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This study is designed to evaluate the use of MRI in screening patients that are at high risk for breast cancer. Patients that based on family pedigree meet a 30% lifetime risk of breast cancer are entered into this study. Patients undergo physical exam, MRI, and traditional mammography. This is a four year study with 75 new patients being enrolled each year. Patients are evaluated yearly under this protocol.

To date, 60 patients have been entered into this study. No formal interim analysis has yet been performed. We anticipate meeting our target accrual of 150 patients at the two year mark at which time interim analysis will be performed.

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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 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 kindreds.(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 have 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 an 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.

3. 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. The initial intent of this study was to recruit patients that were demonstrated to carry a breast cancer susceptibility gene such as a BCA1 or BRCA2 gene. Unfortunately in the current insurance climate, patients are very concerned about confidentiality of genetic tests for breast cancer susceptibility genes and, thus, although many patients with extreme family histories present in the high risk evaluation clinic of Barbara Weber, M.D. every year, less than a handful agreed to have genetic testing. Therefore in collaboration with Dr. Weber, it was decided that the entrance criteria would be modified to include patients that based on a family history would have greater than a 30% lifetime risk of breast cancer. These patients would have greater than a 50% chance of carrying a breast cancer susceptibility gene. Pregnant patients and patients with a contraindication to MR examination are excluded from this study. These include patients with pacemakers, magnetic aneurysm clips, and other implanted magnetic prosthesis.

A detailed clinical history including a detailed family pedigree with respect to breast cancer were obtained from each patient. Family pedigree information is collected by Dr. Barbara Weber at the Cancer Risk Evaluation Clinic.

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 a yearly MRI examination. The MR examination consist of an axial localizing scan followed by a slab interleaved 3D gradient echo T1 weighted images before and after the administration of intravenous contrast. In order to obtain these images a four-coil biplane array is applied to each breast. The coils are dynamically switched to correspond to the interleaved slab. Fat suppressed images are obtained over an 18 cm field of view using a 512 x 256 matrix and 2-3 mm slice thickness in a sagittal plane. The entire acquisition time for both breast is approximately three minutes. Two sequential acquisitions are obtained after the administration of contrast.

The high resolution MR images are interpreted using an architecture based interpretation scheme (36). Suspicious lesions detected by MRI that are not visualized on conventional techniques are biopsied under MR guidance.

Results

As indicated in the methods section above there has been one significant change in this protocol. In order to accommodate the fact that very few women are undergoing genetic testing to assess the risk of breast cancer, a pedigree based entrance criteria has replaced the need for a positive genetic

test. The entrance criteria requires a 30% lifetime risk of cancer as judged by the family pedigree. To date, 60 women have been entered into the first year of this protocol. The initial research plan has suggested that 75 patients would be recruited in the first year. Although we have had many interested patients, there was approximately a three month period during which time we were technically unable to perform this study. This was due to the fact that our GE MR imaging system was upgraded to a 5.6 system requiring modification of the software and hardware needed to perform the slab interleaved sequence and associated coil switching. These modifications were accomplished on October 1 and we are currently back to recruiting patients. We anticipate making up the decrease in first years accrual rapidly in the second year. We currently have a list of approximately 60 patients awaiting the MR study.

To date, we have not performed a formal interim analysis. A formal interim analysis is not anticipated until after year two of this program. However, a brief review of year 1 data indicates that MRI detected two otherwise occult carcinomas in the study group to date. A fuller interim analysis will be submitted with the next report. At that time we anticipate having met the 150 patient recruitment target that we have established over the first two years of this study.

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