Use of human chorionic gonadotropin in the prevention of breast cancer

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Cancer of the breast, the most common type of cancer diagnosed in US and northern European women, is the leading cause of cancer death among women aged 20–59 years [1]. Although mortality rates have significantly decreased in the USA since 1990 [2], over the last few decades, the incidence of breast cancer has been gradually and steadily increasing in women from all ethnic backgrounds in most western countries and in societies that are recently becoming westernized [3]. It has not been possible up to now to prevent this disease because both the cause of breast cancer and the reasons for its increasing incidence are still largely unknown. In those cases in which the cause is known, such as frequent x-ray exposure for diagnosis and follow up of chest diseases [4] or radiation therapy for Hodgkin’s disease [5,6], smoking at an early age [7], and exposure to chemical carcinogens in experimental models of mammary cancer [8–10], there is clear indication that breast cancer is initiated at a young age and before a first pregnancy.

Changes in lifestyle and environmental exposures that have occurred during recent decades in the western world might exert a significant influence in the global increase in number of new breast cancer cases diagnosed. These changes include the tendency to postpone motherhood until later in life, the reduction in family size in modern societies, and the rising of infertility with aging [11] and with environmental exposures [12,13]. A confirmation that these factors play a role in this increase is provided by the lifetime reduction in breast cancer risk resulting from the completion of a full-term pregnancy before age 24 years [14], and the even greater reduction when the number of pregnancies increases [14,15]. Experimental studies have confirmed that full-term pregnancy prevents the initiation of chemically induced cancer [16], a phenomenon mediated by the induction of differentiation of the mammary gland [17]; these observations led us to postulate that activation of this mechanism was the most physiological approach for breast cancer prevention.

However, for reaching a stage of differentiation that confers protection, the breast needs to traverse specific ‘high-risk windows’ during development from infancy to puberty [18,19]. As puberty approaches, the breast develops under the stimulus of pituitary and ovarian hormones and of locally produced growth factors. The mammary ducts grow from the nipple into the surrounding fat pad as the result of a combined process of lengthening and branching into smaller ducts that sprout into primitive lobules type 1 (Lob 1). Under the influence of the cyclic hormonal stimuli of the menstrual cycle, Lob 1 become larger and more complex, originating Lob 2, which remain mostly unchanged as long as a woman does not become pregnant [18,19]. When the first pregnancy occurs, the fertilized egg, or ovocyte, becomes a new endocrine gland by secreting human chorionic gonadotropin (hCG) [20]. After implantation during the first week of pregnancy, hCG is detected in the maternal serum and urine, serving as a biomarker confirmatory of pregnancy [21]. As pregnancy progresses, the hypothalamic–pituitary–gonadal axis responds to placental and fetal stimuli by changing the maternal endocrinological milieu, which in turn stimulates the breast parenchyma to branch more profusely and form new and larger lobules type 3 (Lob 3).

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By the last trimester of pregnancy Lob 3 further enlarge into Lob 4 and begin to secrete milk, activity that becomes more intense after delivery and continues during lactation. After weaning, all the secretory units of the breast regress, reverting to Lob 3 and then to Lob 2. Each new pregnancy will repeat the cycle of lobular development and lactation. After menopause, all
remaining differentiated lobular structures regress; they appear morphologically similar to Lob 1 of nulliparous women but differ in proliferative activity and genomic profile [10], which becomes a permanent biomarker of reduced breast cancer risk conferred by the changes induced in the breast by the gestational events.

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How to utilize this knowledge for the prevention of breast cancer in the general population? Recent progress in defining the early premalignant phases of breast cancer has made secondary prevention a real possibility. Although the detection of the inheritance of cancer-predisposing genes, such as BRCA1/BRCA2, identifies women under a definitive threat, since their lifetime breast cancer risk increases by 85%, this knowledge does not suffice for predicting whether a carrier of deleterious mutations in these genes is going to develop breast cancer and, if so, when. Furthermore, the prognosis of these tumors is worsened by the significantly lower age of onset of the disease than for sporadic breast cancer and by the tumors' lack of estrogen receptor-α, which makes them unresponsive to endocrine therapy [22,23]. These uncertainties have required the implementation of broad, population-based strategies utilizing antiestrogen preventive measures that have significant side effects, require protracted treatment and might not benefit women that would develop estrogen receptor negative tumors [22].

In order to overcome these hurdles it became necessary to develop a new approach for breast cancer prevention capitalizing on the preventive effect of the hormones of pregnancy, which, by inducing differentiation of the breast, imprint a permanent genomic signature that is associated with reduced breast cancer risk [10,17]. The experimental demonstration that hCG [24], the hormone synthesized by the embryo and the placenta, is the one mediating the preventive effect of pregnancy, made it natural to select this specific hormone for the prevention of breast cancer. Both historical and experimental evidences support this selection. hCG is the first hormone noted in the human species prior to its recognition in animals [25]. It has served as a biomarker of pregnancy since as early as the eighteenth Dynasty in ancient Egypt, circa 1530 BC, as described in the Berlin papyrus [26].

