Nationwide Study of Breast Cancer Risk Factors in Latinas

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This clinical study has already been subject to IRB approval, and can be found at www.clinicaltrials.gov

Introduction & Project Aims

Breast cancer is the most common cancer among American women. Any woman can be affected by breast cancer, with risk for the disease increasing with age. Risk for breast cancer is also exasperated in women who have certain genetic alterations. Mutations in the BRCA1 and BRCA2 genes predispose women to breast and ovarian cancer, and are increasingly recognized in prostrate and pancreatic cancers (1-3). In Caucasian and Asian ethnicities BRCA mutations are associated with basal-type/triple-negative disease. However this association between BRCA gene mutations and basal/triple-negative disease has been understudied in other ethnicities (4-6). The incidence and mortality of breast cancer of Hispanics and Native Americans are lower than other ethnicities; however they are underrepresented in epidemiological and clinical studies. Further, it is known that common recurrent mutations in BRCA1 and BRCA2 genes exist in Hispanic/Latino communities which account for 35-45% of mutation carriers (7, 8). The objective of our study is thus to investigate triple negative disease and BRCA gene mutations in Hispanic women.

The BRCA1 and BRCA2 proteins play a role in the repair of double-stranded breaks in DNA. A synthetic lethal strategy for cancer therapy has been developed using DNA damaging chemotherapy agents to cause single-stranded breaks, combined with poly-ADP ribose polymerase (PARP) inhibitors to inhibit single-stranded DNA repair. This approach may be particularly effective in BRCA mutation carriers, as the tumor will be unable to repair the double-stranded breaks (9, 10). A recent trial of one PARP inhibitor demonstrated partial response or stable disease in breast, ovarian and prostate cancer subjects (11). Thus there is a unique opportunity to identify Hispanic/Latino women that may be eligible for new targeted therapies. However it is important to validate the frequency of mutations in the BRCA genes in this underserved minority and their association with triple-negative disease. The objectives are to collect a sample of Hispanic/Latino women with triple negative breast cancer to identify genomic control samples, validate published data on the frequency of recurrent mutations, and analyze the association between

BRCA mutation and pathology. The target distribution of the 2000 subjects will be 1000 samples with triple negative disease, and 1000 with ER/PR positive tumors.

Data Sharing Plan & Collaboration Policy

The investigators are open to data sharing and collaborating with extramural groups in the form of combination of data and patient referrals.

We are currently collaborating with the groups below, and are open to increasing collaborations as the project continues to develop. If you are interested in partnering with us on this project, please contact Michael Dean.

- American Cancer Society
- Avon Foundation for Women
- Breast Cancer Network of Strength
- Howard University Cancer Center
- Nueva Vida, Support Network for Latinas with Cancer

For further Information

Please contact Michael Dean or visit our websites for further information about this study.

http://clinicaltrials.gov/ct2/show/study/NCT01251900

Study Design

Initially all women who self identify themselves as being Hispanic/Latina and having breast cancer will be recruited, followed by targeted sampling of triple negative subjects in an approximately 1:1 ratio. All subjects will be given a copy of the consent form, and the subjects will be registered for the study. All subjects will be asked to permit the release of a copy of their pathology report. Upon receipt of consent and saliva sample, the PI or an authorized BTRIS user will register the subject into the BTRIS system, and barcode the saliva sample with a coded ID number. All subjects will complete a validated questionnaire on known lifestyle and reproductive risk factors for breast cancer. The DNA sample will be "Unlinked", that is irreversibly stripped of all identifiers. A new data file will be created taking only the essential data for the research objectives (age of onset, year of onset, tumor grade, pathology type, age at menarche, age at first childbirth, family history of cancer) and replacing any personal identifiers (name, address, SS# etc) by a single coded number. That coded number will be used to link to the DNA data. Finally, the mapping from the personal identifiers to the coded ID number will be destroyed. Thus, there will be no way to link genetic data generated using the DNA to individuals. Nor will it be possible to send the DNA testing results to the subjects from whom the sample was taken. The original questionnaire data and the pathology report will remain in the research record, as coded information. Figure 1 demonstrates the secured unidirectional flow of data in this study.

