical models was compared with those determined using the HSM developed by Byng et al., (Byng et al., 1996) for validation. The methodology described in this proof-of-principle study has the potential for automation.

Materials and Methods

Study Design

Screening digital mammograms from pre- and post-menopausal women were the data sources for this method-development study. The pre-menopausal women had previously volunteered for a dietary intervention study and provided written informed consent. The digital mammographic images of postmenopausal women were retrieved from the Breast Imaging Clinic of the University of Texas Medical Branch (UTMB) after removal of patient identifiers. Recruitment involved all major races and ethnicities. The study was approved by the Institutional Review Board of the UTMB and the Human Subject Research Review Board of the US Department of the Army Medical Research and Materiel Command.

Breast imaging by a FFDM unit

Screening mammographic exams were performed on each subject using an FDA-approved FFDM unit (GE Senographe 2000D, GE Medical Systems, Waukesha, WI). Each exam consisted of a cranio-caudal (CC) view and a medial-lateral-oblique view of each breast (for a total of 4 mammograms). A duplicate CC view of one breast (most often the left breast) also was obtained from participating pre-menopausal women during the same exam (after repositioning) for reproducibility studies. Thus, a total of 5 mammograms was obtained from each woman.

The GE Senographe 2000D captures each mammographic image using a cesium-iodide scintillator coupled to an amorphous-silicon panel (photodiode/transistor array) (Vedantham et al., 2000). The digital image is 2294×1914 pixels in dimension and 14 bits (16,384 shades of gray) per pixel. The GE Senographe 2000D produces two images for each mammogram, a “raw” and a “processed” image. The “raw” image contains all of the original x-ray attenuation data from the acquisition. The “processed” image is created by the proprietary GE image-enhancement software (e.g., edge enhancement, histogram equalization, normalization, noise reduction, etc.) in order to increase the conspicuity of breast lesions, micro-calcifications and other pathological features of the breast. Though these enhancements are critical for the detection of abnormal breast lesions by a radiologist, they can potentially hinder mammographic density analysis. Therefore, for density analysis, the raw images were used.

Transferring, archiving, and displaying image data

The raw images are in DICOM 3.0 (Digital Imaging and Communications in Medicine) format and were transferred via a secure PACS (Picture Archiving and Communications System) network to an eFilm (Merge eFilm, Milwaukee, WI) workstation for archiving. Prior to mammographic density analyses, the images were anonymized and coded using DicomWorks software (version 1.35; © Phillippe Puech and Loic Boussel, <http://dicom.online.fr/>).

Two free software packages were used to perform the mammographic density analyses: ImageTool (version 3.0; © University of Texas Health Science Center in San Antonio, <http://ddsdx.uthscsa.edu/dig/itdesc.html>) and Sante Viewer (version 3.0; © Manos Kanellopoulos, <http://users.forthnet.gr/ath/mkanell/viewer/viewer.html>). ImageTool was the primary software for tissue segmentation and image calculations. ImageTool can analyze 16-bit images. Therefore, mammographic images did not have to be down-sampled which helped to maintain contrast and brightness during the analyses. Sante Viewer was utilized primarily

as an image viewer and was used to display the processed images for guiding tissue density segmentation.

Mammographic (breast) density analysis

The HSM algorithm developed by Byng et al., (Byng et al., 1996) was adapted and modified, as described below, in order to analyze digital images. Mammographic density (%-density) analyses were performed on 14-bit raw, anonymized left and right cranio-caudal (CC) images (Fig. 1A). The raw GE FFDM images represent exposure domain data (breast tissue appearing dark, while completely exposed areas of the detector appearing white). For the analyses, the raw images were transformed to represent attenuation data, in which the appearance of the image matches a standard, clinical mammogram (i.e., breast tissue appearing white with areas outside of the breast appearing dark). The processed, anonymized images (Fig. 1B), though not used directly in the analysis, were viewed to guide tissue segmentation during the density analysis. Sante Viewer was used to retrieve and display the processed image (Fig. 1B) on one of the two monitors of a standard workstation computer (2.4 GHz Pentium IV processor, 1024 MB of RAM and a 40 GB hard drive). The analyst responsible for performing the density analyses was blinded to all relevant information that could be used to identify the patient. Each mammogram was also classified by a radiologist using the BI-RADS (Breast Imaging Reporting and Data System) classification metric. The four BI-RADS density levels used were: entirely fatty (BI-RADS level 1, the least dense), scattered (BI-RADS level 2), heterogeneously dense (BI-RADS level 3), and extremely dense (BI-RADS level 4, the most dense). BI-RADS density data was not available to the analyst performing density determinations.

