AD NUMBER

ADB288221

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies only; Proprietary Info.; Dec 2002. Other requests shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott St., Ft. Detrick, MD 21702-5012.

AUTHORITY

USAMRMC ltr, DTD 01 Jul 2003

AD_____

Award Number: DAMD17-00-1-0612

TITLE: Is Breast Densitometry a Measure of Breast Cancer Risk?

PRINCIPAL INVESTIGATOR: John A. Shepherd, Ph.D.
Karla Kerlikowske, M.D.
Sven Prevrhal, Ph.D.
Steve Cummings, M.D.

CONTRACTING ORGANIZATION: University of California, San Francisco
San Francisco, California 94143-0962

REPORT DATE: December 2002

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

NOTICE

USING GOVERNMENT DRAWINGS, SPECIFICATIONS, OR OTHER DATA INCLUDED IN THIS DOCUMENT FOR ANY PURPOSE OTHER THAN GOVERNMENT PROCUREMENT DOES NOT IN ANY WAY OBLIGATE THE U.S. GOVERNMENT. THE FACT THAT THE GOVERNMENT FORMULATED OR SUPPLIED THE DRAWINGS, SPECIFICATIONS, OR OTHER DATA DOES NOT LICENSE THE HOLDER OR ANY OTHER PERSON OR CORPORATION; OR CONVEY ANY RIGHTS OR PERMISSION TO MANUFACTURE, USE, OR SELL ANY PATENTED INVENTION THAT MAY RELATE TO THEM.

LIMITED RIGHTS LEGEND

Award Number: DAMD17-00-1-0612
Organization: University of California, San Francisco

Those portions of the technical data contained in this report marked as limited rights data shall not, without the written permission of the above contractor, be (a) released or disclosed outside the government, (b) used by the Government for manufacture or, in the case of computer software documentation, for preparing the same or similar computer software, or (c) used by a party other than the Government, except that the Government may release or disclose technical data to persons outside the Government, or permit the use of technical data by such persons, if (i) such release, disclosure, or use is necessary for emergency repair or overhaul or (ii) is a release or disclosure of technical data (other than detailed manufacturing or process data) to, or use of such data by, a foreign government that is in the interest of the Government and is required for evaluational or informational purposes, provided in either case that such release, disclosure or use is made subject to a prohibition that the person to whom the data is released or disclosed may not further use, release or disclose such data, and the contractor or subcontractor or subcontractor asserting the restriction is notified of such release, disclosure or use. This legend, together with the indications of the portions of this data which are subject to such limitations, shall be included on any reproduction hereof which includes any part of the portions subject to such limitations.

THIS TECHNICAL REPORT HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION.

Kath Moe 9/1/03 _____

_____ _____

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	December 2002	Final (1 Sep 00 - 30 Nov 02)

4. TITLE AND SUBTITLE
Is Breast Densitometry a Measure of Breast Cancer Risk?

5. FUNDING NUMBERS
DAMD17-00-1-0612

6. AUTHOR(S)
John A. Shepherd, Ph.D., Karla Kerlikowske, M.D., Sven Prevrhal, Ph.D., Steve Cummings, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of California, San Francisco
San Francisco, California 94143-0962

john.shepherd@oarg.ucsf.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution authorized to U.S. Government agencies only (proprietary information, Dec 02). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

12b. DISTRIBUTION CODE

13. Abstract *(Maximum 200 Words)* *(abstract should contain no proprietary or confidential information)*

Perhaps the least recognized risk factor for breast cancer is breast density. Other than age, breast density, as measured using the radiographic contrast in mammograms between fat and nonfatty tissue, has been shown to be one of the strongest indicators of breast cancer risk available. The primary aim of our research is to fully develop new technologies, dual and single energy x-ray absorptiometry (DXA and SXA), for breast densitometry that could be used to clinically assess the risk of breast cancer and to serve as a sensitive and highly reproducible surrogate marker for testing new methods for preventing breast cancer. DXA %FAT was found to be highly correlated to phantom percent glandular density ($r > 0.998$). In addition, DXA %FAT was found to be highly correlated to mammographic density using excised cadaveric breasts ($r_{adjusted} = 0.83$). DXA precision (SD) on whole breast tissue samples was 0.5% without repositioning and 1.1% with breast repositioning. Based on this validation of the DXA technique, we have constructed an In vivo DXA positioning aid to be used on commercial DXA equipment and in planned clinical validation trials. With regards to SXA, a workstation and a dynamically adjustable phantom have been designed and constructed. However, full validation of precision and accuracy has not been completed. We plan to follow these encouraging initial results with a case-control study to show that compositional breast density is as highly or more highly predictive of cancer risk than mammographic density alone.

14. SUBJECT TERMS	15. NUMBER OF PAGES
breast density, mammographic density, breast cancer risk, DXA, SXA	22
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Introduction

Perhaps the least recognized risk factor for breast cancer is breast density. Other than age, breast density, as measured using the radiographic contrast in mammograms between fat and nonfatty tissue, has been shown to be one of the strongest indicators of breast cancer risk available. Women who have greater than 50% of total breast area that is "mammographically" dense are at 3 to 5 fold greater risk of breast cancer than women with less than 25% mammographically dense breasts. The primary aim of our research is to fully develop new technologies for breast densitometry that clinically assess the risk of breast cancer and to serve as a sensitive and highly reproducible surrogate marker for testing new methods for preventing breast cancer. Developing the ability to quantify breast density could lead to new risk stratification strategies for screening and treatment of breast cancer, and to increased collaboration between epidemiologists and basic scientists working to better understand how proliferated breast stroma (mammographic breast densities) may interact with breast epithelium to promote the growth of breast tumor cells. The studies we propose are essential pilot studies that we believe will make a strong case for funding of larger studies to establish the value of our new method.

Body

Our aim is to develop new methods to measure the breast tissue composition on a pixel by pixel basis. Breast tissue can be modeled as being composed of just two materials: fat and glandular tissue. Using this two-component model, the combination of fat and lean mass that produces the x-ray attenuation is calculated for each pixel. Summing all pixels in the mammogram would result in a total fat and glandular mass and could be represented as a percentage glandular density (%GD). This method has many advantages. First, it eliminates the subjective evaluation of dense areas or uncalibrated thresholds. Second, it is a true measure of breast compositional density instead of x-ray opacity. Third, breast compositional breast should be more selective (higher odds ratio for cancer risk) than mammographic density since it uses all the contrast information in its measure. That is, all the image gray scale values contribute to the compositional density. This increases the accuracy, dynamic range and precision of the measurement. This is the principal difference between mammographic density and compositional density.

We are developing two techniques for measuring breast compositional density based on dual (DXA) and single (SXA) x-ray absorptiometry. The advantages of DXA and SXA over MRI and CT are that these examination are already part of the annual clinical procedures women are recommended to undergo. DXA is the most common diagnostic method for osteoporosis. A low-dose breast examination added to the standard hip or spine DXA would add little cost. SXA is a modification of standard mammography using film and well suited for new technologies such as digital mammographic detectors or computed radiographic screens. An SXA breast density examination does not add any additional views or dose to the mammography examination and is automatically evaluated.

DXA is most commonly used to solve for bone density to diagnose osteoporosis but is also used to quantify in vivo whole body %FAT. By subtracting two x-ray images acquired at different x-ray energies, one component (say soft tissue) of a two component model (say bone and soft tissue) can be eliminated from the subtraction image and leave a bone mass image (when soft tissue is subtracted) or a %FAT image (when the model just include fat and lean tissue is and lean is subtracted). DXA is a highly developed technique with very high precision, approx. 1% C.V. for bone and soft tissue density, and is available on over 10,000 dedicated clinical densitometers around the world. It is low dose in comparison to mammograms since the image can be spatially noisy since tissue mass is typically quantified in large regions of interests. Several investigators have suggested using DXA techniques on mammographic equipment to better identify calcification or improve image contrast (*1-5*) but to the author's knowledge, no one has actually performed a DXA study of breast density and this technique is not available on standard mammography devices.

