

## **Linkages Between Genome Disorder and Breast Cancer Development**

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Approximately 3-4% of all women in Europe and America who develop breast cancer each year do so by inheriting a mutant copy of a gene that normally operates to suppress breast cancer development. Several such genes have been identified and are under active investigation. Among them, two, BRCA1 and 2, are the best studied and are, collectively, responsible for approximately 60% of these inherited cases. Germ line mutant BRCA1 and 2 genes also elicit high frequency ovarian cancer development.

Interestingly, much of this collection of inherited, breast cancer- suppressing genes operates to promote the maintenance of a stable and integral genome. Indeed, the majority of the genome integrity maintenance/ breast cancer suppressor genes in this group function in a coordinated way to support cellular responses to the development of double strand genomic breaks (DSB). More specifically, they do so by participating in the process that repairs these lesions in an error-free manner, so called homologous recombination (HR). Thus, insuring the proper repair of these DNA lesions, which develop normally in most, if not all, replicating cells, is a breast cancer- suppressing process.

Recently, evidence has emerged showing that at least some of these genes encode proteins that participate in cellular responses to yet other forms of genome damage, as well as in the processes which insure that breast epithelial cells maintain a standard, modal chromosome number. There is also evidence which suggests a role for some of these events in breast cancer suppression.

What has been particularly mysterious is why breast (and ovarian) cancer, in particular, as opposed to tumor development in other organs, is the prime outcome of BRCA1 - driven tumor development and the major clinical result of BRCA2 dysfunction. This subject will be discussed in some detail.