PROJECT TITLE:

ABSTRACT:

Breast cancer is the most common invasive cancer in women and the second leading cause of cancer deaths in women (1). Since 1990, the mortality rate from breast cancer has decreased more than 30% in the United States (2), and this is likely related to both the implementation of screening mammography and significant advances in the treatment of breast cancer (3). The sensitivity of mammography has been shown to be decreased in patients with dense breasts (4). Since 2009, thirteen states have passed breast density legislation that requires women with increased breast density (BI-RADS categories 3 and 4) be informed of their breast density and a bill has been introduced recently in the US House of Representatives. Currently, there is limited data to guide recommendations for additional or alternative imaging evaluation in women with dense breasts and average risk. An initial study of dual-energy (DE) contrast-enhanced (CE) digital mammography showed that this novel technology had better sensitivity when compared to mammography alone (93% vs 78%) (5). The positive predictive value of enhancing lesions identified on DE CE mammography is reportedly higher than those identified with contrast enhanced breast MRI (97% vs 85%) (6). The central hypothesis of my proposed research is that DE CE digital mammography is superior to full field digital mammography (FFDM) for the detection of invasive breast cancer in patients with increased breast density (BIRADS category 3 or 4). This study will prospectively evaluate DE CE digital mammography as an adjunct or as a potential alternative to yearly mammographic screening women with dense breasts and average risk. This pilot data will be utilized to assess the value of a future randomized trial to compare novel breast imaging with DE CE digital mammography as an alternative to routine screening recommendations for women with dense breast tissue.

DETAILED PLAN AND BIBLIOGRAPHY

A. TITLE:

B. SPECIFIC AIMS

Primary Aim:

To determine the accuracy of DE CE mammography when compared to full field digital mammography (FFDM) in patients with increased breast density (BI-RADS category 3 or 4 breast density). We hypothesize that DE CE digital mammography will have improved diagnostic accuracy when compared to FFDM in patients with increased breast density. The proposed study will invite women meeting eligibility criteria to undergo routine screening FFDM and DE CE digital mammography. Sensitivity, specificity, positive predictive values (PPV1 and 3), negative predictive value (NPV), call back rate, false negative rate, and accuracy will be assessed. This imaging technique is hypothesized to improve detection of masses (particularly those that enhance post contrast administration) in patients with dense breasts; thereby decreasing the false negative rate. Additionally, the ability of this technique to demonstrate contrast enhancement of masses may decrease call back rate as compared with FFDM. This trial is unique because to our knowledge this technology has not been assessed in this group of patients and this study will provide data to prepare for a larger clinical trial to determine the accuracy of this novel imaging technique as an alternative to screening mammography in this patient population.

Secondary Aims:

1. To determine through questionnaires and study screening assessments whether DE CE digital mammography has associated factors that make it a less desirable patient

experience than FFDM, and determine the acceptability of a randomized screening trial to compare the two modalities. We anticipate that this patient population will support further study to evaluate new modalities that might enhance accuracy for breast cancer detection.

2. To assess interobserver variability observed with DE CE digital mammography as compared to FFDM. We hypothesize that DE CE digital mammography assessment will have less interobserver variability than FFDM. Each study will be interpreted by 4 radiologists with varying levels of experience blinded to results with separation of time.

3. To evaluate in an exploratory manner any breast cancer identified by each modality including pathologic diagnosis, histologic grade, tumor size, receptor profile, axillary nodal status, and distant metastases. We hypothesize that CE DE digital mammography will identify additional malignancies and that these cancers are more likely to represent invasive disease. We recognize that this will be a small number given the pilot nature of this study and small sample size yet improved detection of clinically significant breast cancer in this population would be valuable.

