

A. SPECIFIC AIMS

Genetic factors contribute to an ill defined proportion of breast cancer incidence, estimated to be about 5-10% of all cases, but approximately 25% of cases diagnosed before age 40. Dominant *BRCA1* mutations are highly penetrant for early-onset breast cancer and there appears to be striking similarities between *BRCA1*-related breast cancers and breast cancers that occur in young black women. For example, *BRCA1* associated breast cancers occur at an earlier average age (44 years) than sporadic breast cancers and it has been observed that African American patients have a greater breast cancer incidence between 30-49 years than Caucasians. Additionally, compared to non-carriers, *BRCA1*-associated breast cancers are characterized by higher than expected frequencies of medullary or atypical medullary carcinoma, poor differentiation (high tumor grade), aneuploidy, high S-phase fraction and hormone receptor negativity. These aggressive histological features are also characteristic of breast cancer in African American women. These similarities suggest that alterations in *BRCA1* or related pathways might contribute to breast cancer in young Black women but limited data are available from this population to evaluate this possibility.

It is important to also evaluate environmental and socio-cultural factors that modulate the expression of breast cancer predisposition genes because genetic factors do not act in isolation. While conducting research on the pheromonal and social control of fertility and reproductive senescence, Dr McClintock and her colleagues discovered that socially isolated female rats die 30% earlier than female rats living with other females, and have a mortality rate that is two and one-half times higher than group housed animals (see project 1). These animals also have a higher incidence of mammary tumors; by 18 months of age, isolated rats are almost three times as likely to have mammary tumors as grouped animals but the tumor incidence was lower as they get older. It appears that social isolation of Sprague-Dawley female rats changes the pattern of ovarian-cycles throughout their reproductive life span and thus differences in life long exposure to estrogen and progesterone. This pattern of mammary tumor development in the isolated rats appears similar to the pattern of breast cancer incidence and its association with estrogen exposure in African American women ---a higher risk of premenopausal breast cancer but lower risk of breast cancer after menopause.

The proposed study will recruit clinic-based African American breast cancer patients from the South side of Chicago as well as Nigerian women diagnosed with invasive breast cancer, all of who will complete an extensive interview regarding exposures prior to diagnosis, social environment and psychological risk factors. We will collect comprehensive family and exposure history, conduct medical record reviews and establish a large bio-specimen repository of breast tumors from Black women that will be invaluable for assessing the reasons why Black women develop earlier onset and pathologically more aggressive breast cancer. The hypotheses being evaluated by this project are:

Hypothesis 1: A genetically or behaviorally-induced modulation of *BRCA1* and *ER* gene expression occurs in a significant proportion of breast tumors in black women
Hypothesis 2: The clinico-pathologic features and secondary genetic changes in breast tumors from women with *BRCA1* dysfunction caused by somatic epigenetic changes are similar to those with germline *BRCA1* mutations.
Hypothesis 3: Social Isolation, vigilance for potential threats and ovarian function all interact in breast cancer causation.

To address these hypotheses, we propose the following specific aims:

1) Assess the relationship of hypermethylation of the *BRCA1* and *ER* promoters with the patients' demographics, family and reproductive histories, environmental exposures, loneliness, hypervigilance and social supports/demands. Based on our preliminary findings, we will estimate the prevalence of *BRCA1* and Estrogen Receptor (*ER*) promoter methylation in tumors from Black women. Since social disruption has been associated with down-regulation of genes important in physiologic processes, we will determine whether *BRCA1* or *ER* promoter hypermethylation is associated with social isolation and vigilance, in addition to clinicopathologic, reproductive, neighborhood, family and epidemiological risk factors.

2) Examine the secondary genetic changes in tumors with *BRCA1* dysfunction. We will evaluate the differential contribution of oncogenes such as *HER2* and *MYC* in relation to *BRCA1* inactivation status and correlate with lifelong exposure history.

Project 2

Principal Investigator, Program Director: Gehlert, Sarah; Project 2:Olopade O.I.

3) Examine gene expression profiles in a 100 Black patients to identify if any "Black-specific" gene expression profiles exist. A second and related outcome that we believe to be more likely is that there are not any "race specific" profiles, but that the proportion of tumors within a given subtype might be different.

In collaboration with Dr Perou from University of North Carolina, we will profile tumors from Black women (African ancestry) and tumors from White women (Northern European ancestry) and use supervised analysis to identify genes that correlate with this supervising parameter. In addition, we will examine the proportion of tumors within a given "intrinsic gene expression" subtype and correlate with breast cancer risk factors. Based upon the epidemiological finding that Blacks show a higher proportion of ER-negative tumors, we would predict that they would show higher numbers of basal-like tumors than Whites.