Received:
01 January 2018

Revised:
30 January 2018

Accepted:
31 January 2018

<https://doi.org/10.1259/bjr.20180032>

Cite this article as:

Suleiman ME, Brennan PC, Ekpo E, Kench P, McEntee MF. Integrating mammographic breast density in glandular dose calculation. *Br J Radiol* 2018; **91**: 20180032.

FULL PAPER

Integrating mammographic breast density in glandular dose calculation

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Objective: This work proposes the use of mammographic breast density (MBD) to estimate actual glandular dose (AGD), and assesses how AGD compares to mean glandular dose (MGD) estimated using Dance et al method.

Methods: A retrospective sample of anonymised mammograms (52,405) was retrieved from a central database. Technical parameters and patient characteristics were exported from the Digital Imaging and Communication in Medicine (DICOM) header using third party software. LIBRA (Laboratory for Individualized Breast Radiodensity Assessment) software package (University of Pennsylvania, Philadelphia, USA) was used to estimate MBDs for each mammogram included in the data set. MGD was estimated using Dance et al method, while AGD was calculated by replacing Dance et al standard glandularities with LIBRA estimated MBDs. A linear regression analysis was used to assess the association between MGD and AGD,

and a Bland-Altman analysis was performed to assess their mean difference.

Results: The final data set included 31,097 mammograms from 7728 females. MGD, AGD, and MBD medians were 1.53, 1.62 mGy and 8% respectively. When stratified per breast thickness ranges, median MBDs were lower than Dance's standard glandularities. There was a strong positive correlation ($R^2 = 0.987$, $p < 0.0001$) between MGD and AGD although the Bland-Altman analysis revealed a small statistically significant bias of 0.087 mGy between MGD and AGD ($p < 0.001$).

Conclusion: AGD estimated from MBD is highly correlated to MGD from Dance method, albeit the Dance method underestimates dose at smaller CBTs.

Advances in knowledge: Our work should provide a stepping-stone towards an individualised dose estimation using automated clinical measures of MBD.

INTRODUCTION

Screening mammography is an effective tool for the early detection of breast cancer, and has been shown to reduce cancer mortality by 25–40%.^{1–3} Since screening mammography was first instigated at a national level in Sweden in 1977, there has been continuous debate about the extent of benefits and the nature of the risk.⁴ The risks arising from screening mammography are two-fold: risk from radiologist's errors such as false positives, false negatives and over diagnosis;⁵ radiation-induced cancer risk arising from the high radiosensitivity of rapidly dividing epithelial cells in the fibroglandular tissues.⁶ Therefore, it is increasingly important to appropriately account for the effect of radiation when assessing the risk vs benefit of screening mammography.⁵ The relative risk of radiation-induced cancer from mammography is quantified by the mean glandular dose (MGD).

MGD is an estimate of the energy deposited per unit mass of glandular tissue averaged over all glandular tissue in the

breast.⁷ MGD is estimated using conversion factors derived from Monte-Carlo simulations.^{8–10} All estimates use assumptions and the available MGD estimation methods operate on the assumption that the breast is 50% glandular and 50% fatty (50:50 model)¹¹ or that glandularity is proportional to compressed breast thickness.^{12,13} The 50:50 model proposed by Hammerstein et al¹¹ was based on a phantom with homogeneous distribution of glandular tissue and the authors suggested that the 50:50 model can be used for comparing mammography doses delivered using different techniques and equipment. MGD calculation models such as Wu et al^{10,14} and Boone et al^{8,15,16} are based on the 50:50 model. However, it is well known that the breast composition is not homogeneous.¹⁷ Additionally, it has been shown, in a volumetric breast density study, that about 80% of females have breasts with less than 27% fibroglandular tissue.¹⁸ Thus, the assumptions made in the 50:50 model are clearly not true for all breasts, and do not represent the glandularity of the population. To address these limitations, another model was established by Dance

et al.^{12,13} To account for the increased cancer risk in glandular tissue, this model incorporates estimates of breast glandularity taking into consideration patient age and compressed breast thickness (CBT).

