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To date, breast MRI screening studies have been performed in 134 women. These examination prompted breast biopsy in 11 women, 3 of which yielded malignancy. Results to date demonstrate the feasibility of using breast MRI to screen high risk women. In particular, adherence to strict architectural interpretation criteria has minimized false positive findings. Additional data are required before any statements of the potential efficacy of MRI can be made.

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FOREWORD

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Annual Report for Contract Number DAMD17-96-C-6059

Introduction

The incidence of breast cancer has been increasing. The National Cancer Institute estimates that approximately 1 in 9 women in the U. S. will have breast cancer in her lifetime. This translates into 180,000 American women developing breast cancer each year. This will result in approximately 45,000 deaths due to the disease.(1) As a result of public awareness of the increasing incidence of breast cancer in Western women, combined with media coverage of recent advances in the genetics of breast cancer, women are increasingly concerned about their individual risk of developing breast cancer. Multiple risk factors for the development of breast cancer have been reported. These include family history and obstetrical history. Studies have shown that a women's risk for breast cancer is strongly related to the number and types of relatives that have had the disease. In fact, Familial clustering of breast cancer was first described by physicians in ancient Rome (2) and first documented in the medical literature in 1866 by a French surgeon who reported ten cases of breast cancer in four generations of his wife's family.(3) Although non-inherited factors certainly play a role in familial clustering of breast cancer, recent advances have provided unequivocal evidence for the presence of breast cancer susceptibility genes responsible for 5-10% of all breast cancer.

Early epidemiologic studies were performed by comparing breast cancer incidence in relatives of breast cancer cases to healthy controls. Although often flawed by unverified diagnoses, lack of rigorously defined control groups and the absence of adjustments for family size, these studies demonstrated familial clustering of breast cancer. These studies were followed by more controlled studies that consistently demonstrated a two- to three-fold increase in breast cancer risk in mothers and sisters of breast cancer patients, figures compatible with current studies.(4-6) Using modern epidemiological methodology, several population-based studies have attempted to estimate breast cancer risk associated with a positive family history. The largest of these is a study conducted in Sweden, involving 1330 women with a confirmed diagnosis of breast cancer in a defined geographic region and 1330 age-matched controls without a previous diagnosis of breast cancer.(7) Within this study cohort, breast cancer in a first degree relative was reported in 11.2 % of breast cancer cases as opposed to 6.7% of controls ($p<0.01$), yielding a standardized relative risk of 1.7. If this observation was extended to include breast cancer in first and/or second degree relatives, the findings remained significant, with 19.8% of breast cancer cases and 12.9% of control women reporting an affected relative, yielding a standardized relative risk of 1.6. Relative risks of a similar magnitude were found in a Canadian population-based study (8) and the U.S. Nurses Health Study (9), a large retrospective case-control study. Higher risks were reported in the Breast Cancer Detection Demonstration project (10) and the American Cancer

Society cohort.(11). These cohorts, though large, were comprised of volunteers, so may be biased.

Population based studies have demonstrated the heterogeneity of risk among breast cancer families. The primary factors which increased risk within families were menopausal status at time of diagnosis and bilateral disease in the primary proband. Additionally, first degree relatives of primary probands were found to be at higher risk than second degree relatives. Data from these studies (12-18) are summarized in Table 1.

Table 1. Relative Risks for First Degree Relatives of Women with Breast Cancer
(14,17)

Characteristics of Affected Mother/Sister	**Relative Risk**
Premenopausal Diagnosis	3.0
Bilateral Disease	5.0
Bilateral Disease and Premenopausal Diagnosis	9.0
Postmenopausal Diagnosis	1.5

By 1980 a significant body of evidence supporting the presence of inherited factors responsible for familial clustering of breast cancer had accumulated and efforts shifted in an attempt to determine the inheritance pattern of breast cancer within these families. In 1984, Williams and Anderson (19) examined 200 Danish pedigrees obtained by contacting more than 300 breast cancer patients entered into the Danish Cancer Registry, a population-based registry based in Copenhagen. Ninety-five percent of cancer cases were confirmed. The Danish study provided evidence for an autosomal dominant breast cancer susceptibility gene with an age-related penetrance. This study was supported in 1988 by King and colleagues who studied 1579 nuclear families of breast cancer probands diagnosed before age 55. Again, all patterns of inheritance, with the exception of a highly-penetrant susceptibility gene transmitted as an autosomal dominant trait, were excluded by this analysis.(20)

