

Use of hCG in the prevention of breast cancer in young nulliparous women

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Breast cancer is an invasive and ultimately fatal disease whose incidence has sharply increased in younger women, especially those belonging to certain ethnic groups or that have inherited cancer-predisposing genes. In BRCA1 populations the lifetime breast cancer risk can be increased up to 85%. Although cancers develop at a significantly younger age than sporadic cancers, are generally negative for estrogen and progesterone receptors and Her2, and are therefore unresponsive to endocrine and immunotherapy, it is not yet possible to identify who will develop breast cancer among asymptomatic carriers. It is known that the lifetime risk of developing breast cancer is markedly reduced by an early full term pregnancy and by multiple pregnancies. This effect is mediated by the induction of differentiation of the breast, which imprints a specific genomic signature that is comprised of 232 deregulated genes representing 18 functional categories (*Russo J et al, CEBP 17:51, 2008*). This signature serves as a biomarker indicative of a lifetime decreased breast cancer risk, therefore we hypothesized that the genomic profile of breast epithelial cells of asymptomatic nulliparous women carriers of BRCA1 germline mutations would be characteristic of high cancer risk.

The aim of our studies is to establish the proof of principle that treatment of this high risk population with r-hCG will change their breast epithelium's genomic profile to one similar to that identified in women with a history of early full first term pregnancy. For this purpose, breast epithelial cells are collected by fine needle aspiration (FNA) from women carriers of BRCA1 deleterious mutations. FNA specimens are analyzed for genomic expression by cDNA microarray, cytomorphology, cell proliferation index and steroid hormone receptor status. After a 90 day treatment with r-hCG differentially expressed genes are identified at the following time points: before, at the end of r-hCG treatment and 270 days after its termination. Of special interest are genes related to immune surveillance, DNA repair, programmed cell death, transcription, and chromatin structure/activators/co activators in comparison with the pre-treatment genomic profile. The comparison of profiles across the different time points are of particular interest because they identify those genes that had become either permanently activated or downregulated.

Our studies indicate that the protection conferred by pregnancy imprints a specific and permanent genomic signature in the breast. Knowledge gained at the completion of this project will serve as the basis for establishing novel genomic signatures as intermediate biomarkers for larger preventive clinical trials. (This work is supported by NCI-NIH grant R21CA124522).