The second technique, which is the subject of a pending patent, may have equivalently high precision and accuracy to the DXA technique with several advantages. Like the DXA method, the advantages are that: 1) it is not subjectively measured like mammographic density, 2) It is an accurate representation of breast density versus mammographic opacity, 3) it can be measured from standard mammograms with the inclusion of a novel reference phantom, and 4) it is easily adaptable and optimal for the new solid state digital mammography devices. However, there are several challenges to solve that may limit the accuracy of SXA. First, the method relies in the fact that the object being measured is of a constant thickness. This is true for approximately 75% of the compressed breast area, but the assumption breaks down in the surrounding breast perimeter. Second, the technique relies on a novel reference phantom to be in the field of measure and that it automatically adjusts

to the compression thickness of the breast without interfering with the technologist or patient. In addition, calcifications are more dense (lean) that pure glandular tissue and if not discriminated could increase the glandular density measure above it actual value. These challenges can only be address in future clinical studies.

The SXA methodology is described below. The compressed breast is modeled as a uniformly thick tissue mass of two materials, fat and glandular tissue. If a reference of fat and gland-equivalent materials is imaged with the compressed breast (a phantom), and if the reference materials are defined to be the same thickness as the breast, then the image attenuation measurements (the digitized gray scale values) can be converted to percent glandular density, %GD. Mathematically, this is expressed as

$$\%GD = 1 - \frac{\sum_{i,j=0}^{N,M} \frac{\ln(\frac{I_{i,j}}{I'})}{\ln(\frac{I''}{I'})} a_{i,j}}{\sum_{i,j=0}^{N,M} a_{i,j} \left(\frac{\ln(\frac{I_{i,j}}{I'})}{\ln(\frac{I''}{I'})} + \left(1 - \frac{\ln(\frac{I_{i,j}}{I'})}{\ln(\frac{I''}{I'})}\right) \frac{\rho_l}{\rho_f} \right)} * 100$$

where I' = the transmission through the fat reference, I" is the transmission through the gland reference, $I_{i,j}$ = transmission at pixel row i and column j, ρl and ρf are the density of the lean (gland) and fat materials respectively, and $a_{i,j}$ is the cross sectional area of each pixel. M and N are the row and column size of the digitized image. Thus the percent glandular density can be quantified without knowing the absolute compression thickness or the exact x-ray technique. The reference phantom is measured at the exact same time and x-ray conditions as the breast and the two reference points bound the expected gray scale values. Thus, the mammogram can be acquired to maximize contrast for diagnostic work without putting limitation on the x-ray technique and still be useful for SXA. At this time, we have conducted preliminary tests with novel SXA phantoms to know that the method is sound and may be as accurate as DXA.

We report on our study progress by listing the specific aims from our proposal and discussing our progress for each.

1. Calibrate and characterize breast densitometry using tissue-equivalent phantoms.

A. DXA Methodology

Methods/Materials: DXA devices assume a two-component soft-tissue model of fat and muscle when quantifying soft tissue composition. To investigate the validity of using DXA techniques for determining percent breast glandular tissue density (%GD) the M17 phantom (CIRS, Inc., Norfolk, VA) was used as a breast density calibration tool. The M17 is a density step phantom of constant thickness that simulates different ratios of breast glandular tissue and adipose fat. See Figure 1. This phantom is an approximate atomic equivalent to adipose fat and breast glandular tissue as reported by Hammerstein, et al. (*6*). The phantom's attenuation coefficients are within 1% of their respective fat/gland ratios from 10 to 200 keV. The density ranged from 0 percent glandular density to 100% glandular density in 6 steps. Note that the inner clear acrylic section was not included in our comparison since acrylic is not a stable representation of tissue across a wide x-ray energy range. The M17 phantom was scanned 10 times on the DXA scanner without repositioning. A second M17 phantom was then placed on top of the first to simulate a thicker breast. The %GD, as reported by the phantom manufacturer was compared to the percentage fat (%FAT) reported by DXA.

Results: The relationship between true %GD of the phantom and %FAT by DXA was

$$\%GD = -0.627 * \%FAT_{DXA} + 72.5$$

with a r^2 value of 0.998 and a SEE = 1.85 g. See Figure 2 below.

B. SXA Methodology

The SXA method is based on a bone densitometry technique called single x-ray absorptiometry (SXA) in which one x-ray image is used to solve for the composition of two materials (*7*). Our approach is based upon having two reference materials, a fat and glandular tissue reference, of the same thickness as the compressed breast that is imaged with each patient. The two materials we actually use are the approximate atomic and density equivalents to 100% fat and 100% glandular tissue (*6*). The materials were specifically made for this purpose (CIRS, Inc., Norfolk, VA). The phantom consists of two wedges (right triangles of a uniform thickness), one

small and one large, such that, when held together along their longest edges, they create parallel surfaces on the top and bottom. See Figure 3. When the smaller wedge is attached to the top compression paddle and the lower wedge allowed to slide along the lower compression surface (Bucky grid) while maintaining contact with the smaller wedge (a spring), the two wedges conform to the compression thickness and provide areas of pure fat and gland sample in the mammogram the same thickness as the breast. A conceptual drawing of how the phantom is used is shown in Figure 4. Over its height range, the prototype phantom's projected size (4.3 cm x 9.6 cm) allows for a generous 1 sq. inch sample of each reference entirely through the phantom's full thickness. At the moment, the phantom footprint is large but in a review of 377 randomly selected 8" x 10" CC mammograms, the phantom could have been placed in the opposite corners from the film tag and only have overlapped the breast image on 4 films.

The development of the SXA software has been slower than anticipated. Table 1 outlines the software development and where we stand it the development.

Table 1: SXA development progress

Task	Completed
1. Create SXA algorithm in Medx software	Done
2. Write Import tool for mammograms	Done
3. Create Flat field algorithm to create uniform gray-scale field.	Partially Done
4. Create algorithm to select uniform thickness portion of breast	Done
5. Integrate the algorithm from 4. Into workstation	Not Done
6. Develop robust digitizing technique for mammograms	Done
7. Validate the SXA method using density step wedge phantom	Not Done
8. Compare precision and accuracy of SXA to standard mammographic density	Not Done

Figure 5 is a screen capture image of the SXA workstation as it is now. The image is of a cadaver breast. The image was generated before correcting for the x-ray field nonuniformities. In summary, we did not completely validate the SXA image in this year study period. We are seeking additional funds to finish this part of the project.

2. *DXA scans and mammograms of breast pairs will be measured to determine if left/right differences exist.*

This aim was to be carried out using the cadaver breasts. Collecting cadaver breast was very difficult. Although we had assurances from the Anatomy Department we could expect approximately 20 pair of breast in the 1-year study period, we only received 5 pair (10 breasts). The first 4 pair were analyzed completely. The last pair has yet to be analyzed and is in frozen storage. 1 pair of the four breasts came back with hepatitis positive test such that we could not complete some of the examinations.

Methods: 3 pairs of breast were compared for left right differences in the DXA measurements. The significance of the difference was determined using a paired t-test to calculate a Pearson's p-value.

Results: The results are summarized in Table 2 below. None of the measures were shown to be statistically significantly different with a p-value less than 0.05. However, it is difficult to generalize since there were only three paired comparisons.

Table 2: Statistical significance of the difference between left and right breasts. This test was severely limited by the small number of samples.

Measure	p-value
Total Mass (g)	0.17
Total Fat (g)	0.05
Total Lean (g)	0.84
Percent Fat (%)	0.64
Percent Glandular Density (%)	0.64

3. *A subset of breasts will be radiographed several times and DXA scanned several times with repositioning of the breast to quantify precision of the mammographic and DXA density measures.*

These results are summarized in Appendix 1.