Linkage analysis has been performed to determine the loci of breast cancer susceptibility genes. Narod, Lynch and colleagues demonstrated unequivocal linkage between the genetic marker D17S74 on 17q21 and the appearance of ovarian cancer with breast cancer in several kindred's.(21) The genetic marker, now referred to as BRCA1, is felt to be responsible for the breast ovarian cancer syndrome. Carriers of mutations in BRCA1 are estimated to have an 85% lifetime risk of breast cancer and a 60% lifetime risk of ovarian cancer.(22,23) Although BRCA1 is felt to be responsible for only 3-5% of all breast cancer,(4,5) it is estimated at as many as 1 in 500-1000 women carry a BRCA1 mutation.(27) In addition, cancer is these women tends to

occur at a young age making BRCA1 responsible for 10-15% of breast cancer that presents under the age of 35.(22)

A recent analysis of 22 pedigrees with a dominant inheritance pattern for female breast cancer and at least one case of male breast cancer provides strong evidence against linkage to BRCA1 in these families, with a LOD score of -16.63 (odds less than 1 in 10-16.(25) These results indicated that there is a gene or genes other than BRCA1 which predisposes women to early onset breast cancer and which confers an increased risk of male breast cancer, now confirmed with the finding of BRCA2 on chromosome 13.(26) It is likely that other genes that are linked to breast cancer will also be discovered. It is estimated that between 5 and 10 % of all breast cancer is hereditary.

Testing for mutations in BRCA1 is now available at several centers around the world. Once a family with a mutation at BRCA1 is identified, the testing of interested family members can be performed. Counseling women who test positive for a BRCA1 mutation is a difficult problem. There are no studies to demonstrate the risk reduction of prophylactic mastectomy in these women. The impact of chemoprevention on the risk of breast cancer in these patients is not known. Most experts suggest aggressive surveillance consisting of a mammogram and physical examination every 6-12 months beginning at age 25-35. However, no data exist to indicate that mammographic screening of this population has any effect on breast cancer mortality.

MRI represents an alternative approach to breast imaging. It has the advantage of high soft tissue contrast that can demonstrate breast cancers in radiodense breasts. The first studies using MRI to detect both benign and malignant breast lesions concluded that it was not possible to detect and characterize lesions on the basis of signal intensities on T1 and T2 weighted images.(27-29) However, reports on the use of gadolinium enhanced breast MRI were more encouraging. Cancers were shown to enhance relative to other breast tissue following the administration of intravenous Gd-DTPA.(30) In one MRI study, 20% of cancers were seen only after the administration of Gd-DTPA.(31) Two early studies reported the MRI detection of breast cancer not visible on mammography.(31,32) The detection of mammographically occult multifocal cancer in up to 30% of patients has led some investigators to recommend its use to stage patients that are candidates for breast conservation therapy.(32)

Although the absence of contrast enhancement has a high negative predictive value, the presence of contrast enhancement alone is not specific for cancer. In fact it has been reported to have a specificity of 40% (32). Fibroadenomas, benign proliferative change and inflammatory change have also demonstrated enhancement after Gd injection. Preliminary results of dynamic contrast examinations that studied the kinetics of enhancement kinetics suggested that increased tissue specificity is possible (30,31,33). In these studies, cancer demonstrated the most intense enhancement, particularly in the initial phases of contrast bolus. Benign solid tumor such as fibroadenomas were shown to demonstrate variable contrast enhancement,

but it also appeared to be more delayed than that seen in malignant tumors.(30,33-35). In addition to contrast enhancement kinetics, the use of lesion architecture has been used to differentiate benign from malignant breast lesions. Orel et al (36) reported the architectural characteristics of benign and malignant breast lesions on high resolution post contrast MR images. Others have shown that lesion border irregularity demonstrated on high resolution post contrast MRI is very predicative of malignant disease. Details of our experience with architectural feature analysis in breast MRI are included in the preliminary data section.

