LAY ABSTRACT

TITLE: Genetic variation in sensitivity to estrogens and breast cancer risk.

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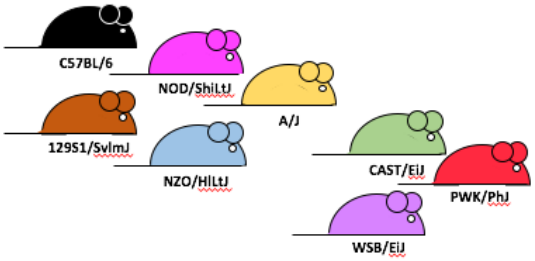
- Natural estrogens and environmental chemicals contribute to breast cancer, but women differ in the risk posed by these exposures.
- Animal models also vary in the effect of estrogen on breast tumors and are being used to identify the genetic differences that make some individuals susceptible and others resistant to breast tumors.
- These animal models are providing new ways to identify women for whom estrogen-like chemicals may pose a significant risk of breast cancer

Estrogens are hormones produced by a woman's ovaries, and they play an essential role in directing breast development. However, prolonged exposure to high levels of estrogen has been associated with increased risk of breast cancer. Therefore, estrogens appear to be a critical factor that can lead to breast cancer which affects 1 in 8 women during their lifetimes. Many common environmental chemicals also have been shown to have estrogen-like effects and may increase risk of breast cancer. So how does estrogen cause breast cancer? Equally important, why do 7 out of 8 women never develop breast cancer despite exposure to estrogens from puberty to menopause?

In this review, we examined the differences in sensitivity to estrogens in rodents. By careful breeding, "families" of mice and rats, referred to as "strains", can be produced that are closely related. Each individual mouse or rat within the strain are nearly identical genetically - essentially identical twins. While the characteristics within a strain is uniform, there are dramatic differences among strains. A similar diversity in responses to estrogen is also observed among women.

Studies in different strains of rats have identified the genetic differences responsible for sensitivity to mammary tumors induced by estrogen. Additional genetic differences that affect development of mammary glands in mice overlap with differences in DNA associated with breast cancer risk in women. The differences in susceptibility and resistance among these strains of rodents is helping to develop tests to identify individuals who are especially sensitive to estrogen-like chemicals and may pose a significant risk of breast cancer.

Diversity in our genes.



TECHNICAL ABSTRACT

Breast cancer risk is intimately intertwined with exposure to estrogens. While more than 160 breast cancer risk loci have been identified in humans, genetic interactions with estrogen exposure remain to be established. Strains of rodents exhibit striking differences in their responses to endogenous ovarian estrogens (primarily 17β-estradiol). Similar genetic variation has been observed for synthetic estrogen agonists (ethinyl estradiol) and environmental chemicals that mimic the actions of estrogens (xenoestrogens). This review of literature highlights the extent of variation in responses to estrogens among strains of rodents and compiles the genetic loci underlying pathogenic effects of excessive estrogen signaling. Genetic linkage studies have identified a total of the 35 quantitative trait loci (QTL) affecting responses to 17β-estradiol or diethylstilbestrol in five different tissues. However, the QTL appear to act in a tissue-specific manner with 9 QTL affecting the incidence or latency of mammary tumors induced by 17β-estradiol or diethylstilbestrol. Mammary gland development during puberty is also exquisitely sensitive to the actions of endogenous estrogens. Analysis of mammary ductal growth and branching in 43 strains of inbred mice identified 20 QTL. Regions in the human genome orthologous to the mammary development QTL harbor loci associated with breast cancer risk or mammographic density. The data demonstrate extensive genetic variation in regulation of estrogen signaling in rodent mammary tissues that alters susceptibility to tumors. Genetic variants in these pathways may identify a subset of women who are especially sensitive to either endogenous estrogens or environmental xenoestrogens and render them at increased risk of breast cancer.