4. *Finally, we will compare the new breast densitometry method to conventional mammographic density. The DXA densities will be correlated to the mammographic density as well as the density scores. DXA Percent Breast Fat thresholds will be defined to correspond to the scoring classification and to percentage mammographic densities.*

These results are summarized in Appendix 1.

5. *Additional Studies:*

The purpose of the trial was to validate if DXA and SXA are valid densitometery methods for measuring breast composition. As seen in Appendix 1, we did validate the DXA method. The SXA method is still under development. In addition, to now use DXA in clinical trials, we also performed the work.

A. DXA Positioning Aid for in vitro studies

We have designed and constructed a positioning aid for the in vivo measurement of breast compositional density. The positioning aid is made of acrylic and rests on top of the DXA scanner's tabletop. It allows for one breast to protrude through the positioner and hang in the x-ray path. This is shown in schematic in Figure 6. A subject being positioned on the Hologic device and positioning aid is shown in Figure 7. The entire breast is imaged in the prone pendulous view without compression.

Key Research Accomplishments

1. DXA %FAT was found to be highly correlated to phantom percent glandular density ($r > 0.998$).
2. DXA %FAT was found to be highly correlated to mammographic density using excised cadaveric breasts ($r_{adjusted} = 0.83$).
3. DXA precision (SD) on whole breast tissue samples was 0.5% without repositioning.
4. DXA precision (SD) on whole breast tissue samples was 1.1% with breast repositioning.
5. In vivo DXA positioning aid has been designed to be used on commercial DXA equipment.

Reportable Outcomes

Publications

1. **Shepherd, J.A.**, K. Kerlikowske, R. Smith-Bindman, H.K. Genant, and S.R. Cummings. Measurement of breast density with dual x-ray absorptiometry: feasibility. Radiology 223(2): 554-7.
2. Prevrhal, S., **J.A. Shepherd**, R. Smith-Bindman, S.R. Cummings, K. Kerlikowske. Accuracy of mammographic breast density analysis: results of formal operator training. *J. Cancer, Epi. Bio. & Prev.* 11(11):1389-93.

Conference Presentations

3. **Shepherd, J.A.**, Kerlikowske, K., Genant, H.K., Cummings, S.R. Can Dual X-ray Absorptiometry Accurately and Precisely Measure Breast Density to Quantify Cancer Risk? Presented at the UCSF Breast Oncology Program Retreat, February 9th, 2001.
4. Swarnakar, S., S. Prevrhal, K. Kerlikowske, S. Cummings, H.K. Genant, and **J.A. Shepherd**. A Mammographic Density Reading Service for Clinical Drug Trials. InfoRAD presentation at the Annual Meeting of the Radiological Society of North America (RSNA), November 28th, 2000, Chicago, IL.
5. **Shepherd, J.A.**, Prevrhal S., Genant, H.K., A New Method for Monitoring Osteolysis using Dual X-Ray Absorptiometry Difference Imaging. Presented (Shepherd) at the Annual Meeting of the Radiological Society of North America (RSNA), November 28th, 2000, Chicago, IL.
6. **Shepherd, J.A.** Compositional Breast Density Techniques. UCSF Breast Densitometry Workshop, UCSF, San Francisco, CA.

Patent Submissions

FILED 5/11/01 (date filed) A Device and Method for Determining Proportions of Body Materials

Funding Applied for Based on this Work

1.	Period:	01/01/02 – 12/31/02
	Source:	The American Cancer Society
	Title:	A Prospective Measure of Cancer Risk and Breast Density
	Role:	Principal Investigator
	Annualized Support:	15 %
	Total Funding:	$466,740
	Desc:	This study was to continue the development of the SXA methodology as well as measure actual ca associated with the DXA and SXA measurement.
	Status:	Submitted 04/01/01. Not funded. Proposal in revision for resubmission.
2.	Period:	07/01/02 – 06/30/03 (ACTIVE)
	Source:	California Breast Cancer Research Program
	Title:	Compositional breast density as a risk factor
	Role:	Principal Investigator
	Annualized Support:	5 %
	Total Funding:	$100,000
	Desc:	This hypothesis-driven research is to quantify breast cancer risk using a unique compositional brea technique.
	Status:	Funded. Awaiting IRB approval

Conclusions

The conclusion to the study is that we have shown that commercial DXA devices can be used to measure breast compositional density. Furthermore, although we did not meet our goal to have a validated workstation for the SXA method, we have demonstrated that the workstation is in progress and is near completion such that validation may proceed soon.

The impact of compositional density has yet to be seen. Now that we know we can measure compositional density with high precision and accuracy, it must be shown that compositional density is as good or better risk factor that mammographic density. We are now initiating a clinical prospective pilot study to compare DXA, SXA, and Mammographic Density on women with recently diagnosed cancer versus non-cancer controls.

The So What Test?

Research on breast cancer is severely handicapped by the lack of a reliable marker of the effect of promising drugs for prevention of cancer. Trials to test new drugs to reduce cancer risk require on the order of 10,000 high-risk women studied for 4 or 5 years at a cost of well over $30 million. Markers of change in risk, such as decrease in breast density, are gaining interest and widespread use in clinical trials with an aim to substantially decrease the size, duration and cost of early-stage trials to test new drugs (*8, 9*).

Thus, we believe that a measurement of breast compositional density (DXA or SXA) that is integrated into routine mammography or densitometry will have several important roles in clinical practice and clinical research:

1. To give women and doctors an estimate of breast cancer risks.
2. To identify women who will benefit most by available (and coming) treatments to prevent breast cancer.
3. To monitor preventive treatments and behavioral changes.
4. To determine whether these treatments reduce breast density and the associated risk of breast cancer.
5. To enable pharmaceutical companies and researchers to test the potential value of promising new drugs for reducing risk of breast cancer before committing to hugely expensive Phase III and Phase IV trials.

References

1. T. Asaga, C. Masuzawa, A. Yoshida, H. Matsuura, *J Digit Imaging* 8, 70-3 (1995).
2. C. C. Shaw, T. P. Wang, D. S. Breitenstein, D. Gur, *Med Phys* 24, 1293-302 (1997).
3. C. G. Shaw, D. B. Plewes, *Med Phys* 14, 956-67 (1987).
4. P. C. Johns, D. J. Drost, M. J. Yaffe, A. Fenster, *Med Phys* 12, 297-304 (1985).
5. P. C. Johns, M. J. Yaffe, *Med Phys* 12, 289-96 (1985).
6. G. R. Hammerstein *et al.*, *Radiology* 130, 485-91 (1979).
7. H. W. Wahner, I. Fogelman, *The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice* (Martin Dunitz, London, 1994).
8. J. A. Knight *et al.*, *Cancer Epidemiol Biomarkers Prev* 8, 123-8 (1999).
9. N. F. Boyd *et al.*, *J Natl Cancer Inst* 89, 488-96 (1997).

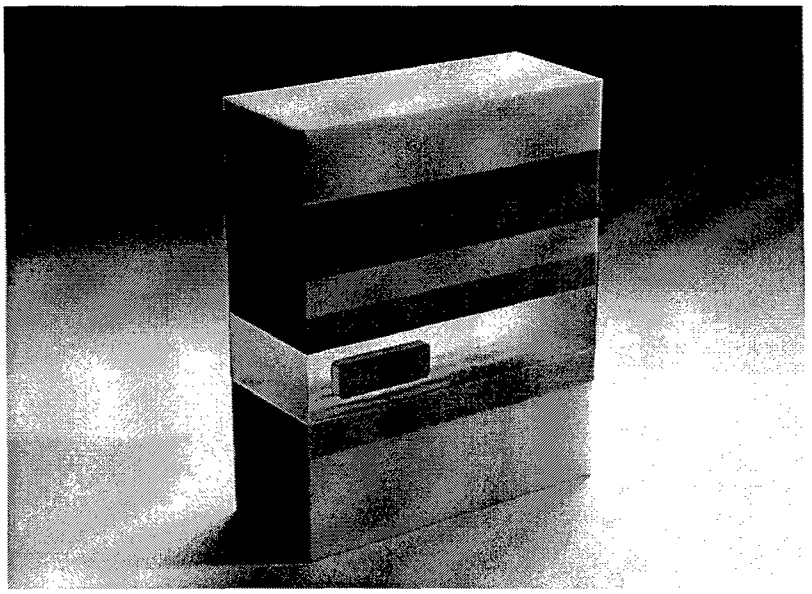

Figure 1: Model 17 phantom by CIRS, Inc. Phantom is made of constant thickness steps of varying thickness from 100% fat (0% glandular tissue) to 0% fat (100 % glandular tissue). Acrylic mid step is ignored since it is not a stable tissue equivalence over both the SXA and DXA energy range.