The early success of contrast enhanced breast MRI has lead to considerable enthusiasm about its potential clinical impact. A number of potential clinical roles for this technique have been suggested, however those which have gotten the most attention include: 1. evaluating patients with suspicious clinical or mammographic findings in order to determine if biopsy is required, and 2. determining the extent of cancer within an affected breast to allow informed treatment planning. The high sensitivity would make MRI a good screening tool for breast cancer, yet its cost prohibits its routine use to screen for breast cancer. However, it may be efficacious and cost effective for screening women determined to be at particularly high risk for breast cancer on the basis of a positive test for a germline mutation in BRCA1.

Development of MRI guided Breast Biopsy

In order to clinically utilize the high sensitivity of MRI to detect clinically and mammographically occult cancer, an MRI guided breast biopsy system is essential. This allows pathologic confirmation of the MRI diagnosis, in cases when the lesion is only observable with MRI. Toward this end, we have developed and tested an MRI guided breast biopsy system. The biopsy system is derived from our bilateral compression breast array. In addition to being an outstanding imaging coil, the compression breast array is naturally configured to accommodate MRI guided breast biopsy. In order to perform MR guided breast biopsies, a single coil lateral plate is used. This consists of a PVC plate with a detachable coil.

The plate itself contains a grid of closely spaced holes through which a needle can be passed. The plate is sterilized for each use. The grid consists of approximately 4000 18 gauge holes placed at 2.5 mm intervals over the face of the plate. This yields a maximal error of 1.75 mm in the needle position if the target is at the center of the square formed by 4 adjacent holes. At the Hospital of the University of Pennsylvania we have performed 42 MR guided biopsy procedures. This includes 38 needle localizations, 2 cyst aspirations, and 6 core needle biopsies. The needle was identified to be in proper position on the first needle pass in all but four cases. In these four cases positioning errors were due to patient motion between scanning and needle placement and clerical error in calculating the proper hole within the needle guide to be used for the biopsy. The average distance from the target to the actual needle position was approximately 2 mm.

Approximately 50% of our biopsies have yielded carcinoma, 30% fibroadenoma, and 20% fibrocystic change (38). In ten cases, MRI guided biopsy have demonstrated occult multifocal carcinoma which have changed patient management. In two cases, MRI guided biopsy has demonstrated occult cancer in patients with positive lymph node biopsies for carcinoma.

Body

Methods

Patients of all races and ethnic backgrounds older than 18 years of age that presented with a documented high risk for breast cancer were considered eligible for this study. As described in our previous report, we have adopted a risk entrance criteria of a 30% lifetime risk of cancer or greater for entrance. Patients who have already had breast cancer would be considered eligible for screening of their contralateral breast if their probability of carrying a breast cancer susceptibility gene was greater than 50%.

A detailed clinical history and family pedigree with respect to breast cancer were obtained from each patient.

All patients undergo a physical examination at the Cancer Risk Evaluation Center. In addition, as part of their normal clinical care, all patients have a routine mammogram.

Under this protocol patients undergo yearly MRI examinations. The MR examination consist of an axial localizing scan followed by a slab interleaved 3D gradient echo T1 weighted imaging sequence before and after the administration of 20 cc of intravenous gadolinium chelate. An eight-coil bilateral biplanar array coil is utilized for this study. Fat suppressed images are obtained over an 18 cm field of view using a 512 x 256 matrix and 2-3 mm slice thickness for each breast. The entire acquisition time for both breast is approximately three minutes. Two sequential acquisitions are obtained after the administration of contrast material.

The high resolution MR images are interpreted as showing suspicious contrast enhancement, probably benign contrast enhancement, or no suspicious findings. Patients with probably benign contrast enhancement were followed at six months and then one year to ensure stability. Patients with suspicious contrast enhancement underwent short term follow-up exam to ensure the lesion continues to enhance and continues to appear suspicious. During the time of that exam if the lesion continued to appear suspicious it was biopsied.

