Does digital deliver?:

Full-field digital mammography for breast cancer screening and its possible advantages for imaging dense breast tissue

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Abstract

Although medical physicists and radiologist have long suspected that the high contrast-resolution of full-field digital mammography and the power of digital image manipulation have the potential to significantly improve mammographic screening of women with a significantly high proportion of dense breast tissue, early clinical studies on the detection accuracy of this technology did not show that its use offered significant advantages over traditional film mammography. However, a very recent study in the *New England Journal of Medicine* has finally provided evidence of such an advantage. This paper discusses the basics of mammographic imaging and provides an overview of studies comparing digital mammography to film mammography, with particular emphasis on the challenges of imaging dense breast tissue, which is common in women under 50 and women receiving hormone replacement therapy.

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Introduction

Jemal et al. estimate that, in 2005, 32% of new cancer cases in American women will be from breast cancer.[1] With such a high rate of breast cancer incidence, doctors recommend that all women over the age of forty get a yearly mammogram. This creates the need for clinical practice that is reliable, quick, efficient, and cost effective. As a former employee of a New York medical equipment company, the author became interested in workflow issues for busy radiology clinics. He witnessed first-hand the disruptions caused to medium- and high-traffic clinics by equipment failures, especially failures of mammography equipment.

However, mammography poses unique problems for busy clinics. First, the Mammography Quality Standards Act of 1997 (MQSA) and its Reauthorization Acts of 1998 and 2002 create regulations that have been deemed necessary to assure the quality of these procedures. Though such regulations are surely proper, the demanding nature of these standards puts a strain on medical physicists and mammography technologists—who must perform very frequent quality assurance (QA) testing—and equipment technicians—who must service these machines when they fail to operate as required, as they often do.

Second, because mammography is most often used as a screening technique, the vast importance of accurate breast imaging has slowed the adoption of digital detection methods in this modality. The Food and Drug Administration (FDA) only very recently approved the American College of Radiology (ACR) to accredit a full-field digital mammography (FFDM) unit—the Siemens Mammomat Novation DR.[2] Even with such approval, though, the gains in adopting digital mammography are not as clear cut as for digital radiography in general.

This paper traces the development of FFDM (hereafter referred to as "digital mammography") for screening purposes. It first introduces some general principles of mammography and describes the imaging of two types of breast tissue: fatty and dense. Next, it discusses the advantages of performing screening mammography with digital equipment. Finally, it briefly assesses present recommendations about further adoption of digital mammography technology.

Basics of screening mammography

At typical radiographic diagnostic energies, the Compton effect dominates photon interactions in matter. The attenuation coefficient for the Compton effect is given in Equation 1:

$$\sigma = {}_e\sigma \ \frac{N_A Z \rho}{A} \qquad (1)$$

Mammography is performed at lower energies, where the photoelectric effect also provides a significant contribution to photon attenuation. The attenuation coefficient for the photoelectric effect is approximated in Equation 2:

$$\tau \ \propto \ \frac{Z^{3\to4} N_A \rho}{(h\nu)^{2\to3} A} \qquad (2)$$

Contrast is obtained in radiographic images because different structures in the body have different effective Z, Z/A, and ρ values. Regions that scatter or absorb photons more effectively will allow fewer photons to penetrate the body and reach the film or detector. Obviously, the greater the differences in attenuation among various structures, the higher the contrast in the image obtained will be.

The principal problem with mammography is that, compared to bone or chest x-rays, the different structures being imaged in mammography have much more uniform composition and density. Further complicating this modality, as noted by a quick survey of mammography articles in back issues of *Medical Physics*, is the need to reduce the radiation dose to the patient. This is extremely important for a screening procedure that is recommended for a significant portion of the population on a regular basis; as Gur noted in 1978, "in mammography, it is the possible late induction of breast cancer that concerns us."[3]

To keep doses low, x-ray tubes for mammography use a molybdenum-anode x-ray tube operated at roughly 25-28 kVp. This tube produces a photon spectrum with peaks at 17.5 and 19.6 keV. Figure 1 shows the contributions of the photoelectric effect, the Compton effect (incoherent scattering), and the Rayleigh effect (coherent scattering) at low photon energies. Note that the photoelectric effect provides a majority of the attenuation at mammography energies, but approximately 35% of the photons are still scattered, which reduces the signal-to-noise ratio and degrades the image.[4]

