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Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: A prospective, observational study☆

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ABSTRACT

Objectives: There is evidence that androgens are breast protective and that testosterone therapy treats many symptoms of hormone deficiency in both pre and postmenopausal patients. However, unlike estrogen and progestins, there is a paucity of data regarding the incidence of breast cancer in women treated with testosterone therapy. This study was designed to investigate the incidence of breast cancer in women treated with subcutaneous testosterone therapy in the absence of systemic estrogen therapy.
Study design: This is a 5-year interim analysis of a 10-year, prospective, observational, IRB approved study investigating the incidence of breast cancer in women presenting with symptoms of hormone deficiency treated with subcutaneous testosterone (T) implants or, T combined with the aromatase inhibitor anastrozole (A), i.e., T + A implants. Breast cancer incidence was compared with that of historical controls reported in the literature, age specific Surveillance Epidemiology and End Results (SEER) incidence rates, and a representative, similar age group of our patients used as a 'control' group. The effect of adherence to T therapy was also evaluated.
Results: Since March 2008, 1268 pre and post menopausal women have been enrolled in the study and eligible for analysis. As of March 2013, there have been 8 cases of invasive breast cancer diagnosed in 5642 person-years of follow up for an incidence of 142 cases per 100 000 person-years, substantially less than the age-specific SEER incidence rates (293/100 000), placebo arm of Women's Health Initiative Study (300/100 000), never users of hormone therapy from the Million Women Study (325/100 000) and our control group (390/100 000). Unlike adherence to estrogen therapy, adherence to T therapy further decreased the incidence of breast cancer (73/100 000).
Conclusion: T and/or T + A, delivered subcutaneously as a pellet implant, reduced the incidence of breast cancer in pre and postmenopausal women. Evidence supports that breast cancer is preventable by maintaining a T to estrogen ratio in favor of T and, in particular, by the use of continuous T or, when indicated, T + A. This hormone therapy should be further investigated for the prevention and treatment of breast cancer.

1. Introduction

Excluding skin cancer, breast cancer is the most common cancer among women, with a lifetime risk of 1 in 8. It is well recognized that estrogen and progestin therapy stimulates breast tissue and increases the incidence of breast cancer. However, the long-term effect of T therapy on the incidence of breast cancer has not been previously documented in a prospective study. This is becoming increasingly important as more research is being performed, and more studies are being published on the benefits of T therapy in women [1–7].

There is some concern about T and breast cancer risk. Although some epidemiological studies have shown an increased incidence of breast cancer associated with endogenous T levels [8–12], others have not [13–16]. In addition, some studies have found T levels to be protective [17,18]. Overall, the evidence from epidemiological studies is conflicting. Furthermore, there are methodological

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limitations, both for these studies, and for T assays, which have been shown to be inaccurate in women.

Another concern is that T is the major substrate for estradiol and therefore has a secondary 'stimulatory' effect at the estrogen receptor (ER). Anastrozole (A), combined with T in a pellet implant, has been shown to prevent aromatization and provides adequate levels of T without elevating estradiol in breast cancer survivors [19,20]. Also, T has been shown to safely relieve side effects of aromatase inhibitor therapy in cancer survivors [21,22].

T therapy is being increasingly prescribed, and its long-term effect in the breast need to be further elucidated. The Testosterone Implant Breast Cancer Prevention Study, i.e., 'Dayton study', is a prospective, observational study that was specifically designed to investigate the incidence of breast cancer in women treated with subcutaneous T implants for symptoms of hormone deficiency. This 5-year interim analysis addresses the incidence of breast cancer in women treated with subcutaneous T, or T + A without concurrent use of systemic estrogen or synthetic progestins.

2. Methods

2.1. Study design, setting, and participants

All patients enrolled in the study are part of an ongoing, 10-year observational, longitudinal prospective IRB approved study, investigating the incidence of breast cancer in women treated with subcutaneous T implants. The study was approved in March of 2008 at which time recruitment was initiated. An interim analysis was planned for year 5, March of 2013.