Although the incorporation of glandularity and CBT in the Dance et al model is logical, this approach to estimation of glandularity has some limitations. First, the Dance et al method estimates changes in glandularity using CBT and age. However, breast composition differs across females within age groups and CBTs. Second, breasts with similar CBT can have different glandular compositions. Third, females of the same age and CBT can have different amount of glandular tissues. Thus, it is increasingly relevant to explore alternative models that account for a female's actual breast composition when estimating glandularity. Also, breast density, which is the amount of fibroglandular tissue in the breast, is a determinant of X-ray attenuation and risk of cancer.¹⁹ The fibroglandular tissue contains high concentrations of primitive epithelial cells, the most susceptible to radiation damage, and from which 80% of cancers arise.²⁰ As the proportion of dense breast influences susceptibility to cancer, it is important that we should be exploring mammographic breast density (MBD) data when estimating radiation-induced risk from mammography. This makes individualised MBD a promising alternative to the 50:50 and Dance models for estimating glandularity and patient-specific dose estimates.

MBD is a representation of the fibroglandular tissue of the breast as seen by the X-ray attenuation patterns on a mammogram. MBD can be assessed qualitatively (visual grading) and quantitatively (area-based (2D) or volumetric (3D) methods).^{21,22} However, qualitative visual methods are prone to intra- and inter-reader variability,²³ suggesting a need to automate MBD measurement for dose calculation. The automated use of MBD for dose assessment has been developed²⁴ and a white paper by Highnam et al²⁴ was the first to report MGD using MBD. This approach has now been incorporated into Volpara™ software (Volpara Health Technologies Limited) to propose Volpara Dose for patient-specific MGD estimation from mammography unit firmware.²⁴ Although Volpara Dose is robust and automated, it has a hardware and software cost, it requires networked systems and needs to be supported by the mammography equipment vendors. Furthermore, Volpara Dose only works on the "Raw Projection" data. These challenges limit its applicability for low-resource facilities and countries, and highlight the need for less costly, accessible and versatile automated alternative. Automated area-based methods utilise computer-assisted interactive thresholding techniques to measure the percentage area covered by the dense tissue on a radiograph and uses this as a proxy for fibroglandular tissue. The Laboratory for Individualized Breast Radiodensity Assessment (LIBRA) software for MBD estimation uses post-processed images, can do batch processing, is freely available and is therefore a possible low cost and low man-power alternative. LIBRA is freely available, fully automated software for the estimation of MBD. It estimates MBD on both "raw projection" data and "post processed" images, and has been validated for GE and Hologic digital mammography systems.²⁵

The current work proposes the use of a female's automatically generated actual MBD to estimate the actual glandular dose (AGD) to the breast. This work explores the use of MBD measured by LIBRA to estimate AGD. It also assesses whether the AGD estimated using MBD compares to MGD estimates from Dance et al method.

METHODS AND MATERIALS

The work involved a retrospective sample of screening mammograms. A total of 52,405 mammograms from 12,034 females were used. Mammograms were acquired on 63 mammography units across 50 Breast Screen centres in New South Wales, Australia between September and October 2014. The data were retrieved from the Cancer Institute of New South Wales Picture Archiving and Communication System, following ethics approval (HREC2014/08/552) from the Cancer Institute Human Research Ethics Committee.

Patient-related information such as mammographic projections, age and breast thickness, exposure parameters, and mammography unit information (make, model) were exported from the Digital Imaging and Communication in Medicine (DICOM) image header to MS Excel using a third party software (YAKAMI DICOM Tools v. 1.4.1.0, Kyoto University, Japan).²⁶ Medical physics annual reports were also obtained from participating centres, as the calculation of MGD requires these data.

MBD was estimated for the data set using LIBRA software.²⁷ LIBRA uses a thresholding technique to detect the boundaries of the breast and the pectoral muscle on the mammogram. An "adaptive multi-class fuzzy c-means" algorithm is then applied to partition the mammographic breast tissue into clusters of similar intensity. These clusters are then aggregated to a dense tissue area. The software package then generates quantitative estimates of breast area, dense tissue area, and calculates MBD by dividing the dense area by the total breast area.^{27,28}

LIBRA has only been validated for GE and Hologic mammography units.²⁵ Therefore, mammograms obtained using Philips and Fujifilm units (14,065 mammograms) were excluded in the current work. Further exclusion criteria related to the calculation method were applied on the data. These included mammograms reported to have 0% glandularity by LIBRA (180 mammograms) which were considered as an indicative of measurement error, mammograms with breast implants (1337 mammograms), mammograms not within 20–110 mm CBT (39 mammograms), incomplete calculation data (1971 mammograms). The final data set was imported to an excel workbook developed in-house which calculated MGD and our proposed AGD.