C. SIGNIFICANCE

Breast cancer is the second leading cause of cancer mortality in women, and the American Cancer Society estimates 232,340 new cases of invasive breast cancer in women in 2013 and 2240 new cases in men (1). Since 1990, the mortality rate from breast cancer has decreased more than 30% in the United States (2), and this is likely related to both the implementation of screening mammography and significant advances in the treatment of breast cancer (3). Mammography remains the standard of care for early detection of breast cancer prior to clinical symptoms, facilitating treatment of malignancy when it is more likely

curable; however, this may also result in some overtreatment (7-10). Additionally, certain women have been shown to benefit from additional screening with contrast enhanced breast (MRI) (11); therefore, a given patient's screening regimen is optimized after discussion with a health care professional regarding personal risk assessment as well as the benefit and potential harms of various imaging studies. Several randomized controlled trials and meta-analyses have shown a reduction in breast cancer mortality, with general agreement of a 15 to 20% relative risk reduction in breast cancer mortality resulting from invitation to screen (12-17). While mammography has shown proven benefit, it is not a perfect screening test, with documented limitations (18-28) including false negative rates ranging from 6 to 46% (4;29-31). Retrospective and prospective studies have shown screening breast MRI is valuable for early detection in women at increased risk for breast cancer (32-39). Breast MRI has been shown to have a higher sensitivity for detecting breast cancer (71-93.8%) when compared to mammography (19-58.8%) (33,36-40).

One condition where screening might be more likely to fail is in women with dense breasts. According to the Breast Cancer Surveillance Consortium data from 1994-2009, false negative rates for mammograms according to breast density were 50.56% and 13.93% in heterogeneously dense and extremely dense breasts respectively as compared to exams categorized as scattered fibroglandular tissue 32.25% and almost entirely fat 3.25%. Since 2009, thirteen states have enacted dense-breast legislation requiring mammography providers to notify women categorized as having dense breast tissue about their condition. A similar bill is proposed in the United States House of Representatives currently. There is little evidence to direct supplemental or alternative imaging evaluation in patients with dense breast tissue who are not eligible for high risk screening using contrast enhanced breast MRI. The Digital Mammography Imaging Screening Trial (DMIST) compared film mammography with digital mammography to reveal a similar accuracy between the two modalities for the general screening population (41). However, digital mammography was

more accurate than film mammography in pre- or peri-menopausal women, women with dense breasts, and women under the age of 50 (42). Mean glandular dose per view averaged 2.37 mGy for film mammography and 1.86 mGy for digital mammography in DMIST (43). Breast density has been associated with decreased sensitivity of mammography (68%) in dense breasts versus 85% sensitivity in non-dense breasts (4). According to the breast cancer surveillance consortium data from 1994 to 2009, approximately 38.65% of women have heterogeneously dense and 9.56% women have extremely dense breasts. Aside from the use of digital mammography little data is available to direct additional or alternative imaging evaluation in this population.

Contrast enhanced mammography was first described in 1985 by Watt et al. utilizing digital subtraction angiography of the breast (44,45). This technique is based on the principle of digital subtraction between two images. One of the images has morphological data and the second image has information relative to breast vascularization. Weidner et al demonstrated the hypervascularity of invasive malignant breast tumors in 1991 (46). Initial studies focused on temporal subtraction CE mammography (47-50); however, no significant difference has been shown between the kinetic enhancement patterns observed for malignant or benign breast lesions. Dual-energy CE mammography was first described in 2003 by Lewin et al. as an alternative to the temporal subtraction technique (51). This technique is based on the interaction between gamma rays and iodine. A "high energy" image above the k edge of iodine (33.2 keV) is obtained to distinguish vascular structures after iodine contrast administration. A "low energy" image (below 33.2 keV) is obtained for morphological information. The digital subtraction of these images highlights the vascularized structures similar to a temporal subtraction method. This technique allows for bilateral breast imaging after a single contrast administration. Dromain et al. showed that DE CE digital mammography had a higher sensitivity (93%) than mammography alone (78%) with no reduction in specificity (63%) (4). This group subsequently showed increased

diagnostic performance in 6 readers with better detection of malignancy and no increase in false positives with the addition of DE CE digital mammography with or without ultrasound (3). Recently, Jochelson et al. compared DE CE digital mammography with breast MRI in patients with known breast carcinoma to reveal similar levels of primary tumor detection (6). MRI detected additional ipsilateral lesions better than DE CE digital mammography (6). However, CE DE digital mammography had a higher specificity with fewer false positives (6). The positive predictive value of an enhancing lesion was higher with DE CE digital mammography than for MRI (97% vs 85%, $p<0.01$) (6). These preliminary results suggest that DE CE digital mammography may be a feasible adjunct or an alternative to routine breast screening using conventional digital mammography in specific groups, such as the population of women with dense breasts.

