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TITLE: Is Breast Tissue from Women Who Carry Germ-Line BRCA1 or BRCA2 Mutations "Normal"? An Immuno-Histopathological Study

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Is Breast Tissue from Women Who Carry Germ-Line BRCA1 or BRCA2 Mutations "Normal"? An Immuno-Histopathological Study

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Background and Hypothesis: BRCA1/2 mutations confer a substantially elevated risk of breast cancer. It is not known whether breast tissue from BRCA1/2 mutation carriers is normal or not. We hypothesize that breast tissue in BRCA1 or BRCA2 mutation carriers exhibits particular morphological and biological features resulting from BRCA1 or BRCA2 haplo-insufficiency or from other additional non-characterized genetic changes, when compared to age-matched non-carriers.

Methods: Forty BRCA1 or BRCA2-related breast cancers and 80 age-matched breast cancers in BRCA1/2 non-carriers diagnosed in Ashkenazi Jewish women will be analyzed. So far we have examined 510 pathology blocks from 43 women with breast cancer. In order to maintain blinded status, the pathologist does not know how many of these women have BRCA1 mutations or BRCA2 mutations. Slides have been cut, mounted, stained and independently reviewed by two pathologists. We plan to evaluate the following biological characteristics: hormonal pathways (estrogen and progesterone receptors, pS2), cell cycle regulation (p27, p53, cyclin D1, cyclin E), proliferation (MIB-1, PCNA), proto-oncogene expression (ERBB2), apoptosis (Bcl-2, caspase3), and androgen receptor.

Subject Terms: breast cancer, immunohistochemistry, BRCA1, BRCA2

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Introduction

Germ-line mutations in BRCA1 and BRCA2 genes are the major causes of genetic predisposition to breast cancer. BRCA1 and BRCA2-related breast cancers are characterized by certain pathological features. Increased incidence of medullary type, higher grade, poor differentiation, absence of steroid receptor expression and aneuploidy are all characteristics of BRCA1-related breast cancer. BRCA2-related breast cancers also tend to be higher-grade tumors than non-hereditary cases. Notably, it has been suggested that BRCA1 and BRCA2-related breast cancer may follow different carcinogenic pathways when compared to sporadic breast cancer. One preliminary study showed a significantly lower expression of the progesterone receptor in the non-neoplastic mammary tissue from a small number of BRCA1 and BRCA2 carriers. Interestingly, recent data suggested physiological differences in BRCA1 and BRCA2 carriers, such as a reduced period of lactation, when compared with women without mutations. Moreover, contrary to what is observed in the general population, early pregnancy and multiparity are associated with an increased breast cancer risk in BRCA1 and BRCA2 mutation carriers. Despite these findings, very little is known about morphological and biological features of non-neoplastic breast tissue in BRCA1 and BRCA2 mutation carriers. Here, we plan to study non-neoplastic breast tissue from women identified as being at high risk of developing breast cancer due to the presence of a mutation in one of these genes. This proposal was awarded a Concept grant.

Body of text

Task 1: Collect normal breast tissue and cancers from BRCA1/2 mutation carriers and controls

The study was considerably delayed by the need for a modification of page 10, paragraph 19, prohibition of use of human anatomical substances (Nov 2000) (USAMRAA). At the Sir M.B. Davis-Jewish General Hospital, we have collected and are in the process of reviewing 510 pathology blocks from 43 women with breast cancer. In order to maintain blinded status, the pathologist does not know how many of these women have BRCA1 mutations or BRCA2 mutations. To increase our potential for recruitment, we have submitted the proposal to the McGill University Health Centre Research Ethics Board (MUHC REB). The Board asked for changes to the consent form. We have submitted these for approval. The amended consent form will be forwarded to the DOD for approval (as it differs slightly from the one approved at the primary site). Once the study is approved at the second site, we expect recruitment to increase considerably. The MUHC REB has also questioned the need for paragraph 18 modification. There is some debate within the REB whether or not this project actually involves human subjects, or rather tissue from human subjects. This debate has further delayed our progress at the second site.

Task 2: Creation of a grid to score the abnormalities noted in normal breast tissue

This has been completed by Dr. Alpert
Task 3: Scoring of abnormalities

This is underway but has not been completed

Task 4: Immunohistochemical analysis of tumours

This is has not be started

Key Research Accomplishments

Nil

Reportable outcomes

1. Publications
No publications have followed from this work as yet. However, obtaining this grant has provided impetus to other, closely related work (please see next section).

2. Other grant support
As a result of this award, we have obtained further funding from the Fonds de la Recherche en Santé du Québec (FRSQ) to collect tissue from BRCA1 or BRCA2 mutation carriers. We will collect both normal and cancer tissue. This will allow us to compare the results obtained in this study with those obtained in the FRSQ-funded proposal.

Conclusions

The demonstration of differences in the morphological or biological features of non-neoplastic breast tissue in an ethnically restricted population of BRCA1 and BRCA2 mutation carriers will be a crucial step in the understanding of hereditary breast cancer. Moreover, preventive strategies could be influenced by these observations. We have commenced the study, but due to unforeseen circumstances, have not yet completed the work, and as such have no scientific data to report at this time. We have requested a no-cost extension to complete this study.

References


