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Review

Testosterone and breast cancer prevention

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ABSTRACT

Testosterone (T) is the most abundant biologically active hormone in women. Androgen receptors (AR) are located throughout the body including the breast where T decreases tissue proliferation. However, T can be aromatized to estradiol (E2), which increases proliferation and hence, breast cancer (BCA) risk. Increased aromatase expression and an imbalance in the ratio of stimulatory estrogens to protective androgens impacts breast homeostasis.

Recent clinical data supports a role for T in BCA prevention. Women with symptoms of hormone deficiency treated with pharmacological doses of T alone or in combination with anastrozole (A), delivered by subcutaneous implants, had a reduced incidence of BCA. In addition, T combined with A effectively treated symptoms of hormone deficiency in BCA survivors and was not associated with recurrent disease. Most notably, T + A implants placed in breast tissue surrounding malignant tumors significantly reduced BCA tumor size, further supporting T direct antiproliferative, protective and therapeutic effect.

Contents

1. Importance of T in women

Testosterone (T) is referred to as a 'male' hormone; however, it is the most abundant biologically active hormone in women. It is produced in the ovaries, adrenal gland, and abundantly (i.e., over 50%) at the cellular level from androgen precursors [1]. Testosterone and its active metabolite, dihydrotestosterone, have a direct physiologic effect at the androgen receptor (AR), located in virtually every tissue and organ system including the breast [2]. T is also the precursor hormone for estradiol (E2) and has an indirect effect at the estrogen receptor (ER) via aromatization. Adequate levels of T are critical for overall mental and physical health, immune function, glycemic control and

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reducing inflammation, all of which may impact cancer occurrence [3,4].

Evidence that women become T deficient has been largely ignored. As in men, T and its precursor hormones peak in women in their twenties and decline with age [5]. Symptoms of androgen deficiency occur as early as the mid-thirties in some women and physicians are slowly recognizing the benefits of T supplementation. Subcutaneous T implants have been shown to be a safe and effective method of T delivery for over 70 years in both sexes [6,7]. Adequate levels of continuous T released from the implants also provide a major source of E2 in postmenopausal women through aromatization.

2. Effects of T on the breast and the role of aromatase

There is abundant evidence that androgens are breast protective. In vitro breast cell cultures and in vivo primates studies support that T's direct effect at the AR is antiproliferative, proapoptotic, and inhibits ERα activity and breast cancer (BCA) cell growth [8–10]. Long-term female to male transgender studies and other clinical evidence also support the protective role of androgens in the breast [11,12]. Eighty to 85% of BCA are AR positive. AR positivity is associated with more favorable tumor characteristics and better prognosis including increased disease free and overall survival [9,13]. Androgens, including T pellet implants, have been used to treat BCA in the past with success and a recent study reports a 58.5% response rate in hormone resistant metastatic BCA [14].

Correlations between sex steroid levels and BCA have been inconsistent and controversial. Some epidemiological studies show an association between T levels and BCA, while others do not, and some report lower levels of bioavailable T in women with BCA [11,15,16]. Nevertheless, association does not infer causation. The association between high T levels and BCA may reflect the correlation between high androgen levels and higher estrogen levels as evidenced by studies that adjusted for estrogens and no longer found an association between T and BCA [15]. Also, most epidemiological studies do not address the 'Obesity-insulin-testosterone' connection. Obesity and insulin increases inflammation and appear to have direct and indirect causative roles in BCA through numerous pathways including increased aromatase expression. Furthermore, insulin stimulates the production of T, accounting for 'associated' increased T levels [17–20]. Many studies also suffer from methodological limitations including the inaccuracy of T assays in women and do not address or acknowledge the 'immeasurable' paracrine, autocrine and intracrine aromatization of T to E2 [21].

Aromatase is located throughout the body including breast adipose, stromal and parenchyma cells where T can exert a direct growth inhibitory effect by binding to the AR, or an indirect growth stimulatory effect via aromatization to E2 and activation of the ER [21–23]. Multiple factors, many of which are independent risk factors for BCA, can increase aromatase activity altering the homeostatic balance of E2 to T and thereby increasing proliferation of normal and BCA cells [3]. In addition, invasive and non-invasive BCA overexpress aromatase resulting in increased local tumor production of stimulatory estrogens [21–23].

