

McClintock Project for Center for Health Disparities Research

Title: Mammary cancer risk: social isolation and hypervigilance

Abstract:

Black women suffer more aggressive, lethal breast cancers at a younger age than do White women of Northern European ancestry. While Blacks of African ancestry may have a higher frequency of cancer promoting genes, e.g. specific rat *BRCA1* mutations, this dramatic health disparity may also have psychosocial origins. Our animal model demonstrating larger mammary carcinomas in socially isolated and hypervigilant rats enables us to identify specific mechanisms of ovarian and adrenal function that increase the penetrance of mammary cancer promoting genes. Group-living female rats typically develop mammary tumors in late adulthood, in a logarithmic pattern similar to breast cancer dynamics in White women of Northern European ancestry. In stark contrast, socially isolated and hypervigilant rats, with the same genome, develop mammary cancers 40% younger, at 4 times the rate and have larger and more aggressive tumors, similar to breast cancer dynamics in Blacks of African ancestry. Our distinctive animal model permits study of tumor development against the backdrop of normal endocrine function. Because puberty is a sensitive period, we will also characterize peripubertal ovarian function in socially isolated and group living rats as predictors of different dynamic patterns of life-long exposure to estrogen and progesterone during spontaneous ovarian cycles. Finally, we will determine how social isolation and hypervigilance alter the timing of mammary gland development relative to ovarian function and pregnancy, increasing sensitivity to carcinogens. In this project we will compare the mammary tumors of socially isolated and group-living rats to determine if both spontaneous and carcinogen-induced (7,12-dimethylbenz(a)anthracene, DMBA) tumors in the two psychosocial conditions are (1) morphologically different (2) have different expression of estrogen and progesterone receptors, and (3) have somatic alterations of rat genes *Brca1*, *ErbB-2/Neu*, or *c-myc*, whose homologs are known to be dysfunctional in Black women with early breast cancer. We will create a tissue bank from all tumors collected in these experiments enabling future collaborative studies by investigators using both proteomic and functional genomic approaches to test additional hypotheses generated by this and other Centers. Insights from this animal model will inform a test of the hypothesis that hypervigilance and social isolation in Black women of African ancestry increase their risk of early, lethal breast cancers.

Research Plan

A. Specific Aims

Social isolation and sustained hypervigilance for threats may contribute to the marked disparities between Blacks and Whites in the rate of developing spontaneous aggressive mammary tumors. This project will use rats as a model of health disparities in human breast cancer in order to identify the pathways by which psychosocial and hormonal modulators regulate the function of specific mammary cancer promoting genes. Our model is unique in studying tumor development in the context of normal dynamic ovarian function throughout the life span. This project builds on our previous discovery that Sprague-Dawley rats spontaneously develop mammary tumors in an age-dependent rate similar to that of White women. Mammary tumors develop late in the life span and accelerate in rate with increasing age. In marked contrast, socially isolated rats develop mammary tumors in an age-dependent rate similar to that of Black women. For ~~f~~ half the population, the mammary cancer rate accelerates dramatically in middle adulthood and then slows towards the end of life to a rate slower than that of old animals ~~who~~ that have lived in a group.

These effects may be mediated through the ovarian axis, since social isolation of rats also (1) accelerates puberty and (2) increases estrogenization during middle adulthood, as well as increasing the rate of early, aggressive and lethal tumors in midlife. Psychological state interacts with the social environment, particularly during puberty, to exacerbate the risk of mammary tumors. Socially isolated rats become hypervigilant and act as if unfamiliar environments are threatening. When sustained throughout the life span, this psychological state is also associated with greater mortality from mammary tumors. Moreover, the effect of hypervigilance is greatest in rats that are socially isolated temporarily during puberty, although still present in those that continued to live with their siblings or live, temporarily with strangers. Because these psychosocial variables profoundly affect spontaneous mammary tumors, we will also determine if social isolation also exacerbates the effects of a carcinogen, given to relative to two key reproductive events (1) the onset of puberty and (2) the age of first pregnancy and lactation. These two events were chosen because they occur at different ages in Black and White populations.

We will use our rat model to identify predisease-pathways by which social isolation and psychological coping style, hypervigilance and the persistent perception of threats, increase risk for early and aggressive mammary tumors among some women. The human projects in our Center for Research in Health Disparities are studying Black women who live in neighborhoods with varying levels of stressors to identify the particular social features associated with both hypervigilance and aggressive mammary tumors. In this project, we shall take a targeted gene approach, parallel to the human studies, to answer the following questions:

Specific Aim 1. Determine whether social isolation induces qualitatively different mammary tumors than those developing in rats living in a group. We shall classify both spontaneous and carcinogen (7,12-dimethylbenz(a)anthracene, DMBA) induced tumors by (1) type, (2) steroid receptor status (3) expression of *Brcal*, *c-myc* and *ErbB-2/neu* genes, parallel to Project 2. We will make tissue arrays to be stored in our Rat Mammary Tumor and Tissue Bank for future analyses of other targeted genes and future hypothesis-driven gene arrays for functional genomics based on results of this and other Centers. These or other significant histological, steroid receptor, and targeted gene measures, will then be made on all mammary tumors in the following Specific Aims (2 – 5).

Specific Aim 2. Compare the effects of hypervigilant and non-vigilant psychological states on formation of aggressive tumors of rats.

Specific Aim 3. Assess the predictive power of early puberty onset and high estrogenization in puberty as risk factors for mammary tumors later in mid-life. Quantify the interaction of other aspects of ovarian function throughout adulthood to identify single or multiple independent risk factors for aggressive malignant disease.

Specific Aim 4. Characterize breast tissue development during the first and fourth ovarian cycle after puberty, both of which are periods for low and high risk for aggressive mammary tumors induced by a carcinogen (DMBA).

Specific Aim 5. Compare the effects of “teenage” and “mature” pregnancies on aggressiveness of mammary tumors developed in response to a carcinogen (DMBA).