ImageTool was used to retrieve the raw image (Fig. 1A) and a *window/level* was set to allow the operator to choose breast region of interest (ROI) by removing extraneous items in the image (Fig. 1C), such as removing any chest wall or muscle areas. Through experimentation, it was observed that the choice of the settings for the *window* (setting the contrast of tissues, see definition below) and the *level* (setting the brightness of the tissue image, see definition below) that were used to display the image could affect the visual selection of the threshold used to segment fibroglandular tissue from adipose tissue. The consequence of this was variable tissue segmentation. To minimize this variability, a standardized method for choosing the *window* and the *level* settings for displaying the image for density analysis was necessary, as described below.

Software was developed to extract the breast pixel intensity data from the DICOM data file, to calculate frequency information from the DICOM image for generating a histogram for segmentation, to calculate the mean and the standard deviation of the pixel intensity distribution within the breast ROI, and to find the maximal intensity level of the pixels in the breast ROI. The one standard deviation value is chosen as the width value of the window (variable label “*window*”). The maximal pixel intensity level (variable label “*level*”) was used as the *level* parameter for displaying the final images for density analysis. Window and level are common ways to display and provide contrast for radiologic image data. This process of selecting the *window*- and the *level*-generated images on a computer (as shown in Fig. 1D) closely resembled the processed images (Fig. 1B), and therefore, were suitable for segmentation.

To segment all of the breast tissue, the intensity histogram (inset in Fig. 1E) of the ROI (selected by the analyst to remove all non-breast tissue) was displayed, and an initial intensity level was selected to provide a level above the background level allowing only the breast area (Fig. 1C) to be displayed. ImageTool makes a binary mask of the segmented whole breast that has pixels with intensities greater than the initial background intensity and provides the sum counts of the pixels in the binary mask area, which consists of the total breast area (Fig. 1C). Although this process is subjective, there is very little error involved. Because the breast intensities are narrowly distributed in the upper 1/4 of the pixel intensity range and the digital images are

background-corrected, the breast is easily segmented from the background. By observing the processed image (displayed using Sante Viewer, Fig. 1B) and the intensity histogram (inset in Fig. 1E) of the ROI image generated by ImageTool, another intensity threshold level (the vertical line dividing the histogram into a black and a white region as shown in the Fig. 1E inset) was selected from the histogram that highlights only the high-density fibroglandular tissue (Fig. 1D). The dense tissue is represented with a white solid color overlay (Fig. 1E). The pixel count in the segmented high-intensity area (Fig. 1F) is provided by ImageTool. The percent density is the ratio of the number of pixels in the high-density area (Fig. 1F) divided by the number of pixels in the entire breast area (Fig. 1C).

Box-filter-assisted histogram segmentation

By applying a box-filter to the image, boundary layers between fibroglandular tissue and adipose tissue become more delineated and are thus easier to segment and threshold. The image was smoothed, using a 27×27 box-filter, and processed as described in Figure 1. The effect of the box-filter on breast density analysis was tested by comparing the reproducibility of results with and without applying the box-filter to the image.

Mathematical model for objectively selecting threshold value

After gaining experience in tissue segmentation using a training set of images, the performance of the density analysis protocol was tested on 37 sets of duplicate images of the breasts (two images for each of 37 breasts). These are the “reproducibility/validity set”, with each image repeatedly analyzed, at least twice, on separate occasions for %density. When the intra-class correlation coefficient (ICC) from the reproducibility/validity set was satisfactory (>0.9), the trained analyst then blindly analyzed a new, independent set of 184 images (the “model building set”). The observed threshold values, from the model building set, after verification by another trained analyst, were used as the dependent variable for a multiple regression analysis (stepwise selection) for finding strong predictors of observed threshold values. The parameter estimates for strong predictors were then used to calculate predicted thresholds. These predicted threshold values were used to obtain predicted %-density values on images from the reproducibility/validity set for validating the ability of the predicted threshold values to estimate %-density. The independent variables for the final regression model analysis included all FFDM imaging variables and the image brightness intensity variables of the imaged breasts.

Statistical analysis

The dependent variables (italicized throughout the text with unit of measurement given if appropriate) were breast density analysis outcomes of interest, including *total breast area (unit is pixel)*, *dense breast area (pixel)*, and *%-density* (dense breast area divided by total breast area $\times 100$). The independent variables were the image brightness intensity variables of the imaged breasts (i.e. *mean intensity*, *window*, and *level*), and the pre- and final-exposure instrument setting variables. Table 1 describes these statistical variables.