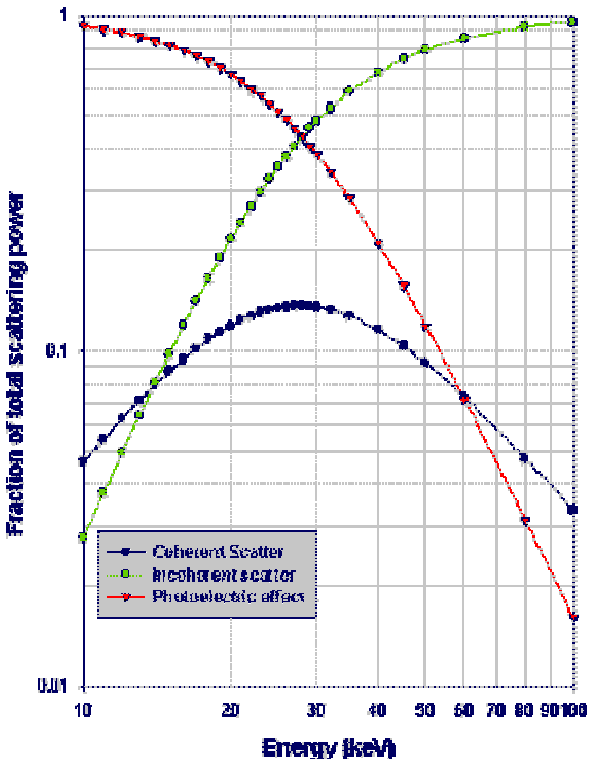

Figure 1: Contribution of the photoelectric effect, Compton effect (incoherent scattering), and Rayleigh effect (coherent scattering) to scattering at low photon energies. Mammography beams have energies of approximately 15-20 keV. (From *Mammography: Introduction*. (2003). Retrieved December 16, 2005, from Monash University Centre for X-ray Physics and Imaging Web site: http://cxpi.spme.monash.edu.au/index.htm)

As if these challenges were not great enough, some types of breast tissue are more difficult to image than others. Although there is much variation in breast tissue composition from woman to woman, the most general classifications of tissue (and, as we will see, the most important from the perspective of evaluating digital versus film mammography) are fatty breast tissue and dense breast tissue.

Fatty breast tissue is the most common in older patients, who are at the greatest risk of breast cancer. Fatty breast tissue is less dense than diseased tissue. As seen in Equations 1-2, both the photoelectric effect and Compton effect attenuation coefficients are linear functions of density.[a] Thus, a higher percentage of photons penetrate the healthy tissue than the cancerous tissue. This make a tumor show up as a light mass in the midst of the darker surrounding tissue. Figure 2 shows a tumor within fatty breast tissue.

[a] For a rigorous treatment of x-ray transmission in the breast, see, for example, the Appendix of Sabol, J. M. & Plewes, D. B. (1996). Analytical description of the high and low contrast behavior of a scan-rotate geometry for equalization mammography. *Medical Physics*, 23(6), 887-898.

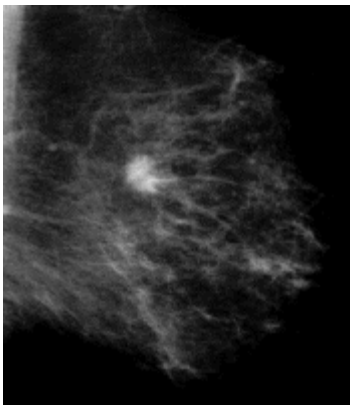

Figure 2: Mammogram of a tumor in fatty breast tissue. The diseased tissue attenuates photons more effectively, so the tumor shows up light against a darker background of fatty tissue. (From *Mammography: Introduction*. (2003). Retrieved December 16, 2005, from Monash University Centre for X-ray Physics and Imaging Web site: http://cxpi.spme.monash.edu.au/index.htm)

Dense breast tissue is more common in younger women and women being treated with post-menopausal hormone replacement therapy.[5] Unfortunately, dense breast tissue has a higher attenuation coefficient than fatty tissue—one much closer to the coefficient of cancerous tissue. This effect is evident in comparing Figure 2 with Figure 3, which shows a much more "opaque" mammogram of a dense breast.

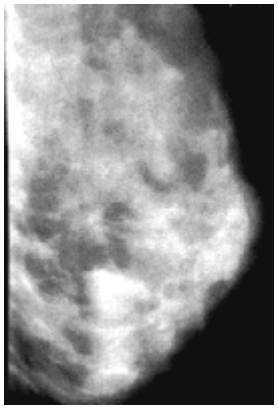

Figure 3: Mammogram of a dense breast. Comparison with Figure 2 suggests the much greater relative difficulty of spotting a tumor in dense breast tissue. (From *Mammography: Introduction*. (2003). Retrieved December 16, 2005, from Monash University Centre for X-ray Physics and Imaging Web site: http://cxpi.spme.monash.edu.au/index.htm)

Unfortunately, the tumors that dense breast tissue may hide are often a good deal more dangerous than the comparatively easy to find ones in fatty breast tissue. While cancer rates are higher in older women, who tend to have fatty breast tissue, Buist et al. report that higher breast densities not only obscure tumors, they also increases a younger woman's risk of developing breast cancer compared to same-aged women with less dense

breast tissue. In addition, oncologists believe tumors in dense breast tissue grow more quickly than those in fatty tissue.[6]

Though logic and the theoretical principles of medical physics only predict the differences between dense and fatty breast mammography described above, the consequences of these differences have been experimentally verified through a number of clinical studies. The most comprehensive was a study by Carney, et al. They attempted to determine "how breast density, age, and use of [hormone replacement therapy] individually and in combination affect the accuracy of screening mammography." They studied 329,495 women who had mammograms between 1996 and 1998. This study used data submitted to the National Cancer Institute's Breast Cancer Surveillance Consortium by seven different states. The researchers excluded patients receiving diagnostic mammography procedures, patients with incomplete records, and patients with breast implants.[7]

Table 1 shows their data regarding the breast densities of the women studied, divided by age group and whether or not the patient was receiving hormone replacement therapy.

