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Molecular Markers in Hereditary Breast Cancer

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The promise of research into breast cancer genetics is that it will provide us with new insights into the etiology of breast cancer that can be translated to strategies for early diagnosis and treatment for the larger population of women who develop breast cancer without having a genetic predisposition.

An academic award represents an outstanding opportunity for me to critically appraise the emerging role of genetics in clinical breast cancer care and forge new avenues of research. Toward this goal, I plan to accomplish the following during the award period:

1) perform a thorough review of the cytogenetic and molecular genetics literature to identify potential chromosomal regions that may harbor genes whose abnormal function is critically involved in the development of breast cancer.

2) develop a robust panel of markers that can be used for clinical correlative studies of hereditary breast cancers.

3) develop a tissue repository composed of biological specimens from 500 patients with inherited breast cancer (e.g. fresh frozen tumor specimens, or paraffin embedded tumor specimens and normal blood lymphocytes, DNA and sera whenever possible).

These studies will lead to an improved understanding of the biology of breast cancer which will ultimately translate into more effective therapies.
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INTRODUCTION
As a physician-scientist, I have had extensive training in clinical oncology and in molecular biology and genetics; I am ideally positioned to bridge the gap between the two. The academic award has represented an outstanding opportunity for me to critically appraise the emerging role of genetics in clinical breast cancer care and forge new avenues of research. Toward this goal, I plan to accomplish the following during the period of my academic award.

1) perform a thorough review of the cytogenetic and molecular genetics literature to identify potential chromosomal regions that may harbor genes whose abnormal function is critically involved in the development of breast cancer.
2) develop a robust panel of markers that can be used for clinical correlative studies of hereditary breast cancers.
3) develop a tissue repository composed of biological specimens from 500 patients with inherited breast cancer (e.g., fresh frozen tumor specimens, or paraffin embedded tumor specimens and normal blood lymphocytes, DNA and sera whenever possible).

Using these unique resources, my future studies will characterize the molecular pathways which allow a normal breast cell to become cancerous in individuals who are genetically predisposed. I will also develop longitudinal follow up studies to correlate clinical outcomes with molecular characterization and epidemiologic risk factors. These studies will no doubt lead to an improved understanding of the biology of breast cancer which will ultimately translate into more effective therapies.

Task I

perform a thorough review of the cytogenetic and molecular genetics literature to identify potential chromosomal regions that may harbor genes whose abnormal function is critically involved in the development of breast cancer.

This year we published two reviews on the genetics of breast cancer. In the next year, we are completing two manuscripts which will focus on the chromosomal abnormalities and genetic alterations in breast cancer.

Publications


Task II

develop a robust panel of markers that can be used for clinical correlative studies of hereditary breast cancers.

We have developed several probes for fluorescent in situ hybridization and have begun to apply these probes to a panel of breast tumors in our tumor bank.

Breast cancer is a heterogenous disease caused by the progressive accumulation of genetic changes in a growing number of oncogenes and tumor suppressor genes. Germ-line mutations in the BRCA1 tumor suppressor gene result in breast cancers characterized by young age of onset, estrogen receptor negativity (ER-), and distinctly high grade tumor phenotype. The secondary genetic changes required for tumor development in BRCA1 carriers are largely unknown. Somatic amplification of HER2/neu, a neighboring gene to BRCA1 on 17q, is also associated with aggressive high grade, (ER-) breast tumors. C-MYC interacts with the BRCA1 protein, and the gene is amplified in 5-50% of breast cancers. We have assessed the relative
contributions of HER-2/neu and/or C-MYC amplification to the aggressive biology of BRCA1-associated tumors.

We performed FISH using the PathVysion™ HER-2 and C-MYC assays on formalin-fixed paraffin-embedded tumor tissues from women with known deleterious BRCA1 mutations. HER-2/CEP17 and C-MYC/CEP8 ratios were scored and compared with clinico-pathological data and immunohistochemical studies. With more than 98 primary breast tumors and cell lines examined by FISH, we are yet to find a single BRCA1-associated tumor with high levels of HER2/neu gene amplification (n=53). In contrast, 6/41 (15%) sporadic tumors demonstrated HER-2/CEP17 ratio ≥ 2 in 10/16 (62%) BRCA1 tumors including 4 tumors with ratios ≥ 4. Our data suggest that a germ-line mutation in the BRCA1 gene inhibits the ability of somatic cells to highly amplify the adjacent HER-2/neu oncogene but C-MYC amplification occurs in a significant proportion of BRCA1 tumors. Thus, it is likely that BRCA1 and HER-2/neu associated tumors progress through distinct molecular pathways.

Publications


Task III

develop a tissue repository composed of biological specimens from 500 patients with familial or hereditary breast cancer (e.g fresh frozen tumor specimens, or paraffin embedded tumor specimens and normal blood lymphocytes, DNA and sera whenever possible).

We have developed a clinical protocol for the tumor bank. The protocol has not yet been approved by the DOD Human Subjects Review Panel. Hence we have not enrolled any patients specifically to this study. However, we have identified collaborators and other sources of tumor materials that will be ready and available for recruitment once our study is approved.

KEY RESEARCH ACCOMPLISHMENTS:
Too early to report

REPORTABLE OUTCOMES:


**CONCLUSIONS:**

N/A Too early

**REFERENCES:**

N/A

**APPENDICES:**

N/A