To produce quality screening mammographic images, while minimizing radiation dose to the breast, the FFDM unit performs a pre-exposure experiment by giving a small dose of x-rays to the breast tissue for a preliminary estimation of the breast's x-ray attenuation characteristics (Shramchenko et al., 2004;Chevalier et al., 2004;Kaufhold et al., 2002;Klausz et al., 2005). Using the instrument setting data and the x-ray attenuation data of the breast from the pre-exposure, a new set of imaging parameters is computed by the FFDM unit for setting the FFDM unit for acquiring each of the final screening mammograms. In many cases, the pre-exposure and the final exposure instrument setting data and the breast's x-ray attenuation data had been recorded in the header of each image report, and were retrieved (see Table 1) for inclusion in the statistical analyses.

The pre-exposure variables (see Table 1) included for statistical analyses were: dose to the air at the detector entrance plane intended for main exposure (variable label, “*expdose*”, nGy), pre-exposure entrance dose to the detector (“*predose*”, nGy), % glandular tissue based on pre-exposure data (“*precompo*”, %), acrylic-equivalent thickness based on pre-exposure data (“*prethick*”, mm), kVp (“*prekVp*”, kV), glandular tissue estimate (“*raddose*”, %), the average glandular dose for the imaged breast tissue (“*orgdose*”, dGy), mean radiation intensity in the pre-exposure region of interest (“*anatmean*”), acrylic-equivalent thickness of the imaged breast based on the final image, not the pre-exposure image, radiological thickness (“*radthick*”, mm), and two unit-less threshold variables used for thickness equalization processing for preparing processed images (variables, “*dthresh*”, and “*segmthresh*”, no units).

The final exposure instrument setting variables (Table 1) were: x-ray beam energy (variable label, “*kVp*” and unit of measurement, kV), x-ray current, (“*x-ray current*”, mA), compressed breast thickness (“*thickness*”, mm), x-ray exposure (“*x-ray exposure*”, μ G), exposure time (“*exptime*”, ms), sensitivity (“*sensitivity*”, counts/nG), force (“*force*”, daN), target (Mo or Rh, “*target*”) and filter (Mo or Rh, “*filter*”). In the statistical analysis, filter type was coded as 1 for molybdenum (Mo) and 0 for rhodium (Rh).

Pearson correlation coefficients were computed for all variables shown in Table 1, i.e., between pre-exposure variables, between final exposure variables, and between %density, total breast area, dense breast area, and BI-RADS density level data with pre- or final-exposure variables. Multiple regression analyses (analysis of covariance) were used to determine the strength of the association between one of the following dependent variables: %-density, total breast area, dense breast area, or the observed threshold value with the independent variables described above (see also Table 1).

Each mammogram was analyzed by an analyst two to three times for computing the within-image analysis CV (coefficient of variation = standard deviation divided by the mean and expressed as a percent). To determine reproducibility, intra-class correlation coefficients (ICC) were computed for breast density parameter outcomes of interest for duplicate mammographic images. The reproducibility analyses were performed for HSM-observed and model-predicted threshold values and the HSM-observed and model-predicted %-density. Ordinary least squares regression analyses were performed to determine the relationship between breast density, retrieved from mammogram reports (BI-RADS score) and assessed by the HSM described above, and the relationship between the HSM-observed and model-predicted threshold values.

Results

Breast (mammographic) density analysis

The HSM developed by Byng et al., (Byng et al., 1996) was adapted and modified to analyze breast density on digital mammograms. All available images (N=474) were divided into four different sets: a “training set” containing duplicate images of the left breast and a single image of the right breast from 11 women (N=33 images), a “reproducibility/validity test set” (N=85 images) containing duplicate images from 37 left breasts (i.e. 74 images for the reproducibility study) and a single left breast image from an additional 11 women (un-related to the women in the training set), a “model building set” (N=184 images), and a “final confirmation set” (N=172 images).

To facilitate threshold selection, a box-filter approach was tested to determine if this could facilitate the visual cue of histogram features for selecting the threshold. The anonymized CC views of left and right breast images from 11 women (the “training set”) with and without applying the box-filter, were analyzed multiple times to determine within-analyst variability.

The CV of the within-analyst variability of density analyses was 7.9% for the unfiltered method and 5.3% for the box-filtered method. To determine the reproducibility of the instrument for imaging the same breast, a duplicate CC view of one of the breasts from each of the 11 women was analyzed. The CV for the duplicate images was 8.5% for the unfiltered method and 5.3% for the box-filtered method.