Pre and post menopausal patients participating in the study were either self-referred or referred by their physician to the clinic (RG) at the Millennium Wellness Center in Dayton, Ohio for symptoms of relative androgen deficiency including hot flashes, sweating, sleep disturbance, heart discomfort, depressive mood, irritability, anxiety, pre-menstrual syndrome, fatigue, memory loss, menstrual or migraine headaches, vaginal dryness, sexual problems, urinary symptoms including incontinence, musculoskeletal pain and bone loss. Female patients with no personal history of breast cancer were asked to participate in this study. Study size was not predetermined. All patients continuing T therapy were invited to participate in the study. No patient was excluded from participation based on age, prior hormone use, oral contraceptive use, endometrial pathology, breast density, increased cancer risk, menopausal status or body mass index (BMI). Mammography and clinical breast exam were not protocol determined. Screening mammograms were recommended, but not required, prior to enrollment. As predetermined, patients with a single T pellet insertion were not included in this analysis. Patients who had received T implants prior to the IRB approval date were not excluded from participation and were recruited to the study beginning March 2008. An IRB approved, written informed consent was obtained on all patients enrolled in the study. As per IRB protocol, the incidence of breast cancer in our study population was to be compared to historical controls as well as age specific Surveillance Epidemiology and End Results (SEER) data.

Although a control group was not part of the original IRB approved protocol, it was predetermined that patients receiving only one pellet implant, i.e., 3 month of therapy, would not be eligible for analysis. Such short-term hormone use would not have a long-term affect on the incidence of breast cancer. This group of 119 patients, enrolled and treated prior to 2010, was followed prospectively as a 'control' group. As of January 2010, only patients who continued T therapy (>1 insert) were enrolled in the study.

Table 1
Indications for aromatase inhibitor therapy in female patients.

History of breast cancer
Increased risk for breast cancer
Atypical ductal hyperplasia
Strong family history
Lobular carcinoma in situ
Severe fibrocystic breast tissue, breast pain
Endometriosis, uterine fibroids, dysfunctional uterine bleeding
Weight gain, increased abdominal obesity/fat
Insulin resistance, metabolic syndrome with elevated estradiol
Menstrual or migraine headaches
PMS, anxiety, irritability, aggression, fluid retention, bloating

Adapted from the 9th European Congress on Menopause and Andropause [10].

2.2. Subcutaneous implants, the evolution of testosterone therapy in clinical practice, testosterone combined with anastrozole

The T and T + A implants used in this clinical practice (RG) are compounded by a pharmacy in Cincinnati, Ohio. They are composed of non-micronized USP testosterone (T) and steric acid, or non-micronized USP T, steric acid and USP anastrozole (A); compressed with 2000 pounds of pressure using a standard pellet press into 3.1 mm (diameter) cylinders; sealed in glass ampoules, and sterilized at 20–25 psi of pressure at 121 °C (250 F) for 20–30 min. The sterile implants are inserted into the subcutaneous tissue of the upper gluteal area or lower abdomen through a 5 mm incision using a disposable trocar kit.

This clinical practice (RG) has evolved over the past 6 years. Systemic estrogen therapy was used in the majority of patients through 2008. However, it became evident that subcutaneous T was able to treat symptoms in over 95% of patients, and the routine use of estrogen, including estradiol (E2) implants, was discontinued. In this practice, T implant dosing is weight based with an average starting dose of 2–2.5 mg/kg and is adjusted based on clinical response; the average interval for T pellet insertion is 13.8 ± 3.8 weeks [1,24].

We began using anastrozole (A), an aromatase inhibitor, combined in the pellet implant in 2008; initially, to treat symptoms of hormone deficiency in breast cancer survivors and men on T implant therapy [19,20]. Subsequently, beginning early 2010, women who presented with signs or symptoms of hyperestrogenism, obesity or increased risk for breast cancer were offered A in combination with T as a pellet implant. We have also found that pre-menopausal patients with symptoms of excess estrogen including migraine headaches, dysfunctional uterine bleeding, endometriosis, uterine fibroids, breast pain or severe premenstrual syndrome, also benefit from the 'low dose' (compared to 1 mg/day oral) A delivered subcutaneously with T. As previously reported, current indications for aromatase inhibitor (AI) therapy followed in this clinical practice are listed in Table 1 [20].

The amount of A in the pellet implant is 4 mg combined with 60 mg of T, which allows for consistent, simultaneous release of both the T and A. Two implants, a total of 8 mg of A, has been shown to prevent elevation of E2 in breast cancer survivors treated with subcutaneous T [19]. We have subsequently found that 4 mg of A, one T + A pellet, is able to prevent symptoms of excess estrogen in many women without breast cancer. The T and T + A dosing is based on clinical history, symptoms, clinical observation, weight, amount of fatty tissue, T dose and laboratory evaluation. Often, heavier, more obese patients require higher doses of both T and A, Table 2.

2.3. Data analytics, patient follow up

From March of 2008 through February of 2010, all data were entered into an excel format. In February 2010, a custom web-based application using Microsoft Active Server Pages with a MySQL