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Potential benefits of estrogens and progestogens on breast cancer.

Schneider HP[1], Jackisch C.

Abstract

The mammary gland seems to be the only organ that is not fully developed at birth. Estrogens stimulate breast tissue via estrogen receptors (ERs). In the mammary gland, ER-mediated mechanisms have been shown to regulate: various growth factors, such as TGF-alpha and TGF-beta; enzymes, such as cathepsin D and plasminogen-activator; proto-oncogenes, such as c-fos, c-myc and HER-2/neu; cyclines and other regulatory substances that provide signaling systems for cell division and differentiation; other steroid receptors and epidermal growth factor receptors. Estrogen target genes contain estrogen-responsive elements. In these genes, transcription will be activated through interaction with the estrogen/ER protein complex. Subsequent activation of proto-oncogenes provides an explanation for the stimulating effect of estrogens on the glandular breast. Progesterone may be the key in influencing the risk of breast cancer with the peak of mitotic activity in the breast during the luteal phase of the menstrual cycle. On the other hand, in human breast cancer cell lines, both proliferation and inhibition have been observed with various progestational agents. Relevant biological and clinical issues are pregnancy and exposure to exogenous hormones. The intense hormonal stimulation of pregnancy (both estrogen and progesterone) has no adverse impact on the course of breast cancer. Pregnancy, with its mammogenetic differentiation, results in the protection of this organ from carcinogenesis. Characterization of specific lobular morphology serves as an indicator of the level of differentiation achieved by the organ, and thus provides means to assess the risk of the gland undergoing neoplastic transformation when exposed to given agents. Sufficient evidence exists to indicate the possibility of a slightly increased risk of breast cancer after approximately one decade of postmenopausal estrogen use. A review of the epidemiologic studies of postmenopausal hormone replacement and the risk of breast cancer fails to provide definitive evidence. Recent information derives from observations of cellular proliferation, plasma and tissue estradiol and progesterone receptor levels, and the percentage of apoptotic epithelial cells in human breast tissue. Several studies suggest that short-term, continuous combined HRT does not increase breast cancer recurrence or mortality. The participation of sexual hormones in the mammogenetic process during pregnancy might serve as an intermediate end point in assessing the effectiveness of hormones as chemopreventive agents. Investigations based on history, and breast morphology, should enable us to select estrogens and progestogens for HRT, and adopt optimal therapeutic regimens.

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