The box filter-analysis procedure was tested in an additional 37 sets of duplicate mammogram images of 37 breasts in the “reproducibility/validity set”. Figure 2 shows that the HSM-observed %-density within each of the 37 pairs of duplicate images correlated strongly ($r=0.98$) with each other with an ICC of 0.98. The ICC was 1.00 for the total breast area and 0.99 for the dense breast area of the 37 pairs of duplicate images (results not graphed). These results suggest that the box-filter method is reproducible. The box-filter procedure was then applied to the analyses of the remaining image samples.

Figure 3 shows the relationship between %-density measured by our HSM and the BI-RADS density levels previously recorded in the mammogram reports from a set of 184 samples (the “model building set”) from pre- and post-menopausal women. The four BI-RADS breast density levels are described in the Materials and Methods section above. The box-plot for each level of BI-RADS density is shown in Figure 3. Linear regression analysis reveals that there is a strong linear relationship ($r=0.83$) between the BI-RADS density levels and the %-density measured by the computer-assisted HSM.

Predictors and statistical modeling of threshold and breast density measurements

Pearson correlation analyses between most variables listed in Table 1 show that, with a few exceptions, the pre-exposure variables and the final exposure variables are inter-related. Additionally, there is also a strong correlation between breast density measurement outcomes of interest and the variables of both pre-exposure and final exposure. The results of Pearson correlation coefficients are not shown, but some results are highlighted below. Percent-density correlated strongly with all exposure variables (r between 0.15 and 0.81) except *exposure* and *force*. BI-RADS density levels correlated strongly with all variables (r between 0.22 and 0.71) except *segmthresh* (a variable used by the FFDM to create processed image), *exptime*, *exposure*, and *force*. Of particular interest are the strong correlations between *BIRADS* density levels and the data in *precompo* ($r=0.70$, $P < 0.0001$), and between the HSM-observed %-density and *precompo* ($r=0.81$, $P < 0.0001$). *Precompo* is the breast density of a segment of the imaged breast estimated by the GE Senographe 2000D based on pre-exposure data (Kaufhold et al., 2002; Klausz et al., 2005). Total breast area correlated strongly with all variables (r between 0.19 and 0.44) except *expdose*, *orgdose*, *anatmean*, *dthresh*, *exptime*, and *x-ray exposure*. Dense area correlated strongly with all variables (r between 0.17 and 0.62) except *prekVp*, *exptime*, *thickness*, and *x-ray exposure*.

Multiple regression analyses were then performed to explore the independent predictors of threshold, %-density, total breast area, and dense breast area using data in the model building set by three different approaches. The independent variables (Table 1) entered into the models were one of the following three groups: (I) pre-exposure variables, (II) final exposure variables or (III) a combination of pre-exposure-, final exposure- and image intensity-variables. Table 2 summarizes the results of these analyses. Based on the overall model R^2 , the strongest models for predicting threshold, %-density, total breast area, and dense breast area are all models constructed with group III variables (i.e. a combination of all variables from pre-exposure, final exposure, and image intensity).

Figure 4A shows the residual plot for the strongest prediction model for threshold (overall model $R^2=0.93$, see Table 2). In this model, anatomical mean intensity (*anatmean*), maximal intensity (*level*), window (*window*) and breast compression thickness (*thickness*) explained

56%, 15%, 12%, and 8% of the variances, respectively (see partial R^2 in Table 2). Using the parameter estimates of this model, the predicted threshold values for the duplicate images in the reproducibility/validity set were computed and found to be very reproducible with a CV of 9% (± 12) and an ICC of 0.95 (Fig. 4B). There is also a strong relationship ($r=0.93$) between the observed threshold values and the model-predicted threshold values (Fig. 4C). These predicted threshold values were used to segment dense tissue and to compute %-density using the mammographic images from the reproducibility/validity testing set. Figure 4D shows that there is a moderate relationship between the observed %-density and the predicted %density with an r of 0.66 if all samples were included, and a strong relationship with an r of 0.82 if data from the entirely fatty (BI-RADS density 1) breasts (Δ in Fig. 4D) were excluded. The ICC for predicted %-density derived from the predicted threshold between duplicate mammograms is 0.80.

The purpose of objectively determining a threshold is to compute %-density. Indeed, Table 2 shows that the observed %-density by our HSM, using the algorithm of Byng et al. (Byng et al., 1996) could be predicted directly from existing instrument parameters and image brightness intensity variables with an overall R^2 of 0.84. In this model, the pre-exposure radiation dose to the detector (*predose*), %-tissue glandularity (*raddose*), and breast compression thickness (*thickness*) explained 59%, 10%, and 10% of the variances, respectively (see Table 2). The residual plot of this model is shown in Figure 5A. Using the parameter estimates of this model, the predicted %-density was calculated for images in the reproducibility/validity test set. Figure 5B shows that there was a strong relationship between the model-predicted %-density of the duplicate images ($r=0.89$, $ICC=0.94$). There was also a strong correlation between the model-predicted %density and the HSM-observed %-density of images in the reproducibility/validity test set ($r=0.86$, Fig. 5C, $N=85$ images) and in the final confirmation set ($r=0.83$, Fig. 5D, $N=172$ images).