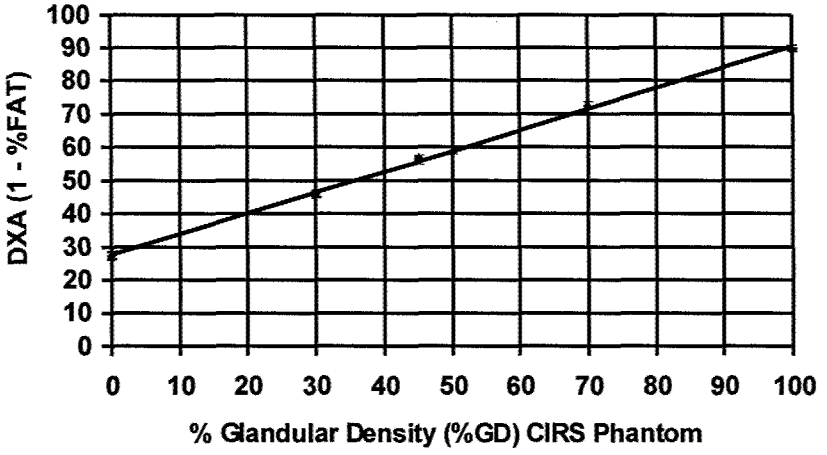

Figure 2: Calibration of %FAT DXA to % Glandular Density using M17 phantom

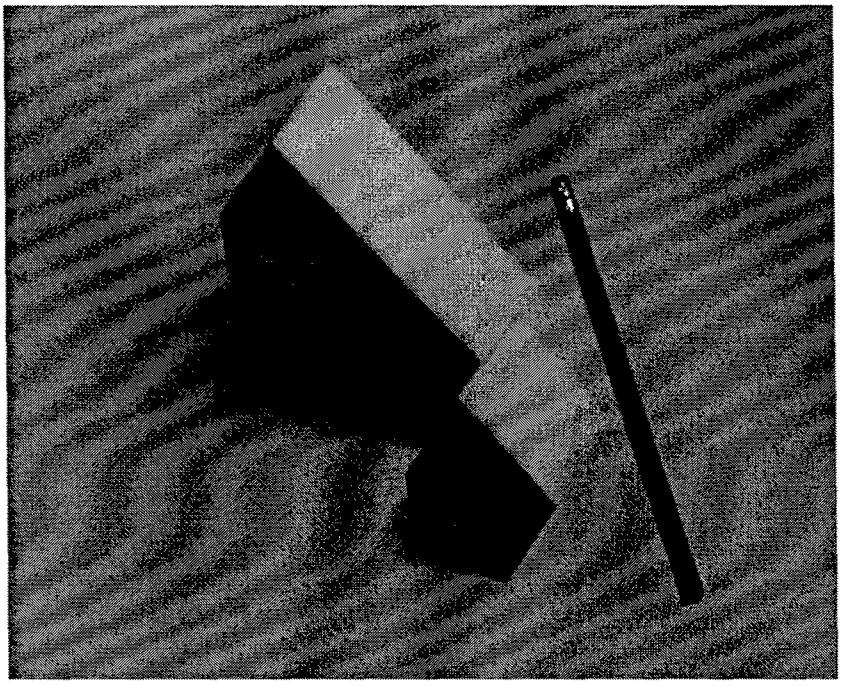

Figure 3: Two separated pieces of dual wedge SXA phantom. Each wedge is made of two materials: 100% fat equivalent, and 100% glandular equivalent. The wedges joined together to form the SXA compressible phantom.

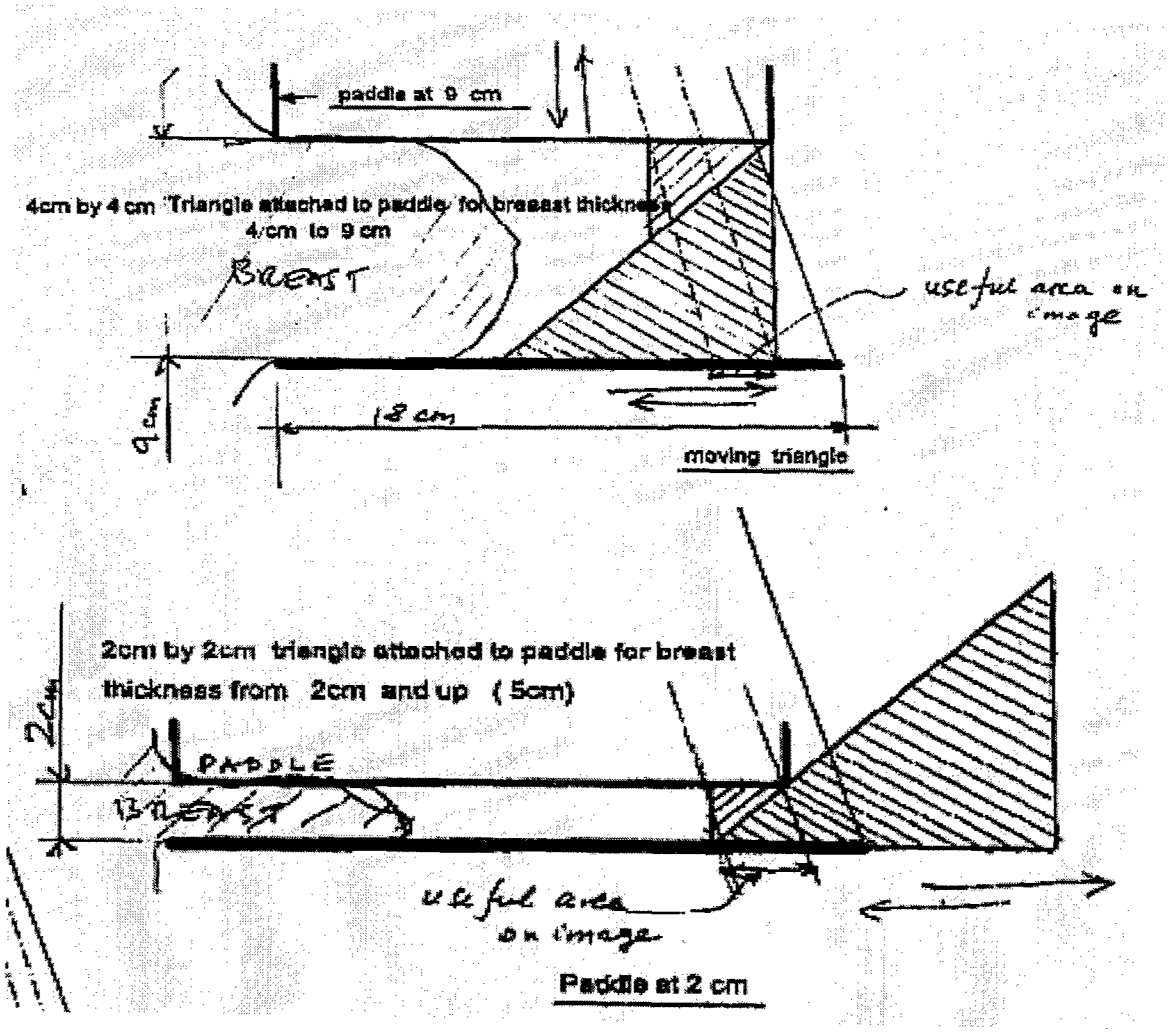

Figure 4: Concept drawing of the dual wedge SXA phantom positioned for a thick (top) and thin (bottom) breast. In both cases, the phantom creates reference areas of fat and gland at the same thickness as the compressed breast.