Table 1: Breast density data, divided by age group and hormone replacement therapy status, from Carney, et al. study

Age Group	No HRT		HRT	
	Total	Dense	Total	Dense
y	*n*	*n (%)*	*n*	*n (%)*
40–44	46 947	28 628 (61.0)	4782	2537 (53.1)
45–49	55 362	32 112 (58.0)	16 023	8304 (51.8)
50–54	43 079	20 551 (47.7)	37 860	18 987 (50.2)
55–59	28 458	9905 (34.8)	39 105	17 832 (45.6)
60–69	57 542	16 511 (28.7)	47 379	20 336 (42.9)
70–79	49 854	13 389 (26.9)	20 551	8812 (42.9)
80–89	13 795	4107 (29.8)	2935	1295 (44.1)

These data clearly show that the probability of a woman having dense breast tissue decreases as a function of age and that older women receiving hormone replacement therapy are more likely to have dense breast tissue than older women not receiving such therapy. These data are important because they allowed the researchers to measure the effects of the presence of dense breast tissue on mammography screening accuracy. Table 2 shows the overall study results.

Table 2: Overall results of Carney et al. study

Variable	Screening Mammograms	Cases of Cancer	Adjusted Cancer Rate per 1000 Screening Examinations†	Adjusted True-Positives per 1000 Screening Examinations†	Adjusted False-Negatives per 1000 Screening Examinations†	Sensitivity	Specificity
	← n →					%	
All eligible women	463 672	2223	4.8	3.6	1.2	75.0	92.3
Age group							
40–44 *y*	51 729	125	2.0	1.4	0.6	65.6	90.9
45–49 *y*	71 385	218	2.7	2.0	0.8	69.7	90.7
50–54 *y*	80 939	328	3.9	2.9	1.0	72.9	91.6
55–59 *y*	67 563	325	4.8	3.6	1.2	73.8	92.3
60–69 *y*	104 921	611	5.9	4.2	1.7	73.3	93
70–79 *y*	70 405	501	7.1	5.7	1.4	81.4	94.1
80–89 *y*	16 730	115	7.3	5.9	1.5	86.1	94.3
Breast density group							
Almost entirely fatty	42 237	110	2.2	1.9	0.2	88.2	96.5
Scattered fibroglandular tissue	218 129	975	4.2	3.5	0.8	82.1	93
Heterogeneously dense	167 003	945	5.8	4.1	1.8	68.9	90.8
Extremely dense	36 303	193	6.1	3.9	2.2	62.2	89.9
Current use of HRT							
Yes	168 635	1319	4.7	3.5	1.3	76.6	92.6
No	295 037	904	4.6	3.5	1.1	72.7	91.7

In particular, note the high false negative rates for women with heterogeneously dense and extremely dense breast tissue and the low sensitivity of screening mammography for women aged 40-49 and for women with heterogeneously dense and extremely dense breast tissue. With its large sample size and carefully controlled methodology, Carney et al.'s conclusion that "mammographic breast density, [hormone replacement therapy] use, and age were all important predictors of the accuracy of screening mammography" is well founded.[8] Studies by Buist et al.[9] and Kerlikowske et al.[10] further confirmed these results.

Thus, physical analysis and clinical experience both suggested that measures needed to be taken to improve screening mammography accuracy for women with dense breast tissue, especially young women and women on hormone replacement therapy. The next section will, in part, discuss the role of digital mammography in facilitating that improvement.

Digital mammography as a solution to the challenges of imaging dense breast tissue

A thorough discussion of the advantages and disadvantages of both film and digital mammography was provided by Feig and Yaffe in 1998. They first noted the obvious advantage that, in digital mammography, separate components perform the duties of "image acquisition, storage, and display," whereas film bears the responsibility for all of these functions in film mammography.[11] Thus, digital equipment can be optimized to perform each of these various tasks. Figure 4 shows their schematic process diagrams for film and digital mammography.