D. PROGRESS REPORT:N/A.

E. EXPERIMENTAL DESIGN

Study Overview: The proposed prospective pilot study will invite women meeting eligibility criteria to undergo screening digital mammography and DE CE digital mammography. This trial is unique because to our knowledge this technology has not been assessed in women with BI-RADS category 3 and 4 dense breasts as an adjunct to routine screening, and we aim to determine potential of this imaging technique as an alternative to screening mammography for this patient population. Patients will undergo either bilateral digital mammography with 4 views or bilateral digital mammography with 4 views plus DE CE digital mammography. Dual-energy CE digital mammography will be performed with bilateral craniocaudal and mediolateral oblique views at high and low energy levels. These images will be obtained after iodinated contrast administration. Intravenous injection of iodinated contrast agent (Omnipaque 350 (iohexal, GE, Shanghai, China) at a dose of 1.5

mL per kilogram of body weight will be injected at a rate of 3mL/sec (similar dose used for computed tomography studies). Standard departmental protocols for contrast administration will be followed. Imaging will begin 2.5- 5.0 min after contrast administration. Case report forms (CRFs) will be completed for each imaging study to record technique, views, dose, breast compression force, compressed breast thickness and image time.

Screening digital mammogram images will be initially read by a radiologist specialized in breast imaging with 5 to 25 years of breast imaging experience. A different breast radiologist will read the DE CE digital mammogram with a routine screening interpretation of only the low energy views initially. Subsequently, the entire DE CE digital mammography exam will be interpreted with all images by the same reader. Readers will interpret their designated study independently blinded to the additional study and results will be documented on the CRFs. Additional clinical work up will be performed based on both studies after the initial independent reads. All lesions will be further evaluated by standard of care. Both digital mammograms and DE CE mammograms will be assessed for quality. Truth will be determined using pathologic diagnoses when available or one year negative follow-up imaging. Calculations will be performed for sensitivity, specificity, negative predictive value, positive predictive value 1 for call back (PPV1), positive predictive value 3 for biopsy performed (PPV3), cancer detection rate, false negative rate, and call back rate.

To evaluate for interobserver variability, all studies will be read by 2 additional radiologists blinded to truth and randomized over time to minimize memory recall. Interobserver variability will be assessed utilizing raw data agreement, Kappa coefficients, and Intra-Class Correlations (ICCs).

Brief questionnaires will be administered to the patients prior to and following DE CE digital mammography to determine if there are any aspects of the exam that would deter a patient from participating in a future clinical trial. These short questionnaires will be administered by the nurse coordinator before the initial FFDM and after the DE CE digital mammography exam to determine if there were any changes in patient response.

Recruitment/Consent: Cases will be accrued via the Department of Radiology from a volume of 12,000 to 14,000 screening exams per year under the direction of the PI (Breast Imaging Section Chief). Patients will be contacted for study participation from patients scheduled for routine screening mammography that meet eligibility criteria for dense breasts (BI-RADS category 3 or 4) and will subsequently be screened for additional eligibility criteria. Data on age, race and eligibility criteria will be collected on all patients contacted; these data will be de-identified and stored in a screening log with the stated reason for refusal or reason(s) for ineligibility. Upon completion of the study, we will analyze data from recruitment screening to discern if patients who refused or were ineligible differed from enrollees on demographic factors since this is important to assess generalizability of findings (52) and possible recruitment for a future randomized control trial. At our facility, approximately 1000 to 1200 women undergo screening mammography each month with approximately 30-45% having heterogeneously or extremely dense breasts (BI-RADS category 3 or 4). Research nurse will assist with patient recruitment. co-director of the breast health center will also assist with patient recruitment.

Eligibility: This study will accrue women undergoing routine screening mammography who:

1) Have heterogeneously or extremely dense breasts (BI-RADS category 3 or 4);

2) Have GFR >60;

3) Are 40 years of age or greater;

4) Have no history of iodinated contrast allergy;

5) Are not pregnant or lactating;

6) Have no personal history of breast cancer;

7) Have no history of prior breast excisional biopsy but can have history of core needle biopsy;

8) Have no history of prior breast reduction mammoplasty surgery;

9) Have no history of prior breast augmentation surgery; and

10) Are not currently being screened annually with breast MRI.