This 'pregnancy test' consisted of moistening a cloth bag containing barley and another bag containing wheat with a woman's urine; if both seeds sprouted, the test was positive. It also served for predicting the sex of the baby: when only barley sprouted, it predicted a male; when only wheat sprouted, it was a female conceptus. This test was based on hCG's curious property of stimulating plant germination through a mechanism similar to that ascribed to the phytohormones gibberellins [27]. More than 3400 years elapsed until, in 1928, Ascheim and Zondek reported their new discovery that the urine of pregnant women contained something that stimulated the ovaries of mice and rats, and Friedman reported the same phenomenon in rabbits, thus initiating a new era in pregnancy testing [25,28]. The isolation, purification and characterization of this substance present in the urine of pregnant women (urinary hCG) identified it as a water-soluble glycoprotein hormone composed of an α and a β subunit [29]. The development of antibodies specific for the β subunit set the basis for the development of a standardized method for the diagnosis of pregnancy, including the currently used home pregnancy test [30].

Urinary hCG is currently used for the treatment of male and female infertility, corpus luteum insufficiency, habitual or threatened abortion, hypogonadism and cryptorchidism in the male [31], treatment of Kaposi's sarcoma in AIDS patients [32], and weight reduction [33]. A recombinant preparation (r-hCG) that has the same physicochemical, immunological and biological activities of the urine-derived hCG [34] has been approved by the US FDA for its use as a subcutaneous injection and for patient self-administration in assisted reproductive technologies [35,36]. In preclinical studies using the 7,12-dimethylbenz(a)anthracene-induced mammary tumor model, treatment of virgin rats with r-hCG exerted both a cancer preventive and a therapeutic effect, inhibiting cancer development when administered before carcinogen exposure and tumor growth when given to tumor-bearing animals [37]. The effect of r-hCG on primary breast cancer in postmenopausal women has been tested in a pilot double-blind, placebo-controlled study. Postmenopausal women with primary operable breast cancer (T1-T3) that was diagnosed by core biopsy received, on alternate days for 2 weeks, an intramuscular injection of either r-hCG (500 µg) (n = 20) or placebo (n = 5).
Therapeutic mastectomies or lumpectomies were performed on day 15. The proliferative index, steroid hormone receptor and inhibin immunoreactivity were determined in the core biopsies and in the final surgical specimens. In r-hCG-treated patients, the proliferative index was reduced from 18 to 4% (p < 0.00006) and inhibin expression was significantly increased in comparison with the placebo group. The hormonal treatment was well tolerated and no local or systemic side effects were seen at any time [38].

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For developing a protocol for breast cancer prevention, it is necessary first to identify the specific population or populations at risk and, within these populations, the specific windows during which hormonal stimulation of breast development will result in protection. Who would benefit from hCG treatment for breast cancer prevention? In principle, all women who have not borne children, since parous women have already been exposed to hCG during pregnancies. An additional risk is associated with the inheritance of cancer-susceptibility genes, namely BRCA1 and BRCA2 [39], as well as other genes, such as TP53 and ataxia-telangiectasia [40–42], that encode essential products for the normal cellular response to environmentally induced damage, such as ionizing radiation-induced cluster damage and double-strand breaks that affect cellular repair processes [40]. In addition to the gene-environment interaction [43] BRCA1 might be involved in the pathogenesis of sporadic breast cancer, such as the basal-like type [44,45]. Inherited breast cancer accounts for less than 5% of all the newly diagnosed breast cancer cases. The overwhelming majority of cases are sporadic, occurring in women with no family history or no known risk factors, except for a history of exposure to radiation [46,47], alcohol consumption [48,49] and smoking at a young age [7]. Thus, those asymptomatic female carriers of inherited deleterious mutations and women with a history of noxious environmental exposures at a young age represent groups in which there is an urgent need for implementing measures for breast cancer prevention.

An ongoing study has been designed with the primary objective of establishing the proof of principle that treatment of asymptomatic nulliparous female carriers of BRCA1 germline mutations 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. Eligible candidates are women aged 25–40 years. They will receive a 3-month treatment with r-hCG after evaluating their breast epithelium genomic baseline in samples obtained by fine-needle aspiration. This procedure will be repeated at the end of treatment and 6 months after the termination of treatment. Participating women will be asked to complete a weekly symptom checklist while on study medication. Potential risks will be minimized by the choice of a study drug with known low-toxicity profile and by the short duration of treatment required to meet study objectives.

Results obtained through these studies will reveal whether the induction of breast differentiation in nulliparous high-risk women will revert the ‘high-risk’ to a ‘low-risk’ signature by virtue of the treatment with r-hCG; the new signature would serve as a biomarker indicative of decreased breast cancer risk. These studies are preceded by a large body of work designed for understanding normal breast differentiation and the hormonal basis of cellular regulation in mammary tissue. Given the prevalence of breast cancer in the general population and the identification of hereditary forms of breast cancer susceptibility with significantly increased breast cancer risk, the need to apply what is known about breast differentiation to novel applications of preventive and therapeutic drug regimens is urgent. This series of inter-related studies will not only explore physiological bases of breast cancer prevention and treatment, but will also establish novel biomarkers predictive of cancer risk and prevention.

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The authors hold the patent (7183251) for a method of treating metastatic mammary tumors in postmenopausal women. They have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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