Review of Studies Related to Breast Cancer Involved Hormonal Imbalance in Menopausal Women

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1) Estrogen/androgen balance is important for normal development of breast tissue. Estrogen possesses proliferative effects on breast and uterine tissues. Unopposed estrogen is known to cause breast and uterine cancer.

2) Progesterone works to counteract the harmful effects of unopposed estrogen at the uterine level but not at the breast tissue. Women's Health Initiative Study showed that combination of estrogen/progesterone (Premarin/Provera) led to a 26% increase in risk of breast cancer after 5.2 yr of follow-up (1).

3) The issue exists of which hormone or any hormone could counter actions of estrogen at the breast cancer tissue. It is difficult to study normal breast tissue because normal breast tissue loses its steroid receptors as soon as it isolated and placed in culture. Many studies found that androgens have antiproliferative effect on breast tissues to counter the effects of estrogen. The antiproliferative effects of androgen depend on few factors.

    a) Estrogen status and type of androgen used:
    (Ando et al (2) reported that DHEA-S and androstenediol stimulate growth of MCF-7 cells in absence of estradiol but reduced cell proliferation in presence of estradiol with 1 nmol/L whereas testosterone and dihydrotestosterone (DHT) at 1-100 nmol/L inhibit MCF-7 cell proliferation)

    b) Androgen concentration:
    (Boccuzzi et al. (3) reported very high concentration of dihydrotestosterone (DHT) of 200nmol/L (normal 0.2 - 0.8 nmol/L) stimulate MCF-7 cell growth whereas lower concentration inhibit cell growth)

    c) Type of breast cancer cell line
    MCF-7; MDA-MB-453; BT-20; T47-D; and ZR-75-1

4) Zhou and colleagues studied testosterone on ovariectomized rhesus monkeys
    a) Treatment of estradiol alone increase mammary epithelial proliferation by six folds and estrogen receptors mRNA increase by 50%
    b) E2/P (E2= estradiol; P=Progesterone) Progesterone did not alter E2 proliferative effects in rhesus monkey ovariectomized. This data is in contrast to the finding from Dr. Ben Formby and Dr. T.S. Wiley at UC Santa Barbara. They found that two genes that stimulates estrogen (estradiol) and progesterone. The estradiol turns BCL2 gene and the cell grows rapidly. However when progesterone which upregulates P53 gene added to tumor cell lines with estradiol, the tumor cell stop growing rapidly. This finding suggested progesterone decreases breast cancer risk with estrogen therapy (10). This study from Dr. Firmly and Wiley contrast with the Women's Health Initiative Study which showed that combination of estrogen/progestin (Premarin/Provera) led to a 26% increase in risk of breast cancer after 5.2 yr of follow-up.
    c) E2/T (T=testosterone) Testosterone reduced E-2 proliferation by 40%
    d) Tamoxifen produces a threefold increase in mammary epithelial proliferation but it also reduced ER expression below placebo level

5) The Women Health Initiative (WHI) found no statistical differences in the effect of doses other than 0.650 mg of estradiol (5). Pickar and colleagues found the rates of endometrial hyperplasia is lower with lower doses but endometrial cancer risk was not changed (6). In the WHI study, investigators found that there are no statistical differences among women who currently used estrogen therapy for 5 to 10 years with body mass index of 25 or higher. The risk increases for women with ER+/PR+ in leaner women and who use estrogen therapy longer than 10 years. The study concluded that women who used estrogen therapy for treatment of osteoporosis usually require long-term therapy should explore other options, given the increased risk of breast cancer with long-term use.

6) Dimitrakakis and his colleagues did a retrospective and observational study that followed 508 postmenopausal women receiving testosterone from 1987 to 1999 (7). The average age of women was 56 years and the mean duration of follow-up was 5.8 years. Breast cancer incidence was compared to untreated women and women using usual hormone therapy reported in literature.
    a) In the 508 postmenopausal women receiving testosterone study, investigators found the rates of invasive breast cancer were 238 per 100,000 woman-years.
    b) Rate for women with estrogen/progestin and testosterone was 293 per 100,000 woman-years
    c) The Women Health Initiative study, the rate incidence of women using estrogen for breast cancer is 380 out of 100,000 woman-years
    d) In the Million Women study, the rate of breast cancer incidence is 521 per 100,000 woman-years

e) For women who never use hormone therapy, the rate of breast cancer incidence was 283 per 100,000

The results showed that women using testosterone have similar breast cancer rates as those women who do not have hormone therapy observed in general population. This observational study suggested that addition of testosterone to conventional hormone therapy for postmenopausal women does not increase induced breast cancer risk. To confirm this finding, a randomized and placebo-controlled study will be necessary to verify the point.