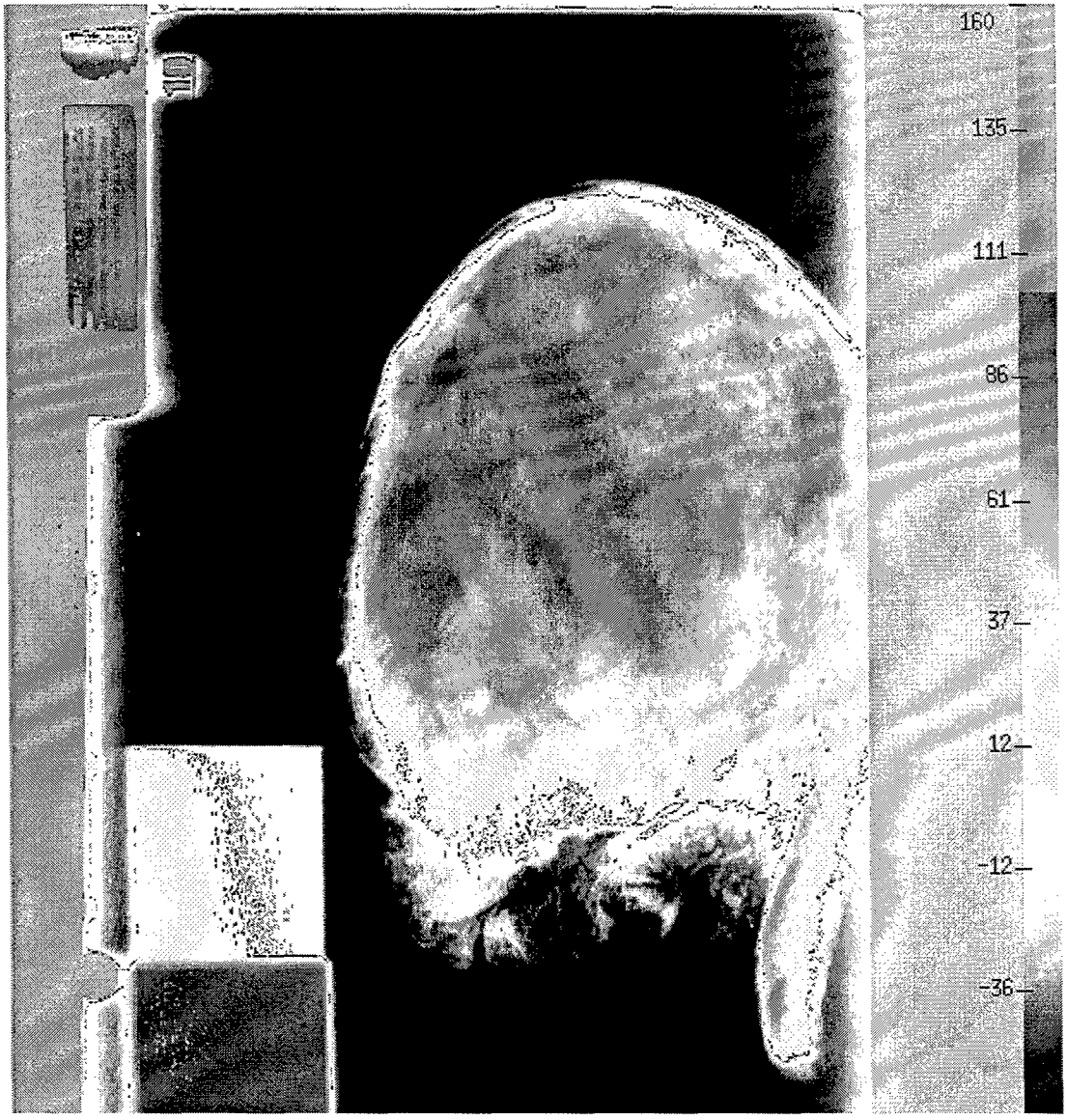

Figure 5: SXA analyzed image of a cadaver breast. The yellow tissue is pure adipose fat while the red is lean tissue. Green is super lean (over 100% glandular tissue) which would highlight calcifications. The gray scale part of the image is super fat. Parts of the breast tissue that are less thick than the phantom (peripheral edge for in vivo scans) will be in the super fat region.

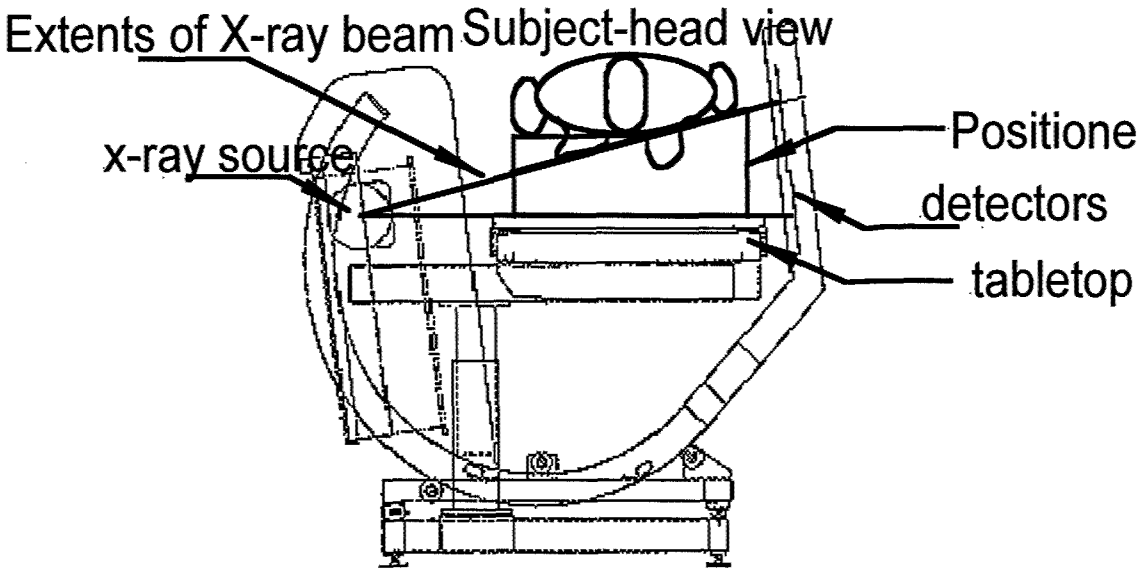

Figure 6: Schematic of a patient positioned for a DXA breast compositional density scan. The densitometer is shown in cross section with its x-ray gantry in the lateral position.