The strongest prediction model for total breast area explained 57% of the variances (Table 2). In this model, compression force, breast compression thickness, *window*, and *segmthresh* (a parameter used by the FFDM to create processed images) are all strong predictors, explaining 19%, 14%, 14%, and 9% of the variances, respectively. These four strong predictors will confound total breast area measurement by the HSM. However, because the model explains only 57% of the total breast tissue variance and it is relatively easy to segment breast ROI from background, it is more accurate to obtain the total breast area by the HSM than by computing from the regression models. For dense breast area, all three models explained about the same variances. In the model including pre- and final-exposure variables, the strong predictors are breast compression thickness (partial $R^2=0.33$, Table 2) and radiological thickness (partial $R^2=0.17$).

Discussion

The HSM that we have described can reproducibly measure the breast density of duplicate mammograms. Reproducibility was excellent ($ICC>0.98$) for all breast density measurements of interest, i.e. total breast area, dense area (glandular tissue), and %density. The method also has validity based on the following three observations. The mean %-density measured by our method for each category of BI-RADS density increased linearly with increasing BI-RADS levels recorded in the mammogram reports (Fig. 3) and also correlated strongly ($r=0.81$, $P<0.0001$) with %-glandular tissue recorded in *precomp* of the digital mammogram reports. Additionally, the BI-RADS density level recorded in the mammogram reports correlated strongly ($r=0.70$, $P<0.0001$) with the %-glandular tissue values recorded in *precomp*.

The usual goal of x-ray mammography is to detect breast cancer. For this reason, there are a significant number of internal manipulations that are normally made by the FFDM machine,

at the level of both instrument settings and data processing by the software. These manipulations are essential for producing quality mammograms because the attenuation of x-rays, thus the dose reaching the detector, is a function of the amount of glandular tissue in each breast. However, this manipulation can be a significant confounder for assessing breast density in mammograms, as shown by the number of instrument variables that are significant predictors of the breast density measurement of interest, *per se* (Table 2 and Figs. 4A and 5A).

Taking advantage of recorded information about instrument settings unique to each imaged breast, we explored whether mathematical models could be constructed to objectively predict threshold values that could then be used to compute %-density values. This would bypass the step of visual selection of threshold for dense tissue, the only subjective step in the current HSM (as shown in Fig. 1). Indeed, data in Figure 4 show that the model-prediction approach appears to be feasible, because the %-density of duplicate images were highly reproducible and the model-predicted %-density calculated from the threshold prediction model (Table 2) also correlated strongly with the HSM-observed %-density. More importantly, Figure 5 shows that %-density can also be directly predicted from the existing instrument parameters associated with each mammogram acquisition and from the maximal pixel intensity level in the breast ROI (for models see Table 2). This approach bypasses the threshold segmentation step, a labor intensive and subjective step. Therefore, the %-density obtained using model parameter estimates (Fig. 5) is also objective, and it appears to be more reproducible (Fig. 5B, ICC=0.94) and more reliable (Fig. 5C–D, $r=0.83$ and 0.86) than those estimates that are obtained using the predicted threshold (Fig. 4D, model 3, ICC=0.8 and $r=0.66$). Because the histogram distribution of the breast's pixel intensity is typically very narrow for the entirely fatty tissue and the homogeneously dense tissue, a small variation in threshold value can cause a very large difference in the sum pixel count of the segmented dense tissue. This may explain why the percent density is less reliable if estimated from the model-predicted threshold value than when computed directly from %-breast density prediction model. It is not clear why models (for both threshold and %-density) built from a combination of pre-exposure and final exposure variables are consistently more reliable in predicting threshold and %-density than those built with either pre- or final-exposure variables. We speculate that this may relate to the intent of mammography to equalize signal intensities of final screening mammograms across all levels of breast density in order to maximize image contrast and improve the sensitivity for detecting breast cancer.