Results

To date, 134 patients have been formally entered into our database. One-hundred and one patients underwent bilateral examinations while the remaining underwent unilateral screening examinations. Thirteen patients had associated clinical findings that were not considered suspicious enough to warrant intervention at the time of entry (breast pain, nipple discharge, vague palpable abnormalities. The MRI study was read as demonstrating no

suspicious findings in 115 cases. Follow-up revealed stable lesions in all cases. Biopsy was performed in 11 cases. In 8 cases the biopsy yielded benign results (including one case of atypical hyperplasia, and one case of LCIS). In 3 cases MRI guided biopsy revealed malignant findings. In one case an angiosarcoma was detected in a patient who was diagnosed with angiosarcoma in the contralateral breast. In two cases invasive ductal carcinomas were diagnosed by MR guided excisional biopsies. One of these cases involved a patient who underwent ipsilateral screening and had a history of contralateral breast cancer, the second case involved a patient who had a coexistent nipple discharge at the time of study entry.

Conclusion

We have successfully performed an MR screening study on 134 patients at high risk for breast cancer. Abnormal findings prompted a total of 11 biopsies, 3 of which yielded malignant findings.

References:

1. National Institutes of Health Consensus Development Conference Statement: Treatment of Early Breast Cancer. (June 18-21, 1990) Bethesda, MD.
2. Lynch HT: Introduction to Breast Cancer Genetics. In Lynch, HT (ed): Genetics and Breast Cancer, pp1-13. New York, Van Nostrand Reinhold.
3. Broca P. Traite de tumeurs. Paris: Asselin; 1866.
4. Sattin RW, Rubin GL, Webster LA, et al. Family history and the risk of Breast cancer. JAMA 253 (13):1908-1913, 1985.
5. Colditz GA, Willett WC, Hunter DJ, et al. Family history, age and risk of breast cancer. JAMA 270:338-343, 1993.
6. Slattery ML, Kerber RA. A comprehensive evaluation of family history and breast cancer risk: the Utah Population Database. JAM 270:1563-1568, 1993.
7. Adami HO, Hansen J, Jung B, Rimsten A. Characteristics of familial breast cancer in Sweden: absence of relation to age and unilateral versus bilateral disease. Cancer 48(7):1688-1695, 1981.
8. Lubin JH, Burns PE, Blot WJ, et al. Risk factors for breast cancer in women in Northern Alberta, Canada, as related to age at diagnosis. J Natl Cancer Inst 68:211-217, 1982.
9. Bain C, Speizer FE, Rosner B, et al. Family history of breast cancer as a risk indicator for the disease. Am J Epidemiol 111:301-308, 1980.
10. Brinton LA, Williams RR, Hoover RN, et al. Breast cancer risk factors among screening program participants. J Natl Cancer Inst 62(1):37-44, 1979.
11. Seidman H, Stellman SD, Mushinski MH. A different perspective on breast cancer risk factors: some implications of the nonattributable risk. CA Cancer J Clin 32(5):301-313, 1982.
12. Anderson DE. Some characteristics of familial breast cancer. Cancer 28:1500-1504, 1971.
13. Anderson DE. A genetic study of human breast cancer. J Natl Cancer Inst 18:1029-1034, 1972.
14. Anderson DE. Genetic study of breast cancer: identification of a high risk group. Cancer 34:1090-1097, 1974.
15. Anderson DE. Genetic predisposition to breast cancer. Recent Results Cancer Res 57:10-20, 1976.
16. Anderson DE. Breast cancer in families. Cancer 40:1855-1860, 1977.
17. Anderson DE, Badzioch MD. Risk of familial breast cancer. Cancer 56:383-387, 1985.
18. Anderson DE, Badzioch MD. Combined effect of family history and reproductive factors on breast cancer risk. Cancer 63:349-353, 1989.
19. Williams WR, and Anderson DE. Genetic epidemiology of breast cancer: segregation analysis of 200 Danish pedigrees. Genet Epidemiol 1:7-20, 1984.
20. Newman B, Austin MA, Lee M, King MC. Inheritence of breast cancer: evidence for autosomal dominant transmission in high risk families. Proc Natl Acad Sci USA 85(9):3044-3048, 1988.