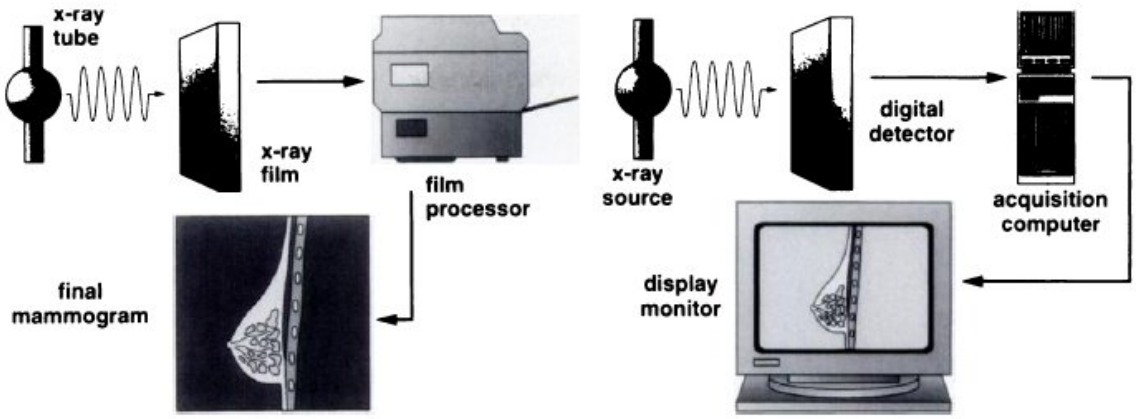

Figure 4: Schematic diagram of film (left) and digital (right) mammography processes. Note that film bears the responsibility of image acquisition, storage, and display. (From Feig, S. A. & Yaffe, M. J. (1998). Digital mammography. *Radiographics*, 18, 893-901.)

The digital equipment customized to each task gives digital mammography several advantages. First, Feig and Yaffe note, digital detectors have a much wider dynamic range, and they have a linear response curve because the size of the electronic signal from the detector is a linear function of exposures.[b] Even more important, however, is the ability to perform digital image manipulation without the need to digitize the film with a scanner.[12]

Figure 5 shows the possible benefits of digital image manipulation. Recall Figures 1-2, which compared tumor images in fatty and dense breast tissue. Figure 5 shows how digital mammography can help bring tumors in dense breast tissue closer to tumors in fatty breast tissue with respect to ease of detection. The figure shows the unaltered image of a dense breast and the same breast with an inset region of interest where digital image enhancement darkens the background and makes a tumor in the dense tissue more visible.

[b] The density-exposure curves of film have a more complicated dependence. See Feig and Yaffe, p. 894.

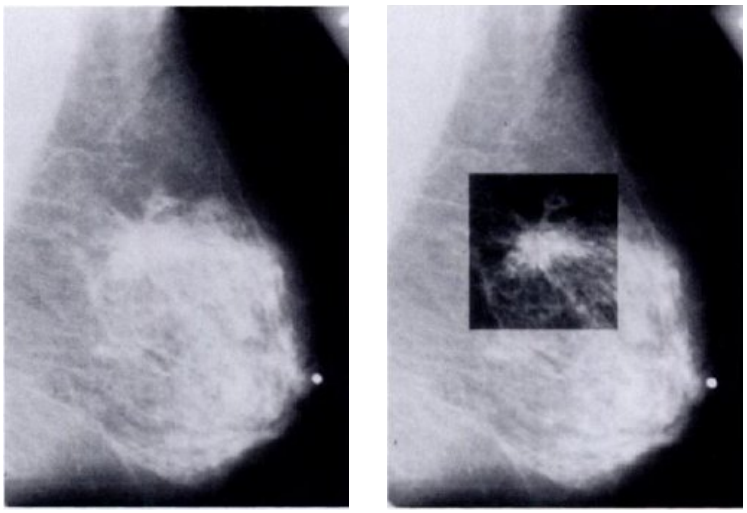

Figure 5: Two mammograms of a dense breast. The inset at right has been altered with digital image enhancement, in this case darkening the bright dense tissue background so that the underlying tumor can be seen. (From Feig, S. A. & Yaffe, M. J. (1998). Digital mammography. *Radiographics*, 18, 893-901.)

These images, combined with the improved intrinsic contrast resolution in digital mammography,[13] suggest the benefits of the technique for screening young women, women with particularly dense breasts, and women on hormone replacement therapy. However, these results were only suggestive. Lewin, et al. summarize the main source of uncertainty in speculating on the different detection capabilities of digital and film thusly: "Compared with film, the digital detector has greater contrast resolution…However, the digital detector does not have as high a spatial resolution for high-contrast objects as film does, and the effect on cancer detection of this trade-off between spatial resolution and contrast resolution cannot be predicted, because both play a role in revealing the features of breast cancers."[14]

Thus, digital mammography showed promise, but still had to prove itself on two key points: (1) it had to be shown to be just as reliable for general use as film mammography, and (2) it had to demonstrate a significant advantage over film mammography for certain demographics (e.g., women with dense breasts).

While acknowledging the potential benefits of digital mammography, one medical physics study, performed by Kuzmiak, et al., was not particularly reassuring with respect to the performance of digital mammography versus film. The researchers studied phantom object detection for both techniques. They found that digital systems did not have a higher phantom object detection rate than film systems, and for two of the systems studied (models made by Fischer and and Spectra), the object detection rate for digital was actually worse than for a standard film system, and that difference was statistically significant.[15] Far from showing that digital was an improvement over film, these results do not even suggest that digital is as effective.

However, these results are tempered by several observations. Most importantly, the study used a film scanner to digitize the film results. Thus, the improved detection from the film system may have been partially the result of the benefits of digital image manipulation. In clinical settings, few screening mammograms are scanned in a viewed in this "soft copy" form, so this benefit would not be born out in practice. Second, although this study did utilize phantoms simulating increasingly dense breasts and found no improvement in the digital systems' ability to image them, density was not the variable of interest in this experiment. An experimental design more specifically tailored to studying the effect of tissue density on object detection may have yielded different results.