Safety: This prospective pilot study will be approved by the Institutional Review Board with a data safety monitoring plan developed under the guidance of the CCTS. In addition, approval by the Radiation Safety Committee is necessary since patients who participate will be undergoing additional radiation associated with the DE CE digital mammographic study. The estimated dose from the combined low and high energy levels for DE CE is reported as 1.2 times that delivered during a routine single mammographic view (53). Imaging will be performed on GE Senographe DS and Essential mammography units with software upgrades for DE CE digital mammography. The breast imaging section is an ACR accredited Breast Center of Excellence with mammography equipment certification by the FDA and ACR. The device under investigation is considered a non-significant risk device per the 21 CFR 812.3 definition 1) it is not intended as an implant; 2) is not purported or represented to be for a use in supporting or sustaining human life; 3) is

not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; 4) and it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject." Non-significant risk devices do not require a formal Investigation Device Exemption.

Quality Control: Quality control activities are as follows: 1) all study databases will be monitored for out-of-range data; 2) screening criteria, surveys, technical and case report forms, and medical data will be reviewed by study staff for missing responses or inconsistencies with resolution of any problems as they occur; 3) the PI will train study staff on data collection; and 4) mammographic studies will be performed on FDA and ACR accredited equipment in compliance with MQSA regulations. Participant safety will be monitored closely by the PI in accordance with a formalized data and safety monitoring plan developed under the guidance of the   CCTS.

Power/Statistical Analyses: We hypothesize that DE CE mammography will outperform routine FFDM in patients with heterogeneously or extremely dense breasts (BI-RADS category 3 or 4). As a pilot study, data will be collected to assess for a potential larger randomized control trial to assess this technology as an alternative to routine screening mammography. We propose a sample size of 200 patients to conduct this study. This will provide over 90% power to detect differences in performance and accuracy (i.e., sensitivity; specificity) between the two methods even at a small significance level of 0.001 using the McNemar's test.

Project Timeline/Benchmarks –The projected timeline denotes major study phases. The strength of this study lies in the effort to answer a clinical question made timelier by new

legislation regarding breast density. We hope to reveal findings that could ultimately influence the standard of care and improve our current approach to breast cancer screening in women with dense breasts.

Benchmarks (qtrs)	1	2	3	4	5	6	7	8
Development	▓							
Recruitment	▓	▓	▓	▓	▓			
Screening Imaging	▓	▓	▓	▓	▓			
Additional Work-up	▓	▓	▓	▓	▓	▓		
Follow-up			▓	▓	▓	▓	▓	▓
Data analysis					▓	▓	▓	▓
Reports							▓	▓

F. MENTORS/ CO-INVESTIGATORS

MENTORS
                    is a Professor of Radiology and the Vice Chair of Research. Her vast experience in imaging research will provide excellent guidance for this project.

                          is a Professor of Nutritional Sciences and the Associate Director of the   She has expertise in clinical outcomes and cancer prevention research, and has an extensive track record of mentoring junior faculty and will serve as a mentor for this project.

            is a Professor of Oncology at the who has extensive experience in clinical trials and will provide mentorship.

CO-INVESTIGATORS
            is an Associate Professor of Biostatistics at the and will provide statistical expertise for the project.

              is a Professor of Radiology with extensive clinical experience in breast imaging who will be a reader for the study.

              is an Associate Professor of Surgery and Co-Director of the Breast Health Clinic and   and will contribute to patient recruitment.