The calculation of MGD in our study followed the methods described by Dance et al.^{9,12,13} This method calculates MGD using entrance air kerma and three conversion factors that depend on age, CBT, half value layer (HVL), and anode/filter combination. A full explanation of the methodology has been previously described²⁹ (Figure 1). AGD in our work was calculated by replacing the original *c* factor values (6 in Figure 1) with

Figure 1. Dance calculation method: input information that needs to be available for the calculation of MGD, the steps taken to calculate MGD for a mammogram and the equations utilised for that process. MGD, mean glandular dose.

a look-up table of interpolated c values for MBDs ranging from 1 to 100%.

The data were stratified by age (40–49 and 50–64) and CBT (20–110 in 10 mm increments). For each age group, our estimated median MBD was compared to Dance's glandularity for each CBT (Figure 2). The distribution of the data was assessed using a D'Agostino & Pearson normality test, and a non-parametric Spearman's correlation was used to assess the relationship between median MBD and age.

MGD and AGD medians were calculated per mammogram. The median MGD and AGD were compared across different breast thicknesses (Figure 3). Bland-Altman analysis was performed to show the mean difference between the two dose estimation

methods. Bland-Altman analysis also provided a measure of the bias and 95% limits of agreement (LOA) between MGD and AGD.³⁰ A linear regression analysis was performed to assess the linear correlation between MGD and AGD. AGDs and MGDs were stratified by CBT, and the median differences between AGD and MGD as well as their 95% confidence intervals were calculated for each range of CBTs.

RESULTS

A further 3716 mammograms failed LIBRA analysis, and the final data set comprised of 31,097 mammograms (7728 females) from 48 Breast screen centres. Table 1 provides a descriptive summary of the data set, including the minimum, maximum, 1st and 3rd quartiles, median, mean, variance, and standard deviation for age, CBT, MBD, MGD, and AGD. Both MGD and AGD

Figure 2. Median glandularity vs breast thickness for 31,097 mammograms, glandularity estimated using LIBRA, and compared to Dance method typical glandularities for two age groups (40–49, 50–64). LIBRA, Laboratory for Individualized Breast Radiodensity Assessment.

Figure 3. MGD and AGD variation with different CBT. The difference between median AGD and MGD for different CBT ranges becomes insignificant at CBTs greater than 80 mm. AGD, actual glandular dose; CBT, compressed breast thickness; MBD, mammographic breast density.

Table 1. Statistical description of the included data set (31,097 mammograms)

Statistic	Age	CBT1	MBD	MGD	AGD
Minimum	40	20	0.01	0.37	0.40
Maximum	89	110	0.99	14.53	13.93
1st quartile	54	50	0.04	1.27	1.37
Median	60	59	0.08	1.53	1.62
Mean	60	59	0.13	1.71	1.80
3rd quartile	66	68	0.17	1.96	2.03
Variance (n-1)	63	175	0.02	0.58	0.55
SD (n-1)	8	13	0.13	0.76	0.74

AGD, actual glandular dose; CBT, compressed breast thickness; MBD, mammographic breast density; MGD, mean glandular dose; SD, standard deviation.

showed skewed distributions with medians of 1.53 and 1.62 mGy respectively. MBD showed a skewed distribution with a median and a mean of 8 and 13% respectively.

Findings show that the median MBD decreased at higher CBTs but were lower than the Dance method at corresponding phantom CBTs for all age groups (Figure 2). There was a direct relationship between dose and compressed breast thickness. The AGD calculated using MBD followed a similar trend as the MGD estimated using Dance Method. However, the Dance method MGD underestimated dose at lower CBTs (below 80 mm) compared to AGD (Figure 3). Further analysis showed that the 95% confidence interval of the difference between median AGD and MGD for different CBT ranges becomes insignificant at CBTs greater than 80 mm (Figure 4).

