

**Dr. David Sidransky, Professor and Dr. Rafael Guerrero-Preston, Instructor,
Otolaryngology-Head and Neck Cancer Research, Johns Hopkins School of Medicine,
Baltimore, MD.**

Genetic mutations in *BRCA1* and *BRCA2*, *BRIP1*, *CHEK2*, *ATM* and *TP53* are estimated to account for only 5% to 10% of breast cancer cases. In addition to genetic alterations, epigenetic modifications such as changes in DNA methylation patterns are associated with sporadic and hereditary breast cancers. The spectrum of alterations includes both gain and loss of DNA methylation involving multi-copy elements as well as single-copy genes. Recent data suggest that epigenetic changes are involved in the earliest phases of tumorigenesis, and that they may predispose stem/progenitor cells to subsequent genetic and epigenetic changes involved in tumor promotion. Extensive cancer-associated hypomethylation of juxtacentromeric satellite DNA and global DNA hypomethylation have been found to be common in all stages of breast cancer, including grade-1 or stage-1 carcinomas, which suggests that global demethylation of the genome is an early event in breast carcinogenesis.

In addition, genome wide analyses have identified over 50 gene specific hypermethylated loci in breast cancer, but the molecular mechanism of hypermethylation in breast cancer initiation and association with breast cancer risk is not well understood. Hypermethylation of the *BRCA1* promoter has been observed in sporadic breast cancer. An overall average methylation of the *BRCA1* promoter region of 25% among non *BRCA1*-linked cancers and 40% among *BRCA1*-linked cancers has been previously reported. The most notable difference was found at five particular CpGs of the *BRCA1* promoter region, each of which exhibited a greater than twofold increase in methylation in the *BRCA1*-linked group compared to the non *BRCA1*-linked group. Methylation of certain critical CpGs may also represent an important factor in transcriptional repression of the *ER(alpha)* gene in *BRCA1*-linked breast cancers. Separate studies have identified *ER(alpha)* and *BRCA1* genes to be specifically targeted for methylation in sporadic breast cancers.

Furthermore, *BRCA1* promoter methylation has been identified as an important factor to consider in predicting breast cancer survival. Promoter-CpG island hypermethylation has been proposed as an alternative mechanism to inactivate *BRCA1* in the breast where somatic mutations of *BRCA1* are rare. A majority of breast cancer tumors (59%) in a population based study were found to be methylated at the promoter of *BRCA1* in a recently published study. The *BRCA1* promoter methylation was more frequent in invasive cancers and among pre-menopausal cases. *BRCA1* promoter methylation was also associated with increased risk of breast cancer-specific mortality and all-cause mortality.

The Sidransky Laboratory is interested in the molecular mechanisms by which global and gene specific DNA methylation affects the onset and development of both, sporadic and hereditary, breast cancer. Our specific Aims in this collaborative project with the Matta laboratory are:

Aim 1. To evaluate the association between global and gene specific DNA methylation levels in genomic DNA obtained from plasma and breast cancer risk in a case control population

Aim 2. To examine the association between DNA methylation levels, DNA repair enzyme

activity, BRCA carrier status in a population based breast cancer.