Gene polymorphisms identified that are responsible for breast density and cancer risk

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It has long been known that breast density, or mammographic density, is a strong risk factor for breast cancer, and that estrogen and progestin hormone therapy increases dense breast tissue. Now, a study published in BioMed Central's open access journal *Breast Cancer Research* has identified several gene variants in hormone metabolism and growth factor pathways that may be associated with breast density and, hence, breast cancer risk.

Mammographic density relates to the fact that x-rays permeate different types of breast tissue in different ways, leading to white areas on the mammogram. Fatty tissue appears on the mammogram as relatively translucent, whereas dense breast tissue contains more stromal tissue and epithelial cells, appearing as white areas. Women with a breast density of 75% or more have a 4-5 times higher risk of developing breast cancer than women of the same age with little or no density.

Controversy exists over why breast density is a cancer risk. Many studies suggest that density is at least partially inherited, and twin studies show that genetic factors do play a role in the variation observed. Breast density decreases naturally with older age and menopause, but also increases with hormone therapy. Merete Ellingjord-Dale and co-authors, from academic centers in Norway and Los Angeles, set out to investigate which genes could play a role in determining breast density. Because of the clear involvement of hormones, they were looking particularly for genes involved in hormone metabolism.

Using data from 2,036 women who participated in the Norwegian Breast Cancer Screening Program in 2004, and separating the participants into hormone therapy users and non-users, the authors found that different gene variants appeared to be important depending on the women's hormone therapy usage.

There was evidence to suggest that variants in the prolactin (PRL) gene were associated with breast density in users of estrogen and progestin, as well as norethisterone acetate (a common regimen in Nordic countries). In non-users of hormone therapy, variants in the tumor necrosis factor (TNF) and SULT1A1/2 genes were significantly associated with breast density.

The findings suggest that several genes in hormone metabolism and growth factor pathways are indeed implicated in determining breast density, and might increase breast cancer risk. Commenting on the findings, lead author, Merete Ellingjord-Dale said, "One reason it has been so difficult to pinpoint which genes are responsible for mammographic density is that the effect of some genetic variants may be amplified in combination with hormone therapy. Consequently in the presence of hormone therapy these genes cause increased density."

She continued, "It is important to consider both the genetic and non-genetic factors simultaneously. Exploring the functional role of gene variants associated with mammographic density could further clarify the biological mechanisms involved. "

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