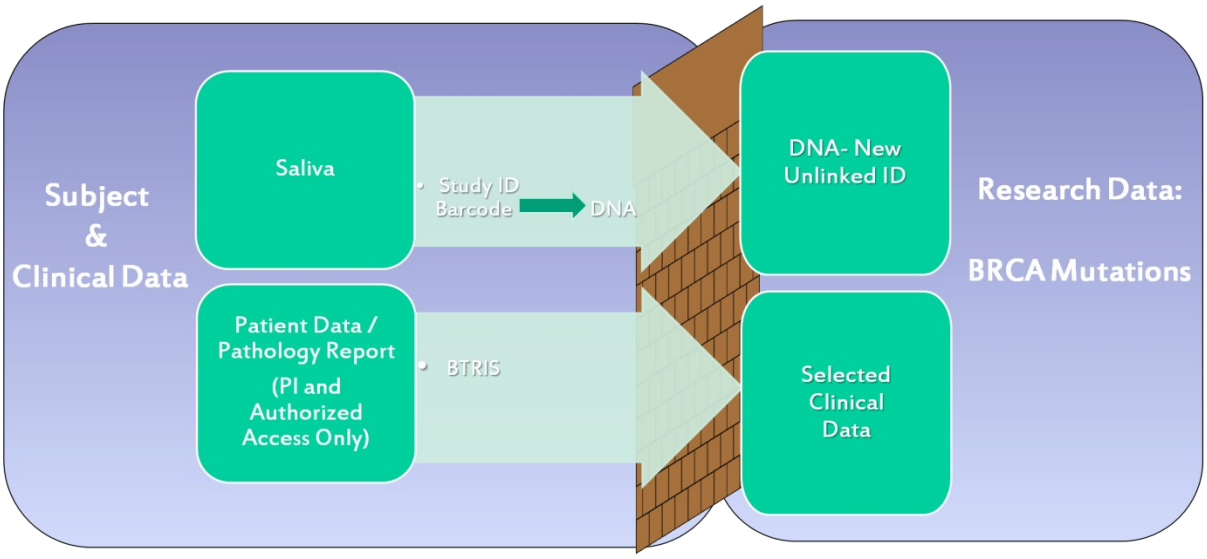

Figure 1. Mapping of separation of Subject and Clinical data (saliva and pathology reports) from Research and Genetic data (BRCA Mutations)

Data Quality and Analysis

Saliva samples will be collected by the subjects using Oragene saliva collection kits with instructions provided in English and Spanish with extensive use of graphics. The DNA is stable long-term at room temperature. Once received saliva will be stored in secure freezers or the NCI-Frederick repository without personal identifiers.

Saliva samples will be used for the extraction of DNA and the DNA will be typed for a panel of ancestry-informative markers specific to Hispanic/Latino populations, and typed for the known recurrent mutations in BRCA1 and BRCA2 identified in published studies. Hispanic/Latino populations have a diverse set of genetic backgrounds. To control for this diversity we will type each sample for a set of 50-100 polymorphisms that have different frequencies in the major racial groups (European, African, Asian) and that are known to be useful for identifying the percent European/Native American/African ancestry of a subject. This data will be used as a covariate in the above analyses.

We estimate that 2000 subjects, 1000 triple negative and 1000 non-triple negative are needed for adequate power. Assuming that 11% of triple negative subjects (110 subjects) and 2-4% of the non-triple negative subjects (up to 40 subjects) have BRCA mutations, then a total of 150 subjects with BRCA1 or BRCA2 mutations would be identified. From that total, we estimate that we will be able to identify a subset of about 80 subjects with the common recurrent mutations. This sample will allow a preliminary analysis of the association of triple negative disease and BRCA status, and an analysis of haplotype structure for the most common alleles. As we complete development of technology to use high throughput sequencing to scan the entire BRCA1 and BRCA2 genes, the numbers with identified mutations will increase.

For the objective to estimate the prevalence of BRCA1 and BRCA2 mutations in Hispanic/Latina women

with breast cancer, we will estimate mutation prevalence in the TN and non-TN groups separately and reweigh the non-TN data to take into account the fact that only a fraction of the non-TN population was sampled, whereas all TN women were sampled. This will give estimates of mutation prevalence in the entire Hispanic/Latino population of women with breast cancer. We will also examine whether similar results hold for recently diagnosed women versus women diagnosed long before, to see if survival bias is important.

