LAY ABSTRACT

TITLE: The proliferative response to p27 downregulation in estrogen plus progestin hormonal therapy is lost in breast tumors

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Increased breast cancer risk is observed in postmenopausal women receiving estrogen + progestin (synthetic progesterone) hormone replacement therapy (HRT). The current study examines hormonal regulation of the progesterone receptor in the normal postmenopausal human breast and the mechanism(s) by which progestins may increase cell division and breast cancer risk. Benign breast tissue from postmenopausal and premenopausal women, and breast tumor tissue from postmenopausal women, were analyzed for changes in progesterone receptor expression in response to estrogen-alone HRT (E HRT) compared to combined estrogen + progestin HRT (E+ progestin HRT). In postmenopausal women who did not receive HRT, the expression of progesterone receptor decreased compared to premenopausal women. Both E HRT and E + progestin HRT in postmenopausal women were associated with increased progesterone receptor expression in the breast, as well as changes in the levels of two proteins that regulate cell division or cell growth in the breast, compared to no HRT. The two proteins whose levels changed are cyclin E and p27. With both types of HRT, the amount of cyclin E in the nucleus of a breast cell increases, while the amount of p27 in the nucleus of a breast cell decreases. The nucleus is where DNA, the cell's genetic material, is duplicated in the process of cell division. The changes in cyclin E and p27 that we see usually indicate increased cell division. Interestingly, with E + progestin HRT, the decrease in nuclear p27 is greater than that seen with E HRT. In breast cancers, E + progestin HRT was also associated with decreased nuclear p27 compared to E HRT, but this was not associated with increased cell division. This result suggests that p27 has a role in cell division in the normal human breast, but not in breast tumors. RANKL is another protein that is increased by E+ progestin HRT, but not by E HRT. RANKL can increase cell division in breast cells, as well as increase breast stem cells. Many breast cancer investigators believe that these stem cells are a primary target in causing breast cancer. This raises the possibility that progestin in E+ progestin HRT may increase breast cancer risk by both increasing the number of susceptible stem cells in the breast and promoting cell division in breast cells. Of note, our results also show that "natural" progesterone and progestin act similarly on the genes that control cell division and maturation of breast cells. Given that the exact functions of progestins to promote breast cancer risk are not fully understood, treatment with any progestin, whether natural or synthetic, should be viewed with caution.