Of course, it is in the clinic that screening digital mammography must ultimately prove itself versus film, and the results of these studies have been more favorable for digital systems than the study by Kuzmiak, et al. Four large clinical trials that compared film to digital screening mammography showed little to no difference between digital and film systems for studies of the general public.

Lewin has performed two such studies with other researchers. The first studied 4,945 women over 40 who received mammograms at one of two participating institutions. The researchers chose a sample population of screening patients, rightly pointing out that earlier studies—performed to aid manufacturers in obtaining FDA approval of the FFDM equipment—had probably introduced bias by analyzing a group of patients who were receiving diagnostic mammography procedures; these procedures receive much more time and attention from radiologists, and do not fairly test the detection accuracy of mammography equipment in its much more common deployment as a screening tool.

Eligibility for the study required women to be at least 40 years old, to be breast implant-free, and to have breasts that could be completely imaged on a 24 cm x 30 cm detector. The women who participated had a digital and a film mammogram taken within three days (91% of them had the procedures on the same day, with the same technologist).

This study concluded that there was no statistically significant difference between digital and film screening mammography in terms of detection rate.[16] Another, larger study by Lewin, et al. reached the same conclusions.[17] Two studies in Oslo, Norway, also found no statistically significant difference between detection rates in screening populations for digital and film systems, and these studies included roughly 10 times the participants.[18,19]

On the whole, these studies suggest that digital mammography probably meets the first criterion of performing at least as well as film units for screening mammography. However, until very recently, there was really no evidence of a reason to switch to digital mammography. After all, as will be discussed later, the cost of making this switch is by no means insignificant. Thus, as Dershaw rightly points out, some kind of *significant* gains must be demonstrated before most hospitals and clinics will seriously begin to think about adding digital mammography capability, let alone switching to its exclusive use.[20]

A couple months ago, a study in the *New England Journal of Medicine* provided convincing evidence of such gains. The study there reported was performed by Pisano, et al. for the Digital Mammographic Imaging Screening Trail (DMIST). This was a huge study, analyzing data from 49,333 eligible asymptomatic patients who received both digital and film mammograms at one of 33 participating sites. These mammograms were each read by two radiologists.

Of all of the participants studied, 42,760 had verifiable cancer status at the end of the two year study. This status was carefully defined; women were classified as positive for cancer if, within 455 days of screening, pathology tests confirmed that the cancer identified in the screening mammogram was present. They were confirmed as being cancer negative if pathology tests of possible tumor masses from the mammographic screening were negative and/or if a one-year follow up mammogram was read as normal by the radiologists. Table A-1 in the Appendix summarizes the demographic information both for all the participants in the study and those whose cancer status was confirmed within its time constraints.

Once again, this study concluded that, for the general population, there are no significant gains to be had from either technology. However—and this was the evidence that had been searched for for quite some time—the study did find that digital mammography was a more effective screening tool for women under the age of 50. As stated by the authors, "The performance of digital mammography was…significantly better than that of film mammography among women under the age of 50 years…, women classified by the readers as having heterogeneously dense or extremely dense breasts…, and premenopausal or perimenopausal women."[21]

This is best illustrated by Figure 6, which plots sensitivity—the ability of a mammogram to correctly identify the presence of breast cancer—versus specificity—the ability to correctly identify the non-presence of breast cancer—for several different demographics.