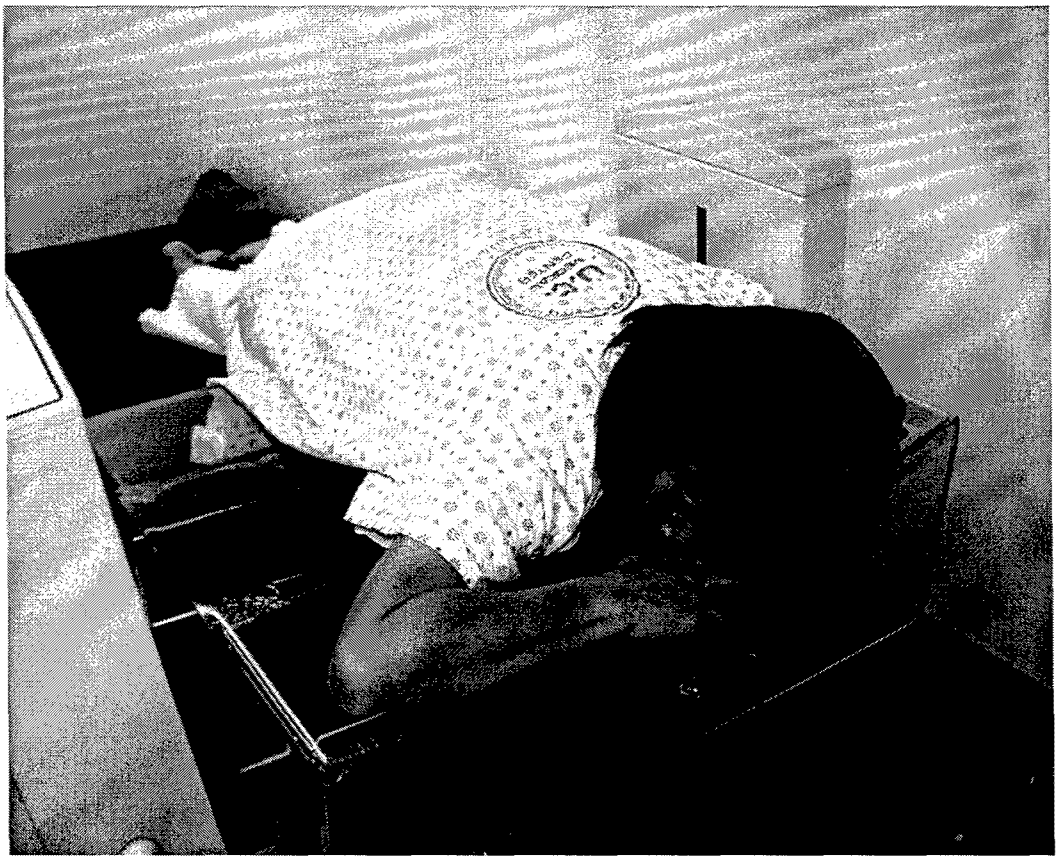

Figure 7: Volunteer positioned on top of the DXA breast positioner.

Appendix 1: Paper accepted for publication to Radiology. (attached)

Measurement of Breast Density with Dual X-ray Absorptiometry: Feasibility[1]

John A. Shepherd, PhD
Karla M. Kerlikowske, MD
Rebecca Smith-Bindman, MD
Harry K. Genant, MD
Steve R. Cummings, MD

Index terms:
Breast
Breast neoplasms, 00.30
Cancer screening
Phantoms

Published online before print
10.1148/radiol.2232010482
Radiology 2002; 223:554–557

Abbreviation:
DXA = dual x-ray absorptiometry

[1] From the Department of Radiology, Osteoporosis and Arthritis Research Group (J.A.S., H.K.G.) and Department of Medicine and Epidemiology and Biostatistics (K.M.K., S.R.C.), University of California at San Francisco, 350 Parnassus Ave, Suite 607, San Francisco, CA 94143; Veterans Affairs Medical Center, San Francisco, Calif (K.M.K.); and Department of Radiology, UCSF/Mt Zion Medical Center, San Francisco, Calif (R.S.B.). From the 2000 RSNA scientific assembly. Received February 19, 2001; revision requested March 28; final revision received November 28; accepted December 10. Supported by Breast Cancer Research Program Concept Award DAMD17-00-1-0612 from the Department of Defense and by UCSF Academic Senate Committee on Research. **Address correspondence to** J.A.S. (e-mail: *john.shepherd@oarg.ucsf.edu*).

Author contributions:
Guarantor of integrity of entire study, J.A.S.; study concepts, J.A.S., K.K., S.R.C.; study design, J.A.S.; literature research, J.A.S., K.M.K.; experimental studies, J.A.S.; data acquisition, J.A.S., R.S.B.; data analysis/interpretation, R.S.B., K.M.K., J.A.S.; statistical analysis, J.A.S.; manuscript preparation, J.A.S., K.M.K.; manuscript definition of intellectual content, S.R.C., K.M.K., J.A.S., H.K.G.; manuscript editing, K.M.K.; manuscript revision/review, H.K.G., S.R.C., R.S.B.; manuscript final version approval, all authors.

Dual x-ray absorptiometry (DXA) was used to quantify breast density with a phantom and with cadaveric breasts. With DXA, percentage of fat correlated with percentage of glandular density of the phantom ($r > 0.998$) and with density at mammography ($r_{adjusted} = 0.83$). DXA precision (SD) was 0.5% without and 1.1% with breast repositioning. DXA devices can be used to accurately and precisely estimate breast tissue density.

Perhaps the least recognized factor for breast cancer risk is breast density. Other than age, breast density has been shown to be one of the strongest indicators of breast cancer risk. Women who have greater than 50% of total breast area that is mammographically dense have a three- to fivefold greater risk for breast cancer than women with less than 25% mammographically dense breasts (1–4). Recently, breast density has been linked to specific biological processes in the breast that give rise to histologic features (5), such as atypical hyperplasia and carcinoma in situ, that are known to be related to increased breast cancer risk. For these reasons, breast density may be an important measure to monitor in clinical drug trials and epidemiologic cancer risk studies.

Breast density was initially described with a semi-quantitative classification system that categorized breast density into one of four categories by taking into account the quantitative (amount) and qualitative (diffuse or pronounced ductal structures and dense parenchymal patterns) nature of the density (3,4,6,7).

A more quantitative approach is to measure the area of mammographically dense breast relative to the total projected breast area. In this article, we will refer to this as mammographic density (3,8,9). Mammographic density (10) is a quantitative continuous grading from 0% to 100% measured by means of delineating the radiographically dense areas on the mammogram from the entire breast area and providing a percentage of breast density. The percentage of breast density is calculated as follows: (high radiographic density area)/(total breast area) × 100. Although quantitative, this method is limited by the fact that films are calibrated for optical density, not mass density, and a unique threshold of breast density is selected by a reader for each image. In addition, the total and dense projected areas will change on the basis of the amount of breast compression. The reproducibility (coefficient of variation) of delineating dense regions combined with patient repositioning errors is generally approximately 5% or more (11). Therapy with tamoxifen, which reduces cancer risk, decreases breast density by 4.3% per year in patients with cancer (12). Thus, the sensitivity of the percentage of breast density in the prediction of risk of breast cancer or in the detection of response to therapy may be similar to that of categorical methods and insufficient to monitor therapeutic changes in breast density for individuals.

There are compelling reasons to use dual x-ray absorptiometry (DXA) techniques to measure breast composition: *(a)* DXA is the reference standard for measuring whole-body composition because of its low radiation dose and high accuracy and precision (13). *(b)* The precision and accuracy of DXA have been characterized in small animals that are less than 600 g (14), which is similar to the size of a human breast. *(c)* The technique does not require a subjective interpretation of results. *(d)* Breast compression is not required. *(e)* The technique is

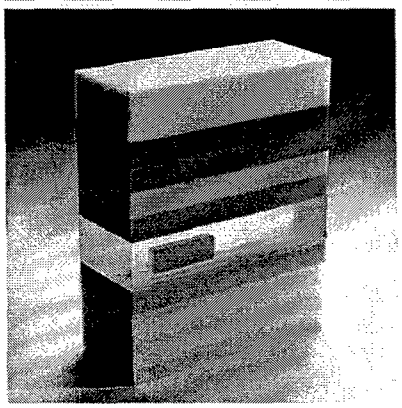

Figure 1. Density-step phantom used to calibrate the DXA device to units of percentage of glandular density. Phantom has a six-step range in percentage of glandular density from 0% (pure adipose fat) to 100% (pure breast glandular tissue).

