Pregnancy Levels of Estrogen and Progesterone: The Double-Edged Sword

To the Editors: Pregnancy-associated breast cancer has a poor prognosis, and there is a transient increase in breast cancer risk after each birth (1). Albrektsen et al. (2) recently reported that pregnancy hormones may have a progressive effect on breast tumors in addition to a possible promoting effect. In their study, the largest proportion of stage II to IV tumors was found among women diagnosed during pregnancy or <2 years after birth. The long duration of elevated levels of estrogen and progesterone is also associated with increased breast cancer risk (3). Pregnancy hormones per se have been described to also exert a possible progressive or promoting effect on breast cancer: Placental weight is positively associated with maternal risk of breast cancer (4), and Hispanic women, who are at lower risk of breast cancer than Anglo women, have been reported to have the lowest pregnancy values of progesterone (5).

On the other hand, in the general population, pregnancy is associated with a reduced risk of breast cancer, and full-term pregnancy early in life is the most effective natural protection against breast cancer in women (6). The short duration of estradiol and progesterone pregnancy levels is associated with reduced breast cancer risk over the host lifetime (3). The hormonal milieu of pregnancy affects the developmental fate of a subset of mammary epithelial cells such that they become resistant to neoplastic transformation (3).

It has been recently reported that pregnancy is associated with a reduced risk of breast cancer in BRCA1 and BRCA2 mutation carriers, although the extent and pattern of this association could be different from that observed in the general population (7). These authors assert that “pregnancy furthers the differentiation of the terminal end buds and induces dramatic changes in the parenchymato-stroma ratio of breast tissue, thereby conferring protection against the development of breast cancer” (8). By contrast, following pregnancy and lactation, the mammary gland regresses to its prepregnant state. The gland involution phase, which is matrix protease dependent, resembles that of a wound-healing environment. Fibroblasts secrete proteases that degrade the extracellular matrix proteins, with the consequent release of bioactive matrix fragments promoting tumor growth, motility, and invasion. These changes in the microenvironment are enhanced by the tumor cells, which are activated by the cytokine-enriched microenviron-

ment, becoming motile and invasive. These activated tumor cells, through the fibrillar collagen-rich interstitial matrix, gain access to local vasculature and lymphatics (9).

In conclusion, multiple full-term pregnancies seem to be associated with a moderate reduction in the risk of breast cancer in BRCA1 and BRCA2 mutation carriers (7). Further studies are needed to understand the mechanisms underlying the observed long-term protective effect of full-term pregnancies on breast cancer risk, as the cross-talk between the tumor cells and their microenvironment could activate them during the postpregnancy gland involution phase (9). The next logical step could be to target the breast microenvironment after pregnancy to avoid its promoting effect on occult cancers.

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