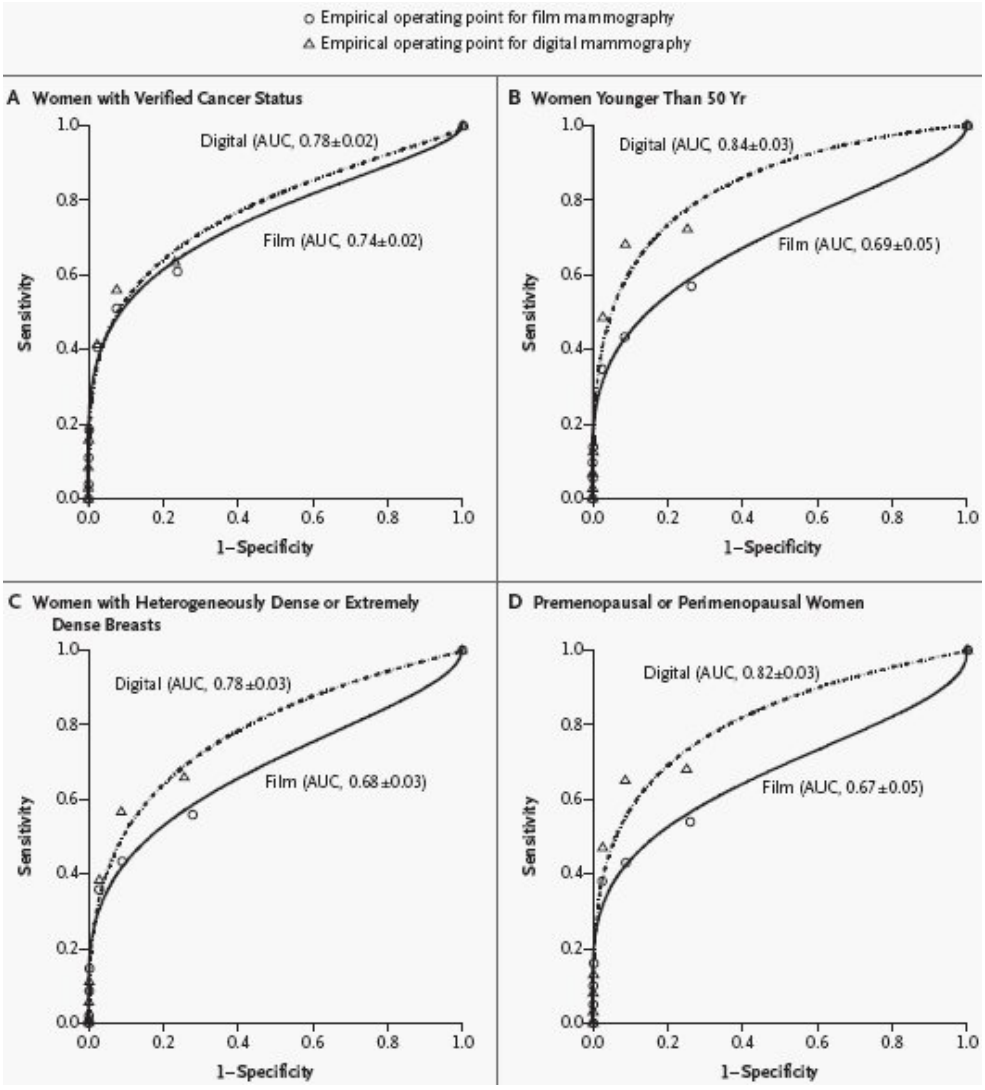

Figure 6: Sensitivity versus specificity in for digital and film mammography for patients with confirmed cancer status, divided by demographic. (From Pisano, E. D., et al. (2005). Diagnostic performance of digital versus film mammography for breast-cancer screening. *New England Journal of Medicine*, 353(17), 1773-1783.)

These estimates of specificity and sensitivity are based on the Breast Imaging Reporting and Data System (BIRADS) standard seven-point malignancy scale, which the participating radiologists all received training in.[22] They support the authors' conclusion that screening with digital mammography is more effective for the demographics shown in plots B, C, and D in Figure 6.[c] Greater sensitivity for a given specificity means significantly more present tumors were identified in patients from these demographics with the digital systems, which should be the goal of any improvement to the breast cancer screening system.

[c] The relevant data are presented in greater detail in Table 2-A of the Appendix.

Although medical physicists and radiologists had suspected this was the case for years, this study represents the first reasonably conclusive proof. Although all previous studies yielded very equivocal results, the enormous scope of this study, and its superior experimental methodology—designed, as it was, to account for flaws in earlier clinical trials[23]—should assuage any doubts about its results. Thus, there are now reasonable grounds to motivate a field-wide discussion about how best to implement digital mammographic imaging into this country's screening system.

Conclusions and recommendations

In an editorial published simultaneously with the DMIST study, Dershaw perceptively defined the terms of this discussion. After praising the results of the study, he summarized the very significant barriers to acting on them:

> These advantages must be weighed against the cost of digital-imaging systems, which are often one and one half to four times as expensive as film mammography systems. Women with large breasts who undergo digital mammography may require multiple exposures to ionizing radiation because the smaller image size requires the acquisition of multiple images to image the breast fully. Workstations for viewing digital mammograms are frequently not user-friendly and more time and effort are often required to read digital mammograms than film mammograms. It can also be difficult to compare digital images with older film studies.[24]

Dershaw is quite right to point out these problems, and DMIST is currently conducting a study on the cost-effectiveness of implementing more digital mammography within the breast cancer screening system. As an erstwhile x-ray and mammography equipment technician and observer of the everyday operations in many New York hospitals and radiology clinics (some of them extremely busy and efficient ones), this author hopes and suspects that decision-makers currently considering whether to increase their capacity for digital mammography screening will answer in the affirmative.

First, while "workstations for viewing digital mammograms" may not be user-friendly at present, increased demand for these systems will eventually drive market forces to improve these workstations. Bioinformatics is a growing field that is getting better and better at keeping pace with technological improvements on the hardware side of medical imaging. Though this will require the commitment of resources—and, more importantly, responsiveness to customer feedback—on part of equipment and software manufacturers, the current state of digital workstations should not unduly influence the future of digital mammography in this country.

Second, while mammography procedures performed with digital equipment may take much longer to perform and read than their film equivalents *now*, this state is also unlikely to persist as technologists and radiologists become more adept with these procedures. Though they may not, in the end, end up being any faster than film, digital

techniques will undoubtedly get faster and may approach equivalent film system speeds. Again, the point is that it is too early to tell, and current imaging and reading times should not be assumed to be constant.

Third, increasingly efficient clinics are demonstrating the serious benefits of going all digital and implementing facility-wide PACS systems. Provided that studies continue to show no medical detriment to using digital images for mammographic screening, it will be important for mammography departments to consider digital systems so as not to be left out of the digitalization process.