The slope for the relationship between the model-predicted %-density and the HSM-observed %-density in Fig. 5C–D is about 0.7, a deviation from the expected “1”. The reason for this deviation is not entirely clear, but we speculate this to be a combination of the bias of the breast density rater and the function of the window/level setting. The HSM is a vision-based image analysis technique and human eyes may not be sensitive enough, i.e. saturated, to the change in optical densities at both extreme ends of the breast densities. At the extreme ends of breast densities we have noticed a tendency for our objectively calculated window/level settings to display a different amount of dense tissue than processed images, leading to deviation in density estimation. In contrast, the variables used to construct the prediction models are all instrument-derived measurements, and data in these variables at the extreme ends of breast density are less likely to show any saturation behavior, as is possible with optical density. Investigation of this deviation by comparing density data from mammography and breast MRI is in progress. The ability of these predicted %-density values to assess the effects of intervention and the biological factors (i.e. non-instrument related factors) that may predict breast cancer risk are under investigation.

The glandular tissue measurements described in this paper can only be viewed as relative, not absolute, density measurements, because a “gold standard” of breast density is not currently available for calibration. In this work we have used multiple regression analyses to estimate

the contribution to breast density measurement of the various instrument imaging parameters available from the FFDM unit. There are, however, other factors that will influence the signal intensity recorded by the digital detector, including estimation error of compressed breast height (a readout from the digital compression paddle height), spatial variation in radiation scatter (especially near the skin-line), the heel effect, quantum mottle, beam hardening, and detector non-uniformity. All of these might impact the detected x-ray fluence as seen by the detector (Highnam et al., 1999; Kaufhold et al., 2002). It is also anticipated that images produced by an FFDM unit may exhibit temporal changes due to aging of the x-ray tubes, variation between FFDM unit manufacturers, and differences between radiology facilities. Many of these factors should be controlled for, either at the instrument or statistical analysis levels, in order to isolate the true biological factors relating to density changes. An ideal approach would be to include a calibration standard with each mammogram acquisition. The density reading of the calibration standard could then be an additional variable in the multivariate regression analyses to correct for instrument drifting or could be used to normalize signal intensity across all mammograms. Because the ground truth of the mammographic (breast) density is hard to obtain due to the inherent overlapping of tissues from breast compression during mammography, it is important to note that the parameters and parameter estimates of regression models may change from installation to installation, site to site, and analyst to analyst. However, the regression analysis process may represent a useful and convenient approach for computing breast density. Additional collaborative research in these areas will enable automation of breast density measurements using approaches similar to the one described here.

In summary, we have adapted the HSM method of Byng et al. (Byng et al., 1996) for breast density analysis on screen-film mammograms to measure breast density from digital mammographic images and have found that %-density is highly associated with many instrument imaging variables. Mathematical models were constructed that could potentially be used to objectively predict threshold, which can then be used to calculate %-density or to directly compute %-density, thus bypassing the labor-intensive and subjective threshold segmentation step. An important advantage of this statistical model-based approach for computing breast density is its potential for automation.

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Abbreviations used

FFDM	full-field digital mammography
CC	cranio-caudal view
ROI	region of interest
kVp	x-ray beam energy

mA

x-ray current

BI-RADS

Breast Imaging Reporting and Data System

HSM

histogram segmentation method

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Figure 1.

Steps taken to segment dense breast tissue by the histogram segmentation method (HSM). A, raw 14-bit digital mammogram image acquired using the GE Senographe 2000D; B, processed digital mammogram; C, raw digital mammogram with background and chest wall removed; D, box-filtered image using objective *window* and *level* settings; E, segmentation of dense breast tissue using the raw box-filtered image in panel D and a histogram (inset in Fig. 1E). In both, the white area represents the dense tissue area. The dark area in the histogram is the non-dense tissue area of the breast region of interest. F, binary representation of segmented dense tissue. Percent density was calculated from the total number of remaining black pixels in Fig. 1F divided by the number of black pixels in Fig. 1C.

Figure 2.

Reproducibility of %-breast density assessed from the duplicate mammograms of 37 breasts (74 images). Two mammograms were obtained sequentially from the same breast on the same day, after repositioning of the breast, and analyzed as described in Fig. 1. Dotted line is a 45° line representing a 1:1 correlation between duplicate images; solid line is ordinary least squares regression; and ICC is the intra-class correlation coefficient.

Figure 3.

Breast density relationship assessed by the HSM described in Fig. 1 and the BI-RADS density classification recorded in mammogram reports. Box plots show the 25–75% interquartile range. Black circles represent points outside this range. Both mean (dashed lines) and median (solid lines) %-density values are shown in the box plots. An ordinary linear regression line (solid line) together with 95% confidence intervals (dashed lines) are shown.

Figure 4.