Bland-Altman analysis revealed a small yet statistically significant bias of 0.087 mGy between MGD and AGD (Figure 5), with 95% confidence intervals and *p* value of $-0.08-0.26$ and <0.0001 respectively. Linear regression analysis demonstrated a strong positive correlation ($R^2 = 0.987$, $p < 0.001$) between MGD and AGD.

Figure 4. Median difference between AGD and MGD at different CBTs and the 95% confidence intervals (shown in bars). AGD, actual glandular dose; CBT, compressed breast thickness; MBD, mammographic breast density.

DISCUSSION

Previous studies estimating radiation risk from mammography made assumptions that are not necessarily true for all breast compositions. Given that the breast is infrequently 50% glandular, and that breasts with the same CBT and age vary in glandularity, the current work argues the importance of integrating actual measures of glandularity in dose calculation. The current work proposes the use of MBD to quantify individual's glandularity for the purpose of patient-specific dose estimation during mammography. Our work demonstrates that MBD is inversely related to CBT, with our median MBDs being lower than the glandularity estimated by Dance *et al*^{12,13} at corresponding CBTs for all age groups. Findings also demonstrated a direct association between CBT and AGD as well as MGD. MGD was lower than AGD at smaller CBTs, with the difference becoming insignificant at higher CBTs (>80 mm). Bland-Altman analysis showed a small yet statistically significant bias between MGD and AGD.

The median breast glandular tissue content in our data set was 8%, with a mean of 13%, similar to that previously reported (17.4–27%) elsewhere^{18,31} and for Australian females (8.1%).³² These values are substantially lower than the 50% glandularity

Figure 5. Bland-Altman plot for MGD and AGD showing a Bias of 0.087 and 95% LOA of $-0.08, 0.26$ for 31,097 digital mammography images. AGD, actual glandular dose; MBD, mammographic breast density.

used in the standard breast composition model for mammography dose optimisation. These findings suggest that the 50:50 model overestimates glandularity and that there is in reality the same dose going to less glandular tissue. Therefore the mean glandular dose is actually higher than estimated by the 50:50 model. This same finding is explained by Dance et al¹² in a different way; they indicate that “The increase of the c-factor with decreasing glandularity is due to the increased percentage depth dose for fattier breasts”. In other words, fattier breasts allow more photon penetration. Therefore, underestimating the dose absorbed per 1 gm of fibroglandular tissue, leading to an underestimation of radiation risk from mammography. Similarly, in comparison to the current work, the Dance et al method, which accounted for variation in breast composition using CBT, overestimated glandularity at smaller CBTs for all ages. We found that the glandularity estimated using the Dance method was almost double the actual glandularity at smaller CBTs, suggesting an overestimation of glandularity in small breasts. Such overestimation may result in an underestimation of dose and risk to patients undergoing mammography procedures, limiting the applicability of Dance model for patient-specific dose estimation, particularly for small breasts.

Further analysis demonstrated a linear increase in AGD and MGD with CBT. MGD was consistently significantly lower (6% difference; $p < 0.001$) than AGD at CBTs < 80 mm. However, Bland-Altman analysis, revealed a small but significant positive bias towards AGD and a narrow LOA. Although the bias was statistically significant, it represents less than 5% of the average dose to the standard breast described by the European protocol.³³ Nonetheless, when females were stratified into different CBTs, the differences in MBD for smaller CBTs resulted in a higher difference (10%) between MGD and AGD, while larger CBTs (over 80 mm) demonstrated under a 2% difference, with narrower 95% confidence intervals (Figure 4). Smaller breast may have lesser fibroglandular content than larger ones but demonstrate higher percentage glandularity. This is perhaps the reason why AGD was higher in smaller breast when individuals' MBDs were accounted for. This finding implies that Dance et al model may not be suitable for dose calculation in smaller breasts. The high correlation between AGD and MGD reported in the current work may be due to the use of a similar methodology for estimating both parameters.