However, this is no denying that the hurdles of going digital are still significant, despite the above points. For a procedure with already low reimbursement values, the burden of spending several times current costs for digital mammography equipment cannot be ignored. Furthermore, Pisano et al. note that, unlike women with mostly dense breast tissue, women with mostly fatty breast tissue might still be better served by film.[25] Obviously, these women—who are, on average, at higher risk for breast cancer—need to be screened as effectively as possible.

But, if it financially possible, so should women with mostly dense breast tissue. Thus, in this author's opinion, Dershaw's recommendation that hospitals and clinics cautiously proceed with the process of gradually supplementing their film mammography screening capabilities with digital ones is the best course of action at this time. Doing so will help mammography departments stay connected with the general trend of increased digitization, and it will help them provide better care for a significant—though not a majority—patient demographic.

Appendix

Table A-1: Demographic information for patients in Pisano, et al. study performed by DMIST

Characteristic	Eligible Women (N=49,333)	Women with Verified Cancer Status (N=42,760)
Age at enrollment — yr		
Mean	54.6	54.9
Interquartile range	47–61	47–62
Race or ethnic group — no. (%)†		
White	40,409 (81.9)	36,079 (84.4)
Hispanic or Latina	2,012 (4.1)	1,266 (3.0)
Black or African American	5,439 (11.0)	4,243 (9.9)
Native Hawaiian or other Pacific Islander	64 (0.1)	61 (0.1)
Asian	923 (1.9)	793 (1.9)
American Indian or Alaskan Native	46 (0.1)	37 (0.1)
Other race specified	396 (0.8)	244 (0.6)
Unknown or data missing	44 (0.1)	37 (0.1)
Menopausal status — no. (%)‡		
Premenopausal	14,349 (29.1)	12,024 (28.1)
Perimenopausal	4,294 (8.7)	3,779 (8.8)
Postmenopausal	29,569 (59.9)	26,087 (61.0)
Unknown or data missing	1,121 (2.3)	870 (2.0)
Breast density — no. (%)		
Almost entirely fat	5,184 (10.5)	4,364 (10.2)
Scattered fibroglandular densities	21,171 (42.9)	18,480 (43.2)
Heterogeneously dense	19,089 (38.7)	16,793 (39.3)
Extremely dense	3,690 (7.5)	3,104 (7.3)
Data missing	199 (0.4)	19 (<0.1)