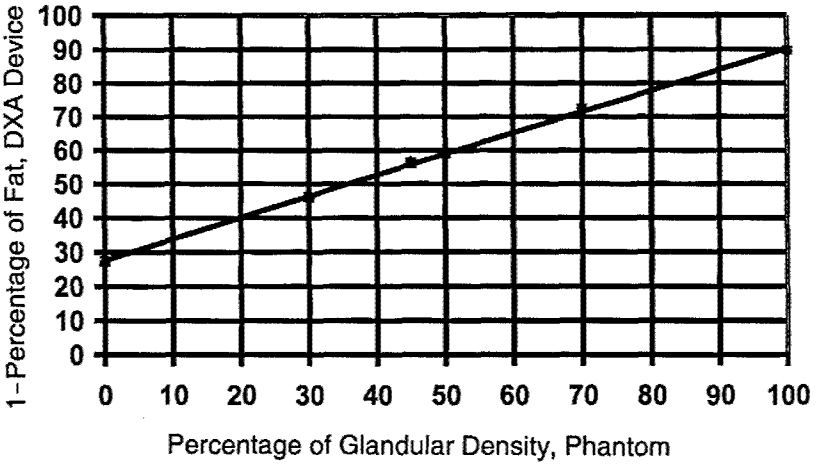

Figure 2. Plot shows results of calculation of 1 minus the percentage of fat measured with the DXA device and the percentage of glandular density reported with the phantom. Error bars are shown but do not extend beyond the dimension of the plot symbol.

readily available throughout the world for measuring bone density and diagnosing osteoporosis. Our specific goals for this study were to calibrate a commercially available DXA device to measure breast glandular density, to quantify in vitro precision by using cadaveric breasts, and to compare our measurements with conventional mammographic density measurements.

Materials and Methods

Devices

For this study, a DXA densitometer (Hologic QDR-4500A; Hologic, Bedford, Mass) was used. The software version was V9.10, and scans were acquired with the small animal/rat whole body scanning protocol. The scanning area was 18 × 36 cm^2 with a pixel size of 1.0 × 1.5 mm. Low- and high-energy images were acquired at 100 and 140 kVp, respectively, with the scanner. The entrance dose was 0.3 mGy (30 mR). Values from the densitometer were recorded as percentage of fat, total fat, total lean, and total mass. The objects were placed on the table and scanned with the x-ray gantry in the standard vertical position.

Phantom Measurements

For this study, a phantom (M17; CIRS, Norfolk, Va) was used as a breast density calibration tool. This model is a density-step phantom of constant thickness that simulates different ratios of breast glandular tissue and adipose fat (Fig 1). This phantom is an approximate atomic equivalent to adipose fat and breast glandular tissue, as reported by Hammerstein et al (15). The phantom's attenuation coefficients are within 1% of their respective fat-gland ratios from 10 to 200 keV. The density ranged from 0% to 100% glandular density in six steps. The inner clear acrylic section was not included in our comparison, since acrylic is not a stable representation of tissue across a wide x-ray energy range. The phantom was scanned 10 times with the DXA scanner without repositioning, and the average percentage of fat value from each density step was determined.

Cadaveric Breasts

Four whole cadaveric breast pairs (eight breasts) were examined by using both DXA and mammography. The breasts were excised whole, and all residual muscle tissue was removed. Each breast was scanned by using DXA twice without repositioning and once after flipping the breast 180° on the table to simulate repositioning owing to a second visit. The breasts were positioned in as close to a craniocaudal view as could be constructed. The precision of the DXA scanner was defined by the variance (PROC GLM; SAS Institute, Cary, NC) of the breast tissue scans without repositioning. The precision associated with repositioning, an estimate of the expected in vivo precision for follow-up examinations, was defined with PROC GLM in the same way by using the first scan and the last scan with repositioning.

For mammographic density, the films of the cadaveric breasts were acquired with a mammography machine (Sensorgraphe DMR; GE Medical Systems, Waukesha, Wis). The films were read by a trained radiologist, and the mammographically dense regions were delineated on the film with a wax pencil. The films were digitized at 100-μm spatial resolution with a digitizer (Lumisys 200; Lumisys, Sunnyvale, Calif). The mammographic density was then quantified by a research assistant with a workstation designed by Swarnakar et al (16) by tracing the pencil lines with a cursor.

Results

Calibration of Percentage of Glandular Density

The percentage of glandular density as defined by the phantom was compared with the percentage of fat measured with the DXA scanner. Each step was analyzed by using an 8.7-cm^2 region of interest. Figure 2 shows a plot of the reported percentage of glandular density of the phantom and the percentage of fat measured with the phantom for each density step. The relationship can be expressed with the following equation: percentage of glandular density = −0.627 × percentage of fat at DXA + 72.5. The slope of −0.627 shows a compression of the range of the percentage of glandular density to that of the percentage of fat such that 100% fat is 9.8% glandular density and 0% fat is 72.5% glandular density.

Characteristics of Cadaveric Breasts

The characteristics of cadaveric breasts are shown in Table 1. There was a wide range of values of total mass, fat mass, lean mass, and percentage of fat. The precision of the DXA scanner was characterized by using the cadaveric breast without repositioning. Table 2 presents a summary of the precision results with the DXA scanner. The precision (determined with the SD) is approximately 1 g for a mean mass of 1 kg, or 0.1% coefficient of variation. By using the previously noted equation to convert percentage of fat to percentage of glandular density, the precision of the percentage of glandular density is 0.5% SD, with a mean value of 32%. The precision results with repositioning in cadaveric breasts are shown in Table 3. The SD for all values increased slightly. Thus, the overall precision was limited by repositioning more so than by x-ray noise. The cadaveric breast mammographic density and the percentage of breast glandular tissue density were correlated with an r value adjusted for the sample size, or $r_{adjusted} = 0.83$. However, because the number of samples was small, the regression analysis relationship was highly influenced by each data point.

TABLE 1
Ranges of Mass and Percentage of Fat in Cadaveric Whole Breasts

Variable	Range
Fat mass (g)	149.1–1,303.6
Lean mass (g)	141.8–371.4
Total mass (g)	554.6–1,675
Fat (%)	13.8–82.5

TABLE 2
Precision Results with DXA Device without Repositioning in Cadaveric Breasts

Variable	Mean	SD	CV (%)*
Fat mass	645.5 g	4.1	0.6
Lean mass	263.2 g	3.7	1.4
Total mass	908.7 g	0.8	0.1
Glandular density	32.0%	0.5	NA

* CV = coefficient of variation, NA = not applicable.

TABLE 3
Precision Results with DXA Device with Repositioning in Cadaveric Breasts

Variable	Mean	SD	CV (%)*
Fat mass	708.0 g	16.3	2.3
Lean mass	263.0 g	8.0	3.0
Total mass	971.8 g	9.3	1.0
Glandular density	30.9%	1.1	NA

* CV = coefficient of variation, NA = not applicable.

Discussion

We found that the percentage of fat of breast tissue measured with DXA was highly correlated and linearly related to the percentage of breast glandular tissue density measured with a standard mammographic phantom. In addition, the percentage of breast density was moderately to highly correlated with the percentage of glandular density measured by using DXA.

It is of interest that the percentage of breast glandular tissue density does not equal one minus the percentage of fat. This is most likely, since the percentage of fat is measured relative to a two-compartment model of fat and muscle, not fat and glandular tissue. Even so, this relationship should result in a slope difference between the percentage of fat and the percentage of breast glandular tissue density. The offset is most likely caused by the DXA densitometer being calibrated to the in vivo four-compartment model of body composition. With this model, underwater weighing is used to derive body density, which has a known offset to absolute standards of fat and lean tissue (17). We expect the in vivo precision to be similar to the cadaveric precision with repositioning, since flipping the breast 180° would be a worst-case repositioning error.