To examine features of the tumor that may be associated with the prevalence of such mutations, such as histopathology (especially triple negative (TN) status), and other features, we will study associations with factors that may affect the prevalence of mutations. One approach will be to look at subgroups defined by factors such as TN status, other aspects of tumor histopathology, and features of the reproductive or exposure history. In addition to computing prevalence within various categories of this type, we will use logistic regression to determine what factors influence the odds of carrying a mutation.

For the objective to estimate penetrance of mutations, we will use the kin-cohort method to estimate the cumulative risk of breast cancer (and of other cancers) in carriers and in non-carriers of mutations. These estimates will be produced by the method of Struewing et al (12).

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APPENDIX

FREQUENTLY ASKED QUESTIONS (FAQS)

Why are you doing this study?

Each human being is different from one another. These differences affect our health and the chance that we will be diagnosed at some point in our life with a form of cancer such as breast cancer. Some of these differences are inherited (or genetic). Genetic differences, called mutations, can be found in families in which breast cancer is very common. While many families with cancer have been closely studied in Caucasian women, and genetic mutations have been found, relatively few breast cancer survivors and families have been studied in Hispanic/Latino communities.

Are the ethnic groups very different?

Yes and no. The long-term goal of research such as this is to find out and give the best treatment for each individual patient, regardless of their race, ethnicity or genetic background. This is known as 'Personalized Medicine'. But we do not have the information that we need to study all of the many populations that are in the United States, including the diversity that exists within Latino/Hispanics (Mexicans, Cubans, Central Americans, Puerto Ricans, South Americans, etc).

How long until this work actually helps someone?

The results of this study may provide information about genetic differences in Hispanic/Latino women who have had breast cancer. Therefore, this information may lead to improvements in breast cancer therapy. There are new treatments currently being tested that are shrinking or slowing the growth of tumors in women who did not previously respond to traditional therapy. At least one of these new therapies may work best in patients with genetic defects (mutations) in BRCA1 or BRCA2, which are the genes that most often cause inherited breast cancer. One of the things we hope to learn in this study is how many Hispanic/Latino women with breast cancer have these mutations and might benefit from these new therapies.

How common are BRCA mutations in non-Caucasian women?

Recently published information from over 45,000 women that had genetic testing for BRCA1 and BRCA2 mutation showed that 13-16% of African American, Native American and Latina/Hispanic women, who are known to have a high risk of breast cancer, had a mutation in either a BRCA1 or BRCA2 gene.

Does this have anything to do with the more aggressive breast cancers that some women have, which is called 'triple-negative' breast cancer?

This is possible. The breast cancers found in women who carry a BRCA1 mutation are more frequently of the so called 'basal-like' or "triple negative", type. Triple negative means that the tumor does not have estrogen and progesterone receptors, and does not over-express the HER2 protein. These basal-like or triple negative tumors require different treatment than other types of breast cancer, and in general fewer of these women are cured and many die more rapidly from their cancer. If the cancer is found early however the treatment is more effective. We know very little about whether BRCA mutations in Hispanic/Latino women are associated with triple negative breast cancer.

OK. I am convinced and will send in my sample. But why won't you send me MY results?

There are a number of important reasons:

For this research study we are required to remove your name from your DNA samples, so that no one can learn the results of your test. These studies are being done in a research lab, not in a clinical testing lab.

We are not necessarily going to analyze the entire BRCA1 and BRCA2 gene in every patient. But we do hope that this study will tell us more about breast cancer in Hispanic/Latino women and the role of inheritance.

How will the research team protect the confidentiality of my information to guard against genetic discrimination?

We take these concerns very seriously as well. Your personal information will be kept in a secure facility with access only to a limited number of study personnel. We will also disconnect your personal data from the genetic results. The research information collected in this study is covered by a Certificate of Confidentiality issued by the National Cancer Institute on behalf of the Secretary of the Department of Health and Human Services. A Certificate of Confidentiality should prevent researchers involved in this project, to the full extent permitted by the Courts, from being forced to disclose your identity or any information about you collected in this study in any legal proceedings at the Federal, State, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, a Certificate does not prevent the review of your research records under some circumstances (for example, under the Federal Food, Drug, and Cosmetic Act, or during the course of any internal program audit or evaluation).