Final multiple regression model for predicting threshold ($threshold = 118563 - 155.7 * prethick - 5.2082 * anatmean + 390.39 * kVp + 0.012 * exposure + 101.2 * thickness + 0.6509 * window - 7.5705 * level$), and for calculating %density. A, studentized residual plot for the final model; B, relationship between model-predicted threshold values of 37 sets of duplicate images; C-D, relationship between model-predicted and HSM-observed values of threshold (C) and %density (D); Δ in Fig. 4D, entirely fatty breast tissue; dotted line, a 45° line representing a 1:1 correlation between duplicate images; solid line, ordinary least squares regression; dashed line, ordinary least squares regression excluding Δ samples in this figure; regression equation y_{1-4} including all data and y_{2-4} excluding Δ samples; and ICC, intra-class correlation coefficient.

Figure 5.

Final multiple regression model for predicting %-density ($\%density = -161.02 - 0.0072 \cdot predose + 6.7221 \cdot prekVp - 0.2253 \cdot raddose + 1.4842 \cdot radthick - 0.0373 \cdot anatmean - 0.5416 \cdot x\text{-ray current} - 2.5283 \cdot thickness - 0.0701 \cdot force + 26620 \cdot sensitivity - 0.0075 \cdot level$). A (images from model-building set), studentized residual plot for the final model; B, relationship between model-predicted %-density values of duplicate images of a breast (N=37 breasts) taken sequentially on the same day, C-D, two independent sets of images for testing the relationship between the model-predicted and the HSM-observed %-density. Dotted line, a 45° line representing a 1:1 correlation between duplicate images; solid line, ordinary least squares regression; and ICC, intra-class correlation coefficient.

Table 1
Definition of variables used to acquire properly exposed mammographic images
and to construct multiple regression models

Variable	Description	DICOM Attribute (Tag)
Variables of the imaged breast		
<i>window</i>	Window setting	
<i>level</i>	Maximal pixel intensity	
<i>mean intensity</i>	Mean pixel Intensity	
<i>threshold</i>	Pixel intensity for segmentation	
<i>total area</i>	Total breast area, pixel	
<i>dense area</i>	Dense breast area, pixel	
<i>%-dense</i>	%-Density	
<i>BIRADS</i>	Radiologist's breast density classification	
Final exposure variables for producing the imaged breast		
<i>kVp</i>	Voltage for exposure, kV	KVP (0018,0060)
<i>exptime</i>	Exposure time, ms	Exposure Time (0018,1150)
<i>x-ray current</i>	X-Ray current, mA	X-ray Tube Current (0018,1151)
<i>exposure</i>	Exposure, mAs	Exposure (0018,1152)
<i>thickness</i>	Body part thickness, mm	Body Part Thickness (0018,11A0)
<i>force</i>	Compression force, daN (newton)	Compression Force (0018,11A2)
<i>x-ray exposure</i>	Relative X-ray exposure, μ G	Relative X-ray Exposure (0018,1405)
<i>filter</i>	Filter, Rh or Mo	Filter (0018,7050)
<i>sensitivity</i>	Detector sensitivity (counts/nGy)	Sensitivity (0018,6000)
Pre-exposure variables for calculating the final exposure variables		
<i>expdose</i>	Exposure dose ¹ , nGy	EXP DOSE (0018,7062)
<i>predose</i>	Pre-exposure dose ¹ , nGy	PRE-EXP DOSE (0018,7062)
<i>prethick</i>	Pre-exposure thickness ¹ , mm	PRE-EXP THICK (0018,7062)
<i>precompo</i>	%-Glandular tissue ¹	PRE-EXP COMPO (0018,7062)
<i>prekvp</i>	Pre-exposure kVp ¹ , kV	PRE-EXP KV (0018,7062)
<i>raddose</i>	Breast glandularity in %	Comments on Radiation Dose (0040,0310)
<i>orgdose</i>	Organ dose, dGy	Organ dose (0040,0316)
<i>anatmean</i>	Estimated anatomical mean	Estimated Anat mean (0045,1020)
<i>radthick</i>	Radiological thickness, mm	Radiological Thickness (0045,1049)
<i>dthresh</i>	Threshold ²	Threshold (0045,1059)
<i>segmthresh</i>	Segmentation threshold ²	Segm Threshold (0045,1064)

¹Data obtained from Exposure Control Mode Description

²Processing algorithm parameters for equalizing processed image, no associated unit of measure

Table 2

Multivariate regression models.