3. Subcutaneous T hormone therapy and the incidence of BCA

T supplementation in ovariectomized women is well established and in some countries T is prescribed for postmenopausal women in addition to usual hormone therapy. A retrospective, observational study following women receiving T implants in addition to conventional hormone therapy found no increase in BCA in women on T therapy compared to historical control groups, suggesting that T therapy was able to reduce the estrogen/progestin therapy associated BCA risk [24].

Table 1
Indications for aromatase inhibitor therapy including signs and symptoms of estrogen excess [6,25,26].

- BCA
- Increased risk of BCA

ADH, LCIS, family history, BRCA positive

- Severe fibrocystic breast disease, breast pain
- Endometriosis, uterine fibroids
- Dysfunctional uterine bleeding
- Abdominal obesity, weight gain, insulin resistance
- Menstrual or migraine headaches
- Premenstrual syndrome, anxiety, irritability
- Fluid retention, bloating
- Elevated estradiol levels

BCA, breast cancer; ADH, atypical ductal hyperplasia; LCIS, lobular carcinoma in situ.

A prospective observational study (Dayton, Ohio) was specifically designed to investigate the incidence of BCA in pre and postmenopausal women treated with T or T combined with anastrozole (T + A) subcutaneous implants for symptoms of hormone deficiency [25]. Indications for aromatase inhibitor therapy are listed in Table 1. Over 95% of women in this study did not receive concurrent estrogen therapy, as continuous T (no estrogen) was able to adequately relieve symptoms in these patients [6].

A 5-year interim analysis of the Dayton study reported a BCA incidence rate of 142 per 100,000 person-years in the intent to treat group. This represents a significant reduced incidence of BCA in women treated with T implant therapy compared to both the age-matched control group and age-specific Surveillance Epidemiology and End Results (SEER) incidence rates; the reduced incidence was even more significant in women who were adherent to T therapy (Fig. 1) [25]. An 82-month updated interim analysis continued to demonstrate a reduced incidence of BCA in women adherent to T or T + A therapy (76/100,000) compared to calculated age-matched SEER incidence rates (297/100,000), RR 0.26 [26]. Being cognizant of signs and symptoms of excess estrogen and individualizing patient therapy to selectively include A in the implant may partially account for the reduced incidence of BCA in this patient population.

4. Subcutaneous T + A therapy in breast cancer patients

BCA treatment often results in ovarian failure or hormone depletion, which can negatively affect sexual desire and cause unpleasant urogenital and vaginal symptoms. Symptoms of hormone

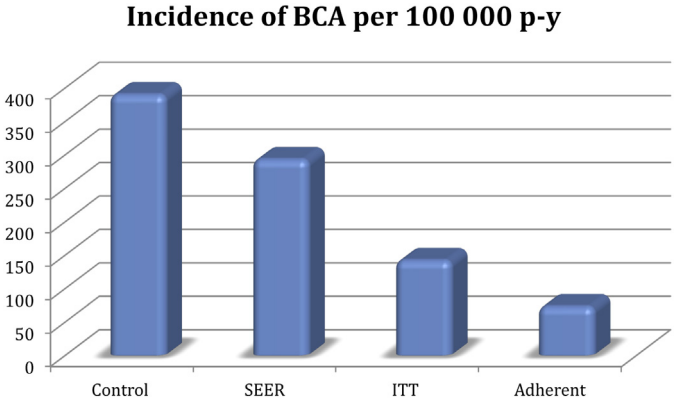

Fig. 1. Incidence of BCA per 100,000 person-years, 5-year interim analysis results: Age-matched controls (390/100,000), Age-specific SEER expected incidence rates (293/100,000), T therapy, intent to treat group (142/100,000), T therapy, patients adherent to therapy (73/100,000) [25].