The 2–10% difference in AGD and MGD at different CBTs has implications for risk and lifetime effective risk, as MGD contributes to 98% of effective lifetime risk, while the other body parts (irradiated during mammography) such as contralateral breast, thyroid and lungs contribute to only 2%.³⁴ Furthermore, according to the Linear Non-Threshold (LNT) model, which is often used for radiation-induced risk assessment, cancer risk from radiation exposure increases linearly with dose. This suggests that underestimation of dose using MGD will result in an underestimation of risk. Although the LNT model is still being debated due to the lack of drop-off effect from death at higher doses and the paucity of data at lower doses, it is still used to quantify risk. There are contentions about the effects of radiation at low doses. While one theory suggests that the processes by

which our cells repair damage (hormesis) and destroy unrepairable cells (apoptosis) occur at low doses³⁵ another asserts that cells are hypersensitive to low level doses.³⁶ Importantly, it has been shown that radiation-induced genetic effects vary between individuals.³⁷ These individual differences in risk emphasise the need to personalise glandularity and dose measurements in order to provide patient-specific estimates of radiation-induced risk.

The overestimation of glandularity at lower CBTs and underestimation of dose by Dance et al model highlights the limitations in the current mammography dosimetry approaches. The current work provides a more objective clinical approach to patient-specific mammography dose estimate. Although the difference between AGD and MGD was small (2–10%), it constitutes a significant difference in terms of risk according to the LNT model, and should be considered when estimating radiation-induced risk from mammography.

Another factor supporting individualized dose and risk estimation is the fact that risk from radiation and DNA repair differ between individuals even at similar dose levels.³⁶ For example, females with BRCA1 & 2 mutations as well as those with single nucleotide polymorphisms (SNPs) are less likely to successfully repair and more likely to develop breast cancer.^{38,39} Unfortunately, because 45–65% of females with BRCA mutations will develop breast cancer by the age of 70,⁴⁰ they are targeted for more regular screening. Cancer risk will also vary between individuals due to difference glandular content. Therefore, it is important to take into consideration these differences when estimating risk from mammography.

Although doses from medical procedures are relatively small, the effect of medical exposure to radiation is well established. A longitudinal study has reported an overall 24% increase in cancer incidence in individuals exposed to low doses compared to unexposed individuals.⁴¹ Evidence also shows that oncogenicity in younger females may be higher at low mammography doses compared to higher doses.³⁶ A significant relationship has also been established between low doses and cell repair.⁴² Therefore, one cannot definitely say that low doses are beneficial, harmful or have no effect, as radiation effects may vary between individuals.

The uncertainty of radiation effects at all doses suggests a conservative risk strategy should be adopted, and that actual measures of the radiosensitive fibroglandular tissues be included in dose calculation models for individualised dose estimation. Thus, AGD may be a better dosimetric parameter, as it accounts for the actual glandular content at risk. Importantly, advances in technology and automation of MBD measurement should facilitate easier estimation of breast glandular tissue content and AGD. This will provide actual measures of dose received by each patient and the potential risk from screening mammography.

The current work is limited in that only images retrieved from two mammography vendors were used. LIBRA is currently being tested on mammography units from different vendors, and may become more versatile in the future. Future work will explore AGD with LIBRA MBD measures from Philips (Sectra), Fuji,

and Siemens systems. The strengths of our work include the use of clinical images rather than phantoms for dose calculation as well as a large sample. Furthermore, the use of an automated MBD measurement software package (LIBRA) eliminates the variability associated with subjective human assessment. It does not, however, deal with heterogeneous glandular tissue distribution in the breast. Using a voxel phantom Dance et al⁴³ found that accounting for different glandular distributions in the breast could give up to 48% error in the conversion factors estimated using simple homogenous phantoms. He concluded, "For accurate breast dosimetry, it is therefore very important to take the distribution of glandular tissues into account". Therefore the

MBD proposed in the current work, although not yet accounting for heterogeneity, is a reasonable alternative. Our work should provide a stepping-stone towards an individualised dose estimation using automated clinical measures of MBD.

CONCLUSION

The use of MGD underestimates dose from screening mammography compared to AGD. There are inconsistent differences between AGD and MGD at different CBTs, with larger differences seen in smaller breasts. This inconsistency may result in the underestimation of radiation risk during mammography for females with smaller CBTs.

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