

## Direct hCG Actions Afford Protection Against Breast Cancer.

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Breast cancer, the fatal disease most frequently diagnosed in American women, is steadily increasing in incidence in most westernized societies. Although the prevention of this disease has been hindered by the lack of identification of an etiologic agent, the epidemiological observations that breast cancer risk is higher in nulliparous women than in women that have completed one or more pregnancies at a young age provide physiological basis for intervention. These findings highlight the role of endocrinological and reproductive events in breast cancer prevention. This phenomenon has been experimentally confirmed through the demonstration that in rats, one pregnancy or a 21-day treatment with human chorionic gonadotropin (hCG) before administration of a chemical carcinogen significantly reduce the incidence of mammary tumors. In addition, hCG administered to tumor bearing animals, is therapeutic, since it inhibits tumor progression. The *in vivo* cancer protective effects of hCG are in great part mediated by its stimulatory effect on the ovary through the G protein-coupled lutropin-choriogonadotropin-receptor (LH-CG-R) present in the granulosa and luteal cells of the ovary. This novel hormonal milieu induces mammary gland differentiation, inhibition of cell proliferation, and activation of tumor suppressor genes like inhibin and apoptotic genes, i.e., TRPM2, ICE, p53, c-myc, WAF-1/CIP-1, bcl-XS, and p53. Rat gene microarray analyses, real time RT-PCR, and cluster analysis performed at different time points of hCG treatment have revealed that the genomic profile of the mammary gland varies as a function of the length of treatment and correlates with the stage of development or regression of the organ. A direct effect of hCG on human breast epithelial cells has been demonstrated *in vitro* in the normal immortalized MCF-10F cells and in its derived chemically transformed cell lines. In these cells a 24-hour treatment activated apoptotic genes, a phenomenon preceded by induction of the CAMP-PKA, p53, and TGF-beta pathways, for acting on their target gene p21<sup>WAF1/CIP1</sup>, before proceeding towards cell cycle arrest. HCG inhibits tumor growth in a dose dependent manner in Balb/c nude mice (*nu/nu*) injected with the breast carcinoma cell line MCF-7. In post-menopausal women with primary operable breast cancer diagnosed by needle core biopsy, a 2-week treatment with recombinant hCG prior to therapeutic surgery significantly reduced the tumor's proliferative activity (Ki67 index) and the percentage of steroid hormone receptor positive cells; it also increased the synthesis of inhibin, all effects independent of ovarian function and of the estrogen and progesterone receptor status of the host tissue. Future studies are geared towards the elucidation the genetic and epigenetic pathways through which hCG inhibits cancer, knowledge necessary for unfolding the potential of this model for the prevention and treatment of breast cancer based on physiological mechanisms of gene expression regulation.