Dependent Variables	Independent Variables	Overall Model R ²	Final Prediction Model Equations	Partial R ² for each variable in the model equation as it appears ^d
Threshold (N=177)	Pre-exposure ^b	0.67	$threshold = -529.68 - 0.1234 \cdot predose - 2.6765 \cdot anatmean - 18.352 \cdot raddose + 13.401 \cdot segmthresh + 40805 \cdot orgdose + 2.8014 \cdot dthresh + 27.151 \cdot radthcik$	0.36 [*] , 0.16 [*] , 0.09 [†] , 0.03 [†] , 0.02 [*] , 0.006 [†] , 0.0009 [†]
	Final-exposure ^c	0.61	$threshold = -44849 + 140.94 \cdot thickness - 0.0735 \cdot exposure + 899.79 \cdot filter + 4.64e6 \cdot sensitivity + 3.7057 \cdot exptime - 354.76 \cdot kVp$	0.35, 0.16 [†] , 0.04, 0.04 [†] , 0.02 [*] , 0.009 [†]
	Pre- & Final- exposure ^d	0.93	$threshold = 118563 - 5.2082 \cdot anatmean - 7.5705 \cdot level + 0.6509 \cdot window + 101.2 \cdot thickness + 0.012 \cdot exposure - 155.7 \cdot prethick + 390.39 \cdot kVp$	0.56, 0.15, 0.12, 0.08, 0.01, 0.007, 0.006
%Breast Density (N=184)	Pre-exposure ^b	0.76	$\%density = 125.84 - 0.0065 \cdot predose - 0.0005 \cdot expdose + 0.3611 \cdot raddose - 0.0377 \cdot dthresh - 0.0564 \cdot anatmean - 1.2185 \cdot radthick + 5.5549 \cdot prekVp$	0.50, 0.11 [†] , 0.09, 0.03, 0.03, 0.007 [†] , 0.006 [†]
	Final-exposure ^c	0.71	$\%density = -121.55 - 1.3668 \cdot thickness + 0.0244 \cdot exptime - 6.2566 \cdot filter + 6.9849 \cdot kVp$	0.61, 0.04, 0.03, 0.002
	Pre- & Final-exposure ^d	0.84	$\%density = -161.02 - 0.0072 \cdot predose - 0.2253 \cdot raddose - 2.5283 \cdot thickness - 0.0373 \cdot anatmean - 0.0701 \cdot force + 26620 \cdot sensitivity - 0.0075 \cdot level - 0.5416 \cdot x-ray current + 1.4842 \cdot radthick + 6.7221 \cdot prekVp$	0.59, 0.10 [†] , 0.10, 0.03, 0.01 [†] , 0.009 [†] , 0.002 [*] , 0.002 [*] , 0.0004, 0.0001
Total Breast Area (N=184)	Pre-exposure ^b	0.29	$total area = -1.55e6 + 91744 \cdot prekVp + 7636.1 \cdot segmthresh$	0.19, 0.10
	Final-exposure ^c	0.36	$total area = -294591 + 9026.6 \cdot force + 19346 \cdot thickness$	0.22, 0.14

Dependent Variables	Independent Variables	Overall Model R ²	Final Prediction Model Equations	Partial R ² for each variable in the model equation as it appears ^a
	Pre- & Final- exposure ^d	0.57	<i>total area</i> = 2.76e6 +7359.8 [*] <i>force</i> +19390 [*] <i>thickness</i> -497.56 [*] <i>window</i> +12102 [*] <i>segmthresh</i> -165.21 [*] <i>mean intensity</i>	0.19, 0.14, 0.14 [‡] , 0.09, 0.005 [*]
Dense Breast Area (N=184)	Pre-exposure ^b	0.54	<i>dense area</i> = 2.54e6 +1868.8 [*] <i>raddose</i> +9504 [*] <i>radthick</i> -890.52 [*] <i>dthresh</i> +2284.7 [*] <i>segmthresh</i> -743.02 [*] <i>anatmean</i>	0.31 [*] , 0.12, 0.07, 0.04 [‡] , 0.004 [‡]
	Final-exposure ^c	0.57	<i>dense area</i> = -2.9e6 -17598 [*] <i>thickness</i> +127965 [*] <i>kVp</i> +2379.6 [*] <i>force</i> +404.58 [*] <i>exptime</i> -76333 [*] <i>filter</i>	0.32, 0.12, 0.07, 0.05, 0.01 [*]
	Pre- & Final-exposure ^d	0.65	<i>dense area</i> = -1.55e6 -19877 [*] <i>thickness</i> +30909 [*] <i>radthick</i> +3700.4 [*] <i>segmthresh</i> +84.697 [*] <i>mean intensity</i> +1246 [*] <i>force</i>	0.33, 0.17, 0.07, 0.05, 0.03 [‡]

^a All P values <0.0001, except as indicated by

^{*}, P<0.15;

[‡] P<0.01;

[†] P < 0.001

^b Instrument setting variables for pre-exposure only. For variable definition, consult text.

^c Instrument setting variables for final exposure only

^d Variables from pre-exposure and final exposure plus image intensity variables