21. Narod SA, Feuteun J, Lynch HT, et al. Familial breast-ovarian cancer locus on chromosome 17q12-23. The Lancet 338:82-83, 1991.
22. Easton DF, Bishop DT, Ford D, Crockford GP and the Breast Cancer Linkage Consortium. Genetic linkage analysis in familial breast and ovarian cancer - results from 214 families. Am J Hum Genet 52(4):678-701, 1993.
23. Easton DF, Ford D, Bishop DT and the Breast Cancer Linkage Consortium. Breast and ovarian cancer incidence in BRCA1 mutation carriers. Lancet 343(8899):692-695, 1994.
24. Claus EB, Risch N, Thompson WD. Genetic analysis of breast cancer in the cancer and steriod hormone study. Am J Hum Genet 48:232-242, 1991.
25. Stratton MR, Ford D, Neuhausen S, et al. Familial male breast cancer is not linked to the BRCA1 locus on chromsome 17q. Nature Genet 7:103, 1994.
26. Wooster R, Neuhausen S, Mangion, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 265:2088-2090.
27. El Yousef SJ, Duchesneau RH, Alfidi RJ. Magnetic resonance imaging of the breast. Radiology 150:761-766, 1984.
28. Stelling CB, Wang PC, Lieber A, et al. Prototype coil for magnetic resonance imaging of the female breast. Radiology 154:457-462, 1985.
29. Dash N, Lupetin AR, Daffner RH, et al. Magnetic resonance imaging in the diagnosis of breast disease. AJR 146:119-125, 1986.
30. Kaiser WA, Zeitler E. MR imaging of the breast: fast imaging sequences with and without Gd-DTPA. Radiology 170:681-686, 1989.
31. Heywang SH, Wolf A, Pruss E, et al. MR imaign of the breast with Gd-DTPA: use and limitations. Radiology 171:95-103, 1989.
32. Harms SE, Flamig DP, Hesley KL, et al. MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. Radiology 187:493-501, 1993.
33. Stack JP, Redmond AM, Codd MB, et al. Breast disease: tissue characterization with Gd-DTPA enhancement profiles. Radiology 174:491-494, 1990.
34. Boetes C, Barentsz JO, Mus RD, et al. MR characterization of suspicious breast lesions with a gadolinium-enhanced turboFLASH subtraction technique. Radiology 193:777-781, 1994.
35. Kelcz F, Santyr GE, Mongin, et al. Clinical experience with a model for distinguishing benign from malignant breast lesions dected with dynamic Gd-enhanced MRI. (Abstr) RSNA 1994:89.
36. Orel SG, Schnall MD, LiVolsi VA, Troupin RH. Suspicious breast lesions: MR imaging with radiologic-pathologic correlation. Radiology 190:485-493, 1994.
36a. Weber BL, Abel KJ, Couch FJ, et al. Progress toward Isolation of a Breast Cancer Susceptibility Gene, BRCA1. Cold Spring Harbor Symposia on Quatitative Biology, 59, 531-536, 1994
37. Nunes LW, Orel SG, Schnall MD. Diagnostic accuracy and lesion characteristic predictive values in the MR imaging evaluation of breast masses. (Abstr) RSNA 1994; 267:853.

38. Orel SG, Schnall MD, Newman R, et al. Initial experience with MRI-guided breast localization. Radiology
39. Orel SG, Schnall MD, Powell CM, Hochman MG, et al. Staging of suspected breast cancer: effect of MR imaging and MR-guided biopsy. Radiology 196:115-122, 1995.

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CONSENT FORM

MRI based screen for
Patients at high risk for
developing breast cancer.
Principal Investigator:
Mitchell Schnall, MD, PhD
University of Pennsylvania
Philadelphia, PA 19104
(215)- 662-7238

CONSENT TO PARTICIPATE IN A STUDY OF MRI BASED SCREEN FOR PATIENTS AT HIGH RISK FOR DEVELOPING BREAST CANCER.

PURPOSE: The purpose of this study is to investigate the utility of high resolution MRI (magnetic resonance imaging) in screening women at high risk for developing breast cancer. You have been selected for participation in this study because you have been identified as having a high risk (greater than 30%) of developing breast cancer in your lifetime. It is hoped that this investigation will result in a new technique to detect tumors in the breast and cancer detection. The principal investigator of this project is Dr. Mitchell Schnall of the University of Pennsylvania. Other investigators involved in this study include Dr. Barbara Weber and Dr. Susan Orel. This investigation will involve a total of 300 subjects.