G.LITERATURE CITED

1. Siegel R, Niashadham, MA, Jemal A. Cancer Statistics. CA Cancer J Clin 2013;63:11-30
2. SEER database Cancer statistics review 1975-2009
3. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-1972
4. Rosenberg RD, Hunt WC, Williamson MR et al. Effects of age, breast density, ethnicity, and estrogen replacement therapy on screening mammographic sensitivity and cancer stage at diagnosis: review of 183,134 screening mammograms in Albuquerque, New Mexico. Radiology 1998; 209;511-8
5. Dromain C, Thibault F, Muller S, et al. Dual-energy contrast-enhanced digital mammography: initial clinical results. Eur Radiol 2011;21(3):565-74
6. Jochelson MS, Dershaw DD, Sung JS, et al. Bilateral contrast-enhanced dual-energy digital mammography: feasibility and comparison with digital mammography and MR imaging in women with known breast carcinoma. Radiology 2013; 266(3):743-51
7. Duffy SW, Tabar L, Olsen AH et al. Absolute numbers of lives saved and overdiagnosis in breast cancer screening, from a randomized trial and from the Breast Screening Programme in England. J Med Screen 2010; 17:25-30
8. Yen MF, Tabar L, Vitak B, et al. Quantifying the potential problem of overdiagnosis of ductal carcinoma in situ in breast cancer screening. Eur J Cancer 2003; 29:1746-54
9. Welch HG, Black WC, Overdiagnosis in Cancer. J Nat Cancer Inst 2010;102: 605-13
10. Zahl PH, Strand SH, Maehlen J. Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening; prospective cohort study. BMJ 328;2004:921-4
11. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;55:75-89
12. Tabar L, Fagerberg CJ, GAD A, Baldetrop LH, Grontoft O, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomized trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet 1985;1:829-32
13. Nystrom L, Andersson I, Bjurstam N, et al. Long- term effects of mammography screening; updated overview of the Swedish randomized trials. Lancet 2002;359:909-19
14. Gotzche PC, Nielson M. Screening for breast cancer with mammography. Cochrane Database Syst Rev 2011;1:CD001877
15. Nelson HD, Tyne K, Naik A et al. Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force. Ann Intern Med 2009;151:727-37, W237-42
16. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review, Lancet. 2012 Nov 17;3,80:1778-86
17. Tabar L, Vitak B, Chen TH et al. Swedish two-country trial; impact of mammographic screening on breast cancer mortality during 3 decades. Radiology 2011;260:658-63
18. Bird RE, Wallace TW, Yankaskas BC. Analysis of cancers missed at screening mammography. Radiology 1992;184:613-7
19. Kalisher L. Factors influencing false negative rates in xeromammography. Radiology 1979;133:297-301
20. Goergen SK, Evans J, Cohen GP, et al. Characteristics of breast carcinomas missed by screening radiologists. Radiology 1997;204:131-5
21. Holland R, Hendricks JH, Mravunac M. Mammographically occult breast cancer: a pathologic and radiologic study. Cancer 1983;52:1810-9
22. Boyd NF, Martin LJ, Bronskill M, et al. Breast tissue composition and susceptibility to breast cancer. J Natl Cancer Inst 2010;102:1224-37

23. Harvey JA, Fajardo LL, Innis CA. Previous mammograms in patients with impalpable breast carcinoma: retrospective vs. blinded interpretations. AJR Am J Roentgenol 1993;161:1167-72
24. Feig SA, Shaber GS, Patchefsky A, et al. Analysis of clinically occult and mammographic occult breast tumors. AJR Am J Roentgenol 1977;128:403-8
25. Wallis MG, Walsh MT, Lee JR. Review of false negative mammography in a symptomatic population. Clin Radiol 1991;44:13-5
26. Martin JE, Moskowitiz M, Milbrath et al. Breast cancer missed by mammography. ARJ AM J Roentgenol 1979;132:737-9
27. Cahill CJ, Boulter PS, Gibbs NM, et al. Features of mammographically negative breast tumors. Br J Surg 1981;68:883-4
28. Mann BD, Giuliano AE, Bassett LW et al. Delayed diagnosis of breast cancer as a result of normal mammograms. Arch Surg 1983;118:23-4
29. Warren Burhenne LJ, Wood SA, D'Orsi CJ, et al. Potential contribution of computer-aided detection to the sensitivity of screening mammography. Radiology 2000;215:554-562
30. Kerlikowske K, Grady D, Barclay J, et. Likelihood ratios for modern screening mammography. Risk of breast cancer based on age and mammographic interpretation. JAMA 1996;276:39-43
31. Porter PL, El-Bastawissi AY, Mandelson MT, et al. Breast tumor characteristics as predictors of mammographic detection: comparison of interval-and screen –detected cancers. J Natl Cancer Inst 91;1999:2020-8
32. Morris EA. Liberman L, Ballon DJ et al. MRI of occult breast carcinomas in high-risk population. ARJ Am J Roentgenol 2003;181:619-26
33. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004 Sept 15;292:1317-25
34. Warner E, Plewes DB, Hill KA, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. Magnetic Resonance Imaging Screening Study Group. N Engl J Med. 2004; 29;351:427-37
35. Lehman CD, Isaacs C, Schnall MD,et al. Cancer yield of mammography, MR, and US in high-risk women: prospective multi-institution breast cancer screening study. Radiology 2007;244:381-8
36. Leach MO, Boggis CR, Dixon AK et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicenter cohort study (MARIBS). Lancet 2005;365:1769-78
37. Passaperuma K, Warner E, Causer PA et al. Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. Br J Cancer 2012;107:24-30
38. Kreige M, Brekelmans CT, Boetes C et al. Efficacy of MRI and mammography for breast cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004;351:427-437
39. Sardenelli F, Podo F, D'Agnolo G et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. Radiology 2007;242:698-715
40. Weinstein SP, Localio AR, Conant EF et al. Multimodality screening of high-risk women: a prospective cohort study. J Clin Oncol 2009; 27:6124-6128
41. Pisano ED, Gatsonis C, Hendrick E et al. Digital Mammographic Imaging Screening Trail (DMIST) Investigators Group. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 2005;353:1773-83