7) Medroxyprogesterone acetate (MPA) is the major progestin used for oral contraception and hormone replacement therapy. It has been implicated in increased breast cancer risk. Ghatge and colleagues wanted to understand if the increase in breast cancer risk is due to progestional or androgenic properties. To address the effects of medroxyprogesterone acetate on androgen receptor, investigators compared receptor expression profile of progesterone, medroxyprogesterone acetate (MPA), and dihydrotestosterone (DHT) in Y-AR cells (breast cancer cell line). The study found that there is extensive gene regulatory overlap between DHT and MPA through the androgen receptor and none with progesterone. They concluded that MPA does not mimic those of endogenous progesterone alone, but it is also possible that increased breast cancer risk and/or the therapeutic efficacy of MPA in cancer treatment is in part mediated by androgen receptor (11).

8) Most of androgens in women, especially after menopause, are synthesized in peripheral intracrine tissues from inactive precursors dehydroepiandrosterone (DHEA) of adrenal origin (8). Administration of DHEA results in beneficial effects in postmenopausal women through its transformation into androgens and/or estrogens in specific target tissues without significant side effects. DHEA does not stimulate endometrium thus avoid the fear of progestin-induced breast cancer added to the well known effect stimulatory effect of estrogens (8). The levels of DHEA and DHEA-S drop dramatically about 50% in women 40 years compare to normal women of 21 years age (8).

In their studies, Li et al. investigated the possibilities of DHEA and its metabolites for prevention of mammary carcinoma (9). They incubated the induced mammary carcinoma in rats with DHEA implants up to 105 days. When DHEA given in a SILASTIC BRAND implants that produce a serum level DHEA of 7.09 and 17.5 nM led to a dramatic reduction of tumor development to 22% and 11% of animals having mammary carcinoma compared with a high 68% in control animals (9). When the dose was given with highest dose of DHEA (6 X 3cm) implant and serum DHEA level is 27.2 nM, the reduction of tumor area is almost complete to 3.8% in tumor size compare to 68% in control animals (8). The physiological DHEA range of a normal 20-30 years women are (8.3 to 17.3 nM).

This data suggests that DHEA has the potential effect for prevention of breast cancer in women.

In another study, Labrie et al, investigated the effect of DHEA on ZR-75-1 breast cancer cell line in vivo in nude mice (8). To avoid the DHEA effect from ovary production, investigators used ovariectomized animals and supplement it with 0.5 microgram estradiol (E_2). They found that with estradiol treatment alone, the tumors increased 9.4 fold over 291 days period in the nude mice (8). When animals treated with estradiol and percutaneous DHEA with 0.3, 1, 3 mg per animal each day, the inhibition of 50%, 77%, and 80% at 9.5 months treatment compared to treatment of estradiol alone. It is believed to be the first time that investigators demonstrated the inhibitory effect of DHEA on growth of human breast cancer xenografts in nude mice.

In addition to DHEA, researchers investigated the additive effects of DHEA and new antiestrogen EM-800 on the growth of DMBA-induced mammary tumors in rat. The result was 95% of control animals developed palpable mammary tumors by 279 days after DMBA administration (DMBA is agent used to induce mammary carcinoma). Treatment of DHEA or EM-800 alone reduced to 57% and 38% development of DMBA-induce mammary carcinoma. Whereas the combination of 10mg DHEA and 75 microgram EM-800 completely inhibit the growth of tumor in the group (no data given for number of animals in each group) (8).

In addition, one of DHEA benefits is to stimulate the effect on bone mineral density by increasing serum osteocalcin (135% over control). Osteocalcin is a marker for bone formation. DHEA could be use to prevent or treat osteoporosis whereas estrogen replacement therapy only reduces the rate of bone loss. Labrie et al, studied the effect of DHEA on 60-70 years old women (n=15). They found that bone mass density was increased by 2.3% at the hip, 2.2% at the lumbar spine. The authors of this review concluded that at physiological replacement doses, DHEA does not stimulate the endometrium, thus removing the need to use a progestin to counteract the stimulation of endometrium by estrogen. Also DHEA has other beneficial effects like increased muscle mass, improved libido whereas minimal negative effect have been observed (8). With the potential benefit effects of DHEA demonstrated in animal and invitro models, a clinical trial of randomized, double-blinded, and placebo control study would prove or disprove the benefits of DHEA.

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