We will exclude pregnant women and any women who can not undergo an MRI exam because of the following reasons:

Pacemaker
Magnetic aneurysm clip or other surgically
Implanted magnetic device
Severe claustrophobia

PROCEDURE: As part of this study, you will undergo sequential yearly breast MRI exams for the four years of the study. This procedure will not require hospitalization, withholding of standard treatments, blood tests or special preparation. There will be no cost to you for these studies. You will be placed in the center of a large cylindrical magnet. The MRI machine produces a strong magnetic field that passes through your body without harming it. Pulses of radio frequency energy will be transmitted into you. Two small wire coils will be placed on either side of your breast to receive the very weak radio signals from the breast. Gentle compression will be applied to the breast. This is less than that used in a mammogram and usually results in no discomfort. A computer attached to the MRI machine will process these signals into a picture and spectrum of the breast. The spectrum gives us information about the chemical composition of the breast. At some point during the examination, an MRI contrast agent called Gadolinium will be injected into a vein in your arm. Although the placement of the needle may cause minor discomfort, Gadolinium is considered safe and is routinely used during MRI examinations in this hospital. This contrast agent helps to improve the images of your breast by making breast tumors more conspicuous. Although routinely used to enhance images of many

areas of the body, gadolinium is under investigation for use in breast cancer. The FDA has given permission to study gadolinium for use in breast cancer but has not approved this agent for this use.

The entire procedure will take 30-40 minutes in total. You will have to lie still during this time. A padded table will be provided to keep you from becoming uncomfortable. A licensed physician will be present throughout the study.

You will be asked to undergo a serum pregnancy test if you have childbearing potential. In order to participate in this study, you should have avoided becoming pregnant from the first day of your most recent menses. A negative pregnancy test does not absolutely prove that you are not pregnant. Regardless of the results of the pregnancy test which you were administered as part of the screening for this study, you should not participate if you think there is a possibility that you might be pregnant.

BENEFIT: You may benefit from participation in this study by having a potentially very sensitive screening test for breast cancer. If a possible cancer is identified, it will be recommended that this lesion be biopsied under MRI guidance. You will also receive the satisfaction of being involved in a study that may help patients with breast disease in the future.

RISK: Although there are no known hazards to this procedure, the possibility of unforeseen hazards cannot be ruled out. It is possible that you may have a claustrophobic reaction to the procedure. The data available at this time indicates that this study will not be harmful. In the past, experimental animals and human beings have been exposed to magnetic and radiofrequency fields stronger than those of the present study without harmful effects. Gadolinium is an MRI contrast which is routinely used in MRI examinations and felt to be safe. Information obtained in this study will be kept confidential, except as required by law, and not released in any way that can be identified with you without your permission.

CONFIDENTIALITY :Informat on obtained in this study will be kept confidential, except as required by law, and not released in any way that can be identified with you without your permission.

It is the policy of the U.S. Army Medical Research and Material Command that data sheets are to be completed on all volunteers participating in research for entry into the Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, social security number, study name and dates. The intent of the data base is tow-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years. Representatives of the U.S. Army medical research and material command are eligible to review research records as part of their responsibility to protect human subjects.

WITHDRAW: You are free to decide whether or not to participate in this study and free to withdraw at any time. Nonparticipation or withdraw will not harm future interactions with the investigators, your physician, or the University of Pennsylvania.

INJURY / COMPLICATIONS: You understand that in the event of physical injury resulting from research procedures, medical treatment in excess of that covered by third party payers will be provided without cost to me, but financial compensation is not covered.
Summary:

I have read and received a copy of the consent form and have been given the opportunity to ask questions.

I understand that in the event of physical injury resulting from research procedures, medical treatment in excess of that covered by third party payers will be provided without cost to me, but financial compensation is not available.

I realize that this consent is voluntary and may be withdrawn at any time without prejudicing continuing care.

I understand that if I wish further information regarding my rights as a research subject, I may contact the director in the Office of Research Administration at the University of Pennsylvania by telephoning 898-7293

I agree to participate in this study.

_____ _____
Name of Subject (print)

_____ _____ _____
Signature of Subject Date

_____ _____ _____
Signature of Investigator Date

_____ _____ _____
Signature of Witness Date