42. Pisano ED, Hendrick RE, Yaffe MJ et al. DMIST Investigators Group Diagnostic accuracy of digital versus film mammography; exploratory analysis of selected population subgroups in DMIST. Radiology. 2008;246:376-83
43. Hendrick RE, Pisano ED, Averbukh A et al. Comparison of Acquisition Parameters and Breast Dose in Digital Mammography and Screen-Film Mammography in the American College of Radiology Imaging Network Digital Mammographic Imaging Screening Trial AJR Am J Roentgenol 2010;194:362-369
44. Watt AC, Ackerman LV, Shetty PC, Burke M, Flynn M, Grodsinsky C, et al. Differentiation between benign and malignant disease of the breast using digital subtraction angiography of the breast. Cancer 1985; 56(6):1287-92.
45. Watt AC, Ackerman LV, Windham JP, Shetty PC, Burke MW, Flynn MJ, et al. Breast lesions: differential diagnosisusing digital subtraction angiography. Radiology 1986; 159(1):39-42.
46. Weidner N, Semple JP, Welch WR, FOlkman. Tumor angiogenesis and metastasis – correlation in invasive breast carcinoma. New Engl J Med 1991;324(1):1-8.
47. Jong R, Yaffe MJ, Skarpathiotakis M, et al. Contrast-enhanced digital mammography: initial clinical experience. Radiology 2003;228(3):842-50
48. Dromain C, Balleyguier C, Muller S, et al. Evaluation of tumor angiogenesis of breast carcinoma using contrast-enhanced digital mammography. AJR Am J Roentgenol 2006;187(5):W528-37
49. Diekmann F, Diekmann S, Jeunehomme F, et al. Digital mammography using iodine-based contrast media: initial experience with dynamic contrast medium enhancement. Invest Radiol 2005;40(7):397-404
50. Diekmann, Fryer M, Diekmann S, et al. Evaluation of contrast-enhanced digital mammography. Eur J Radiol 2009;78(1):112-21.
51. Lewin JM, Isaacs PK, Vance V et al. Dual-energy contrast enhanced digital subtraction mammography: feasibility. Radiology 2003;229:262-8
52. Demark-Wahnefried W, Bowen DJ, Jabson JM, Paskett ED. Scientific bias arising from sampling, selective recruitment, and attrition: the case for improved reporting. Cancer Epidemiol Biomarkers Prev 2011 March;20(3):415-8
53. Dromain C, Thibault F, Diekmann F, et al. Dual-energy contrast-enhanced digital mammography: initial clinical results of a multireader, multicase study. Breast Cancer Research 2012;14:R94.

Budget:

	2014	2015
	YR 1	YR 2
Personnel		
	$49,980	$49,980
Fringe benefits (28.6%)	$20,020	$20,020
Supplies		
Miscellaneous		
Travel		
Sub Total	$70,000	$70,000
	$0	$0
IDC @0%	$70,000	$70,000
Total		$140,000.00