There are other methods available to estimate body fat, but only DXA (18), computed tomography (CT) (19), and magnetic resonance (MR) imaging (20) can be used to measure the tissue composition of isolated body regions. Lee et al (20) reported a 2% accuracy of segmenting breast fat from glandular and ductal tissue in phantoms by using whole-breast MR imaging. The sections were individually segmented into two compartments, and measurements in all sections were summed to calculate a total percentage of breast fat. In 40 women, the SD of the mean value for the group was 18% compared with 30% for mammographic density in the same women, although the techniques were correlated ($r = 0.6$). This suggests that mammographic density is related to segmented compositional density but with a variance that is influenced by nondensity features.

CT can provide a precise measure of tissue composition calibrated to electron density or absolute references. Kalef-Ezra et al (19) described the normal breast electron density from CT volume scans in pre- and postmenopausal women. However, the whole-organ radiation dose with CT limits its usefulness as a screening tool. Neither technique, to the authors' knowledge, has been used to quantify cancer risk on the basis of breast density.

Dual-energy mammographic imaging is not a new concept and has been used for selecting calcifications and for improving imaging contrast (21–25). Breitenstein and Shaw (26) and Shaw and Plewes (27) reported on theoretical calculations of signal-to-noise ratios for single- versus dual-energy mammography to quantify tissue density with idealized phantoms. However, there is a substantial effort necessary to generate precise and accurate quantitative DXA images with standard mammography equipment (ie, filtering, poor dynamic range of film, availability of digital mammography units, x-ray tube stability). The widespread use of digital detectors and the replacement of x-ray film should make DXA imaging more feasible with standard digital mammography machines.

Our study had several limitations. First, there were only a small number of cadaveric breasts available for our estimates of precision and the regression analysis statistics. Second, we used a conventional DXA device optimized for bone density and whole-body composition measurements. In contrast to CT and the more specialized scanning modes possible with digital mammography machines, the DXA images acquired in this study have no diagnostic value beyond their use in determining tissue density and mass. Last, choosing alternative DXA energies may improve the technique's tissue selectivity even further.

In conclusion, findings of this study show that conventional DXA devices can be calibrated to measure the percentage of glandular density; with DXA, breast density can be quantified to approximately 1% precision limited principally by repositioning. The agreement between mammographic density and the percentage of breast glandular tissue density was moderately to highly correlated. Thus, compositional densitometry may be more accurate and precise than mammographic density for quantifying breast cancer risk.

However, it has not been demonstrated whether compositional breast density measured by using any technique is more predictive or discriminating than mammographic density in determining breast cancer risk. In vivo studies to quantify the percentage of breast glandular tissue density and cancer risk are warranted.

Acknowledgments: The authors acknowledge the UCSF Ambulatory Care Center and Department of Anatomy for their participation in the data collection.

References

1. Boyd NF, Byng JW, Jong RA, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 1995; 87:670–675.
2. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995; 87:1622–1629.
3. Wolfe JN, Saftlas AF, Salane M. Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case-control study. AJR Am J Roentgenol 1987; 148:1087–1092.
4. Saftlas AF, Szklo M. Mammographic parenchymal patterns and breast cancer risk. Epidemiol Rev 1987; 9:146–174.
5. Boyd NF, Jensen HM, Cooke G, Han HL, Lockwood GA, Miller AB. Mammographic densities and the prevalence and incidence of histological types of benign breast disease: Reference Pathologists of the Canadian National Breast Screening Study. Eur J Cancer Prev 2000; 9:15–24.
6. Wolfe JN. Breast patterns as an index of risk for developing breast cancer. AJR Am J Roentgenol 1976; 126:1130–1137.
7. American College of Radiology. Illustrated breast imaging reporting and data system (BI-RADS). 3rd ed. Reston, Va: American College of Radiology, 1998.
8. Boyd NF, O'Sullivan B, Campbell JE, et al. Mammographic signs as risk factors for breast cancer. Br J Cancer 1982; 45:185–193.
9. Brisson J, Merletti F, Sadowsky NL, Twaddle JA, Morrison AS, Cole P. Mammographic features of the breast and breast cancer risk. Am J Epidemiol 1982; 115: 428–437.
10. Byng J, Boyd N, Fishell E, John R, Yaffe M. The quantitative analysis of mammographic densities. Phys Med Biol 1994; 39:1629–1638.
11. Sivaramakrishna R, Obuchowski NA, Chilcote WA, Powell KA. Automatic segmentation of mammographic density. Acad Radiol 2001; 8:250–256.
12. Chow CK, Venzon D, Jones EC, Premkumar A, O'Shaughnessy J, Zujewski J. Effect of tamoxifen on mammographic density. Cancer Epidemiol Biomarkers Prev 2000; 9:917–921.
13. Laskey MA. Dual-energy x-ray absorptiometry and body composition. Nutrition 1996; 12:45–51.
14. Makan S, Bayley HS, Webber CE. Precision and accuracy of total body bone mass and body composition measurements in the rat using x-ray-based dual photon absorptiometry. Can J Physiol Pharmacol 1997; 75:1257–1261.
15. Hammerstein GR, Miller DW, White DR, Masterson ME, Woodard HQ, Laughlin JS. Absorbed radiation dose in mammography. Radiology 1979; 130:485–491.
16. Swarnakar V, Prevrhal P, Kerlikowske K, Cummings S, Genant HK, Shepherd JA. A mammographic density reading service for clinical drug trials (abstr). Radiology 2000; 217(P):701.
17. Kelly T. Whole body enhancements: free software upgrades available for QDR-4500A and QDR-4500W users with and without body composition option. In: QDR Insights Newsletter: New Developments in Bone Mineral Measurement. Vol 7. Bedford, Mass: Hologic, 1996; 15.
18. Sutcliffe JF. A review of in vivo experimental methods to determine the composition of the human body. Phys Med Biol 1996; 41:791–833.
19. Kalef-Ezra JA, Karantanas AH, Koligliatis T, Boziari A, Tsekeris P. Electron density of tissues and breast cancer radiotherapy: a quantitative CT study. Int J Radiat Oncol Biol Phys 1998; 41:1209–1214.
20. Lee NA, Rusinek H, Weinreb J, et al. Fatty and fibroglandular tissue volumes in the breasts of women 20–83 years old: comparison of x-ray mammography and computer-assisted MR imaging. AJR Am J Roentgenol 1997; 168:501–506.
21. Johns PC, Drost DJ, Yaffe MJ, Fenster A. Dual-energy mammography: initial experimental results. Med Phys 1985; 12: 297–304.
22. Asaga T, Masuzawa C, Yoshida A, Matsuura H. Dual-energy subtraction mammography. J Digit Imaging 1995; 8(1 suppl 1):70–73.
23. Johns PC, Yaffe MJ. Theoretical optimization of dual-energy x-ray imaging with application to mammography. Med Phys 1985; 12:289–296.
24. Chakraborty DP, Barnes GT. An energy sensitive cassette for dual-energy mammography. Med Phys 1989; 16:7–13.
25. Asaga T, Chiyasu S, Mastuda S, et al. Breast imaging: dual-energy projection radiography with digital radiography. Radiology 1987; 164:869–870.
26. Breitenstein DS, Shaw CC. Comparison of three tissue composition measurement techniques using digital mammograms: a signal-to-noise study. J Digit Imaging 1998; 11:137–150.
27. Shaw CG, Plewes DB. Effects of scattered radiation and veiling glare in dual-energy tissue-bone imaging: a theoretical analysis. Med Phys 1987; 14:956–967.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MD 21702-5012

REPLY TO
ATTENTION OF

MCMR-RMI-S (70-1y) 1 July 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLLIS M. RINEHART
Deputy Chief of Staff for
Information Management

ADB274518
ADB287328
ADB277943
ADB288221
ADB248332
ADB265760
ADB287619
ADB281577
ADB287600
ADB288422
ADB288375
ADB268297