Table 2-A: Pathological information for referred women by type of mammography

Diagnosis	Both Film and Digital Mammography				Film Mammography Alone				Digital Mammography Alone				Neither Type of Mammography				Total
	All	Women <50yr Old	Pre-menopausal and Peri-menopausal Women	Women with Heterogeneously Dense or Extremely Dense Breasts	All	Women <50yr Old	Pre-menopausal and Peri-menopausal Women	Women with Heterogeneously Dense or Extremely Dense Breasts	All	Women <50yr Old	Pre-menopausal and Peri-menopausal Women	Women with Heterogeneously Dense or Extremely Dense Breasts	All	Women <50yr Old	Pre-menopausal and Peri-menopausal Women	Women with Heterogeneously Dense or Extremely Dense Breasts	
	number of women (percent)																
Invasive carcinoma	85 (25.4)	12 (3.6)	16 (4.8)	36 (10.7)	35 (10.4)	3 (0.9)	7 (2.1)	12 (3.6)	38 (11.3)	14 (4.2)	19 (5.7)	26 (7.8)	73 (21.8)	14 (4.2)	18 (5.4)	41 (12.2)	231 (68.8)
Invasive ductal carcinoma +/– DCIS	73 (21.8)	9 (2.7)	13 (3.9)	33 (9.9)	26 (7.8)	2 (0.6)	6 (1.8)	8 (2.4)	30 (9.0)	11 (3.3)	14 (4.2)	19 (5.7)	60 (17.9)	10 (3.0)	13 (3.9)	32 (9.6)	189 (56.4)
Invasive lobular carcinoma +/– DCIS	5 (1.5)	2 (0.6)	3 (0.9)	1 (0.3)	5 (1.5)	1 (0.3)	1 (0.3)	3 (0.9)	6 (1.8)	3 (0.9)	4 (1.2)	5 (1.5)	5 (1.5)	2 (0.6)	3 (0.9)	3 (0.9)	21 (6.3)
Mixed invasive ductal and lobular carcinoma +/– DCIS	7 (2.1)	1 (0.3)	0	2 (0.6)	4 (1.2)	0	0	1 (0.3)	2 (0.6)	0	1 (0.3)	2 (0.6)	8 (2.4)	2 (0.6)	2 (0.6)	6 (1.8)	21 (6.3)
DCIS†	36 (10.7)	14 (4.2)	16 (4.8)	18 (5.4)	17 (5.1)	3 (0.9)	4 (1.2)	7 (2.1)	25 (7.5)	8 (2.4)	14 (4.2)	14 (4.2)	25 (7.5)	4 (1.2)	6 (1.8)	11 (3.3)	103 (30.7)
High grade	15 (4.5)	6 (1.8)	8 (2.4)	9 (2.7)	6 (1.8)	2 (0.6)	1 (0.3)	3 (0.9)	7 (2.1)	3 (0.9)	6 (1.8)	4 (1.2)	12 (3.6)	1 (0.3)	3 (0.9)	4 (1.2)	40 (11.9)
Medium grade	14 (4.2)	5 (1.5)	4 (1.2)	6 (1.8)	4 (1.2)	0	1 (0.3)	1 (0.3)	12 (3.6)	4 (1.2)	6 (1.8)	5 (1.5)	7 (2.1)	1 (0.3)	1 (0.3)	3 (0.9)	37 (11.0)
Low grade	6 (1.8)	3 (0.9)	4 (1.2)	3 (0.9)	6 (1.8)	1 (0.3)	2 (0.6)	3 (0.9)	6 (1.8)	1 (0.3)	2 (0.6)	5 (1.5)	6 (1.8)	2 (0.6)	2 (0.6)	4 (1.2)	24 (7.2)
Unknown grade	1 (0.3)	0	0	0	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0	2 (0.6)
Other malignant cancer‡	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Tstage††	122 (36.4)	26 (7.8)	32 (9.6)	54 (16.1)	52 (15.5)	6 (1.8)	11 (3.3)	19 (5.7)	63 (18.8)	22 (6.6)	33 (9.9)	40 (11.9)	98 (29.3)	18 (5.4)	24 (7.2)	52 (15.5)	335 (100.0)
No stage§	1 (0.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)
Tx	12 (3.6)	4 (1.2)	3 (0.9)	7 (2.1)	4 (1.2)	2 (0.6)	0	0	9 (2.7)	4 (1.2)	5 (1.5)	6 (1.8)	13 (3.9)	0	0	4 (1.2)	38 (11.3)
Tis	36 (10.7)	14 (4.2)	16 (4.8)	18 (5.4)	17 (5.1)	3 (0.9)	4 (1.2)	7 (2.1)	25 (7.5)	8 (2.4)	14 (4.2)	14 (4.2)	25 (7.5)	4 (1.2)	6 (1.8)	11 (3.3)	103 (30.7)
T1mic	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0	1 (0.3)	0	0	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	5 (1.5)
T1a	11 (3.3)	3 (0.9)	2 (0.6)	6 (1.8)	3 (0.9)	0	1 (0.3)	1 (0.3)	4 (1.2)	2 (0.6)	1 (0.3)	1 (0.3)	5 (1.5)	0	0	1 (0.3)	23 (6.9)
T1b	20 (6.0)	0	2 (0.6)	6 (1.8)	8 (2.4)	1 (0.3)	3 (0.9)	4 (1.2)	8 (2.4)	1 (0.3)	1 (0.3)	6 (1.8)	18 (5.4)	1 (0.3)	2 (0.6)	7 (2.1)	54 (16.1)
T1c	29 (8.7)	1 (0.3)	3 (0.9)	13 (3.9)	15 (4.5)	0	1 (0.3)	6 (1.8)	11 (3.3)	4 (1.2)	8 (2.4)	7 (2.1)	18 (5.4)	5 (1.5)	6 (1.8)	13 (3.9)	73 (21.8)
T2	10 (3.0)	3 (0.9)	5 (1.5)	3 (0.9)	4 (1.2)	0	2 (0.6)	3 (0.9)	2 (0.6)	1 (0.3)	1 (0.3)	2 (0.6)	17 (5.1)	2 (0.6)	3 (0.9)	14 (4.2)	33 (9.9)
T3	1 (0.3)	0	0	1 (0.3)	0	0	0	0	3 (0.9)	2 (0.6)	1 (0.3)	3 (0.9)	1 (0.3)	0	0	1 (0.3)	5 (1.5)
Nstage (invasive cancer)‡‡	83 (24.8)	12 (3.6)	16 (4.8)	35 (10.4)	35 (10.4)	3 (0.9)	7 (2.1)	12 (3.6)	38 (11.3)	14 (4.2)	19 (5.7)	26 (7.8)	73 (21.8)	14 (4.2)	18 (5.4)	41 (12.2)	231 (68.8)
Nx	23 (6.9)	5 (1.5)	4 (1.2)	14 (4.2)	9 (2.7)	3 (0.9)	2 (0.6)	3 (0.9)	12 (3.6)	4 (1.2)	5 (1.5)	9 (2.7)	18 (5.4)	1 (0.3)	1 (0.3)	7 (2.1)	64 (19.1)
N0	44 (13.1)	6 (1.8)	7 (2.1)	16 (4.8)	19 (5.7)	0	2 (0.6)	4 (1.2)	20 (6.0)	7 (2.1)	9 (2.7)	12 (3.6)	30 (8.9)	8 (2.4)	8 (2.4)	23 (6.9)	122 (36.4)
N1	16 (4.8)	1 (0.3)	5 (1.5)	6 (1.8)	7 (2.1)	0	3 (0.9)	5 (1.5)	6 (1.8)	3 (0.9)	5 (1.5)	5 (1.5)	13 (3.9)	4 (1.2)	9 (2.7)	8 (2.4)	42 (12.5)
N2	0	0	0	0	0	0	0	0	0	0	0	0	3 (0.9)	1 (0.3)	0	1 (0.3)	3 (0.9)

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